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Executive Summary

February 2013 – Journal coverage for February focused primarily on behavioral health, traumatic brain injury and medical protocol and training with a significant number of relevant articles discussing nutrition, obesity, surgeries and substance abuse. Research on medical protocol and training dominated journal coverage with subjects ranging from tracking tissue for transplantation and evaluating medical personnel’s knowledge of the health issues unique to Soldiers with same sex partners to evaluation of the patient-centered medical home. *Military Medicine* was particularly interested in evaluating the patient-centered home with research discussing patient outcomes, staff satisfaction, facility culture and the potential for budget reduction.

Behavioral health research studied nurses’ post-deployment reintegration, the association between depression and hospital outcomes as well as risk and protectant factors of PTSD, depression and alcohol misuse. TBI continued to draw a significant amount of research including a well-publicized study on the relationship between PTSD and mild TBI and various studies pointing to the potential long-term effects of TBI.

Several journal articles received specific attention in traditional media including, most prominently, research from *Armed Forces & Society* indicating that combat exposure and military-related factors have little to no association with suicide risk. A second study, published by *Military Medicine*, supported these results in indicating that PTSD and depression among veterans who served on the wars in Iraq and Afghanistan is associated with a lack of social support rather than combat experience. Finally, Army researchers’ development of an effective treatment for Cutaneous Leishmaniasis was also widely covered and highlights Army Medicine’s contribution to world healthcare.

Medical Journal Coverage

*Behavioral Health*

**Military Medicine: U.S. Army Nurses’ Reintegration and Homecoming Experiences After Iraq and Afghanistan**

Researchers evaluated U.S. Army nurses’ reintegration experiences after deployments in Iraq and Afghanistan. Five themes arose during recorded interviews including, the belief that “no one cares,” the argument that pre and post-deployment interviews are performed to “check the box,” enhanced stress of being home due to the need to now focus on family responsibilities on top of duty requirements, the belief that those who
have not deployed do not understand their unique stressors, and the belief that a deployment “just changes you.” These themes reveal that nurses experience some of the same outcomes as Soldiers engaged in combat deployments, and they point to the need for improved intervention for nurses returning from deployments.

**Canadian Medical Association Journal: Association between depression and hospital outcomes among older men**

Previous research on the link between depression and hospital outcomes has focused on very specific populations. In widening the research population, this study finds that the presence of depressive symptoms is a significant predictor of hospital admission for non-psychiatric conditions, number of hospital admissions and the length of hospital stay. Research such as this indicates the impact depression can have on Soldiers’ health as well as the burden of the cost of healthcare to Army Medicine. Targeting this high-risk group can help reduce the burden of healthcare cost for Army Medicine.

**Military Medicine: Operation BRAVE Families: A Preventive Approach to Lessening the Impact of War on Military Families Through Preclinical Engagement**

Operation Building Resilience and Valuing Empowered Families (OBF) is a program established by Army Medicine to empower families of wounded warriors. In studying the effects of OBF on the children and spouses of wounded warriors, this study and literature review determines that OBF can be used as a model for other military treatment facilities as well as civilian hospitals. Programs and research such as this highlights Army Medicine’s benefit to its community as well as its contribution to civilian healthcare.

**Military Medicine: Placement of Combat Stress Teams in Afghanistan: Reducing Barriers to Care**

Deploying medical personnel requires leadership to determine which populations have the greatest need for combat stress personnel. The distribution plan for Combat Stress Control teams was created after evaluating ratios of combat stress personnel and troops as well as statistics on troops who may be at-risk to develop stress disorders. An evaluation of this distribution plan confirms its effectiveness and proves the importance of future evaluation of such plans.

**BMC Medicine: Depression pathogenesis and treatment: what can we learn from blood mRNA expression?**

Patients with severe depressive disorders consistently display alterations in biological systems, but these alterations have previously been studied through the use of saliva. This literature review studies the evidence supporting the use of peripheral blood gene expression to determine the pathogenesis of and biomarkers associated with depression. The review finds consensus that patients with major depressive disorders exhibit
altered patterns of expression in several genes. The review also indicates that peripheral blood gene expression is a clinically relevant biomarker approach that can assist Army Medicine in evaluating Soldiers with severe depressive disorders.

**Military Medicine: Risk and Protective Factors Associated With Symptoms of Post-Traumatic Stress, Depression, and Alcohol Misuse in OEF/OIF Veterans**

Given the increase in mental health problems among Soldiers returning from the wars in Iraq and Afghanistan, researchers are interested in determining the risk and protective factors associated with post-deployment mental health issues including, PTSD, depression, and alcohol misuse. Researchers looked specifically at the tendency for negative attitude, pre-deployment life events, combat experience, perceptions of threat and post-deployment social support for mental health symptoms. Results indicate that a negative attitude is most closely linked with mental health problems, and the study shows combat experience only plays a secondary role in the development of depressive disorders. Results indicate that social support appears to be a powerful preventative to mental health concerns, and its effect increases overtime. For Army Medicine, increasing Soldiers’ access to social support systems can, overtime, lower instances of mental health concerns.

**Military Medicine: Treatment of Avoidant Personality Traits in a German Armed Forces Inpatient Psychiatric Setting**

Avoidant personality traits have been known to lead to interpersonal conflict which, in turn, can cause susceptibility to mental disorders. This study examines the German military’s practice of providing enhanced therapy to treat Soldiers who display symptoms of avoidant personality disorder. Data suggests inpatient treatment for these personality traits improves psychiatric symptom severity among Soldiers while social skills group training was not any more effective than individual treatment outcomes.

**Disease**

**The Lancet: Synergies in integrated malaria control**

The article from Lancet’s Infectious Diseases journal urges concern over the spread of insecticide resistance and the implications of resistance on insecticide-based approaches to malaria control strategies. The trial seeks to determine the efficacy of bed nets with either indoor residual spray (IRS) containing carbamates or a carbamate-infused plastic wall covering. The researchers discover no particular benefit with the use of bed nets and supplemental use of carbamate given carbamate’s short half-life.

**HIV Medicine: Determinants of Incident Chronic Kidney Disease and Progression in a Cohort of HIV-infected Persons With Unrestricted Access to Health Care**
In order to control for socioeconomic factors, which may impact the risk of chronic kidney disease (CKD), researchers use a population of 3360 HIV-infected subjects with universal access to health care. Findings indicate a low incidence of CKD that may be due to a younger demographic, early HIV diagnosis, or other factors.

**JAMA: Veterans’ Complex Chronic Illness Requires Personalized Care, Says IOM**

Caring for veterans’ health is complicated by the prevalence of chronic multisymptom illness (CMI) among the military and veteran populations. As medical associations focus on reducing care by automating healthcare treatment, CMI’s provide an obstacle as they are challenging to treat and difficult to automate. The Institute of Medicine recommends The Department of Veteran Affairs continue to use post-deployment patient-aligned care teams that include treatment from primary care clinicians, nurses, mental health professionals, social workers, and other specialists.

**The New England Journal of Medicine: Topical Paromomycin with or without Gentamicin for Cutaneous Leishmaniasis**

Cutaneous Leishmaniasis is a disfiguring disease common in the Middle East and North Africa that can be transferred to humans through sandfly bites. This Army-supported and conducted research developed a successful antibiotic treatment for cutaneous leishmaniasis that is effective in significantly reducing the lesion in less than 42 days. Only a limited number of patients experienced a slight side effect to the topical treatment. The successful development of this treatment was covered in a prominent newswire, and it demonstrates Army Medicine’s ability to assist Soldiers as well as the local population.

**Military Medicine: Texting Away Malaria: A New Alternative to Directly Observed Therapy**

Communicating and complying with medical protocol can be challenging in austere environments. Army medical personnel involved in Operation Onward Liberty began using text messages to remind Soldiers to be aware of malaria dangers and to help ensure total and complete daily accountability as regards malaria prevention. After commanders required Soldiers to report through text message that they took their daily malaria medication there have been no reported malaria diagnoses among U.S. Forces in Liberia. Requiring Soldiers to report medial activity through text messages may be the best alternative for accountability during deployments.

**Medical Protocol and Training**

**Military Medicine: Diagnosis of Right Ventricular Cardiac Sarcoidosis With Cardiac Magnetic Resonance in a Patient Presenting With Ventricular Tachycardia**

The phenomenon of cardiac sarcoidosis, or the collection of chronic inflammatory cells, is rare and potentially fata. This article focuses on the possibility of diagnosing the case study, a 34-year-old African-American male. Through use of chest radiograph, computed tomography, positron
emission tomography, CMR, and transbronchial biopsy, the study urges physicians to consider the possibility of sarcoidosis in any instance of arrhythmia and to use, as a primary line of imaging, CMR. Army Medicine can utilize the information to screen for those at risk for cardiac sarcoidosis.

Military Medicine: The Patient-Centered Medical Home in the Transformation From Healthcare to Health

The Surgeon General of the Navy discusses the long-term trajectory of medicine in the United States and the importance of focusing on preventive care instead of relying on medicine following diagnoses. In an effort to refocus medical attention, Vice Adm. Matthew L. Nathan highlights the Patient-Centered Medical Home (PCMH), a partnership between Naval Hospital Pensacola and Walter Reed National Military Medical Center that is being implemented across the military health system (MHS).

JAMA: Enhanced Tracking of Tissue for Transplantation

Current methods for tracking tissue grafts are not effective in allowing for rapid communication that results in several risks including, the spread of diseased tissue, dangerous infections resulting from bacteria outbreaks at tissue-processing facilities, and the distribution of illegally obtained and potentially tainted tissue. Authors suggest the tissue banking industry adopt the blood bank’s practice of utilizing electronic tracking systems to enhance communication and hospital blood banks assume responsibility for tracking.

Military Medicine: Examining Selected Patient Outcomes and Staff Satisfaction in a Primary Care Clinic at a Military Treatment Facility After Implementation of the Patient-Centered Medical Home

Through evaluation of the Patient-Centered Medical Home (PCMH) model, researchers hone in on comparisons in emergency department visits and a 2-year review after PCMH implementation. In addition to patient outcomes, staff satisfaction was measured after two years. Researchers found improved access to care, fewer emergency visits, and a high level of staff satisfaction as well. The implementation of PCMH, a partnership between Naval Hospital Pensacola and Walter Reed National Military Medical Center, highlights the military’s focus and research on patient-centered care.

Military Medicine: Impact of a Patient-Centered Medical Home on Access, Quality, and Cost

In trying to determine whether the Patient-Centered Medical Home (PCMH) at Walter Reed Medical Center has resulted in reduced costs while improving access to care, the research uses both a patient database and patient surveys, which saw 4,090 subjects respond (39 percent). Factoring in the costs of ER visits and pharmaceuticals, beneficiaries see an approximate decrease in costs of 9 percent. The recognition that patient-centered care such as the PCMH can result in cost decreases offers Army Medicine the potential to highlight the quality of care.
Military Medicine: The Patient-Centered Medical Home: A Case Study in Transforming the Military Health System

Through the study of the Patient-Centered Medical Home (PCMH) implemented across the Military Health System (MHS), the article simply describes the process of implementation and explains how the shift transforms the delivery system at large. By detailing the outcome measures and criteria of evaluation, researchers find the potential to address current inadequacies in the MHS, which would allow Army Medicine to better address the needs of Soldiers.

Annals of Internal Medicine: The Patient-Centered Medical Home: A Systematic Review

This review of patient-centered medical homes (PCMH) describes various facilities' implementation and summarizes evidence of effectiveness for both patients and staff. In 19 studies, researchers report that PCMH had a small positive effect on patient experience and a small to moderate positive effect on preventative care services. Staff experiences were improved moderately while hospital emergency visits decreased. None of the studies reviewed observed that PCMH offered cost savings.

Military Medicine: Leveraging the Military Health System as a Laboratory for Health Care Reform

Researchers sought to utilize the Military Health System (MHS) in order to collect data relevant to the Patient Protection and Affordable Care Act. By sharing many similarities with private sector hospital systems, the article also highlights limitations of the MHS such as the lack of a productivity reimbursement model. The MHS, according to researchers, is almost ideally suited as a test case for the Patient Protection and Affordable Care Act due to the expanse of data available from service members and their families, the standard of care that mirrors the private sector, and the centralized structure of the system.

Military Medicine: Protecting the Culture of a Patient-Centered Medical Home

The study looks at the potential for friction within the Patient-Centered Medical Home, complete with interviews questioning the barriers to practicing medicine, team cohesion, organizational influence, and concerns of PCMH viability. In order to address the concerns, the article points to socialization training, realistic job previews, personnel retention efforts, team-building exercises, and increased managerial support systems. The focus on the PCMH highlights the patient-centered model and reinforces the military’s commitment to preventive care.

Military Medicine: A Pilot Study Describing Knowledge and Practices in the Health Care of Men Who Have Sex With Men by U.S. Air Force Primary Care Providers

February 2013
With the repeal of Don’t Ask Don’t Tell, military medicine is tasked with ensuring military personnel are aware of health issues and requirements that are unique to Soldiers with same-sex partners. Researchers set out to determine if Air Force medical providers were aware of the CDC recommendation that men who have sex with men are encouraged to screen annually for sexually transmitted infections (STI). Results indicate that a significant portion, 42 percent, of medical providers are unaware of the CDC’s recommendation, while the vast majority, 81 percent, had not offered STI screening in the past year. Though this study does not examine Army populations directly, this oversight could exist across all branches of the military.

**Military Medicine: Increasing Educational Indebtedness Influences Medical Students to Pursue Specialization: A Military Recruitment Potential?**

As the cost of medical education continues to rise, medical students are choosing to attend less expensive schools and pick their specialty based on potential future earnings rather than interest. These trends overtime will negatively impact health care availability by causing a dearth of specialists in areas of medicine not known for high income, including primary care. The Department and Defense and Army Medicine can offset this trend by better publicizing programs to provide financial aid in exchange for military service.

**Nutrition and Fitness**

**Annals of Internal Medicine: The Association Between Physical Fitness and Dementia**

In the study of nearly 20,000 healthy middle-aged patients, the researchers sought to determine the relationship between early childhood fitness and the onset of dementia. Findings indicate the “most fit” participants, defined by time spent exercising on a treadmill, were less likely to develop dementia, but the study also suggests it could be due to uncontrolled factors such as healthy eating. The study is relevant to Army Medicine given the concern that TBI may possibly result in dementia and the Army’s continued focus on nutrition and fitness as a comprehensive approach to wellness.

**The Lancet: Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial**

Enteral nutrition, or tube feeding, is essential for patients in intensive care, but it often is not substantial enough to consistently achieve nutrition goals. Researchers delivered 100 percent of a patient’s energy target from days four to eight in intensive care units and supplemented parenteral nutrition (SPN). Results indicate that supplementing enteral nutrition with SPN starting four days after intensive care admission greatly reduces nosocomial infections and improves clinical outcomes.
PLOS Med: Causal Relationship between Obesity and Vitamin D Status: Bi-Directional Mendelian Randomization Analysis of Multiple Cohorts

Researchers have theorized an association between vitamin D deficiency and obesity, though few studies have confirmed this theory. In setting out to determine the association, researchers found that every 10 percent increase in BMI leads to a 4.2 percent decrease in concentration of vitamin D in the body. This indicates that obesity does indeed lead to low vitamin D status, which causes vitamin D deficiency. Results show, however, that vitamin D deficiency is not a cause of obesity. For Army medicine, Soldiers who are obese should be treated for vitamin D deficiency.

Obesity

American Journal of Medicine: Leading Avoidable Cause of Premature Deaths Worldwide: Case for Obesity

Pointing to the exclusion of certain physiological hazards such as smoking and possible effects of obesity (hypertension, diabetes, etc), the article suggests that the harm from obesity is grossly underestimated. In a collaborative analysis of 900,000 people from 57 studies, researchers suggest that 29 percent of cardiovascular deaths and 8 percent of cancer deaths will be in populations with high relative BMI. With reporting on obesity within the ranks emerging in the past months, the rise in obesity in the general population and the public health response to it is of concern to Army Medicine.

Military Medicine: Emerging Technology in Diabetes Care: The Real-Time Diabetes Monitoring System

Through the use of Real-Time Diabetes Monitoring Systems (RT-DMS), the article focuses on the value of telemicine systems in treating pediatric type-1 diabetes through regular uploads of glucometer readings. The consistent data allows physicians to more effectively monitor the patient’s health and, therefore, improve the quality of care. For Army Medicine, the use of medical technology such as RT-DMS allows valuable real-time information to be transmitted between physicians and patients regularly.

BMC Pulmonary Medicine: Obstructive Sleep Apnea and Multimorbidity

Rates of obstructive sleep apnea (OSA) are increasing in North America and research has associated it with specific chronic diseases, most commonly cardiovascular disease. Results of this study indicate a strong association between severe OSA and multimorbidity rather than a correlation between all levels of OSA and multimorbidity. Military primary care providers should be aware of the potential outcomes of severe OSA, and should focus treatment on individuals with OSA to prevent increasing severity.

February 2013
Physiological Injuries and Surgery

Current Opinion in Infectious Diseases: Diagnosis and Management of Prosthetic Joint Infection

The study seeks to determine the treatment for infections on joint surgery, seeing as the incidence of joint surgery is expected to increase significantly over the next 20 years. The prosthetic joint infections (PJI) point largely to a biofilm created by microorganisms, and the best treatments in the study include exchange procedures and debridement and retention of the prosthesis (DAR). Researchers do not feel comfortable, however, in setting standards without a larger data set and urges the use of a registry and collaborative research groups to determine better patient-centered outcomes. The study has implications on Army Medicine due to the high incidence of prosthetic limbs and parts provided to Soldiers; the Army then has the potential to take the lead on PJI research.

Military Medicine: Transforaminal Lumbar Interbody Fusion: Prognostic Factors Related to Retention in an Active Duty Military Population

This article from Military Medicine gathers data from 2005 to 2008, where 143 patients averaged 36.3 years of age and the follow-up occurred just shy of 3 years. The analysis of transforaminal lumbar interbody fusion (TLIF) data, despite its popularity as a surgical intervention, largely focuses on short-term follow-up with fewer than 100 patients, so the author urges more long-term follow-up and a larger set of patients. From the data set studied, only 143 patients were included based on research criteria (with 135 participating in 2-year follow-up). The resulting findings indicate TLIF as an efficacious method to treat various spinal injuries. Due to the vast network of healthcare, Army Medicine can pioneer long-term studies and data sets of TLIF use and efficacy.

JAMA: Comparative Effectiveness Research on Robotic Surgery

Turning to the innovation of robotic-assisted surgery, the authors compare a database of 264,758 women who underwent a hysterectomy at 441 various hospitals. From 2007 to 2010, use of robotically-assisted hysterectomy increased from 0.5 to 9.5 percent. For hospitals already familiar with robotically-assisted procedures, those robotically-assisted hysterectomies accounted for 22.4 percent of all hysterectomies. The article continues on to question the cost, value, and level of commercialization associated with robotics. With regular advances in Army Medicine and the recent coverage surrounding the sequester and budget cuts, Army Medicine should be able to speak on the affordability (or lack) of robotic assistance.

Military Medicine: Vascularized Plantar Myocutaneous Free Flap Transfer for Amputee Stump Preparation: A Proof of Concept Cadaver Study
Researchers estimate that more than 3 million people will have amputations by 2050, indicating the need for research to enhance amputees’ quality of life, including enabling the use of prosthetics. One major deterrent to utilizing lower limb prosthetics is stump ulceration, irritation or pain. This study examines the hypothesis that these issues can be alleviated by insetting a vascularized plantar free flap (VPFF) on the stump. This procedure is simple enough to be accomplished in battlefield care for some amputees under certain circumstances laid out by this study.

**High-performance neuroprosthetic control by an individual with tetraplegia**

This research, funded by The Department of Veterans Affairs, seeks to return limb control through brain-machine interfaces among individuals with tetraplegia. Researchers implanted two 96-channel intracortical microelectrodes in a 52-year-old individual with tetraplegia. The individual gained the ability to control a high performance limb after two days of training and was proficient in making seven-dimensional movements after 13 weeks of therapy. This research points to the need for more concentrated research on the effectiveness of neuroprosthetic limbs.

**PTSD**

**Military Medicine: Stellate Ganglion Block Improves Refractory Post-Traumatic Stress Disorder and Associated Memory Dysfunction: A Case Report and Systematic Literature Review**

Through the prevalence of both PTSD and alcohol abuse, the study looks at the effect of stellate ganglion block (SGB) as a potential treatment for PTSD. The study focuses on the case of one patient who underwent the SGB injection, so the article urges more research to develop a robust database to research. Results indicate favorable health outcomes and improved quality of life of the SGB treatment for a patient with persistent PTSD.

**Psychiatric Annals: Stellate Ganglion Block for the Treatment of Posttraumatic Stress Disorder**

Stellate Ganglion Block is a federally approved treatment for depression, schizophrenia, psychosis and other mental health disorders. The treatment consists of a local anesthetic that is injected into the stellate ganglion, which is located in the back of the neck and connects with the amygdala. Evidence suggests the treatment is also effective in reducing the symptoms of PTSD because of its ability to deter the increase of nerve growth factor, associated with the release of norepinephrine and the onset of PTSD symptoms. This treatment received some coverage from medical trade publications.

**Sleep**

**Military Medicine: Sleep and Resilience: A Longitudinal 37-Year Follow-up Study of Vietnam Repatriated Prisoners of War**
The examination of sleep histories and resilience following an instance of trauma is the focus of a *Military Medicine* article that revisits the subjects after 37 years following a Prisoner of War (POW) experience in Vietnam. The study also seeks to determine factors that contribute to psychiatric illnesses due to trauma, such as PTSD. Data is currently available for 440 of more than 600 who were originally repatriated. Of the 440, only 224 had full sleep information available from 1973. Results indicate those repatriated prisoners of war reporting sleep issues during trauma did not report the same issues post-trauma. Moving forward, Army Medicine can utilize the information on self-reporting sleep quality to further investigate the role of sleep in overall health promotion.

**Sleep: Sleep Disorders and Associated Medical Comorbidities in Active Duty Military Personnel**

Numerous studies have pointed to a consistently high rate of Soldiers diagnosed with sleep disorders, many of which can lead to significant long-term health issues. In order to identify relationships between demographic characteristics, comorbid diagnoses and specific sleep disorders, researchers studied military personnel with sleep disorders who had been referred for polysomnography. Results indicate that service-related illnesses are common in those who participate in polysomnography, and that these illnesses are linked to PTSD, pain syndromes and insomnia. Research such as this highlights the importance of enhanced treatment of sleep disorders to prevent further debilitating and expensive health consequences.

**Substance Abuse**

**Military Medicine: Pharmaceutical Overdose Deaths, United States, 2010**

This comprehensive study of drug overdose deaths in the United States provides perspective for substance abuse in military populations. In studying pharmaceutical overdose deaths in 2010, 74 percent were found to be unintentional while 18 percent were suicides and 8 percent were undetermined. The drugs most commonly involved in overdose deaths were opioids, benzodiazepines, and antidepressants. Researchers note the prevalence of opioid-use in deaths that also involved other pharmaceuticals. This research provides Army Medicine’s substance abuse programming with key information to determine which subsets of the military population are at risk to for prescription medication abuse or unintentional death.

**The Lancet: Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries**

The analysis of a 2011 United Nations meeting on non-communicable diseases (NCDs) points to potential action regarding private sector businesses and industry related to tobacco, alcohol, and ultra-processed food and drink. The international focus on nutrition also profiles various geographic areas and the shift in dietary patterns towards more processed, unhealthy eating habits. The article considers transnational corporations major drivers of NCD epidemics, as these industries use both hard and soft power to counter public health initiatives. As Army
Medicine has an increased focus on nutrition and its impact on Soldier health, the strategies outlined in the analysis provide Army Medicine with an international perspective focused on public health and the impact of transnational business on that public health.


In studying factors that contribute to prescription drug misuse among active duty service members, this research attempts to determine predictors that can help Army Medicine determine which Soldiers have the greatest risk to misuse prescription medication. Results indicate that the strongest predictor of prescription drug misuse was receipt of pain reliever in the past month, year or previous year, and absence of drug testing contributed to an increased level of prescription drug abuse in certain populations. For Army Medicine, service members who have a history of treatment for pain or mood disorders and who work in an environment that does not administer regular drug tests have the greatest risk to misuse prescription drugs.

**Suicide**

**Armed Forces & Society: Perspectives on Suicide in the Army National Guard**

Given the significant increase in suicide in the Army, Marine Corps and Army National Guard, researchers examined data sets including, dispositional risk, social cognitive, stressor-strain, and social cultural/institutional to determine the statistical causes of suicide in the Army National Guard. Results indicate that young, white males are most likely to commit suicide. African American Soldiers have less risk for suicide due to better support systems, higher participation in religious events and increased resilience in adapting to difficulty. Notably, combat exposure and other military-related variables had little to no association with suicide risk. This research received significant coverage in the media from high-profile publications.

**TBI**

**Journal of Head Trauma Rehabilitation: Self-Reported Mild TBI and Postconcussive Symptoms in a Peacetime Active Duty Military Population: Effect of Multiple TBI History Versus Single Mild TBI**

This study is comprised of 224 active duty Soldiers, divided into groups of a singular TBI and more than one TBI, and seeks to investigate the effect of mTBI on postconcussive symptoms. The results indicate a relationship between those Soldiers with 2 mTBI or more and significant postconcussive symptoms. The more Army Medicine understands regarding TBI, and more specifically the symptoms of mTBI, the information can dictate how to diagnose, treat, and rehabilitate mTBI.
The American Journal of Geriatric Psychiatry: PET Scanning of Brain Tau in Retired National Football League Players: Preliminary Findings

Given the partnership between Army Medicine and the National Football League, the distribution of brain tau, a protein deposit from mild TBI, is evaluated in five retired NFL players aged 45-73. Given the small sample size, the authors urge further research into the effect of contact sports on mTBI and chronic behavioral, mood, and cognitive disturbances. An article in Medscape also discusses the findings.

The Journal of Head Trauma Rehabilitation: The Relation Between Posttraumatic Stress Disorder and Mild Traumatic Brain Injury Acquired During Operations Enduring Freedom and Iraqi Freedom

This research sought to elucidate the relationship between mTBI, blast exposure, white matter in the brain and the severity of PTSD. Results of this 4-year study indicate for the first time that PTSD severity is related to both the severity of combat stress as well as physical changes within the brain, but it is not linked to clinical diagnosis of mTBI. In its discussion, researchers note mTBI is likely linked to PTSD and suicide. Coverage such as this is topical given recent focus on TBI as the signature injury of the wars in Iraq and Afghanistan, and this journal article received prominent coverage in the media space.

Medscape: PET Imaging Reveals Damage From Head Injury in Living Athletes

This ground-breaking study reveals protocol to observe visible brain damage after repetitive head injuries in athletes. The long list includes a higher than normal concentration of tau protein deposits in all subcortical regions in the amygdala. This research can help facilitate the early discovery of brain damage to expedite treatment and improve outcome.

Medscape: Hemodynamic Complications Common in Traumatic Brain Injury

This article covers research presented but not yet published on two common outcomes of combat-related TBI including, cerebral arterial vasospasm (VSP) and intracranial hypertension. These outcomes’ severity and prevalence causes researchers, some of which were Army medical personnel, to recommend standard daily transcranial Doppler (TCD) monitoring. This research is pertinent and timely given reporting and research on the difficulty in diagnosing mTBI.

Other
JAMA: Restoring the Blood-Brain Barrier

The Queen Mary, University of London study of mice indicates a relationship between an anti-inflammatory protein and the strength of the blood-brain barrier. The results suggest the supplemental dosage of ANXA1 may help prevent the degeneration of neurological diseases such as multiple sclerosis, Alzheimer disease, and Parkinson disease.

Heartwire: Runner Who Died During Marathon Took DMAA During Race

The article details the implications of drugs such as DMAA on active people, such as in the recent death of Clair Squires and the deaths of two Soldiers in 2012. The past relationship involving Soldiers abusing DMAA displays the need for Army Medicine to inform Soldiers of the risks associated with its consumption.

PLOS Medicine: Socioeconomic Inequalities in Lung Cancer Treatment: Systematic Review and Meta-Analysis

The meta-analysis of data from patients suffering from lung cancer seeks to determine any socioeconomic inequalities in treatment. Twenty-three studies were used for data analysis. The study concludes that patients living with lung cancer from socioeconomically deprived circumstances are less likely to receive any sort of treatment including but not limited to surgery and chemotherapy. Given the varied socioeconomic backgrounds of Soldiers, Army Medicine should be aware of specific socioeconomic limitations that Soldiers and veterans may face.

Military Medicine: Health Care Utilization and Health Indicators Among a National Sample of U.S. Veterans in Same-Sex Partnerships

With the recent repeal of Don’t Ask, Don’t Tell, the research focuses on the impact of veterans being in same-sex partnerships. The data of those in same-sex relationships was derived from a self-reported 2004 Behavioral Risk Factor Surveillance System. The research finds same-sex partners to be more overweight than same-sex partnered nonveterans but less likely to be overweight than opposite-sex veteran partners. Same-sex partnered veterans are also twice as likely to smoke cigarettes. The unique experiences faced by same-sex partnerships provide Army Medicine and Veterans Affairs the opportunity to discuss post-DADT medical care provided to Soldiers.

Medical Journal Clips

Behavioral Health
ABSTRACT

Objective: The aim of this study was to understand U.S. Army nurses' reintegration and homecoming experiences after deployment to Iraq or Afghanistan. Method: Employing existential phenomenology and purposive sampling, 22 U.S. Army active duty nurses were recruited from two military posts and participated in single digitally recorded interviews. Results: Five themes emerged: (1) aspects of command support were articulated as "No One Cares"; (2) fulfilling requirements for attendance at pre/postdeployment briefings were described as merely "Check the Blocks"; (3) readjustments from focusing strictly on duty requirements versus multitasking, such as family responsibilities and daily living, led to the "Stress of Being Home"; (4) nurses stated "They Don't Understand" when referring to anyone without deployment experience (family, friends, other soldiers); and (5) when referencing deployment experiences, nurses emphasized that, "It Just Changes You." Discussion: Nurses in this study felt that the current reintegration process was not meeting their needs for a smoother homecoming; new or improved interventions to assist redeploying nurses with the transition to a noncombat environment would be beneficial. Educational programs to help nursing supervisors provide optimal leadership support through all phases of deployment are needed.

INTRODUCTION

Following the traumatic events of the September 11, 2001 terrorist attacks, combat forces began deploying to Afghanistan to respond to the Global War on Terrorism. In 2003, military units, accompanied by support personnel, were ordered into Iraq. Alongside the combat warriors, U.S. Army nurses have been involved in the Iraq and Afghanistan conflicts since the onset. Over the last decade, approximately 2,700 nurses have deployed to these combat locations. Of those, about 500 have served at least two tours and more than 70 have fulfilled a deployment mission three times or more (MEDCOM Report, G. Braane, personal communication, August 12, 2011).

Literature reports that traumatic experiences encountered by combat warriors during wartime service have led to substance abuse and other psychological symptoms and syndromes, such as post-traumatic stress disorder (PTSD), that linger long after the combat deployment is over. Challenges of reintegration and homecoming have proven to be equally traumatic. Returning to family roles and previous military occupations often results in significant family strain, disproportionate care giving burden on certain family members, elevated risks of major depression, and suicide. Similar research related to reintegration and homecoming has not been completed on nurses returning from combat areas.

By definition, reintegrate means "to integrate again into an entity, restore to unity." For this study "reintegration" pertained to the process of reuniting military nurses with family, community, and work following a deployment to Iraq and/or Afghanistan. Doyle and Peterson opined that...
suffering, both physical and emotional, related to war experiences “frequently becomes most apparent during the reintegration phase” (p 362), and believed that the efficiency of the reintegration process and coming home greatly influences the level of personal readiness. The acute readjustment period may last from 3 to 9 months, with lingering strain for 12 to 18 months. The soldier “may typically experience culture shock, stimulus overload, and emotional overload… there are unresolved feelings about the separation, and unresolved unchannelled aggression” (p 188). Reunited families and the soldiers themselves require several months to readjust to changed roles as they return to a noncombat environment.

Background

Concerns about the process of reintegration have been voiced for decades. Nurses from Vietnam stated they were happy to be home, but found their transition difficult and needed time to “decompress alone.” Adding to transitional stress, they felt their skills were underutilized and devalued at home compared to their work in combat. In other written reports, a nurse described how the sounds of combat had followed her home and spoke of jumping at popping noises, whereas others described having pent-up emotions and very little tolerance for mundane things.

More recent studies have focused on Army medical personnel and their deployment experiences in Operation Iraqi/Enduring Freedom and Operation Desert Storm/Shield. The most often mentioned theme in participant responses concerned leadership; the most often discussed topic within leadership related to subordinates' perceptions that leadership had not met the expected standard to care about those serving under them and the patients whose well-being was their focus. Expectations of leadership, and feelings about whether leaders had met those expectations, influenced how medical personnel experienced unit cohesion, and general feelings of confidence and trust. Negative appraisal of how leaders performed in the field impacted performance during deployment and carried over into postdeployment, in some instances resulting in lower retention.

Derived from her personal experience, Lonsdale commented about her world after coming home from Iraq, how the littlest thing would elicit so much anger and frustration. She indicated that those who stayed at home did not really understand what occurred during deployment and probably never would. Another nurse spoke of the little things that caused distress after returning home. She described having to decide what clothes to wear or what shoes to put on. She indicated that just making those types of decisions were both difficult and frustrating.

Leaving the war behind and fitting back into the predeployment routines has been described as difficult by multiple authors in addition to those already cited. The reintegration process not only affects soldiers' performance at duty stations but can also amplify stressors at home as soldiers and their families renegotiate family roles, further compromising maximal performance and readiness.

In summary, earlier works have reviewed military medical personnel's deployment experiences providing care in the war zone, and critical skills needed within a combat theater. Participants in those studies have overwhelmingly reported concerns encountered during reintegration and homecoming. However, none of the previous studies were tailored to investigate the phenomenon of Army nurses' reintegration and homecoming. No information existed concerning Army nurses' reintegration from theaters of operations in Iraq or Afghanistan. Therefore, the purpose of this
study was to understand the lived experience of U.S. Army nurses' reintegration and homecoming following deployment to Iraq and/or Afghanistan.

METHODS

Research Design

An existential phenomenological research methodology and design, as described by Thomas and Pollio, was used to gain the understanding of the nurses' lived experiences of reintegration and homecoming. This specific approach has its foundation in the philosophical works of Maurice Merleau-Ponty, an existentialist who proposed that humans' interpretations of the world are formed by their perceptions and experiences within the world, wherever they "stand" at any given point in time. Those perceptions reflect an integration of elements of time, body, other people, and world. Furthermore, human perception of experience is never pure, but instead always blends past experience with current perception. According to Merleau-Ponty, phenomenology is a method of describing, not explaining.

Using Thomas and Pollio's method, the study aimed to answer the following research questions: (1) what are the lived experiences of the U.S. Army nurses returning home following a combat deployment to Afghanistan and/or Iraq?; (2) what issues or difficulties did nurses encounter upon returning home from the deployment(s)?; (3) what approaches were effective in managing the process of coming home?; (4) what were barriers to reintegration?

Sample and Setting

A purposive sampling method was used to recruit 22 U.S. Army nurse participants from two different military installations who met the study criteria. These criteria specified that the participants must be English speaking, active duty U.S. Army registered nurses, over the age of 21, and have experienced at least one deployment to Iraq and/or Afghanistan. Emails and posted flyers were employed to advertise the study.

The interviews took place at a location of the participant's choosing. These included homes, offices, and conference rooms where privacy could be achieved. Recruitment continued until saturation within the data was achieved.

Procedures

Before beginning the study, approval from a military institutional review board was obtained. Following approval, arrangements were made for the interviews with nurses who volunteered for the study. Verbal consent was obtained and digitally recorded. Once consent was obtained and any questions concerning the study or procedures were answered, each interview began with the broad question of “What stands out for you when you think about your experience of reintegration and coming home from your deployment?” Probe questions were asked for clarification and understanding, but only for topics already introduced by the participants. In this methodology, new topics cannot be suggested by the researchers, thus precluding pursuing new lines of discussion. Each interview lasted from 30 to 90 minutes. Field notes were recorded following the interview. The digitally recorded interviews were carried to a professional transcriber who had signed a confidentiality statement. Each recording was
transcribed verbatim. When the transcript was returned it was verified with the digital recording for accuracy. A demographic instrument was also completed by all participants.

Data Analysis

Data analysis of the nurses’ \( n = 22 \) stories was performed by following the thematic analysis process outlined by Thomas and Pollio: (1) line-by-line reading of each transcript text by three members of the research team to ensure a thorough understanding of the phenomenon under investigation; (2) identification of meaning units within and across all the transcripts; (3) clustering of similar units into groups, establishing themes, and collapsing the themes; (4) culmination of the process with development of a thematic structure to provide a pictorial representation about the phenomenon, in this case U.S. Army military nurses’ experiences of reintegration and homecoming. The research team used Nvivo 8, qualitative software, to assist with coding and grouping of meaning units. Originally, there were 12 themes. After extensive review and discussion among the team, these 12 themes were further collapsed, resulting in five major themes.

Trustworthiness

To ensure the essence of nurses' reintegration and homecoming was accurately interpreted, measures of validity using the principles of trustworthiness were followed. Specifically, a summary of study results to include the thematic structure was shared with the participants for review and feedback. Their replies indicated that their stories had been represented correctly. Several of the comments stood out from the others. One stated, “Great stuff with the five themes. I really like the ‘new normal’, as you never go back to what was (normal again) …” Another offered, “From the information that was shared within the study summary, I now know I am not alone in my feelings … at least I know I am normal. The picture you provided is a wonderful way for the world to view reintegration and the issues that arise.”

RESULTS

Consistent with the Thomas and Pollio method, the five major themes identified are reported in the words of the nurses: (1) “Command Support: No One Cared,” (2) “Check the Blocks,” (3) “The Stress of Coming Home,” (4) “They Don't Understand,” and (5) “It Changes You.” The thematic structure depicts reintegration as the bridge between deployment and “the new normal.”. In telling about their reintegration experiences, nurses often provided overall opinions of the process. One participant identified a reintegration problem as expecting individuals to go back to life the way it was simply because they had completed the mandatory processing.

“Reintegration is a process. It is not something that happens overnight … it's something that needs to be addressed, because … how do you take someone and say you're a soldier, [then] you put them in this violent environment, and then you pluck them out of it, put them back into society, and think they should behave normally.”

Another participant questioned whom the reintegration training was for and the true purpose behind the reintegration process.

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“We went through the Army reintegration training, which was a joke, and all of us were kind of like, ‘This training is not for us. This training is just to cover their butts in case one of us commits suicide or gets a DUI,’ but was it really that anyone was concerned with our physical or mental well being?”

One nurse shared thoughts on the delivery of reintegration information.

“The stuff they are telling you is so canned, it may not even be their area of expertise or it is their area of expertise but they have been giving it however many times and so they are bored, so they put no effort into it.

Command Support: “No One Cared.”

Of all the themes, the one that evoked the most overt emotion related to command support. The perception among participants was that no one from the command seemed to know or care that the nurses had deployed and finally returned. One nurse commented about the lack of acknowledgment.

“[Nurses] would sit around and talk and they would complain that no one cared that they had deployed; no one acknowledged them.”

Another participant described how her deployment group felt about their nurse leadership upon returning home.

“What would have made it better is if we knew that our leadership really cared …. It was kind of like, another notch on their belt, and well, we're back now, so you’re on your own, and that was kind of, I think, how all of us felt.”

Arriving home, two nurses spoke of how no one met them at the airport and the impact it had on their thoughts regarding their command.

“They had made these comments about how they’d make sure somebody was there to greet you and stuff like that and that just wasn't the case.”

“There was no representation from the unit, there was no phone call from the unit, from the commander or from anybody to say ‘hey, welcome back’ even once they knew I was back … out of sight, out of mind.”

Returning to her unit, one nurse told of her feelings of insignificance when trying to sign out on leave following her deployment.

“I went in to pick up my paperwork they told me that I had to reprocess before I could take my leave. Now I'm just coming off a long flight and just got back in country. It wasn't, ‘Hello. Thank you. Welcome back.’ It was, ‘Oh no. You've got to in-process first’ … all of those things added up and it really left me with a bitter taste in my mouth and … it made me feel so forgotten, insignificant, don't matter.”

“Check the Blocks”

Hallmarks of the reintegration process were rote briefings that did not seem meaningful to nurses in this study. Covering rigidly prescribed topics, these exercises were presided over by trainers perceived as uncaring and focused on getting the briefings over as quickly as possible. One nurse
emphasized the importance of the reintegration process. She indicated that reintegration is not something that can be placed on a timeline as it different for everyone.

“Reintegration is very important. It is not just a matter of checking the block; it is a matter of making sure it is done correctly … people are not going to be up front in the beginning [if they are having problems]. They are not going to say ‘I am a basket case.’ If you are going to only screen people at 90 days, 60 days, or 120 days … you might as well not even check those blocks … Have some [other] type of follow-up … some kind of group that would say … ‘I am following up with you’ … [just] getting a phone call from somebody.”

As expressed by several participants, reintegration training should be something that is useful and could potentially help individuals returning home and their families, not to just say the task was completed.

“If you are going to give me reintegration training … give me meat that I can chew on … that is going to help me, that is going to help my family…they don't teach it for you to learn anything … they teach it to check the block … ‘yes we did it’.”

“My biggest beef is that they don't teach it for you to learn anything … they teach it to check the block … ‘yeah we did it’.”

“Before we left [deployment country] we had a mandatory reintegration thing [briefing] to tell us what they thought we might expect [after returning home] from the mental health people there and you could tell the young specialist was severely bored with giving the class … it was mandatory [just] to check the block and that's what it was—a check in the block.”

“The Stress of Being Home”

While deployed, nurses described having a fairly singular focus of the mission in country. After arriving home, all the responsibilities of families, living situations, and work bombarded the returning individuals. Several of the participants spoke about the difficulty of multitasking and decision making.

“The stress of being back in America is huge! Having to multitask again …. It was hard to come back initially, transitioning … I can't explain why … having to choose and make decisions … going to the grocery store, big bright lights, aisles of food to choose from (not just one thing to choose from and pick but a variety), the cereal aisle for example … what cereal am I going to buy.”

Returning home after deployment was noted as stressful and rather difficult to rationalize as they were actually home. Participants commented on the hardships of trying to discover where they belonged in a noncombat environment.

“It was just so … everything just bombarded me at once … walking into my house felt very, very strange … trying to rationalize the fact that I truly was back.”
“I didn't know what my place was... how I fit back in [with family] and it was very difficult to realize that I had been there ... [in country] I was in a routine and knew where everything was and what was expected of me ... what I was going to do next and then you come back home and you are here and it's like, “Okay, this is a very strange environment.”

“[Reintegration] was very difficult ... I felt totally disconnected from almost everything and everyone ... It was a hard time coming back initially, transitioning, and I can't explain to you why, other than you come from an environment where death is very evident and apparent and you see ... Soldiers with their legs blown off, their arms blown off, and then you come back.”

“They Don't Understand”

Those who have served in a wartime environment typically do not speak to family and friends about their experiences unless those individuals have deployed themselves. Several of the nurses indicated that those who had not been there would not understand or they (family and friends) really did not want to know about their experiences.

“You can't talk to your family about it ... unless they have deployed or served in the military and went through [it] ... maybe Vietnam or Desert Storm, they really don't understand.”

“If you try to explain to somebody who wasn't there, they don't get it, you got to be there. I can't talk to you, because you haven't experienced what I've experienced, and so to sit there and tell me everything is going to be okay, how do you know!!”

“Every time I have been deployed I come back and I am just shocked on how people don't get it, Americans in general don't get what it is like to be deployed ... the sacrifices we have made.”

The nurses conveyed that it was challenging to share what they had seen or felt with family and friends. Often, it brought back memories they had tried to forget.

“You don't understand ... There are not enough words for me to describe some of the things that I saw ... It's a burden. It's hard ... You can't even imagine. Your mind goes back and you kind of relive certain scenes over and over again... that wasn't a good thing.”

“You get over there it becomes real ... bullets are flying ... we're being mortared. You're seeing all these injuries ... people with broken bones, blown off arms, burns, and then ... you come back.”

One nurse had a positive reintegration experience with family and friends, but reintegrating at work mirrored other nurses' negative experiences.

“The homecoming party was about thanking all of them [family and friends] for their support and then being able to kind of tell my story in the slide show—from the day that we left the airport until the day we got home—the last slide is “Freedom Isn't Free” and just to have people have a better idea of what it means to serve.”
“It Changes You”

According to the nurses, the individuals who left are not the same people, who come home, as the experience has permanently changed who they are.

“It just changes you … it probably took about 2 years before I could really say I’m…okay, I’m different, I’ll never be the same because of the experience.”

“How am I still me? I’m not the same person that I was before. This has changed me.”

“I feel that all of the pieces have been put back together, maybe that is where the growth comes from … but they are all in a different mural … it's a better mural.

The participants shared that they reacted to things differently once they returned and that it was an enormous readjustment to come home.

“Things like large crowds really kind of bother me and I still don't do well in traffic …” “Things that would really kind of bother me the most were when people would get upset about stuff that was really not worth getting upset about … so just kind of getting reaccustomed to the American culture.”

One nurse shared regarding her homecoming and reintegration at work.

“They [supervisors] did everything right, but I wasn't right.”

Several participants articulated a greater appreciation for the simple things in life.

“I learned a lot while I was there. I learned what it was to be in an area like that. I learned to be thankful for the little things that we take for granted in this world like being able to wash your clothes at home, having your own space and being able to sit outside in the fresh air … It [deployment] taught me lessons of life …” “You don't realize how good you have it and you just think Americans complain about the silliest things when there is a so much bigger picture.”

Finally, participants described finding their place in the world again, what they called, “the new normal.”

“It was just like this is okay. I am not evil, I am not crazy, it is okay to be this annoyed, frustrated and it is normal.”

“You know [you are] transitioning to a more normal [life] again, the ‘new normal is going on’. “You have to kind of reintegrate yourself and find how you fit in with your spouse and how you are going to interact with them. That is the “new normal.”

DISCUSSION
Previous studies described difficulties with reintegration and homecoming experienced by combat warriors after wartime deployments, and also indicated nursing personnel were challenged by reintegrating after wartime deployments dating back decades. This research built upon those earlier studies, significantly adding to reintegration knowledge by providing data through the lens of nurses who experienced the reintegration process most recently, and indicating that the challenges reported after earlier conflicts such as Vietnam continue to be felt in the present. Our participants acknowledge recent efforts by the military to respond to reintegration needs of its returning personnel, and expressed firm conviction that every discrete element of the reintegration process is vital. But the voices of our participants also speak powerfully to the inadequacy of current reintegration support for nurses, men and women who very often deploy and redeploy alone, outside of a larger group. Participants were unified in describing the urgent need for enhanced reintegration support. The process of reintegration is not merely a series of tasks to be completed, or formalities to be glossed over just to report that they have been done. Instead, nurses indicated that reintegration briefings should contain practical, useful information, not only for themselves but also for their families as well, and the process should be adapted for the unique needs of specific audiences. To that extent their responses also added support for earlier research conducted with non-health-professionals whose families experience significant reintegration stress.

At the administrative level reintegration may be perceived as one experience, with definitive beginning and end points, yet reintegration and homecoming experienced by these participants emerged as a two-stage process. The first begins with mandatory meetings and training required of all soldiers; this is the “official” process. The second phase is more personal, individualized, and ongoing. This stage is similar in nature to the grief process because each person proceeds through it at his/her own pace, sometimes moving forward, but often falling back a few steps. “Falling back” episodes may be triggered by smells, words, or sounds that call to mind thoughts about a previous deployment. Often, elicited reactions cause strife within the family unit, among friends, and at work. In truth, reintegration becomes a lifelong process, never ending. With each added deployment it becomes more complex: thoughts and emotions from one deployment bleed over to feelings and memories from other combat experiences.

The formal, somewhat emotionless, reintegration process combined with the perceived lack of support from command, supervisors, and colleagues created barriers to personal reintegration for participants. Families and friends at times added to the stress of homecoming because they lacked complete understanding of what their significant others had endured and what to expect upon their return. Coping mechanisms that helped the nurses through their reintegration process were their faith, support of family members, supervisors who had previously deployed, and talking with nurses who “had been there” even if they were not deployed at the same time or in the same location.

Limitations

The study was limited only to the extent that it included only active duty U.S. Army registered nurses who had deployed to Iraq and/or Afghanistan. Because all of the nurses were originally deployed from many locations, their experiences were not impacted by base of origin, time of deployment, impressions of nurses from the same base who may have been deployed at the same time, or other issues related to time and place.

CONCLUSION
Nurses returning from combat deployments are encountering difficulties similar to those described by combat warriors across decades. Their words recount a multitude of stressors experienced when giving care in the combat arena. Nurses in this study reported that the current reintegration process frequently did not meet their needs for a smoother homecoming; indeed, at times it complicated instead of facilitating life. Described as isolating and minimally supportive, reintegration routinely placed them in situations where they returned home alone without the mutual support of warriors who deploy as parts of larger units. There was little or no acknowledgment by superiors or family that they were returning from experiences that have left them exhausted, traumatized, and experiencing residual stress disorders that impede maximum functioning. They are asking for, and have earned, a level of support for their reintegration that serves them and their needs well.

Future research can best be focused on addressing nurses’ needs, identifying a revised process that facilitates their return to home and family and supports their adjustment. New or improved interventions to assist redeploying nurses with the transition to a noncombat environment would be beneficial. Educational programs to help nursing supervisors provide optimal leadership support through all phases of deployment are needed. Future studies should also include nurses in other military branches, including the reserves and national guard, to determine whether they are encountering similar issues.

Association between depression and hospital outcomes among older men

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Background: Studies that have investigated the relation between depression and the type, nature, extent and outcome of general hospital admissions have been limited by their retrospective designs and focus on specific clinical populations. We explored this relation prospectively in a large, community-based sample of older men.

Methods: A cohort of 5411 men aged 69 years and older enrolled in the Health in Men Study was assessed at baseline for depressive symptoms, defined as a score of 7 or higher on the 15-item Geriatric Depression Scale. Participants were followed for 2 years for occurrence and number of hospital admissions, type of hospital admission, length of hospital stay and inpatient death as recorded in the Western Australian Data Linkage System.

Results: Of 339 men with depressive symptoms, 152 (44.8%) had at least 1 emergency hospital admission, compared with 1164 of 5072 (22.9%) nondepressed men (p < 0.001). In multivariate analyses, the presence of depressive symptoms was a significant independent predictor of hospital
admission (hazard ratio 1.67, 95% confidence interval [CI] 1.38–2.01), number of hospital admissions (incidence rate ratio [IRR] 1.22, 95% CI 1.07–1.39) and total length of hospital stay (IRR 1.65, 95% CI 1.36–2.01).

Interpretation: Participants with depressive symptoms were at higher risk of hospital admission for nonpsychiatric conditions and were more likely to have longer hospital stays and worse hospital outcomes, compared with nondepressed participants. These results highlight the potential to target this high-risk group to reduce the burden of health care costs in an aging population.

Older people are the most frequent users of health services, and the progressive aging of the world’s population may lead to a saturation of available services. Therefore, we must find ways to reduce preventable admissions to hospital and uncover the factors associated with potentially preventable use of health services. An association between depression and hospital admission for nonpsychiatric conditions has been postulated, although the data have been limited to specific clinical populations and the interpretation of the results hampered by the retrospective study design and the use of self-reported outcomes. Consequently, these findings cannot be easily generalized or used to develop data-driven interventions.

We addressed this gap in the literature by using a community-based population survey with prospective data linkage to measure important health-related outcomes. Our main objective was to investigate whether community-dwelling older men with depressive symptoms were more likely than nondepressed men to be admitted to general hospitals. Our other aims were to determine whether the long-term clinical outcomes of these 2 groups differed in relation to the number of future hospital admissions, length of hospital stay and inpatient deaths.

Methods

Patient sample

We identified and selected participants from a community-derived sample of 5585 men living in Perth, Western Australia, who collectively compose the Health in Men Study cohort. The Health in Men Study is a prospective, follow-up study involving men aged 69 years and older who participated in an earlier trial of screening for abdominal aortic aneurysm. The full details of the cohort, including assessment procedures and enrolment are available elsewhere. In brief, 19 352 men aged 65–83 years were randomly selected between Apr. 1, 1996, and Jan. 31, 1999, from the electoral roll (enrolment is mandatory for Australian citizens) and invited to participate in the study. A total of 12 203 men completed the full questionnaire, which covered aspects of their lifestyle and medical history. The surviving men were invited to participate in a follow-up study between Oct. 1, 2001, and Aug. 31, 2004. The 4263 men who attended a face-to-face follow-up survey and the 1322 who completed a follow-up questionnaire constitute the Health in Men Study cohort (n = 5585). Both the face-to-face survey and the questionnaire included another health questionnaire and an assessment of mood status. All the participants who completed the mood assessment in the Health in Men Study (5411 [96.9%]) were included in this analysis.

This study was approved by the Department of Health of Western Australia and the Human Research Ethics Committee of the University of Western Australia. All participants provided written informed consent.
Data sources

We obtained administrative hospital records from the Western Australian Data Linkage System, which is a complex multiset system for the creation, storage, update and retrieval of links between health- and welfare-related data. The system integrates records from the Western Australian cancer, death and hospital morbidity registers, as well as the Mental Health Information System. The hospital morbidity register records all admissions to private and public hospitals since 1980, including codes for multiple medical diagnoses, admission and hospital type, and length of stay. The proportion of invalid (false positives) and missed links (negatives) were both estimated to be 0.11%.

Measure of depression

We used the 15-item Geriatric Depression Scale (GDS-15) to assess depressive symptoms. Participants who scored a total of 7 or more points were defined as having clinically significant depressive symptoms. The relatively high cut-off was chosen a priori to ensure high specificity for the diagnosis of depression. We used previously published data to group the severity of depressive symptoms as follows: no depression (GDS-15 total score of 0), questionable depression (score of 1–4), mild-to-moderate depression (score of 5–9) and severe depression (score of 10–15).

Other measures

Education level was subdivided into categories and measured as the highest level of education completed: no schooling, primary school, some secondary school, completed secondary school, completed university or other postsecondary degree. To assess social support, we used the Duke Social Support Index, a validated scale that measures individuals’ satisfaction with their network of relationships.

We assessed smoking status by asking men whether they had ever smoked and whether they were still smoking at the time of assessment. Finally, we used the Charlson weighted index, a widely used measure, to assess the presence of substantial medical comorbidity in our sample. Information about co-occurring medical conditions during the 10 years before assessment for the Health in Men Study was derived from the Western Australian Data Linkage System for all participants. We followed the procedures described by Quan and colleagues for the coding of algorithms, and we used Stagg's Stata routine to calculate Charlson index scores.

Outcomes measures

We investigated hospital admission (0 = not admitted, 1 = admitted), number of hospital admissions, mean total length of stay across hospital admissions, median length of stay, type of admission (elective v. emergency), overnight admission and inpatient death. For all analyses, we included only emergency (not elective) admissions, because they are more indicative of acute health problems.

We retrieved participants’ hospital records for 24 months following assessment for the Health in Men Study. We chose this follow-up period a priori because we assessed depression only once and because we wished to generate data that would be comparable to other studies.
Statistical analysis

We identified potential confounding variables by comparing baseline characteristics of participants with and without depression. We analyzed 24-month outcomes separately for all admissions and overnight admissions, and we stratified outcomes by depression status. We reported $p$ values from $\chi^2$ tests for categorical variables. Student $t$ test was used to compare the number of hospital admissions among men with and without depression. We used Mann–Whitney tests to compare length of hospital stay.

We reported incidence rate ratios (IRRs) with 95% confidence intervals (CIs) after performing zero-inflated negative binomial regressions to account for overdispersed count outcome variables (mean length of stay, total length of stay, number of hospital admissions) with excess zeros. We used the Vuong nonnested test to assess the fit of the models.

We plotted adjusted Kaplan–Meier curves, together with log-ranked test results, to compare cumulative admission rates of men with and without depression. We included age group, education level, Duke Social Support Index tertiles, smoking status and weighted Charlson index in the models as confounding variables. We estimated hazard ratios (HRs) by performing Cox regressions after checking that the proportional hazard assumption held. Finally, to investigate the association between depression and high-cost use of health services, we used Poisson regression analysis to determine mutually adjusted prevalence ratios with 95% CIs.

Results

A total of 5411 (96.9%) men provided valid GDS-15 ratings and were included in the analysis. The mean age of participants was 76.8 (standard deviation 3.7) years, and 339 (6.3%) had a GDS-15 score of 7 or greater. Compared to men without depression, those with depression were older, less educated and more likely to be current smokers, and they had a higher number of comorbidities.

Length of stay and number of hospital admissions had very skewed distributions with an excess number of zeros. Potential confounders were therefore investigated by running zero-inflated negative binomial regressions. Length of stay was longer and number of hospital admissions was higher among men with depressive symptoms compared with those without, even after adjustment. The adjusted IRR was 1.25 (95% CI 1.06–1.48) for mean length of stay, 1.65 (95% CI 1.36–2.01) for total length of stay and 1.22 (95% CI 1.07–1.39) for number of hospital admissions. Vuong tests were significant, confirming that the use of zero-inflated models was indicated.

We investigated probability of hospital admission in the 2 groups by plotting Kaplan–Meier curves adjusted for age, education level, smoking status, Duke Social Support Index tertiles and comorbidities. We performed Cox regression analyses after computationally and graphically confirming the proportional hazards assumption. In the fully adjusted model, the presence of depressive symptoms increased the hazard for hospital admission (HR 1.67 [95% CI 1.38–2.01] and inpatient death (HR 1.81 [95% CI 0.82–4.04]), though this was not statistically significant.
Kaplan–Meier estimates of hospital admissions by (A) depression status and (B) severity of symptoms. Adjusted for age, education level, smoking status, Duke Social Support Index tertiles and weighted Charlson index. Severity of symptoms: 15-item Geriatric Depression Scale score = 0 (no depression), 1–4 (questionable depression), 5–9 (mild-to-moderate depression) and 10–15 (severe depression).

Increasing scores in the GDS-15 were also associated with higher HRs for both hospital admission and death, with men scoring 10 to 15 points at baseline having almost twofold higher HRs compared with men who scored 5 to 9 points.

A sensitivity analysis using a cut-off score of 5 points on the GDS-15 was also carried out. The findings were consistent and were not affected by this different cut-off (data not shown).

Interpretation

In this study, the presence of clinically significant symptoms of depression in older men was associated with increased risk of hospital admission, higher number of readmissions and longer use of services. These associations remained statistically significant after adjustment for several confounding variables.

Few studies have investigated the effect of clinically significant depressive symptoms on hospital admission and outcomes in people living in the community. A Danish group explored this association in a general population by following a group of 75-year-old adults over a 5-year period. The group found a weak association between depression and subsequent hospital admission among women, and no association among men. This result is possibly explained by the relatively small sample size and the use of a depression scale not designed for older adults.

Wong and colleagues found a relation between depression and increased length of hospital stay and number of admissions in an older population in southern China, although the magnitude of the association was smaller than in our study. This may be because of a lower prevalence of depression at baseline and the use of self-report measures when recording comorbidities. Similar findings in diverse populations were described by von Ammon Cavanaugh and colleagues, who reported that a diagnosis of major depressive disorder and a history of depression independently predicted inpatient death. Finally, in a similar study by Prina and colleagues involving an older Dutch population, longer length of hospital stay and higher rates of admission and inpatient death were reported among depressed patients. However, only length of stay was associated with depression after adjustment for sociodemographic variables and comorbidities.

Several potential reasons can be proposed to explain the higher risk of hospital admission among older men with depression. Treatment adherence is known to be poor among patients with mood disorders. This could result in patients arriving in hospital at more acute or severe stages of their illness, potentially increasing length of stay and risk of death during admission. Our data show a higher number of emergency admissions than elective admissions among participants with depression, which is consistent with this hypothesis. Depression is also an internalizing disorder that could potentially hamper effective communication with health care professionals, delaying a potential diagnosis and consequent treatment. Depressive symptoms in older adults could aggravate chronic diseases and disability. This could unfavourably influence
older people's ability to look after themselves, leading to poorer self-perceived health, an increase in unexplained physical symptoms and, consequently, a rise in medical admissions. Furthermore, there is an association between the number of physical conditions and depression, and a dose–response relation has been described.

In the current study, we have found that, even after adjustment for a robust measure of comorbidity (Charlson index), depression was a strong independent risk factor for hospital admission, longer hospital stays and worse hospital outcomes. This suggests that the association between depression and comorbidity, disability and hospital admission is complex and cannot be attributed solely to age, prevalent clinical morbidity, social support, education or smoking. However, even after adjustment for comorbidities, it is difficult to know to what extent depression may be a manifestation of early stages of diseases. We cannot therefore exclude the possibility that the findings may partially reflect depression as an epiphenomenon for other diseases.

We found a dose–response relation between depression severity and hospital admission, which suggests that reducing the symptoms may potentially improve hospital outcomes. However, subthreshold symptoms should not be underestimated, because they still have an impact on hospital admission and associated outcomes.

Limitations

Our study population was limited to men aged 69 years and older. We do not know whether our findings are generalizable to younger adults, women and people living outside Australia, although there is no obvious reason that this would not be the case, particularly in other developed countries. Although the GDS-15 has been proven to be a valid instrument for screening for major depressive disorder, it does not have the potential to differentiate between symptoms of major depressive disorder and depressive symptoms caused by other psychiatric diagnoses (e.g., dementia, psychosis), which could affect the interpretation of our results. We measured depressive symptoms only at baseline, and this exposure could have changed during the follow-up period. Hence, we were unable to determine whether change in depressive status could affect hospital outcomes.

Finally, the Charlson weighted index was originally created to estimate death and may not take into account all of the diagnoses that may increase hospital admission. Future research could involve a more comprehensive index to account for comorbidities.

Conclusion

Our study emphasizes the independent association between the presence of depressive symptoms in older men living in the community and hospital admissions, highlighting a possible target to identify men with potentially preventable admissions. Larger studies may be able to investigate effect modification, to determine more clearly what factors, if any, mediate the relation between depression and hospital outcomes. It is not clear whether reducing depressive symptoms would result in fewer hospital admissions, and further research is required to clarify this issue.
Our data extend previous findings on the association between depression and hospital admission, with focus on the general population and admission frequency, length of stay and outcomes.

Placement of Combat Stress Teams in Afghanistan: Reducing Barriers to Care

Military Medicine
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ABSTRACT

This article describes the medical planning process whereby combat stress and mental health clinicians were placed at Forward Operating Bases in southern and western Afghanistan during a period of intensive surge operations in 2009–2010. The distribution plan for the Combat Stress Control teams was based on previously published guidance on ratios of combat stress personnel to troop end-strength, population at-risk data, and kinetic activity associated with current and future combat operations. The article concludes with outcome data that validates the distribution decisions made through the planning process. Through dissemination of this information, it is hoped that future planners and clinicians can improve the processes involved in providing combat stress and mental health services to forward-deployed troops.

INTRODUCTION

Combat and operational stress control doctrine calls for the forward deployment of behavioral health personnel to provide prevention, education, treatment, and consultation services as close as possible to troops serving on combat, peacekeeping, and humanitarian missions. As identified in the Joint Mental Health Advisory Team-7 Report (February 22, 2011), behavioral health personnel are viewed as "low supply/high demand" assets who have been “some of the most active and forward-reaching of all medical occupational specialties” during Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF). Given the critical roles that behavioral health personnel play in support of warfighters in theater, the allocation of Combat Stress Control (CSC) teams becomes both an operational concern in shaping the battle space and a medical concern in reducing barriers to obtaining care. Specific barriers to care identified in Mental Health Advisory Team-7 (MHAT-7) included availability of mental health services, knowing where to get help, and obtaining time off work to receive treatment.

In December 2009, the authors participated in an unprecedented mobilization effort to rapidly distribute new CSC personnel to Forward Operating Bases (FOBs) in southern and western Afghanistan in support of over 15,000 widely dispersed troops operating throughout the region under austere and highly kinetic circumstances. This report documents how joint service teamwork helped shape the battle space by integrating personnel planning processes, medical intelligence, and combat stress service capabilities to ensure that CSC teams could comprehensively
execute their assigned missions. The methodology described here, however, is not meant to be prescriptive, but to document for future planners and medical leaders, key issues and procedures the authors found useful in distributing CSC personnel to both unserved and underserved areas.

BACKGROUND: TRAGEDY AND RESOLVE

In response to recommendations from the Joint Mental Health Advisory Team-6 (MHAT-6) (conducted from April 2009 to June 2009), decisions were made by senior Army leadership to increase the number of behavioral health personnel in support of both OIF and OEF. The units assigned to this mission in August 2009 were the 467th Medical Detachment (CSC) (assigned to Afghanistan) and its sister unit the 1908th Medical Detachment (CSC) (assigned to Iraq). On November 5, 2009, both of these units started in-processing for their respective deployments via the mobilization site at Fort Hood, Texas. As activated Army Reserve Units, the 467th and 1908th were slated to spend approximately 1 month at Fort Hood for required predeployment training in preparation for combat deployments in support of OIF and OEF. November 5th was the first full day of in-processing for these units, but the unthinkable occurred that morning as an Army physician with alleged jihadist sympathies opened fire at the mobilization site killing 13 soldiers and wounding many others. Among the CSC personnel slated to go to Afghanistan, 3 Soldiers were killed or died of their wounds and 6 Soldiers were wounded and thus, unable to deploy. Ironically, as CSC teams, the 467th and 1908th now found themselves the focus of intensive support and debriefing interventions in the ensuing days and weeks rather than serving as the facilitators for such activities in support of other combat personnel.

Immediately after the shooting incident and for several weeks thereafter, the deployment status of both units was unclear because of legitimate medical status concerns from senior Army leaders about the emotional well-being of these units, given the horrific circumstances the units faced during the shooting incident. Also, given the need to attend to their comrades’ funerals and participate in debriefings, there was concern about the units’ ability to meet the timetable of predeployment training requirements. Shortly after the shooting incident, new Soldiers volunteered to take the place of those killed or wounded during the incident. Surviving team members grieved together, and ultimately decided to “push forward.” In doing so, the surviving team members embraced the very doctrine that they apply in supporting others: use adaptive stress reactions to continue on and fulfill the mission. On November 23, the 467th CSC and the 1908th CSC were validated for mobilization and reported for duty in Afghanistan the first week of December 2009.

FORMATION OF THE PLANNING TEAM

Five of the authors (DJ, FJ, AT, PH, and SM) were already in Afghanistan when the 467th CSC arrived. These authors were part of the newly formed Task Force Med South (TFMS) based at Kandahar Airfield (KAF) in southern Afghanistan in November 2009. The remaining author (LS) arrived in theater as the Officer-in-Charge (OIC) of the approximately 45 member 467th CSC. The TFMS team received notification about 1 week before the arrival of the 467th in Kandahar. During the week before the arrival of the 467th CSC, the TFMS team met to define a plan to distribute the 467th into smaller teams (typically comprising 2 to 3 members) throughout the region and to establish a training plan to orient the new CSC personnel to the theater. Prevailing operational limitations in personnel air movement meant that members of the 467th arrived in Afghanistan in a staggered fashion over the course of a week.
The TFMS planning team collaborated with United States Forces Afghanistan Headquarters to create a CSC team distribution plan for southern and western Afghanistan based on population-at-risk (PAR) data, previously published MHAT-6 ratios of combat stress personnel to troop end-strength, and anticipated kinetic activity related to combat operations. Consultation also occurred with coalition partners, most notably Canadian forces. Indeed, a Canadian social worker was assigned as one of the site reviewers for one of the FOB placement teams. Once the 467th was in theater, their OIC and Senior Enlisted Leader joined the TFMS planning team to provide information on who among their staff would work best together. The TFMS planning team briefed higher authorities and obtained concurrence to move ahead with each phase of the CSC team distribution plan.

KEY CONCEPTS IN PERSONNEL PLACEMENT

Information gathering regarding upcoming operations was essential for placement of the 467th CSC teams so that these personnel could operate as close to where the troops were serving as possible. This information gathering process involved obtaining input on current and future operations, casualty estimates, personnel status issues, availability of intelligence information, scheme of maneuver and forces involved, as well as logistical considerations. The use of disease and nonbattle injury estimates, unit medical status and needs assessments, and consultation with organic medical personnel also provided additional information to guide decisions regarding CSC team composition (i.e., types of providers) and placement (i.e., specific location). The MHAT-6 (2009) recommendation of a 1:700 provider to service member ratio was used as a starting point in recommending distribution decisions to various FOBs. In the context of the MHAT report, the term “provider” referred to both credentialed providers and enlisted behavioral health medics/corpsmen.

The decisions regarding the placement and composition of CSC teams was ultimately modified from a strict 1:700 distribution ratio with the following considerations:

- Given that personnel resources were limited, placement priorities were given to high-risk areas or high-risk units, such as those reporting a large number of significant activity (SIGACTS), from improvised explosive device explosions or incidents of troops in combat who sustained direct fire from enemy combatants;
- Additionally, placements had to factor in the number of behavioral health referrals received at the NATO Role 3 Hospital in Kandahar from units residing at different FOBs within the purview of the Hospital; in other words, the placement of CSC personnel also reflected workload independent of SIGACTS.

Unit Intelligence Officers gathered information on the number of SIGACTS occurring in the Afghanistan area of operations using the Combined Information Data Network Exchange (CIDNE). The CIDNE program and data mining tools were used to determine the number and types of improvised explosive devices (found or exploded), the number of direct and indirect fire incidents, and the number of coalition and host national force casualties, local national casualties, and enemy casualties that had occurred by region, province, district, and/or Unit. Regional casualty data were also obtained through the Regional Command's combined joint operations medical operations desk that managed regional medical evacuation (from point of injury) and tactical evacuation (usually from a lower echelon of care to a higher one). These data described those
casualties deemed serious enough to be airlifted and also provided information on urgent mental health cases requiring evacuation to a higher level of care. Data were also obtained on the number of patient encounters experienced at given locations.

Information from all data sources was used to determine CSC team placement and composition. The intent was to ensure that a CSC team would not be underutilized in an area with a high PAR but fewer other stressors when they could be better used in an area with a lower PAR but higher operational tempo, SIGACTS, Unit casualties, and/or historical behavioral health referral volume.

DETAILS ON THE DISTRIBUTION PLAN FOR THE 467TH CSC

1. (1) Upon notification that the 467th was cleared for deployment, TFMS team members created a spreadsheet with listings that included FOB name, level of medical capability at the site, numbers of current (if any) and/or proposed mental health and combat stress personnel at the FOB, population densities at the identified FOBs, and provider to personnel ratios (derived by dividing the PAR by the number of actual and proposed combat stress personnel at a given locale). This spreadsheet was used as the key planning document for all subsequent planning and placement decisions. Appointments were then made with each FOB “Mayor” (i.e., person in charge of base operations) in preparation for a team to assess the FOB and work out final details for the placement of follow-on CSC Teams. Site visits were the best way to evaluate the situation at each FOB and make the best decisions regarding team composition and placement location.

2. (2) Upon the 467th CSC's arrival at KAF, Operations and Logistics Officers received, staged, and integrated (RSO&I) team members. RSO&I activities meant that the unit was met at the airport and escorted to short-term billeting while arrangements were made for teams to be distributed to various FOBs upon completion of site visits. The TFMS team assigned personnel to the each FOB assessment team to conduct reviews of the facilities and work spaces available at each FOB where a CSC team was proposed to deploy. Assessments were conducted at the following FOBs in southern and western Afghanistan: Wilson, Farah/Herat, Ramrod, Tarin Kowt, Wolverine/Lagman, Spin Boldak, Frontenac, and Camp Leatherneck.

3. (3) FOB assessments and site visit checklists were completed by each team. Upon return to KAF, the team leader wrote a trip report that was available to TFMS leaders via a secure web site. The focus of these reports was on billeting and work space capabilities at each FOB, including computer and phone support for the CSC teams. After the assessment teams returned to KAF, the team leader met with the TFMS planning team to provide feedback on possible personnel distribution changes. The Task Force Planning Team gained approval from the various FOB Mayors regarding the final number of CSC personnel assigned to support each FOB and set a timetable for the arrival of permanent CSC teams. These results were briefed to higher Headquarters and approval was obtained for CSC troop movement to their specified FOBs. As surge operations intensified, major constraints were placed on troop movements; in order to ensure that CSC team members moved in a timely manner, the Operations Officer submitted Movement Requests per theater policy, usually within 96 hours of the anticipated movement.
OUTCOMES AND VALIDATION OF THE PLANNING PROCESS

The first CSC team at KAF went to work within a week of arrival. The first team outside of KAF was mobilized the third week of December 2009. By January 2010, approximately 6 weeks after the 467th CSC Detachment arrived in theater, the last of their CSC teams traveled to their identified FOBs. The environments in southern and western Afghanistan were austere, with notable limitations on supply chains and air and ground transport. Delays in transit were common as a result of combat priorities, weather, flight, and logistical considerations. Because of the conditions at many of the FOBs, it was difficult to provide resupply and telecommunications resources for the CSC teams to begin their work. Consequently, several teams began providing services in temporary facilities while either room was made elsewhere on the FOB or new tents and/or prefabricated buildings were constructed.

To provide some perspective, there were other medical teams at single locations that took 6 or more weeks to become fully operationally capable. Given that the 467th CSC teams became fully operationally capable at 10 different locations less than 6 weeks after arrival in theater was a testament to the teamwork of the gaining commands and determination of the 467th staff. All in all, the 467th provided direct support to over 10 new FOBs and brought new support capabilities to over 15,000 troops.

Team members for the additional sites were usually reassigned from existing FOBs based on optempo. In one case, a team was developed after a new provider arrived in theater. The 3-Month and 8-Month Status columns give information on team changes to meet new operational requirements. In general, all the CSC teams were well received and integrated effectively with resident FOB units to provide troops needed CSC services.

During July and August of 2010 (about 7 months into the year-long deployment of the 467th CSC), members of the MHAT-7 team conducted surveys of mental health needs of Soldiers and Marines in Afghanistan from randomly selected maneuver units. Over 900 anonymous surveys were collected from Army personnel representing 40 different platoons. An additional 85 surveys were collected from behavioral health personnel, including members of the 467th CSC. From July to September, the MHAT-7 team analyzed the surveys and conducted focus groups with Soldiers, Marines, and behavioral health personnel in theater. Several findings from the MHAT-7 Report provide indirect support on the placement decisions associated with the 467th CSC teams at FOBs across southern and western Afghanistan.

Perhaps, the most striking finding was reduction in barriers to care identified by troops in the survey between 2010 compared to 2009. The calculated ratio of behavioral health personnel to maneuver troops reduced from 1:1123 in MHAT-6 (2009) to 1:646 in MHAT-7 (2010). Across all measures related to barriers to care (e.g., availability of services, knowing where to get help, difficulties in obtaining appointments, difficulties in obtaining time off work for treatment, difficulties in getting to locations with behavioral health support, and leadership discouraging people from seeking mental health services), troops reported a decrease in barriers to care in 2010 (the time of the 467th's deployment) compared to 2009. In short, it can be argued that the placement decisions associated with the distribution of the 467th CSC across southern and western Afghanistan contributed to the troops' perceptions that barriers to care were reduced in seeking help for combat stress and mental health concerns.

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SUMMARY AND FUTURE DIRECTIONS

In this article, an overview was provided of the medical planning process whereby combat stress and mental health clinicians from the 467th CSC were placed at FOBs in southern and western Afghanistan to support new mission requirements for 15,000 troops without embedded CSC support. As noted, the 467th CSC had to quickly move from managing and overcoming their individual reactions to the Fort Hood shooting to providing combat stress care in Afghanistan within a little more than a month after the incident. That the unit pushed forward under these horrific circumstances was a testament to the courage, resiliency, and perseverance of the 467th CSC. Data from the MHAT-7 Advisory Team helps validate the placement decisions of the 467th CSC as troops reported a decline in barriers to care related to having less difficulty in getting time off to receive treatment and finding their leaders encouraged the use of mental health services. Continued review and analysis of this and other CSC team placements may provide information on outcome measures that future planners can use to test the adequacy of decisions in new situations. Changes in the time it actually takes for troops to receive combat stress support or changes in the number of aeromedical evacuations associated with the placement of CSC personnel could also be used to validate decisions. Other outcomes that could be considered include comparison of “sick call” rates before and after the placement of CSC teams or the length of time it takes for a CSC at one FOB to mobilize to support a nearby FOB without CSC personnel vice having personnel transported from a higher echelon of care such as KAF. All of these evaluation efforts could serve as part of a “Phase II” validation process for placement decisions of CSCs in future conflicts, whereby a new generation of planners can assess the most effective ways to support both gaining units and CSC teams on the ground. Through dissemination of the present information and through validation efforts, it is hoped that planners and clinicians can improve the ways in which new CSC teams meet the challenges of providing services to forward-deployed troops.

Depression pathogenesis and treatment: what can we learn from blood mRNA expression?

BMC Medicine
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Abstract

Alterations in several biological systems, including the neuroendocrine and immune systems, have been consistently demonstrated in patients with major depressive disorder. These alterations have been predominantly studied using easily accessible systems such as blood and saliva. In recent years there has been an increasing body of evidence supporting the use of peripheral blood gene expression to investigate the pathogenesis of depression, and to identify relevant biomarkers. In this paper we review the current literature on gene expression alterations in depression, focusing in particular on three important and interlinked biological domains: inflammation, glucocorticoid receptor functionality and neuroplasticity. We also briefly review the few existing transcriptomics studies. Our review summarizes data showing that patients with major depressive disorder exhibit an altered pattern of expression in several genes belonging to these three biological domains when compared with
healthy controls. In particular, we show evidence for a pattern of 'state-related' gene expression changes that are normalized either by remission or by antidepressant treatment. Taken together, these findings highlight the use of peripheral blood gene expression as a clinically relevant biomarker approach.

Introduction

Major depressive disorder (MDD) is a complex disorder characterized by the interaction between biological, genetic and environmental factors, and by a pathogenesis involving alterations in several biological systems. A large amount of research has been focused on understanding the underlying mechanisms of MDD, and there is already a wealth of evidence demonstrating changes not only in the central nervous system (CNS) but also in the periphery. For example, blood and saliva are useful and accessible systems that, via relatively low-invasive procedures, can be used to analyze several biomarkers, such as proteins or metabolites, using quantitative techniques. Using this approach, hormonal and immunological abnormalities, such as elevated levels of pro-inflammatory cytokines, alterations of the hypothalamic-pituitary-adrenal (HPA) axis, changes in neuroplasticity, and changes in oxidative and nitrosative stress pathways, have all been documented in patients with MDD, and are indicative of the ‘neuroprogressive’ nature of MDD.

An emerging and useful method to investigate the pathogenesis of this disorder is the use of peripheral blood to measure the expression levels of genes. This is a useful approach in biomarker identification, with opportunities for both hypothesis-driven biomarker search and for hypothesis-free transcriptomics-based discovery. ‘Blood gene expression’ usually refers to intracellular RNA from blood, and it is technically associated, in most cases, with two approaches: the use of tubes for blood collection that stabilize mRNA from all cells in the blood; and the extraction of mRNA from separate distinct blood cell populations. What is really of importance for researchers is whether blood mRNA can be used as a proxy for mRNA expression in other tissues that are more relevant to the pathogenic processes of interest - in psychiatry and neuroscience, the brain. In this regard, peripheral blood gene expression is very promising, as several studies have shown that blood cells share more than 80% of the transcriptome with other body tissues, including the brain. For example, Sullivan and colleagues compared the transcriptional profiling of 79 human tissues, including that of whole blood and of several brain areas. They showed that whole blood shares significant gene expression similarities with multiple brain tissues, in particular for genes encoding for neurotransmitter receptors and transporters, stress mediators, cytokines, hormones, and growth factors, all of which are relevant to MDD. As such, investigating peripheral blood gene expression appears to be a useful tool for assessing and understanding MDD.

It is important to mention that biomarker researchers have previously used the term leukocyte gene expression to refer to blood gene expression, implying that the mRNA isolated from blood comes predominantly from leukocytes (white blood cells) - that is, the cells of the immune system. This assumption has been largely based on the notion that erythrocytes, or red blood cells, even if much more abundant than leukocytes (by a factor of approximately 1,000), do not have a nucleus and as such should not have mRNA synthesis.

However, most recent research has suggested that, in fact, whole blood mRNA comes predominantly from erythrocytes. As mentioned above, there is clear evidence that biological systems such as the HPA axis and the inflammatory response are altered and can contribute to the pathogenesis of depression. The dysfunction of these systems is largely thought to be a result of the activation of stress-related mechanisms, as
MDD is often preceded by acute or chronic stressful experiences. We and others have proposed an explanatory model centered on the glucocorticoid receptor (GR), one of the most important receptors and transcription factors governing the stress response. Stress can induce glucocorticoid resistance, that is, a reduction of GR function, which in turn leads to both HPA axis hyperactivity and increased inflammation. As communication occurs between the CNS and the endocrine and immune systems, an activation of one can affect the processes of another, and vice versa.

Based on this, we review the current literature on blood gene expression alterations in MDD. Additionally, we look at bipolar disorder (BPD) studies that consider euthymic or depressed states, but excluding those that look at manic states. We focus in particular on three important and interlinked domains: inflammation, GR functionality and neuroplasticity. We also briefly review the few existing transcriptomics studies.

Alterations in the expression of genes involved in inflammation The inflammatory theory of MDD emphasizes the role of psychoneuroimmunological dysfunctions where there is an activation of the immune system. Moreover, MDD is very common in the medically ill, particularly in conditions with an inflammatory component, such as cardiovascular disease and rheumatoid arthritis, as well as in autoimmune and neurodegenerative disorders. Indeed, patients with MDD have been consistently shown to have altered levels of pro- and anti-inflammatory cytokines in circulation, and postmortem studies have also described gene expression alterations in a variety of these cytokines. However, studies on postmortem brains have several limitations that can affect the results, including the brain region analyzed, the cause of death and the effect of the antidepressant treatments on gene expression. As such, researchers are using peripheral tissues, such as leukocytes, that have several advantages, which we have already mentioned. A few studies have assessed the mRNA levels of genes involved in inflammation in the peripheral blood of patients with MDD. For example, Tsao and colleagues found that the expression of IL-1β, IL-6, TNF-α and IFN-γ genes was significantly higher in the peripheral blood mononuclear cells of patients with MDD compared with healthy controls. Moreover, in a sub-sample of patients, they demonstrated that IFN-γ expression was reduced, though not normalized, after 3 months of fluoxetine treatment, suggesting that antidepressants may have anti-inflammatory properties. Similarly, we have recently shown altered gene expression levels in a number of cytokines in the whole blood of patients with MDD when compared with controls. We have found higher mRNA levels of IL-1β, IL-6, TNF-α and macrophage inhibiting factor (MIF) as well as lower levels of IL-4. Moreover, we have also found that IL-β, TNF-α and MIF mRNA levels are predictors of antidepressant treatment response, as all three show higher baseline expression in non-responders.

Finally, we also demonstrated that IL-6 expression is reduced after 8 weeks of antidepressant treatment (escitalopram or nortriptyline) in responders only, suggesting a unique ability of these biomarkers to both predict and track the therapeutic antidepressant response. The activation of the immune system observed in patients with MDD is of course not limited to changes in cytokines production. For example, apolipoprotein E (ApoE) is a protein produced by macrophages known to act as an immunomodulator. ApoE is thought to interact with many immunological processes including suppression of T cell proliferation, macrophage function regulation and activation of natural killer T cells. One study investigated the expression levels of the ApoE receptor, ApoER2, in lymphocytes of Patients with MDD and healthy controls, demonstrating that patients with MDD had a significantly lower expression of ApoER2 compared with controls. These receptors bind to reelin, an extracellular matrix glycoprotein that plays crucial roles in brain development as well as in synaptic plasticity in the adult brain. Interestingly, blood levels of an isoform of reelin have also been shown to be reduced in patients with MDD. There is also gene expression evidence for the involvement of key inflammatory enzymes, including cyclooxygenase-2 (COX-2), myeloperoxidase (MPO) and inducible nitric oxide synthase, in the development of...
MDD. These enzymes have been shown to be expressed not only in immune cells but also in the CNS. Moreover, increased oxidative and nitrosative stress as sequelae of inflammation have been previously demonstrated postmortem as well as in animal studies. Indeed, a gene expression study showed higher mRNA levels of COX-2, MPO, inducible nitric oxide synthase-2A and phospholipase A2 (PLA2G2A) in patients with MDD compared with healthy controls.

Furthermore, an increase in either reductive or oxidative stress is thought to be involved in the alteration of the expression of several neurotrophic factors, and will be reviewed below (see neuroplasticity). Finally, a recent study in patients with MDD and euthymic BPD disorder investigated three key genes involved in inflammatory processes: triggering receptor expressed on myeloid cells 1 (TREM-1), DNAX-activation protein of 12 kDa (DAP12), and purine-rich Box-1 (PU.1). In this study, peripheral blood mononuclear cells were isolated from whole blood and gene expression carried out using purified monocytes. The results showed a significantly higher expression of PU.1 in patients with MDD and a significantly higher expression of TREM-1 in patients with BPD, with a trend for higher expression in patients with MDD compared with healthy controls, supporting, again, the role of inflammation in these disorders.

Alterations in the expression of genes involved in glucocorticoid receptor functionality Alterations of the HPA axis, including impairments in glucocorticoid-mediated negative feedback, is a well-established and consistent finding in MDD. The GR is involved in this negative feedback and several studies have assessed GR expression and functionality in patients with MDD. These studies have primarily been conducted in peripheral cell types including immune cells (mononuclear and polymorphonuclear leukocytes) and fibroblasts (gingival and skin). Four studies have analyzed mRNA expression of GR or of GR-related molecules in peripheral blood. Katz et al. investigated gene expression of chaperones and co-chaperones of the GR, such as FK506 binding protein (FKBP)-4 and FKBP-5, which influence GR function, and of GR target genes during pregnancy in individuals with a history of depression. They found an upregulation of eight genes during pregnancy in all patients; however, the expression of BAG family molecular chaperone regulator 1 (BAG1), FKBP-5, peptidylprolyl isomerase D (PPID) and nuclear receptor coactivator 1 (NCOA1) was reduced in mothers who were in a current depressive state. This suggests that maternal depression diminishes the pregnancy-related upregulation of these particular GR-related genes. A part of these findings was replicated in our recent study, where we also assessed the expression of FKBP-4, FKBP-5 and GR in patients with MDD and controls. We found higher mRNA levels of FKBP-5 and lower levels of GR in patients with MDD compared with controls. Furthermore, we found that antidepressant treatment significantly reduces FKBP-5 levels after 8 weeks in patients who responded to treatment, and increases GR levels in all patients, suggesting that a successful antidepressant treatment requires a normalization of GR function.

In a third study, Matsubara et al. investigated two isoforms of GR in both patients with MDD and with BPD: GRα, which is able to directly exert glucocorticoid effects, and GRβ, which binds poorly to glucocorticoids and, by forming heterodimers with GRα, impairs ligand binding of this isoform and acts as a dominant negative regulator of GR function. The authors found that GRα expression was lower in patients with MDD and with BPD, in both current depressive states and in remission, compared with healthy controls. This suggests that GRα mRNA reduction is not state-dependent but a trait-dependent finding in mood disorders. These findings may seem at odds with the aforementioned study showing that antidepressant treatment increases GR expression; however, it is important to note that most of the patients with depression in the study by Matsubara et al., even those defined as ‘currently depressed’, were already on antidepressants at the time of the gene expression analysis. They found no significant differences in the expression of GRβ in either patient groups compared with controls. Lastly, a study conducted by the same
group, again in both patients with MDD and with BPD, investigated glyoxalase-1 (Glo1), an antioxidant enzyme involved in oxidative stress and also a GR target gene as it contains consensus sequences for GR response elements. It has been suggested that a GR dysfunction may also have an effect on Glo1 expression and, indeed, the authors found a lower expression of Glo1 in patients with MDD and BPD in a current depressive state compared with controls.

On the contrary, there was no significant difference in Glo1 expression in patients with MDD or BPD in remission when compared with controls. This supports the notion that a reduced GR function, and thus a reduced expression of GR target genes like Glo1, is involved in the pathogenesis of depression, and that antidepressant treatment is able to restore this dysfunction. These data are also consistent with our experimental work showing that antidepressant treatment increases GR function both in vivo and in vitro.

Alterations in the expression of genes involved in neuroplasticity MDD may also involve an inability of neuronal systems, especially under stress conditions, to show adaptive plasticity, a mechanism known as neuronal plasticity. Molecular correlations underlying the mechanisms of the stress response involve the regulation of several neurotrophic factors, one of them being brain-derived neurotrophic factor (BDNF). To this regard, several studies have demonstrated reduced serum and plasma BDNF levels in patients with MDD when compared with controls, and now a few studies have investigated BDNF at gene expression level. Pandey et al. investigated BDNF gene expression in both adult and pediatric patients with MDD and found significantly lower mRNA expression as well as lower protein levels in both MDD groups compared with controls. These findings are supported by another of our studies, where we have also shown significantly lower BDNF expression in the peripheral leukocytes of patients with MDD compared with controls. Additionally, we have found a significant increase in BDNF expression after treatment with the antidepressant escitalopram as well as a parallel improvement in depressive symptoms. In a similar study, we investigated the expression of the neuropeptide VGF (non-acronymic) in the peripheral leukocytes of patients with MDD and controls. VGF is known to be involved in synaptic plasticity and to be induced by BDNF, and we have shown that VGF expression is significantly lower in patients with MDD compared with controls. Interestingly, we also found that expression of VGF is increased after 12 weeks of escitalopram treatment in those patients whose depressive symptoms were ameliorated. We have recently replicated these data in the aforementioned larger study, where again we show that patients with MDD have lower mRNA levels of BDNF and VGF, and that antidepressant treatment (escitalopram or nortriptyline) increases both BDNF and VGF expression in treatment responders.

In a study of patients with MDD and BPD, Otsuki et al. did not find any significant differences in BDNF expression between patients and controls. However, most of the patients were on antidepressant medication, so this may explain the lack of differences. Moreover, Otsuki and colleagues showed state-dependent differences in a number of other neurotrophic factors, including glial cell line-derived neurotrophic factor (GDNF), artemin (ARTN) and neurotrophin-3 (NT-3). These factors have previously been shown to be associated with stress response in animal model as well as with depression and suicide in humans. Specifically, they demonstrated that patients with MDD in a current depressive state have lower expression of GDNF, ARTN and NT-3 compared with those in remission as well as controls. However, they did not find any significant differences in the expression levels of these three factors in BPD patients in depressive or remissive states, suggesting that the changes in the expression of these genes are associated with MDD only, and may be state-dependent.
Another protein related to BDNF is p11, a member of the S-100 family known to be involved in the regulation of a number of cellular processes such as cell cycle progression and differentiation. Interestingly, two studies have found p11 to be overexpressed in patients compared with healthy controls. Su et al. demonstrated that patients with MDD had a higher expression of p11 compared with controls, and Zhang et al. found the same results in patients with BPD [55]. However, in both of these studies the patients were medicated. Conversely, in our recent study we reported lower mRNA levels of p11 in drug naïve patients with MDD compared with controls. Furthermore, after 8 weeks of antidepressant treatment, p11 levels were significantly increased. We have also recently demonstrated the p11 mRNA levels are increased by antidepressant treatment in vitro in a human neuronal hippocampal model, thus showing also the unique ability of a gene expression approach to be used consistently across different experimental approaches.

As mentioned earlier, the expression of neurotrophic factors can be altered particularly in response to oxidative or reductive stress. One such neurotrophic factor is vascular endothelial growth factor (VEGF). Increased expression of VEGF has previously been shown in peripheral monocytes of patients with diabetes with coronary artery disease. Given the high prevalence of depression in patients with coronary artery disease, VEGF mRNA levels have been proposed as a putative biological marker for MDD. Indeed, Iga and colleagues measured VEGF expression in the peripheral leukocytes of patients with MDD and showed that VEGF expression was higher in patients with MDD compared with healthy controls. A similar study by Dome et al. investigated the expression levels of VEGF receptor-2 (VEGFR2) in the peripheral blood of patients with MDD. They showed a lower expression of VEGFR2 in patients with MDD compared with healthy controls. Moreover, the expression of VEGFR2 negatively correlated with depression scores, thus supporting the role of VEGF signaling in MDD pathogenesis.

Two further molecules regulating neurogenesis have been found to be altered in depression: pericentrin 2 (PCNT2) and epithelial membrane protein 1 (EMP1). PCNT2 is a disrupted in schizophrenia 1-interacting protein that regulates cell proliferation, differentiation and migration, and outgrowth of neuronal axons and dendrites. In a study of patients with MDD and BPD, mRNA levels of PCNT2 were found to be significantly higher in drug-naïve patients with MDD compared with controls. Interestingly, PCNT2 expression was also higher in patients with BPD in a remission state when compared with controls. EMP1 is involved in neurogenesis mechanisms as it interacts with transforming growth factor beta signaling. In drug-naïve patients with MDD, EMP1 levels were significantly lower when compared with controls and, after 8 weeks of antidepressant treatment, EMP1 mRNA levels showed a trend towards an increase.

Cell adhesion molecules such as neural cell adhesion molecule (NCAM) and L1 are also known to play important roles in synaptic plasticity, and have been indicated to have altered expression in the cerebrospinal fluid and brain of patients with a mood disorder. Several studies conducted in peripheral blood mRNA confirm this. For example, Wakabayashi et al. assessed the expression of NCAM-140 and L1 in the leukocytes of patients with MDD and BPD, as well as controls. They found a lower expression of NCAM-140 in patients with BPD in a current depressive, but not in a remissive, state compared with both controls and patients with MDD. They also found a higher expression of L1, again in patients with BPD in a depressive state but not in those in remission compared with controls and patients with MDD. Interestingly, they did not find any significant differences in the expression of these molecules in patients with MDD when compared with controls. This suggests that the alterations in the expression of both NCAM-140 and L1 are specific to BPD and are also state dependent. In addition, no changes were found for intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) or E-cadherin expression, in patients with either MDD or BPD compared with controls.

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Repressor element-1 silencing transcription factor (REST) is a modulator protein that is also known to be involved in synaptic plasticity. It has been recently shown that REST is involved in the synthesis of cortisol and in neurogenesis, both of which are of relevance to mood disorders. Otsuki and colleagues investigated the expression of REST and a variety of its target genes including corticotropin-releasing hormone (CRH), adenylate cyclase 5 (Adcy5) and TNF superfamily member 12-13 (TNFs12-13) in patients with MDD and BPD. They found a lower expression of REST in patients with MDD compared with controls. Furthermore, they investigated whether altered expression of these mRNAs were state or trait dependent, reporting a higher expression of CRH, Adcy5 and TNFs12-13 in patients with MDD in a current depressive state compared with those in a remissive state.

Interestingly, they found no significant differences in the expression of REST or any other mRNAs in patients with BPD when compared with controls.

Transcriptomics studies

The use of high-throughput technologies like microarray platforms allows for the exploration of the expression levels of the entire genome and thus the identification of gene expression differences by using a hypothesis-free approach. Beech et al. used microarrays containing >48,000 transcript probes to investigate gene expression in the peripheral blood of patients with BPD compared with healthy controls [69]. They found a total of 1,180 differentially expressed genes, 559 of which were upregulated in patients with BPD and 621 that were downregulated. Using pathway analysis they were able to identify functional pathways that were significantly different between patients and controls, including pathways involved in gene transcription, immune response, apoptosis and cell survival. In particular, they found differences in the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, which plays important roles in transcription regulation and immune response mechanisms. This is in line with a previous study showing increased DNA binding of NF-κB in peripheral blood mononuclear cells of patients with MDD in response to an acute stressor. Another microarray study focusing on postpartum depression identified 73 differentially expressed genes in mothers with postpartum depression compared with control mothers. Of interest, the authors observed a reduction in the expression of genes involved in immune modulation, transcriptional activation, cell cycle and proliferation, as well as DNA replication and repair processes. As previously mentioned, neuronal plasticity as well as cell survival are important processes involved in MDD and even in the effects of antidepressant drugs. Indeed, one microarray study investigated gene expression changes in response to the serotonin-norepinephrine reuptake inhibitor venlafaxine in elderly patients with MDD. The authors found 57 out of 8,000 sequences examined to have an altered expression after 4 weeks of antidepressant treatment. The genes found to be differentially expressed belong to the biological systems we have already discussed, including those involved in cell survival, ionic homeostasis, neural plasticity, signal transduction and metabolism. Lastly, a study in 2012 conducted microarray analysis in lymphocytes from patients with MDD and subsyndromal symptomatic depression (SSD). In patients with MDD, they found 149 differentially expressed genes, enriched in 53 pathways, in comparison with control participants. Pathway analyses identified significant differences for IL-2 and IL-6-mediated signaling as well as TNF receptor signaling pathways.

In patients with SSD, they identified 1,456 genes and 47 pathways that were significantly different when compared with controls, with 20 genes overlapping with those found in patients with MDD. Pathways found to be differentially expressed in patients with SSD included cytokine-cytokine
receptor interactions and G protein signaling. Only two pathways were found to be involved in both MDD and SSD: the mitogen-activated protein kinase signaling pathway and the Wnt signaling pathway, both of which have been previously implicated in mood disorders.

Although strictly speaking not a transcriptomics study in patients with depression, it is worth mentioning our recent study in the human hippocampal cells model. In this study, we mimicked depression ‘in a dish’ by incubating cells with stress-level concentrations of the main human glucocorticoid hormone, cortisol. Transcriptomics analyses have identified inhibition of the ‘Hedgehog pathway’ as a candidate mechanism by which depression can reduce neurogenesis. It is of interest that, in the same study, we also found that Hedgehogsignaling is inhibited in the hippocampus of adult prenatally stressed rats with high glucocorticoid levels, again confirming the ability of gene expression approach to identify findings that are replicated consistently across different experimental models.

Conclusions

We have presented data on peripheral mRNA gene expression in patients with depression across MDD and BPD, obtained from whole blood, isolated mononuclear cells and isolated monocytes. All studies identified a pattern of altered expression in several genes belonging to three biological systems of interest: inflammation, GR functionality and neuroplasticity. Of note is the frequent pattern of state-relate’ gene expression changes that are normalized either by remission or by antidepressant treatment. The association between gene expression and treatment response identifies this biomarker approach as particularly relevant from a clinical point of view. However, the temporal relationship of these gene expression changes with other factors, such as exposure to stress, is still unclear. This is relevant especially considering the frequent occurrence of stressors in these clinical groups. For example, a study on socioeconomic circumstances used transcriptome gene expression measurements followed by bioinformatics analysis of genes whose expression is regulated by specific transcription factors, including the GR and NF-κB. The authors described an upregulation of target genes for NF-κB and a downregulation of target genes for GR, consistent with a pattern of glucocorticoid resistance and increased inflammation, that is, a pattern similar to that described in depression. We also do not know whether some of these changes in gene expression represent the marker of a genetic predisposition to encounter psychopathology; for example, we have previously shown that genetic variants in CNS and immune genes increase the association between depression and inflammation.

It should also be noted that the many pathways involved in the onset of depressive symptoms are of course interrelated and dynamic in nature. Because of this complexity, it has been proposed that a systems biology approach, combining information from gene expression analysis, protein data and well-validated animal models, is necessary to untangle the exact relevant pathways as well as novel molecular mechanisms. Despite these unanswered questions, peripheral blood gene expression is a strong and clinically relevant system to identify biomarkers related to pathology and treatment response, and also to discover unknown mechanisms underlying the development of mood disorders. The identification of both could help in the personalization of therapy and in the future development of novel treatments.
Risk and Protective Factors Associated With Symptoms of Post-Traumatic Stress, Depression, and Alcohol Misuse in OEF/OIF Veterans

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ABSTRACT

Military personnel returning from the conflicts in Iraq and Afghanistan commonly experience mental health problems and efforts are underway to determine risk and protective factors associated with postdeployment mental health concerns. This study examined the contribution of trait neuroticism, predeployment life events, combat experience, perceptions of threat, and postdeployment social support on mental health symptoms at 6 months, 12 months, and 24 months postdeployment. Two hundred seventy-one veterans completed self-report measures. Hierarchical regression analyses demonstrated that neuroticism predicted posttraumatic stress and depressive symptoms at all 3 time points; perceived threat predicted posttraumatic stress symptoms at Time 1 and Time 2 and depressive symptoms at Time 2. Social support was a strong negative predictor of posttraumatic stress and depressive symptoms. Alcohol misuse was not significantly predicted by any of the variables. The present study highlights the role of perceived threat and trait neuroticism on postdeployment mental health symptoms and indicates social support is a robust protective factor. Efforts aimed at increasing sustained postdeployment social support may help defend against significant mental health problems among veterans.

INTRODUCTION

Mounting research highlights the prevalence of post-traumatic stress disorder (PTSD), depression, alcohol misuse, and related problems among Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans. Nearly 1 in 5 OEF/OIF veterans report mental health concerns immediately following deployment, and longitudinal research has demonstrated that the rate of mental health concerns continues to increase in the months following return from deployment. These alarming statistics emphasize the significant impact of deployment on our service members and their families, and highlight related costs such as attrition from the military and increased health care needs for returning soldiers. Consequently, there has been a significant interest in examining vulnerability and protective factors that are associated with mental health concerns among OEF/OIF veterans to more effectively stem the deleterious effects of combat on future military personnel.

Above all other factors contributing to veterans’ mental health concerns, the impact of combat exposure on a variety of negative mental health outcomes has been well documented. In fact, contemporary researchers have suggested that the focus on combat exposure has hindered understanding how other important personal and environmental factors affect mental health outcomes among veterans. In recent years, a number of additional deployment-related factors as well as nonmilitary experiences and circumstances have been implicated in the development of veterans’ mental health concerns. Regarding deployment-related factors, the subjective perception of threat (i.e., concern about safety and
survival) has garnered significant attention with several studies demonstrating that perceived threat is more robustly associated with PTSD than actual combat experiences and that it accounts for the association between combat experiences and PTSD. The extent to which perceived threat is associated with other mental health concerns has received relatively limited attention. Although there is some evidence that perceived threat is associated with depression, the findings have been mixed, suggesting the benefit of additional research in clarifying the association between perceived threat and other mental health problems.

Beyond deployment-related experiences, a growing body of research also highlights the impact of predeployment and postdeployment risk and resilience factors on mental health outcomes of veterans. For instance, prior history of stressful life events has been associated with poor outcomes. In contrast, growing research has emphasized the protective nature of postdeployment social support in buffering against mental health problems. In total, veterans’ mental health outcomes are multiply determined by lifetime experiences both within and outside the military, highlighting the importance of evaluating diverse factors contributing to mental health outcomes in veterans. To that end, King et al have developed a suite of scales known as the Deployment Risk and Resilience Inventory (DRRI) to capture experiences that are relevant to mental health and well-being of military personnel.

In addition to the experiences evaluated by the DRRI, variation in personality traits represents another factor that may confer risk for mental health concerns. In particular, neuroticism is a stable characteristic reflecting vulnerability to negative emotional experiences that has been associated with mental health and substance use problems in veterans. As noted by King et al in the development of the DRRI, neuroticism may reflect an important variable that underlies associations between DRRI scales and mental health symptoms. To date, the extent to which neuroticism and DRRI scales are uniquely associated with mental health symptoms has not been evaluated.

This study examined the contribution of neuroticism, predeployment life events, deployment (combat experiences, perceived threat), and postdeployment social support on mental health symptoms at an initial assessment and two follow-up assessments completed 6 months and 1 year later (i.e., at 12 months and 24 months postdeployment). Specifically, the impact of these factors on symptoms of PTSD, depression, and substance use were evaluated. This is the first study to examine the association of neuroticism and DRRI scales on various mental health symptoms of OEF/OIF veterans at multiple time points. Consistent with prior research, it was expected that neuroticism, predeployment life events, and deployment experiences would each be associated with mental health problems at Time 1. Given the stability of personality traits, neuroticism, but not necessarily predeployment life events or deployment factors, was expected to predict mental health symptoms at subsequent assessments. Finally, social support was expected to protect against mental health symptoms at each assessment.

METHODS

Participants

The sample for this study included 271 OIF/OEF veterans who registered for Veterans Affairs (VA) health care subsequent to their return from deployment. Fewer than half had used any VA services at the time of recruitment into the study and, as requested by the local Institutional Review Board, veterans receiving VA mental health services at the study’s inception were excluded from recruitment. Thus, this was a nonclinical sample.
The initial evaluation (Time 1) took place approximately 6 months following their return, and participants were invited to complete additional evaluations at roughly 12 months (Time 2) and 24 months (Time 3) postdeployment. Over half of the original participants (n = 141) completed the Time 2 evaluation and one-third (n = 97) completed the Time 3 evaluation. In adherence to the Declaration of Helsinki, all participants provided written informed consent before participating. The study protocol was approved by the local Institutional Review Boards.

The veteran participants were largely males (85%) and ranged in age from 19 to 58 (Mean = 31.03, SD = 9.29). Twenty-eight percent of participants did not provide data on their race/ethnicity; the remainder was primarily Caucasian (68% of total). Forty-seven percent of participants described themselves as single/never married, 42% were married, and 8% were divorced. Almost all of the participants (93%) had a high school diploma or equivalent. Regarding the most recent deployment, 33% reported mainly combat duties, 46% reported mainly combat support, and 18% reported noncombat-related duty. The majority of participants (52%) were in the National Guard on the most recent deployment, 22% were reservists, and 21% were full-time active duty status. Eight-five percent served in the Army. The Navy, Air Force, and Marines each accounted for about 5% of participants.

Measures

Neuroticism

Neuroticism was assessed using the Big Five Inventory (BFI), a 44-item self-report measure of the Five-Factor Model personality traits. The BFI requires participants to rate themselves on a variety of characteristics using a 5-point Likert scale, ranging from “disagree strongly” (1) to “agree strongly” (5). Items on the neuroticism subscale assess characteristics such as emotional instability, anxiety, irritability, and sadness. Previous studies have documented high test–retest reliability, internal consistency, and convergent and divergent validity of the overall BFI and its subscales. Internal consistency of the neuroticism subscale in our sample was good (Cronbach’s α = 0.814).

Deployment Risk and Resilience Inventory

The DRRI consists of a series of self-report scales assessing predeployment, deployment, and postdeployment factors that have been linked to veteran physical and mental health outcomes. The present study utilized four of the scales. The Predeployment Life Events scale consists of 15 dichotomous (yes/no) items evaluating exposure to highly stressful or traumatic events (e.g., sexual abuse, domestic violence) occurring before deployment. The Combat Experiences scale is a dichotomous (yes/no) scale that assesses exposure to a variety of combat experiences, such as firing a weapon at the enemy or participating in missions. The Deployment Concerns scale assesses perceived threat and concern about safety with items such as “I thought I would never survive” or “I was worried about getting an infectious disease,” answered on a 5-point Likert scale ranging from “strongly disagree” (1) to “strongly agree” (5). Using the same 5-point Likert scale, the Postdeployment Social Support scale evaluates the extent to which an individual feels understood and able to rely on others for emotional or other support when needed. The DRRI has shown good internal consistency, criterion-related validity, and discriminative validity with OIF veterans. Internal consistency reliability in this study was as follows: Predeployment Life Events (Cronbach's α = 0.713), Combat Experiences (Cronbach's α = 0.858), Deployment Concerns (Cronbach's α = 0.900), and Postdeployment Social Support (Cronbach's α = 0.890)
Post-Traumatic Stress Disorder

Symptoms of PTSD were assessed with the PTSD Checklist-Civilian Version (PCL-C), a 17-item self-report scale that assesses PTSD symptoms based on Diagnostic and Statistical Manual for Mental Disorders (Edition 4) criteria. Each item reflects one of the PTSD symptoms. Participants are asked to rate how much they have been bothered by each symptom in the past month using a 5-point Likert scale, ranging from “not at all” (1) to “extremely” (5). The total score, which ranges from 17 to 85, provides an index of current PTSD symptom severity. For military personnel, a total score of 50 or greater indicates likely PTSD. In this study, 16% of the participants met or exceeded that threshold at Time 1, 12% at Time 2, and 10% at Time 3. At each time point, nearly twice as many veterans met or exceeded a more moderate cutoff of 40. Internal consistency, test–retest reliability, and convergent validity of the PCL-C have all been found to be adequate. Internal consistency in our sample was excellent (Cronbach’s $\alpha = 0.944$, 0.929, and 0.957 at Time 1, Time 2, and Time 3, respectively).

Depression

Symptoms of depression were evaluated with the Beck Depression Inventory-Short Form (BDI-SF), a 13-item self-report questionnaire assessing the cognitive-affective aspects of depression. For each item, participants choose among four response options indicating increasing levels of symptom severity. Item scores range from 0 to 3 with a maximum total score of 39. The BDI-SF is derived from the BDI, one of the most widely used rating scales for depression, and is often used in medical facilities. The BDI-SF has been found to have comparable internal consistency to that of the full BDI, and Pearson product–moment correlation coefficients between the BDI-SF and full BDI support its use as a substitute for the longer version. Internal consistency was good in the present sample (Cronbach’s $\alpha = 0.89$, 0.909, and 0.914 at Time 1, Time 2, and Time 3, respectively). A score of 10 or greater is indicative of at least mild depressive symptoms. In this study, 14% of participants at Time 1 and 21% of participants at Time 2 and Time 3 met or exceeded that threshold. Because of an administrative error, some participants at Time 1 did not complete the BDI-SF. Results for Time 1 depressive symptoms are based on 142 participants.

Alcohol Misuse

The Alcohol Use Disorders Identification Test (AUDIT) is a widely used 10-item questionnaire assessing hazardous alcohol consumption. The items assess the following domains: amount and frequency of alcohol consumption, negative consequences of drinking, and symptoms of alcohol dependence. Possible scores range from 0 to 40, with scores of 8 or more indicating harmful alcohol use and possible dependence. Potentially problematic alcohol use was relatively common in the present sample, with 28% of participants at Time 1 and Time 2 and 20% of participants at Time 3 meeting or exceeding that threshold. Internal consistency of the items was good in the present sample (Cronbach’s $\alpha = 0.814$, 0.858, and 0.881 at Time 1, Time 2, and Time 3, respectively).

Analyses

Preliminary data analyses were conducted to examine for outliers and non-normality. Univariate outliers were brought to the fence by adjusting the extreme values to be equal to the median ± (2 × interquartile range). After adjusting for outliers, all of the variables were normally distributed. Bivariate correlations were calculated to determine the basic associations between variables. The primary analytic strategy involved a series of
hierarchical multiple regressions to evaluate the ability of the DRRI scales and neuroticism to predict symptoms of PTSD, depression, and alcohol misuse at each of the three time points. For each of the regressions, variables were entered in blocks in the following order: neuroticism was entered in Block 1, predeployment life events were entered in Block 2 (i.e., predeployment), combat experiences and deployment concerns (i.e., perceived threat) were entered in Block 3 (deployment), and postdeployment social support was entered in Block 4 (postdeployment). To reduce the likelihood of Type I error, family wise level of significance was set to 0.01. Thus, with Bonferroni correction, independent variables in each of the regression models were considered significant if the $p$ value was less than 0.002 (0.01 divided by 5, the number of predictors in each analysis). All regressions were examined for normal distribution of residuals and multicollinearity, and no problems were detected.

RESULTS

Post-Traumatic Stress Disorder

In the hierarchical regression model predicting PTSD symptoms at Time 1 and Time 2, $F$ change was significant at $p < 0.001$ for Blocks 1, 3, and 4, suggesting that neuroticism, deployment, and postdeployment factors all contributed significantly to PTSD symptoms. At Time 3, $F$ change was significant at $p < 0.001$ for Block 1 (neuroticism) and Block 4 (postdeployment social support) and at $p < 0.005$ for Block 2 (predeployment).

Depression

In the hierarchical regression model predicting depressive symptoms at Time 1, $F$ change was significant at $p < 0.001$ for Block 1 and Block 3 and at $p < 0.02$ for Block 4 suggesting that neuroticism, deployment, and postdeployment factor social support all contributed significantly to depressive symptoms. In the model predicting depressive symptoms at Time 2, $F$ change was significant at $p < 0.001$ for Block 1 (neuroticism) and Block 4 (postdeployment social support) and at $p = 0.006$ for Block 3 (deployment). Finally, in the model predicting depressive symptoms at Time 3, $F$ change was significant at $p < 0.001$ for Block 1 and Block 4 indicating that neuroticism and social support, but not predeployment or deployment experiences, were associated with depressive symptoms 24 months postdeployment.

Alcohol Misuse

In the hierarchical regression model predicting alcohol misuse at Time 1, $F$ change was significant only for Block 1 (neuroticism; $p = 0.027$). At Time 2, $F$ change was significant only for Block 4 (postdeployment social support; $p = 0.012$). At Time 3, $F$ change was marginally significant for Block 3 (deployment experiences; $p = 0.045$); no other blocks were significant predictors of alcohol misuse.

DISCUSSION

The goal of this study was to examine the contribution of neuroticism and several DRRI scales to mental health concerns among a sample OEF/OIF veterans. Overall, the findings suggest that neuroticism and perceived threat during deployment are predictive of subsequent symptoms of PTSD and depression. In contrast, social support protects against symptoms of PTSD and depression. These results are consistent with
independent lines of research highlighting the roles of personality traits and lifetime experiences in predicting veterans’ mental health concerns and extends prior work by demonstrating the unique contributions of each.

A voluminous body of research has documented the association between neuroticism and psychopathology, particularly internalizing disorders such as PTSD and depression. As expected and in line with prior research, neuroticism was a robust predictor of PTSD and depressive symptoms at each of the three time points in this study, even when all other DRRI predictors were included. Thus, results from this study indicate that trait neuroticism appears to be distinct from the DRRI scales and is an important factor that may significantly impact risk for postdeployment mental health concerns. Indeed, recent research has demonstrated that neuroticism interacts with other deployment-related variables to potentiate PTSD symptoms. Neuroticism, however, is a broad trait comprised of a variety of characteristics (e.g., emotional instability, anxiety, depression). Further research aimed at parsing out the relationship between different facets of neuroticism and pathological outcomes in veterans may be useful in terms of more clearly identifying personality factors that may give rise to postdeployment mental health concerns among veterans. Notably, personality traits have also been shown to contribute to resilience; however, it was beyond the scope of this article to investigate resilience factors.

Here, as in previous studies, combat experiences played a secondary role to perceived threat in terms of predicting PTSD symptoms. This finding is particularly compelling in light of the mounting research demonstrating that significant psychopathology is one of several possible outcomes following exposure to potentially traumatic events. In fact, resilience or healthy outcomes following exposure to potentially traumatic events appear to be the norm, and the present findings suggest that threat appraisal may be a factor that distinguishes between healthy and pathological outcomes. Along those lines, a novel prospective study examining neural activity in soldiers before and after deployment to a combat zone found that DRRI-assessed perceived threat, but not combat experiences, was associated with sustained changes in connectivity between the amygdala and other brain regions. These findings suggest that individual differences in threat appraisal are biologically mediated and may represent a vulnerability marker for subsequent PTSD. However, perceived threat appears to be less associated with depression and alcohol use problems. The limited research examining the association between perceived threat and depression has produced mixed results; in the present study, perceived threat predicted depressive symptoms at Time 2 only. Although it is unclear why this relationship was significant only at Time 2, it is possible that individuals prone to depression may ruminate about their combat-theater experiences, thereby increasing the salience of threatening experiences over time. Finally, our findings that perceived threat is not associated with alcohol misuse are consistent with the only other study to examine perception of threat on substance use disorders. Further research is warranted to determine the mechanisms through which threat perception differentially predicts mental health outcomes.

In this study, Predeployment Life Events were not predictive of any outcomes. This finding was somewhat surprising in light of previous research demonstrating that prewar events are associated with postdeployment onset of PTSD. That being said, our null results are largely consistent with other research utilizing the Predeployment Life Events scale from the DRRI, which have also demonstrated no to little association between prior stressors and mental health outcomes. The Predeployment Life Events scale includes a variety of experiences, some of which assess potentially traumatic events (e.g., assault, abuse) whereas others assess more general life stress (e.g., job loss, parental substance use problems). Prior research demonstrating associations between prewar events and postdeployment PTSD have focused on traumatic experiences (e.g., abuse). The inclusion of more general life stressors along with potentially traumatic events on the DRRI scale provides a more comprehensive assessment of prewar experiences but may also dilute scores and limit predictive utility regarding significant mental health outcomes.
In terms of symptoms of PTSD and depression, social support appears to be a powerful buffer that protects against postdeployment mental health concerns. Furthermore, the results of this study suggest that the influence of social support on moderating symptoms of PTSD and depression increases over time. In fact, at Time 2 and Time 3, social support is the strongest predictor of mental health outcomes with high social support exhibiting robust negative associations with PTSD and depressive symptoms. Clinically, the present findings suggest that postdeployment reintegration services that foster continued social support may be particularly beneficial in mitigating mental health problems among returning OEF/OIF veterans. Furthermore, efforts aimed at increasing social support may also reduce suicide risk among veterans. The interpersonal psychological theory of suicide posits that a decreased sense of belonging is a key factor that promotes suicide risk. Thus, increasing opportunities for emotional and instrumental support may increase one's sense of belongingness, providing a buffer against suicide risk.

Notably, neither social support nor any of the other variables were significant predictors of alcohol misuse in the final model for this veteran sample. Although the absence of any significant predictors was somewhat surprising, it is consistent with results from the only other study to examine DRRI scales in relation to problematic substance use. The rates of hazardous drinking in the present sample were consistent with those reported elsewhere and may broadly reflect a feature of military culture rather than individual differences in deployment experiences or personality characteristics. It is feasible that other personality characteristics not included in this study may have significantly predicted alcohol misuse. For instance, disinhibition is a trait characterized by impulsivity and risk-taking behaviors that has largely been associated with drug use; however, recent studies have documented associations between disinhibition and alcohol use problems in military personnel. Particularly given the preponderance of research highlighting morbidity and mortality associated with alcohol misuse, additional research examining factors that predict alcohol misuse in OEF/OIF veterans is warranted.

Overall, this study demonstrates that trait neuroticism and one's perception of threat during deployment are robust predictors of PTSD and depressive symptomatology in the initial years post-deployment; conversely, continued social support protects against those symptoms. Although the findings are novel and highlight important clinical considerations, the present results are not without limitations. First, the results are based entirely on self-report data. Although each of the measures is widely used, self-report assessments, particularly of psychopathology symptoms, fall short of gold-standard diagnostic interviews. Nonetheless, the rates of mental health problems exceeding established cutoffs are consistent with other large epidemiological studies. Second, because this was not a prospective study, veterans' characteristics and experiences were not evaluated before deployment. Consequently, in the case of neuroticism in particular, it is unclear to what extent the responses reflect stable features versus deployment-related negative effect. Although trait neuroticism is considered to be a relatively stable trait, there is some evidence that the relationship between neuroticism and psychopathology is bidirectional. In other words, neuroticism may be a vulnerability factor for future psychopathology that may in turn serve to increase neuroticism. Finally, this is a nonclinical sample comprised primarily of Army and Army National Guard military personnel, and it is unclear whether or not the findings would generalize to other samples.

In conclusion, this study highlights the role of personality characteristics and one's perception of threat in predicting subsequent mental health concerns and indicates that social support is an immensely important protective factor. Efforts aimed at increasing opportunities for sustained postdeployment social support are likely to be beneficial in reducing the deleterious impact of combat-related experiences in our nation's military personnel.
Treatment of Avoidant Personality Traits in a German Armed Forces Inpatient Psychiatric Setting

Military Medicine
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ABSTRACT

Military duty places high demands on the soldiers' social adaptability and competences. Avoidant personality traits can lead to interpersonal conflicts and at least to mental disorders. 192 German Armed Forces soldiers were treated in a multimodal inpatient psychiatric treatment setting at a Bundeswehr hospital between 2007 and 2010. 129 of these patients received a social skills group training (group training of social competence [GSC]) as part of this setting. A comparison group (n = 63) did not participate but got unspecific treatment elements instead. The Symptom Checklist 90-Revised (SCL-90-R) and the Inventory on Competence and Control Beliefs (Fragebogen zu Kompetenz-und Kontrollüberzeugungen [FKK]) were applied. Symptom severity in the SCL-Global Severity Index, sum scale of the SCL-90-R and the four primary scales of the FKK showed significant improvements both immediately after treatment and at follow-up. No significant influence of the form of treatment (with/without GSC), age, gender, diagnosis, and deployments on the treatment result was established in the analysis of covariance. The data suggest that an inpatient psychiatric treatment setting focused on avoidant personality traits has a favorable effect on psychiatric symptom severity in military personnel. Social skills group training as a treatment component does not seem to be significantly superior to the standard setting.

INTRODUCTION

When carrying out their profession, military personnel are exposed to various highly stressful situations. These stressors include participation in missions abroad, coping with social conflict situations, and leadership demands. The frequently traumatizing events that accompany deployments can lead to post-traumatic stress disorders (PTSDs), the pathogenesis of which can be influenced by a number of vulnerability and resilience factors. Studies have repeatedly revealed that a supportive social environment is one of the most important protective factors. Since social skills and the use of social support are directly connected to each other, improvement of social skills can— in particular for deployed military personnel— help to maintain mental health.

Group psychotherapy adopts an approach of this kind and is an effective and well-evaluated treatment component in different therapeutic settings. In the case of military patient collectives, however, the data available is limited. In some studies, particularly in the American and British Armed
Forces, the use of depth psychology or eclectic approaches has resulted in positive changes in military personnel with mental disorders, including those suffering from PTSD.

The choice of the most appropriate therapeutic method and the treatment effects depend on a number of influencing factors. The mental stress level before the therapy is of importance, also the diagnostic entity (e.g., group therapy in the treatment of addiction disorders has the need for interventions different from psychoreactive diseases), personality structure level, existing comorbidities, age, gender, education, or the participant’s social integration.

In due consideration of these factors as well as the specific nature of the military context, a depth-psychology-based treatment concept was initially established at the German Armed Forces (Bundeswehr) hospitals at the beginning of the 1990s as a short-term inpatient group psychotherapy. In comparison to a control group, a prospective study showed evidence that the method is effective for various psychiatric disorders in Bundeswehr soldiers, including stress-reactive mental disorders. However, lower response levels were seen among young soldiers who often present themselves with avoidant personality traits in everyday clinical practice. As a result, consideration was given to establishing and evaluating an additional group therapy component that was suitable for this group of patients.

Group trainings of social competences, e.g., based on Hinsch and Pfingsten (group training of social competence [GSC]), seemed to be an option because this method is available in a manualized and well-evaluated form and has shown to be adaptable to different applications, e.g., for educational purposes. In addition, positive results were obtained in civilian studies performed on young patients with lower levels of personality structure maturity; as by contrast to other group therapeutic approaches, GSC gives detailed instructions for each therapeutic session and thus provides a supporting therapeutic frame.

The aim of this study was to evaluate the effectiveness of an inpatient psychotherapeutic treatment setting on avoidant personality traits as a symptom cluster of psychiatric disorders in Bundeswehr soldiers and the differential effect of social skills group training as a component of this setting.

MEASURES

Study Participants

All study participants were recruited from the military patient clientele of the Department of Psychiatry and Psychotherapy of the Bundeswehr Hospital in Berlin between October 2008 and January 2011. They were referred to this department either by the unit physician or via the department’s outpatient psychiatric clinic.

In total, the group of selected patients consisted of 192 individuals aged between 18 and 27 years (average 23.2 years, SD 3.9). 129 patients took part in the social skills group training. On average, these patients were 23.0 years of age (SD 3.4). 63 patients were included in the comparison group (23.7 years/SD 4.9). 167 test subjects were male (87%) and 25 were female (13%) (social skills training group: 114 male vs. 15 female,
controls: 54 vs. 9). The age and gender differences were not significant. The average duration of the inpatient treatment for the entire group was 30.2 days (SD 15.1) (subgroup differences not significant).

The main inclusion criterion of the study was the detection of avoidant personality traits in the clinical interview manifesting in social anxiety or lack of self-confidence in interpersonal relationships.

The inclusion criterion for the comparison group also was symptomatology indicating participation in a social skills group training. However, for organizational reasons, the training did not take place during the observation period of this group (the social skills group training is only carried out about once per quarter year). Thus a randomization was not performed because of clinical needs. The comparison group was allowed to participate in the training later but was not included in the analyses.

Exclusion criteria were an addictive disorder requiring urgent treatment or acute psychotic symptomatology with distinct formal thought disturbances or agitation. Three patients from the social skills group training and two from the comparison group ended the treatment prematurely.

All patients taking part in the study were informed about the aim of the study and the voluntary nature of their participation, and gave their written consent. The study was authorized by the ethical committee of the Berlin Charité University Clinic, and the ethical standards of the Helsinki Declaration were complied with.

Treatment Procedure

Based closely on the standardized treatment program “Group Training of Social Competence” of Hinsch and Pfingsten, the training group underwent seven core component group sessions lasting 90 to 120 minutes per session. The three topics specified by the authors—“asserting one's rights,” “confident behavior in relationships,” and “gaining sympathy”—were looked at with 2 trainers (under the direction of certified group therapists) within a closed group setting comprising 8 to 10 participants. In addition to theoretical components, practical exercises in the form of video-assisted role plays and exercise-based excursions accompanied by the therapeutic staff were offered. These exercises derived from a list of standardized protocols, which were rated and chosen with respect to expected difficulties by the participants before.

In parallel, the subjects carried out a group project in ergotherapy (1 hour daily for 3 weeks), which was presented by the group at the end of the social skills group therapy.

Training group and comparison group were offered psychotherapeutic one-to-one sessions twice a week over a period of 50 minutes each. These contacts were focused on matters of self-esteem and interindividual relationships, adapted to the given symptoms and the actual interpersonal conflicts, depending on the patients' individual situation at the beginning of the therapy.

Further elements of the standard inpatient setting applied continuously during the whole treatment included relaxation techniques 30 minutes twice a week (progressive muscle relaxation and breathing relaxation), daily sports (aqua-fitness 30 minutes, fitness training 20 minutes), morning rounds (30 minutes twice a week) and one doctors’ round weekly.
The comparison group \((n = 63)\) was exposed to the same standard setting described above over 3 weeks, albeit without the social skills group training elements. Instead of seven group sessions, unspecified therapy components (sports: 90 minutes four times in 3 weeks, outings: three times in 3 weeks) were used. All in all GSC and comparison group received the same hours of activities per week.

Study Procedure

The initial clinical assessment comprised a diagnostic interview to determine Axis I disorders in accordance with DSM IV/ICD-10 (MINI-DIPS), a nonstandardized clinical interview and the following psychological testings:

- SCL-90-R to evaluate general psychiatric symptom severity. In addition to the individual symptom-related scales, a sum scale for the overall severity (SCL-Global Severity Index [GSI]) was used.
- Inventory on Competence and Control Beliefs (Fragebogen zu Kompetenz- und Kontrollüberzeugungen [FKK]) with the scales FKK-SK (self-concept of own abilities), FKK-P (social externality), FKK-I (internality), and FKK-C (fatalistic externality). In addition, two secondary scales, FFK-SKI (generalized self-efficacy) and FKK-PC (generalized externality) can be derived from these primary scales. The questionnaire comprises a total of 32 items. (reliability: Cronbach’s \(\alpha\) for the primary scales: 0.65–0.82). When evaluating the FKK, only the primary scales FKK-SK, FKK-I, FKK-P, and FKK-C were taken into account. It is important to note that, owing to the structure of the scale, improvements in the scales FKK-SK and FKK-I are geared to greater values.

Immediately after the group training had been completed, or—in the case of the comparison group—after 21 days of inpatient treatment, the tests were repeated. For follow-up purposes, the above-mentioned questionnaires were forwarded by post to all patients after 6 months. If no replies were sent back, they were resent after 4 weeks (only 4 additional patients replied after the second forwarding). 89 questionnaires (46.4%) were received, of which 65 (50.4%) were from the social skills training group and 24 (38.1%) were from the comparison group.

Statistical Analysis

First time-dependent differences in the complete inpatient therapy group were assessed. The differences between tested scale values of the four primary FKK scales and the GSI sum scale of the SCL-90-R after therapy and values before therapy as well as the differences between 6 months follow-up values and before therapy were used as dependent variables. Incorrect questionnaires (e.g., missing data) were excluded from further statistical evaluation.

The Kolmogorov–Smirnov test rejected the null hypothesis of normal distribution for the differences of the SCL-90-R. The differences were therefore tested using the \(t\)-test for better comparability with the other results and using the Wilcoxon test for confirmation of significance. The Kolmogorov–Smirnov test failed to reject the null hypothesis of normal distribution for any of the differences of the FKK, which is why parametric methods could be used for evaluation throughout.
Afterward the factors therapeutic approach (GSC/standard), age, sex, deployment abroad, and ICD-10-diagnosis (Group 1: depressive disorders, Group 2: neurotic disorders, anxiety and somatoform disorders, Group 3: PTSD, Group 4: personality disorders) were included in an analysis of covariance (ANCOVA). Age was a covariate; all other factors were blocking factors.

RESULTS

In the SCL-GSI scale of the SCL-90-R, significant improvement could be observed immediately after therapy and at the 6 months follow-up.

In all primary scales of the Inventory on Competence and Control Beliefs FKK (FKK-SK, FKK-P, FKK-I, and FKK-C) symptom severity improved significantly both immediately after therapy and at follow-up.

In the ANCOVA, tested variables therapeutic approach (GSC/standard), age, sex, deployment, and ICD-10-diagnosis (Group 1: depressive disorders, Group 2: neurotic disorders, anxiety and somatoform disorders, Group 3: PTSD, Group 4: personality disorders) had no significant effect on the results of the therapy with regard to the SCL-GSI sum scale of the SCL-90-R and the FKK primary scales immediately after therapy and in follow-up. The results are thus not shown in detail.

DISCUSSION

In summary, the multimodal inpatient psychiatric treatment in a Bundeswehr hospital led to a significant improvement of symptom severity in the SCL-90-R sum scale (SCL-GSI) and in the primary scales of the Inventory on Competence and Control Beliefs (FKK-SK, FKK-I, FKK-P, and FKK-C), both immediately after therapy and in follow-up after 6 months. It is of particular importance that this approach also seems to have a positive effect on soldiers with deployment-related psychiatric disorders, thus suggesting an additional option for the treatment of PTSDs in veterans, which should be a focus of further studies.

In the ANCOVA which included the treatment approach, however, a specific effect of group training of social competence (GSC) was not observed. A series of studies about trainings of social competence and comparable group therapeutic techniques have been performed; these studies demonstrate a significant improvement with regard to the used scales and a significant superiority of the training compared to control groups, with regard both to social adaptability and to the general psychiatric symptom severity of the participants. In contrast to our study, the control groups of these investigations usually received no psychiatric or psychotherapeutic treatment, making significant differences more likely to be detected.

Furthermore, data from other studies indicate that patients presenting with heterogeneous psychiatric disorders may react in different ways to the treatment components of a multimodal setting. The subjective assessment of the effects of inpatient psychodynamic group therapy, for instance, depended to a large extent on the SCID-II personality traits of the participating patients. Thus diagnostic heterogeneity of this study's participants may have led to different perceptions of the therapeutic components and also of individual changes during therapy.
The available data in the military research field is limited. There have been, however, comparative studies in which programs similar to GSC showed no significant effects on the dropout rate or level of distress in military training situations when compared to a control group. Although the results of a patient group and a nonclinical population are difficult to compare, the approaches equally address GSC as a tool for strengthening social resources of young soldiers.

So far, there have been no studies concerning either the treatment of German Armed Forces soldiers with avoidant personality traits or GSC. The only group therapeutic option has been inpatient short-term group psychotherapy in Armed Forces Hospitals yet. By contrast to GSC, therapists provide considerably less therapeutic structure and therefore urge the participants to free interaction, which is accompanied and interpreted by the therapist. The evolving conflicts and interpersonal relationships are supposed to be a model for the patients’ relationships in the private and public environment. The program has a higher frequency of group sessions (90 minutes daily) and thus can be considered as more intense for the patients. The evaluation showed significant improvements of the SCL-90-R after treatment as well as of the scales of the Minnesota Multiphasic Personality Inventory compared to a wait-list control group.

Analysis of the demographic and medical independent variables showed no significant associations with the therapeutic results in this study. This could be an indicator for a broad applicability of GSC in a military population. The low average age of 23.2 years and the small range of age distribution might have contributed to the lacking age effect, though. This may be as a result of the inclusion criterion “avoidant personality traits” as this is clinically seen predominantly in younger German soldiers. In other military-related studies, factors such as age, sex, or education did not have any significant effect on group training programs either. The evaluation of short-term group therapy for Bundeswehr soldiers mentioned above did not provide any significant predictors of change except for age and initial severity of symptoms.

LIMITATIONS

A limitation of this study is the relatively small number of cases. Less than half of the patients returned filled-in questionnaires in the 6 months follow-up, leading to a reduced statistical power.

In addition, the inclusion criterion of clinically manifest avoidant personality traits was based on the initial clinical interview and the participants were not included by means of diagnostic testing.

Furthermore, diagnostic heterogeneity of the examined patients was high, which made the identification of significant effects more difficult. This methodological problem was foreseen during the planning of the study, but the risk was accepted because in a former study, the inclusion of different diagnostic groups was not problematic—presumably because of military cohesion as an equaling factor.

Also it has to be mentioned there was no randomized assignment to groups. Such conditions, however, are difficult to achieve in an inpatient therapeutic setting.

CONCLUSIONS
Although a specific effect of GSC within the framework of a multimodal, inpatient, military treatment setting could not be seen in this study, it provided some indication that such an inpatient setting could have a positive effect on soldiers with avoidant personality traits, even those with experience from deployments. Additionally, it cannot be excluded that the therapeutic impact of GSC was masked by the other therapeutic elements applied. It may be useful to evaluate social skills group trainings in more homogeneous groups of participants, for instance, for primary prevention of psychiatric disorders in association with military deployments.

**Disease**

**Synergies in integrated malaria control**

The Lancet Infectious Diseases
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Combination of malaria vector control strategies, particularly insecticide-based approaches, needs careful consideration. Responsibility to implement a sound strategy goes beyond immediate alleviation of disease burden, to deceleration of the diminishing returns of future control efforts resulting from the spread of insecticide resistance. Vincent Corbel and coauthors present a clustered randomised trial examining the combined efficacy of pyrethroid-impregnated bednets with either indoor residual spray (IRS) with carbamates, or a carbamate-impregnated plastic sheeting placed high up on household walls. The investigators noted no additional benefit, in terms of disease incidence or prevalence, of either combination over a control scenario in which only bednets were used. They suggested the short half-life of carbamate efficacy contributed to the absence of additional benefit provided by these supplements to bednets. In their Comment, Raphael N'Guessan and Mark Rowland express disappointment with this explanation for absence of synergy.

More than just a lack of synergy, however, vector control strategies restricted to a subpopulation of people within a community might risk exacerbation of malaria transmission to the remaining individuals, once that the transient community-wide benefits of enhanced mosquito mortality have faded. Provided that the mosquito survives its encounter with the insecticide, which is increasingly likely with depleted insecticidal potency or increased resistance, its bite is deflected onto the more accessible hosts. Because longitudinal incidence data were not collected from all individuals in the community, speculation about the transmission dynamics is difficult. However, the 32% increased odds in incidence after 18 months of combining targeted bednets with IRS (compared with bednets alone), might allude to the after-effects of potentiated transmission. IRS, or insecticides on sheets placed in houses, combined with bednets can be distributed at the household level in different ways. For example, they can be distributed randomly, preferentially together, or preferentially apart. By simulation of these alternatives, we showed that distribution of nets and IRS preferentially together at the household level, as was done in Corbel and colleagues' trial, is the approach that capitalises least on
any synergistic effect that these control methods might have. In the advent of the President's Malaria Initiative advocating the combined use of bednets and IRS, careful and regular monitoring is particularly crucial to negate any detrimental outcomes of integrated vector management, and to capitalise on any synergisms.

We declare that we have no conflicts of interest.

BACK TO TOP

**Operation BRAVE Families: A Preventive Approach to Lessening the Impact of War on Military Families Through Preclinical Engagement**

Military Medicine
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ABSTRACT

Objectives: Operation Building Resilience and Valuing Empowered Families (OBF) is a preventive, preclinical program that was developed by the Walter Reed National Military Medical Center's Child and Adolescent Psychiatry Service to form a working partnership with families of wounded warrior parents from the war in Iraq and Afghanistan. The OBF staff helps to identify the families' needs and collaborates with many organizations at Walter Reed National Military Medical Center to provide assistance. This article describes OBF, offers a case description, reviews current preventive programs for children exposed to trauma and disaster, and compares and contrasts OBF to these programs. Methods: A literature review was performed, searching Ovid MEDLINE(R) for keywords, such as post-traumatic stress disorder, child and adolescent, family, prevention, and disaster. Results: There are an increasing number of preventive programs for children and adolescents throughout the country, especially over the past 10 years. These programs build upon past prevention models. There are few services that offer primary prevention. Conclusions: OBF is a military treatment facility-focused preventive program that can serve as a program model for other military treatment facilities and civilian hospitals with the mandate to care for the family members and children of parents who are trauma victims and require long-term care.

INTRODUCTION

According to MilitaryTimes and the U.S. Department of Defense, there are 6,364 total casualties of Operation Iraqi Freedom and Operation Enduring Freedom and 48,296 wounded in action confirmed by the U.S. Central Command. Given that there are close to two million children of active duty military parents with 44% under the age of six, it is reasonable to suggest that many families are directly and indirectly affected by the
trauma of the war. Because the families of the soldiers are an important part of their support system and recovery, they assume the role of a caregiver to the wounded warrior. This is a daunting task as the entire family is in a state of transition after an injury has taken place. The children of wounded warriors thus face the dilemma of having to provide support for their parent while they, too, are experiencing their own reactions to their parent's injury.

The literature suggests that the child's response to trauma, to include disasters of war, terror, and nature, can be lumped into a “disaster syndrome” that includes symptoms of post-traumatic stress disorder (PTSD), anxiety, dissociation, depression, and grief. A child's cognitive and emotional reactions result from different kinds of losses: of people, support systems, normal routines, and basic assumptions concerning safety and regularity. The severity of a child's response to a disaster usually correlates to the severity of his or her parents' reaction through social referencing cues and role modeling, and the presence of adults providing care during and after a major stressor is considered the most important protective factor. Individual factors that affect the severity of response to a disaster or trauma include prior anxiety or mental illness, negative coping strategies, and past traumatic experience.

It is clear that children's exposures to trauma can be through secondary means, after a disaster has already occurred. Children of military parents may be studied from this perspective since a parent may return from a war zone with emotional injuries and physical wounds. Although the children have not been directly exposed to the trauma that caused their parent's injury, they must learn to cope with the effect it has created in their parent and their living environment. Therefore, the parent's trauma often is perceived as a direct, primary trauma from the child's point of view.

The majority of soldiers who return from wartime operations, despite exposure to traumatic events, will have transient symptoms of PTSD. The same is true for the majority of children who survive a disaster; when routine and stability return, their symptoms subside. However, there are populations of soldiers and military children who are at higher risk for anxiety and depression after such an exposure. The increased operation tempo of the recent war has caused more and more frequent separation of family members for long periods of time. This situation has led to more than just transient symptoms of depression and increased anxiety for the children involved. The length of deployment for the U.S. Army was recently shortened from 12 to 9 months, and the amount of time between deployments was recently increased from about 1 to 2 years. The changes that have been made have resulted from recognition that these factors had an impact on the amount of mental health challenges faced by soldiers. These separations also served as a predisposing factor that put military children at increased risk for developing further symptoms if their parent was injured.

Clinical treatment for children of military families has been available through Child and Adolescent Psychiatry Services (CAPS) on military treatment facilities before and since the start of the war to address these clinical behavioral health needs. Nevertheless, there is a growing realization that many more service members and their families will require treatment from providers in the civilian behavioral health community because of the length of the war and the fact that many active duty soldiers are exiting the service. As a result of several years of working with wounded warrior families and the acknowledgment of the impact of preclinical secondary trauma on the soldiers’ children, the CAPS at the Walter Reed National Military Medical Center (WRNMMC) decided to address the special needs of families of returning wounded warriors by establishing Operation Building Resilience and Valuing Empowered (BRAVE) Families (OBF). OBF was created because of the empirical needs of families.
who migrated to WRNMMC to support their wounded warrior. Stigma regarding accessing behavioral health services in the military has been well defined. The preventive nature of OBF, providing assistance to military families before disabling symptoms arise also works to overcome problems with stigma that are often a barrier to treatment. This preclinical focus of OBF targets these family needs before they reach the point of need for clinical treatment, but if anxiety, depression, and other symptoms are identified, a referral for the child and/or adults is made. OBF mainly targets families of wounded warriors, those who have had an amputation or other severe injury, and their spouses and children, especially young children. These families will spend about a year and a half up to 3 years on the campus of WRNMMC by the time their treatment, rehabilitation, and administrative requirements have been completed.

Understanding the Post (Wartime) Injury Family and Its Needs

Although military families share many defining characteristics of American families in general, they take on an exceptionally unique set of challenges during their stay at WRNMMC. These families not only have parents serving in the military but also they are facing, what is in many cases, a traumatic assault on the family as a function of the parent's emotional and physical injuries.

There are many different types of military families. Some may have one parent who deploys frequently while the family remains at a large installation. Others may have never experienced a deployment before. In turn, National Guardsmen or Reservists and their families may have never have been linked into a military installation. Just as there is no one type of military family, there is also no one type of family response to trauma. There are, however, trends in how family members of service members adjust to the injury of a loved one.

Role Shifting to Accommodate the Injury

The most obvious change in the family constellation comes from the wounded warrior's status change from child caregiver to receiver of care. This places added stress on the child's parent who accompanies the wounded warrior because that parent is placed into a dual caregiver role. In fact, WRNMMC formalizes this role by putting caregivers on official orders as nonmedical attendants.

Adjustment to WRNMMC From Previous Routines

The comfort and safety of these families' existing life patterns that are found in predictable routines and familiar surroundings are significantly disrupted. To address these stressors, WRNMMC has accommodated these families' basic needs through the creation of housing and parking garages and corroboration with many organizations to include the Red Cross. There are many caring staff and numerous resources from the community and government agencies in addition to many opportunities for family members to engage in social and recreational activities. Nevertheless, families must be extremely flexible in approaching day to day household chores and completing tasks. For example, few families have kitchens to prepare meals or private areas to engage in routine family activities.

Learning How to Operate Within WRNMMC
Military family members quickly learn where and how to meet their needs as they move to new geographical locations about every 2 to 3 years through permanent changes of station. These families are also faced with frequent temporary duty, during which the parent works away from home for a short time. Since many military families are now staying at WRNMMC with the injured parent, they begin to identify with the military system. However, families that are new to the military, such as families of newly recruited service members and activated National Guardsman and Reservists, likely will be less experienced in accessing services and adjusting to a new way of life. The role of OBF is to ameliorate the needs of these families and empower them in their journey of regaining normalcy in their lives.

OBF: Filling the Gap to Mitigate Secondary Trauma

OBF is a system of care which provides clinicians an opportunity to assist families of wounded warriors on multiple levels in an attempt to ameliorate the effects of secondary trauma and accelerate adjustment to their new surroundings. It is an outreach-based component of CAPS, which was engineered to serve spouses, children, and extended family members of wounded warriors who are receiving treatment at WRNMMC. It is a proactive, prevention-based program that emphasizes resiliency and empowerment, offers a broad range of services, and conducts multiple and diverse tasks. It employs a collaborative and educational approach aimed at addressing and reducing myriad stressors that may cause or exacerbate problems or illnesses (be they physical, psychological, emotional, familial, interpersonal, social, vocational, or existential) in the returning injured parents and their families. Much of the work OBF accomplishes is directed most specifically toward the families of wounded warrior parents.

The staff of OBF attempts to form a working partnership with the families of wounded parents to address the families' needs. Education is provided in a nonpatronizing manner based on the family members' report of their responses to war-related injury or illness. A special emphasis is placed on helping to prepare children of wounded warriors as they learn about and cope with the parent's injury. Psychological first aid is provided individually and in groups to the children and families through family, individual, therapeutic art, and therapeutic play sessions. OBF provides support and training to professionals who serve military families, conducts research about the impact of war on families and professionals, and assesses its service effectiveness. Training for professionals is accomplished through weekly rounds with OBF and other services such as psychiatry consult-liason service (PCLS). These are among the core services provided by OBF that are delineated in its manual. Additional core services include a needs assessment, surveillance of symptoms and conditions that evolve, therapeutic activities such as art and play activities, individual and group parent guidance classes, and adult groups. The OBF program also provides outreach, participatory seminars, research, and development through dedicated annual meetings. A process improvement instrument is being developed, which will likely take the form of a satisfaction questionnaire similar to the 45-Item Outcome Questionnaire. A semistructured interview, using the Parent Guided Assessment Instrument (PGA-I), is one of the methods the staff uses to conduct a needs assessment for those who choose to participate. The PGA-I uses a 5-point Likert scale to assess child distress before and after injury as well as perceived family distress.

The process for family work used by OBF is based on the framework delineated by Hoagwood, and it includes identifying, engaging, and staying connected with the family. First, wounded warriors and their family members are identified. The planning for service provision begins when the OBF staff is informed of the pending arrival of the families of wounded warriors, which is before they are in transit to the hospital. This is facilitated
by the Department of the Army sending the travel and transportation orders of the family members directly to WRNMMC, CAPS via the Travel and Transportation Office so staff can prepare to meet the wounded warriors and their families.

There are two major entry points into the OBF program. Staff members of OBF make themselves available and provide information packets to the Fleet and Family Service and the Soldier Family Assistance Center, where weekly orientation meetings are held for family members of wounded warriors who have just arrived at WRNMMC. Family members are provided with brochures, resource materials, and contact information, and these staff members give notice to families to expect to hear from an OBF provider at a later date. The preparation for a child to come visit usually includes a discussion about seeing the wounded parent for the first time. Another point of entry and access to new families is through the PCLS daily rounds where all wounded warriors are offered preventive medical psychiatry services and those who have children are identified. This point of entry helps OBF identify many other family members who have joined the injured parent through means other than military travel channels, and the information gathered is relayed to OBF professionals who attend these rounds twice weekly. Once the wounded warrior family is identified, OBF staff begins engaging with the family and focuses on establishing a connection.

The OBF staff meets the injured parent and family in their inpatient setting within 1 week to inform or remind them of available services and OBF’s potential role in helping them. Families are provided with anticipatory parental guidance and a specially developed educational brochure. The family is offered the opportunity to participate in a screening assessment using the PGA-I, which is similar to other screening measures used with children who are experiencing medical trauma. There is an emphasis on learning from the family about their foremost needs and concerns. Practical assistance, such as how to set up child care on post or how to find a local health care provider, etc., is readily provided or a referral is made to resources that exist to provide this assistance. This meeting with the child and parents enables OBF staff to start an assessment and observation of behavior. Then a preliminary plan is formed and structured activities are provided. Families who choose to participate with the supportive services are followed throughout the course of their loved ones' hospitalization and care at the WRNMMC. Certainly one of the goals of OBF, which is similar to identifying and engaging wounded warriors and their families, is to stay connected with families and empower them to mobilize their energies, resources, and strengths.

To stay connected and foster relational empowerment, OBF staff must help the injured parents and their families to reduce or overcome barriers such as decreased motivation, grief over loss, depression, apathy, withdrawal, anxiety, feelings of worthlessness, and loss of personal freedom because they are bedridden. Part of this work is done through mental health professionals who work in tandem with OBF staff, many of them serve as primary therapists or psychiatrists. OBF strives to increase the sense of strength of injured parents and their family members. Acute symptomatology is addressed in a prompt and yet comprehensive manner.

Case Study

The following case illustrates some challenges faced by the wounded warrior parent, family, and child and showcases some ways that OBF provides preclinical engagement. All identifying information has been removed to protect confidentiality.
In July 2009, Staff Sergeant (SSG) John Jones, a 29-year-old infantry soldier, was admitted to the Surgical Intensive Care Unit (SICU) after sustaining injuries from an improvised explosive device blast, which included a fracture of his right femur and an above the knee amputation of his left leg. He was in critical condition, and his physicians were uncertain as to whether or not he was going to survive. When members of OBF became alerted by the PCLS that SSG Jones had a child who would be coming to visit, an OBF social worker approached the family to provide information about services that were available and to assess how the family could be assisted. The soldier's wife, mother, and sister were present. His wife was shocked by her husband's injuries and wondered how to explain them to their only child, a 3-year-old daughter named Emily. The social worker discussed with SSG Jones' family how to talk to Emily in an age-appropriate language that she could understand, being careful not to give too much information that would overwhelm her.

A couple of weeks later, after Emily had arrived at WRNMMC and spent some time with her father, the OBF social worker introduced herself to Emily in the waiting room of the SICU and stopped by weekly to check in with the family. Eventually SSG Jones' injuries improved and he was moved from the SICU into a room on the general medical floor. During this time, the OBF social worker continued to meet with Emily and her grandmother in the Soldier Family Assistance Center to play games. One play session was at the outside play area of a hotel on base with Emily's maternal grandmother and paternal grandfather. Emily and the OBF social worker went to play on the swing where they talked to one another and then played hide and seek. One day Emily met individually with the OBF social worker to play with toys and she focused on the doll house. Emily's play reflected her desire for her mother's support and for her mother to be more emotionally available to her. One of the dolls she played with was a man in a wheelchair. Emily's play indicated reservations about the man in the wheelchair and what he could and could not do for himself or others.

Emily's mother and grandmother expressed concern that Emily was demanding and difficult, especially during periods of transition of care from mother to grandmother. They were provided with information about stress and how it is manifested to children in her age as well as strategies to reduce the stress. In addition, ways to encourage and improve her relationship with her father were discussed.

SSG Jones and Emily were both hesitant to interact because he had an external fixator on his leg, making it difficult for Emily to get close to him, and he had some injuries to his arms and fingers that made it hard for him to reach out to her. The OBF social worker provided a book for SSG Jones to read to Emily and discussed possible ways for her to get close enough to see the pictures. Both parents felt that Emily became more interactive when the external fixator came off and the bed could be lowered for them to hug each other. Emily's mother also became more relaxed despite her own anxiety about his severe injuries.

Emily's mother planned to return to work when SSG Jones was discharged from the hospital. He began living independently in an apartment just outside of the base. SSG Jones had been spending weekends and holidays at his apartment and reported that everything was going well. Emily's parents attended other functions offered by OBF, including a coffee group at the MATC while Emily stayed at daycare where she developed relationships with peers. After a couple of months, Emily and her mother returned to their permanent home so that her mother could resume work while SSG Jones continued his recuperation at WRNMMC. He decided there was no need for continued involvement at that point, but OBF left contact information and offered to help should the need arise for ongoing support.
This case study typifies how the family volunteers, or elects, to receive services in this preclinical model. Because of the fact that they are not official patients, the goal of the service can appear vague, but the family must still provide social consent to receive OBF's involvement in their lives at WRNMMC.

METHODS

An Ovid MEDLINE(R) search was conducted for keywords such as PTSD, child and adolescent, family, prevention, and disaster. The goal was to find programs with a similar focus of OBF: preventive programs and, if possible, programs with preclinical engagement to compare and contrast them to OBF.

RESULTS

There was a relative paucity of these programs that were found, but there have been an increasing number of preventive programs in recent years that have been created in response to terrorism, war, and natural disasters. The Cohen-Harris Center's Tel-Aviv model was implemented in Israel after attacks by SCUD missiles in the 1991 Gulf War. An acronym that describes the theory behind this program is AREST (anticipate, redifferentiate, empower, supervise and assess, and treat and follow-up). This approach was found most helpful after assessment of the local government structure and evaluation of how the existing services could be unified, although there is no data that assesses this efficacy. Laor asserts that systems are difficult to change after the stress of a disaster, and this systems-based, ecological approach makes available resources accessible to the victims. Another preventive program is the University of California, Los Angeles public mental health model for treatment of children and adolescents traumatized by disaster. This model was implemented in 1995 as a postwar trauma and grief intervention program for adolescents in Bosnia–Herzegovina. It includes three levels of organization: governmental response, school community programs, and intervention teams. There are also three tiers of interventions: a broad-scale school-based intervention, specialized school-based intervention, and a highly specialized community-based intervention through referral. These models form a back-drop to the formation of more recent child focused programs for addressing disaster and terrorism in the United States.

The Child and Adolescent Trauma Treatments and Services Consortium is a program that came into existence to provide services necessitated by the unprecedented World Trade Center terrorism attacks on September 11, 2001. It received referrals of children who saw their school counselors but who needed a higher level of care from the Federal Emergency Management Agency (FEMA)-sponsored Project Liberty. When the Child and Adolescent Trauma Treatments and Services Consortium was created, Trauma Focused-Cognitive Behavioral Therapy (TF-CBT), a treatment modality with proven efficacy in child sexual abuse, was selected for use with the children who were exposed to the attacks on the World Trade Center. In addition, it implemented a modified form of Trauma/Grief-Focused Group Psychotherapy Program with positive treatment outcomes for adolescents (a decrease on the reaction index total score from 31 to 14 at 12 months in one case). In the next step of evolution, TF-CBT, group therapy, and a systems approach were used after the disaster of Hurricanes Katrina and Rita in August and September of 2005 in New Orleans through the program called Project Fleur-de Lis. The project used a three-tiered school-based mental health system to identify, triage, and refer children to more specialized, evidence-based treatment. The first tier was classroom-based interventions. The second tier is school-based
interventions, using Cognitive Behavioral Intervention for Trauma in Schools, a primarily group-focused treatment modality. The third tier, using TF-CBT, was community-based interventions.

These programs share some similarities in that they show innovation and creativity in using the best existing treatment modalities available, which are then adapted to provide services that would otherwise not have been available. OBF is similar in this regard as there was a need for preventive services focused on providing outreach to children and family members of wounded warrior parents. However, the preclinical nature of OBF places it in a unique position because assistance can be offered in conjunction with existing medical services without a referral, in a nonintrusive way, to families who may not perceive a need for assistance. In addition, its preclinical nature overcomes some of the barriers of stigma that are often associated with seeking care from behavioral health. Similar to the described programs, OBF identifies patients using a screening measure, uses general treatment modalities such as various groups, and uses the existing structure and culture of the hospital, helping to unify many hospital services. In addition, the OBF program uses a somewhat tiered system: making itself available and identifying those at risk, providing psychoeducation and assistance, and making clinical care referrals when needed. It provides a microecological model within the structure of the military's flagship hospital and could serve as a model for other military treatment facilities and civilian facilities that have the mandate to adjust existing services to meet the needs of children and family members of injured parents. OBF is a program that has adapted to the wounded warrior demographic and serves as a model for secondary and tertiary prevention. It may eventually move towards a primary prevention model, collaborating with the Families OverComing Under Stress project that targets the military family before a parent deploys.

Determinants of Incident Chronic Kidney Disease and Progression in a Cohort of HIV-infected Persons With Unrestricted Access to Health Care*

HIV Medicine
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Abstract and Introduction

Abstract

Objectives As socioeconomic factors may impact the risk of chronic kidney disease (CKD), we evaluated the incidence and risk factors of incident CKD among an HIV-infected cohort with universal access to health care and minimal injecting drug use (IDU).
Methods Incident CKD was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m2 for ≥ 90 days. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Rates were calculated per 1000 person-years (PY). Associations with outcomes were assessed using two separate Cox proportional hazard models, adjusting for baseline and time-updated covariates.

Results Among 3360 participants [median age 29 years; 92% male; 44% African American (AA)] contributing 23 091 PY of follow-up, 116 developed incident CKD [5.0/1000 PY; 95% confidence interval (CI) 4.2–6.0/1000 PY]. The median first eGFR value was 97.0 mL/min/1.73 m2 [interquartile range (IQR) 85.3–110.1 mL/min/1.73 m2]. Baseline factors associated with CKD included older age, lower CD4 count at HIV diagnosis [compared with CD4 count ≥ 500 cells/μL, hazard ratio (HR) 2.1 (95% CI 1.2–3.8) for CD4 count 350–499 cells/μL; HR 3.6 (95% CI 2.0–6.3) for CD4 count 201–349 cells/μL; HR 4.3 (95% CI 2.0–9.4) for CD4 count ≤ 200 cells/μL], and HIV diagnosis in the pre-highly active antiretroviral therapy (HAART) era. In the time-updated model, low nadir CD4 counts, diabetes, hepatitis B, hypertension and less HAART use were also associated with CKD. AA ethnicity was not associated with incident CKD in either model.

Conclusions The low incidence of CKD and the lack of association with ethnicity observed in this study may in part be attributable to unique features of our cohort such as younger age, early HIV diagnosis, minimal IDU, and unrestricted access to care. Lower baseline CD4 counts were significantly associated with incident CKD, suggesting early HIV diagnosis and timely introduction of HAART may reduce the burden of CKD.

Introduction

Chronic kidney disease (CKD) is a significant concern in HIV-infected individuals. The reported prevalence of CKD in HIV-infected persons ranges from 2 to 15.5%. Ethnicity is reportedly a significant determinant of CKD and end-stage renal disease (ESRD) in HIV-infected persons.[6, 7] In one study, HIV-infected African Americans (AAs) were twice as likely as Caucasians to develop incident CKD and 20-fold more likely to progress to ESRD.

In HIV-uninfected persons, several studies have highlighted the importance of low socioeconomic status (SES) as a determinant of CKD and ESRD. Furthermore, potentially modifiable risk factors such as low SES, differences in access to care, and suboptimal lifestyle behaviours contribute to the excess risk of CKD and ESRD observed in AAs.

In the USA, estimates of CKD in HIV-infected subjects have been largely derived from urban clinics, settings where socioeconomic factors such as poverty and lifestyle factors including injecting drug use (IDU) both complicate the care patients receive and potentially confound these estimates. Moreover, as higher CD4 counts and suppressed HIV replication are associated with a reduced risk of CKD in HIV-infected patients, it is possible that suboptimal access to medical care with delayed diagnosis and treatment of HIV contributes to the increased incidence of CKD in HIV-infected AAs. As socioeconomic factors are inextricably related to the incidence of CKD and may impact ethnic inequities observed in prior studies,[9,14] we determined the incidence of and risk factors associated with CKD and progression to stage 5 CKD or death in a racially diverse cohort of HIV-infected persons with unrestricted access to care and low rates of IDU.
*This work was presented in part at the 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, 16-19 February 2010 [Abstract number 738].

Methods

Study Design and Population

Study participants were enrollees of the US Military HIV Natural History Study (NHS), an ongoing (since 1986), multicentre, prospective cohort comprised of consenting HIV-infected Department of Defense (DoD) beneficiaries. NHS participants have free and unrestricted access to health care and medications. As a consequence of random drug testing policies among active duty service members, IDU is uncommon (historically ≤ 1%), and all service members have a minimum of a high school educational equivalent.

The military health system has a comprehensive HIV screening and treatment programme. All active duty members are screened at entry into the military and every 1–5 years thereafter. NHS study visits are conducted biannually. At each visit, participants are evaluated by an HIV specialist and research personnel collect data on demographics (including self-reported ethnicity), clinical information [including data on CKD-specific comorbidities such as diabetes mellitus (DM) and hypertension], data on the medication regimen, and laboratory measures including serum creatinine measurements, CD4 counts, and HIV-1 RNA levels. All participants provide written informed consent. For this substudy, eligible subjects were > 18 years old at HIV diagnosis with self-reported ethnicity available, enrolled in the NHS prior to 2010, and had a minimum of four quarterly creatinine measures. This substudy was approved by a central institutional review board.

Definitions

The absence of CKD at baseline was defined by a confirmed estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m². Participants were classified as having incident CKD if they had at least two consecutive quarterly eGFR values <60 mL/min/1.73 m² separated by a window of 3–18 months, consistent with the National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines (NKF-KDOQI).[21] Thus, a minimum of four creatinine measures were required to determine both baseline and incident CKD status. Date of CKD diagnosis was defined as the date of the initial eGFR below the specified threshold. Among participants meeting the definition for incident CKD, progression was defined as advancement to stage 5 CKD defined by an eGFR < 15 mL/min/1.73 m². We used stage 5 CKD instead of ESRD, as renal replacement therapy is not captured in the NHS. The eGFR was calculated using both the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease (MDRD) equation; unless otherwise noted, results presented are based on the CKD-EPI equation.

Chronic hepatitis B was defined as surface antigen positivity in at least two determinations 6 months apart, and hepatitis C by a positive antibody test. DM was indicated by physician diagnosis, use of an antidiabetic medication, or elevated glucose (any value >200 mg/dL or a fasting value...
Hypertension was defined by physician diagnosis or use of antihypertensive medication. AIDS was defined according to the 1993 case definition excluding a CD4 count <200 cells/μL, and highly active antiretroviral therapy (HAART) was defined as previously described.

Statistical Methods

Baseline for CKD incidence analyses was defined as the date of HIV diagnosis, and baseline covariates were those measured closest to HIV diagnosis (~1 month to 6 months). To limit bias associated with frequent creatinine measurement during illness, only quarterly creatinine measurements, closest to each 3-month anniversary from HIV diagnosis (± 1 month), were selected. Comparisons between groups used χ2 or Fisher's exact tests for categorical variables, and Wilcoxon two-sample tests for continuous variables.

Follow-up time for CKD incidence rates started on the date of the confirmatory eGFR value used to define CKD-free status at baseline. Incidence rates were calculated per 1000 person-years (PY) with exact Poisson 95% confidence intervals (CIs). Poisson regression was used to test for trends in rates by calendar year, and Cox proportional hazards to model associations between factors and incident CKD. For these models, time zero was set at HIV diagnosis date for the intent of assessing risk of CKD since HIV diagnosis; however, delayed entry was used to specify that participants were not at risk until the date of the confirmatory eGFR value used to define CKD-free status at baseline. Those not meeting the definition of incident CKD were censored on the date of their last creatinine measurement. The latest censoring date was 21 January 2010. Multivariate models were constructed by including variables significant at the 0.10 level in univariate models, then sequentially removing variables that were neither significant at the 0.05 level nor impacted the estimates by >20%. Ethnicity was maintained in the models because this variable was of interest. Multivariate model 1 included baseline covariates. A similar model-building process was used to add time-updated covariates to multivariate model 2, with HAART use modelled as a time-updated covariate that described the proportion of time since HIV diagnosis that HAART was used.

Among participants meeting the definition for CKD, as progression to ESRD and death represent competitive risks, the composite endpoint of stage 5 CKD or death was analysed using incidence rate calculations and Cox proportional hazard models similar to those used for CKD incidence. Baseline for these models was defined at CKD diagnosis. For this endpoint, all events occurring within 3 months of the last creatinine measurement were counted and the remaining participants were censored at 3 months after the last creatinine measurement. Among four subjects diagnosed with stage 5 disease at CKD diagnosis, time to stage 5 disease or death was imputed using the midpoint between CKD diagnosis and the earliest stage 5 disease or death event time observed among the other participants with CKD. A sensitivity analysis for this endpoint was performed excluding these four subjects.

Changes in eGFR (slopes) were modelled among AA and Caucasian subjects with and without incident CKD using linear mixed effects models with random slopes and intercepts. Estimates for the overall slope were adjusted for baseline covariates. Slopes during the first 18 months after incident CKD were also estimated, with adjustment for the following variables: ethnicity, CD4 count and HAART status at CKD diagnosis, and time since CKD diagnosis. To assess whether associations between eGFR slopes varied by ethnicity, an interaction term using ethnicity and time since
CKD diagnosis was tested. All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC). A P-value <0.05 was considered statistically significant.

Results

Study Population Characteristics

Of the 5117 NHS participants, 3360 (66%) met the eligibility criteria. Excluded participants included 1704 with fewer than four creatinine measurements, 14 with CKD at baseline, and 39 whose status could not be determined. Subjects excluded because of insufficient (fewer than four) creatinine measurements were significantly younger [median (interquartile range (IQR)) 27 (23–33) vs. 29 (25–34) years, respectively], were less likely to self-identify as being Caucasian and more likely to identify as ‘other’ (40% vs. 45% Caucasian, respectively), were more likely to be diagnosed with HIV after 1996 (39% vs. 28%, respectively), and had a significantly lower CD4 count at HIV diagnosis [median (IQR) 489 (331–667) vs. 507 (363–672) cells/μL, respectively] compared with those who were included in this analysis.

In this substudy, Caucasians and AAs were similarly represented, and 92% of individuals were male (Table 1), reflective of the military population. The median age and CD4 count at baseline were 28.8 years (IQR 24.5–34.1 years) and 507 cells/μL (IQR 364–673 cells/μL), respectively. The first median eGFR after HIV diagnosis was 97.0 (IQR 85.3–110.1) mL/min/1.73 m2. The majority (72%) of the participants were diagnosed with HIV in the pre-HAART era (prior to 1996). At HIV diagnosis, AAs compared with Caucasians were younger, were more likely to be female, had a lower CD4 count and HIV-1 RNA level, and were more likely to be diagnosed with hypertension.

Incidence of CKD

The 3360 study participants contributed 23 091 PY of follow-up (median 7.5 years; IQR 4.8–12.6 years), and had a median of 10 quarterly eGFR values (IQR 6–17). The median number of research visits (11) and reported tenofovir use at censoring-event date (26%) were identical between AAs and Caucasians. During follow-up, 116 participants met the criteria for incident CKD based on the CKD-EPI equation, for an overall incidence of 5.0/1000 PY (95% CI 4.2–6.0/1000 PY). The median age and CD4 count at CKD diagnosis were 42.2 years (IQR 36.6–51.9 years) and 181 cells/μL (IQR 12–469 cells/μL), respectively. Based on the MDRD equation, 120 participants met the criteria for CKD for an overall incidence of 5.2/1000 PY (95% CI 4.4–6.3/1000 PY).

Figure 1 summarizes incidence rates using both the CKD-EPI and MDRD equations for 5-year calendar intervals (a) and participant categories (b–f). While no significant trend was detected among 5-year intervals from 1996 to 2010 (P = 0.52) (Fig. 1a), the combined CKD incidence rate in the HAART era (4.1/1000 PY; 95% CI 3.2–5.3/1000 PY) was significantly lower than the rate in the pre-HAART era (6.7/1000 PY; 95% CI 5.0–8.8/1000 PY; P = 0.01; data not shown in figure). CKD incidence rates were higher for women (Fig. 1b) and increased with age (Fig. 1c). AAs (4.9/1000 PY; 95% CI 3.6–6.4/1000 PY) and Caucasians (5.2/1000 PY; 95% CI 3.9–6.8/1000 PY) had similar rates of incident CKD (Fig. 1d). Lower rates were observed with increasing category of baseline CD4 count (Fig. 1e) and with HIV diagnosis in the HAART era vs. pre-HAART era.
Within any category, rates based on the CKD-EPI and MDRD equations were similar. In addition, rates of incident CKD were similar among AAs and Caucasians for clinically relevant CD4 cell count categories and for those above and below the median age (Fig. 2). Statistically nonsignificant declines in eGFR slopes were observed among Caucasians (−0.07 mL/min/1.73 m²/year; 95% CI −0.20, 0.06 mL/min/1.73 m²/year) and AAs (−0.08 mL/min/1.73 m²/year; 95% CI −0.21, 0.05 mL/min/1.73 m²/year). Slopes did not differ significantly by ethnicity (P = 0.90).

Factors Associated With Diagnosis of Incident CKD

Estimates for univariate and multivariate models are shown in Table 2. Multivariate model 1 adjusts for baseline covariates only; multivariate model 2 adjusts for both baseline and time-updated covariates. Compared with Caucasians, AAs were not at increased risk of CKD in univariate or multivariate analyses (model 1: HR 0.9, 95% CI 0.6–1.4; model 2: HR 1.0, 95% CI 0.7–1.5). In model 1, older age (HR 1.4 per 5-year increase; 95% CI 1.3–1.6 per 5-year increase), lower CD4 count at HIV diagnosis (reference CD4 count ≥ 500 cells/μL; CD4 count 350–499 cells/μL: HR 2.1; 95% CI 1.2–3.8; CD4 count 201–349 cells/μL: HR 3.6; 95% CI 2.0–6.3; CD4 count ≤ 200 cells/μL: HR 4.3; 95% CI 2.0–9.4) and HIV diagnosis before 1996 (HR 4.3; 95% CI 2.2–8.5) were significantly associated with increased risk of incident CKD. In model 2, associations with baseline age remained significant and the following time-updated covariates were also associated with increased risk of CKD: DM (HR 2.0; 95% CI 1.3–3.3), lower nadir CD4 count (HR 6.6; 95% CI 2.4–18.5; for nadir ≤ 200 cells/μL compared with ≥ 500 cells/μL), chronic hepatitis B (HR 1.8; 95% CI 1.1–3.2), and hypertension (HR 1.6; 95% CI 1.0–2.6). Increased proportion of time on HAART was protective (HR 0.7 per 20% increase; 95% CI 0.6–0.9). Using the MDRD equation, similar estimates were obtained, except associations with gender were observed in multivariate models, HIV diagnosis era was significant in model 2, and hypertension was not significant and therefore omitted from model 2 (Table S1).

Progression From CKD to Stage 5 CKD or Death

Of the 116 participants diagnosed with CKD, 53 self-identified as Caucasian and 51 as AA. As the majority of subjects with incident CKD were either AA or Caucasian, we limited our descriptive comparisons to these two groups. Compared with Caucasians with CKD, AAs with CKD were more likely to be male (96% vs. 79% for Caucasians; P = 0.02), were more likely to be diagnosed with HIV prior to 1996 (98% vs. 85%, respectively; P = 0.03), and had lower median eGFRs at CKD diagnosis [50.2 (IQR 38.4–55.4) mL/min/1.73 m² vs. 54.3 (IQR 45.4–57.6) mL/min/1.73 m², respectively; P = 0.03]. Among those diagnosed with CKD in the HAART era, AAs were less likely to be receiving HAART (56% vs. 85% for Caucasians; P = 0.12) and tenofovir (22% vs. 46%, respectively; P = 0.06) at CKD diagnosis compared with Caucasians, although these differences were not statistically significant. Of note, 69 subjects (66%) were diagnosed with CKD prior to 2001, the year tenofovir received licensure. While not statistically significant, the median CD4 cell count at time of CKD diagnosis was numerically lower in AAs (94 cells/μL; IQR 11–478 cells/μL) compared with Caucasians (219 cells/μL; IQR 14–509 cells/μL; P = 0.31).

As progression to ESRD and death represent competitive risks, we examined the combined endpoint of stage 5 CKD or death. A total of 52 participants (28 AAs and 21 Caucasians) met the combined endpoint (17 with stage 5 CKD and 35 deaths). The overall incidence rate of stage 5 CKD or death was similar among AAs and Caucasians (16.9 vs. 18.8/1000 person-years, respectively; P = 0.66).

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CKD or death was 1.8-fold higher among AAs (22.1/100 PY; 95% CI 14.7–32.0/100 PY) vs. Caucasians (12.0/100 PY; 95% CI 7.5–18.4/100 PY). In the multivariate model, HAART use at CKD diagnosis was protective (HR 0.3; 95% CI 0.2–0.8), whereas a low CD4 count at CKD diagnosis was associated with progressive kidney disease and/or death (HR 5.2; 95% CI 2.3–12.1 for CD4 cell count ≤ 200 cells/μL). AA ethnicity was not associated with progressive CKD or death in either the univariate or multivariate models (Table 3). A sensitivity analysis that excluded the four AAs who had stage 5 CKD at diagnosis and model estimates derived using the MDRD equation afforded similar results (data not shown).

Adjusted models that examined eGFR slopes following CKD diagnosis demonstrated nonsignificant declines among AAs (−3.08 mL/min/1.73 m²/year; 95% CI −8.26, 2.11 mL/min/1.73 m²/year) and a significant increase in eGFR among Caucasians (4.97 mL/min/1.73 m²/year; 95% CI 0.27, 9.67 mL/min/1.73 m²/year). eGFR slopes differed significantly between the ethnic groups (P = 0.02).

Discussion

The overall incidence of CKD, in this predominantly male cohort characterized by unrestricted access to care, was lower than that previously reported. There are several potential explanations. Recognized risk factors for CKD include older age, IDU, and hepatitis C virus coinfection. NHS participants are young (median 29 years), and have low reported rates of IDU (<1%)[19] and hepatitis C virus coinfection (<2% in this subset). Furthermore, our participants are typically diagnosed early in HIV infection and have free and unrestricted access to care. These differences in socioeconomic, demographic, and clinical characteristics may in part explain the lower rates of CKD observed in our study.

CKD risk in our cohort was associated with increasing age and persistent immunological dysfunction reflected by a low time-updated nadir CD4 count, whereas HAART use was protective, confirming the findings of prior reports. However, previously reported ethnic differences were not observed.[8] We examined both incident CKD and declines in eGFR; irrespective of the outcome examined, associations with ethnicity were not observed. Our observations are consistent with a recent report that failed to observe an association between ethnicity and eGFR declines. Among HIV-uninfected persons, ethnic inequities in the incidence of CKD have been attributed to differences in the prevalence of traditional risk factors such as hypertension and DM, biological differences, lifestyle-related variables, and socioeconomic factors that impact health care coverage. While AAs in our cohort had lower baseline CD4 counts and a higher prevalence of hypertension, we did not observe a higher risk of incident CKD. Given the significant protective effect of HAART and preserved CD4 counts observed in our study, our data suggest that reported ethnic differences in CKD incidence among HIV-infected subjects may be attenuated when SES factors such as health care access are equalized among ethnic groups. As unrestricted access to health care does not always mean equal health care utilization, we measured health care utilization by examining visits for blood draws and research visits; AAs and Caucasians had similar numbers of visits, suggesting similar health care utilization.

In addition, we examined associations of CKD with the CD4 count at HIV diagnosis. Because of the mandatory HIV screening policies of the DoD, NHS participants are often dated seroconverters (i.e. with documented HIV-positive and HIV-negative dates) identified relatively early in HIV infection. We observed a graded relationship in the risk of CKD and the CD4 count at HIV diagnosis. An increased risk of CKD was observed even among subjects with relatively preserved (350–499 cells/μL) CD4 counts in comparison with those whose CD4 counts were ≥ 500 cells/μL. The results of our observational study suggest that adopting routine testing to identify subjects early in HIV infection and preserving CD4 counts via the early introduction of HAART may reduce the burden of CKD.

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In multivariate models, progressive kidney disease and/or death in this cohort was closely linked to the CD4 count and HAART use at CKD diagnosis. While numerically AAs had a higher incidence of stage 5 CKD and/or death compared with Caucasians, unlike prior reports we failed to observe an association between ethnicity and progressive kidney disease and/or death in univariate or multivariate models. Our failure to observe an association may be attributable to the small numbers of subjects with stage 5 CKD and the significant beneficial effects of HAART on mortality. However, eGFR slopes following CKD diagnosis differed among the ethnicities. While there were statistically nonsignificant declines in eGFR in AAs with CKD, eGFR improved among Caucasians, and we observed a significant interaction with ethnicity. As HAART use is associated with improvements in eGFR, differential use of HAART among AAs and Caucasians at CKD diagnosis may in part explain our observation. Alternatively, ethnic differences in eGFR slope may reflect differences in the underlying disease process resulting in CKD. HIV-associated nephropathy (HIVAN) is the leading cause of ESRD among AAs; HIVAN is a late manifestation of HIV infection and renal outcomes appear to be poor even after HAART has been introduced and viral suppression has been achieved. Biopsy results were not available to confirm this hypothesis. Other effect modifiers such as angiotensin converting enzyme (ACE) inhibitor use were not captured in this cohort and their impact cannot be assessed.

Our study has limitations. Firstly, the NKF-KDOQI guidelines define CKD as either a persistent decline in eGFR to <60 mL/min/1.73 m2 or the presence of markers of kidney damage such as persistent proteinuria. We did not have urinalysis results available, which may have reduced our ability to detect CKD, especially in AAs, who have higher rates of proteinuria. Of note, a large study that reported ethnic differences in the incidence and progression of CKD among HIV-infected subjects also did not measure proteinuria. Secondly, the MDRD and CKD-EPI equations for estimating GFR have not been validated in HIV-infected subjects. Although the results presented in this analysis are primarily those derived from the CKD-EPI equation, we generally found similar results utilizing the MDRD equation. We believe the use of both estimating equations improves the validity of our estimates. Several recent reports have demonstrated a relationship between cigarette smoking and both CKD and ESRD. As smoking history has not been consistently captured among NHS participants, we were unable to adjust our analysis for smoking, and this could have affected our estimates, as smoking rates vary by race. Finally, because of our strict definitions for CKD status at baseline and incidence during follow-up, approximately one-third of the NHS participants were excluded from our analyses as they did not have sufficient (at least four) creatinine measurements available. Statistically, excluded participants had lower CD4 counts, were less likely to be Caucasian, were more likely to be diagnosed in the post-HAART era, and were younger, but the magnitudes of these differences were small and unlikely to be clinically significant.

The strengths of our analyses include the conduct of this study in an ethnically balanced cohort of HIV-infected participants with limited confounding, allowing us to precisely examine the relationship between HIV-specific factors and CKD, and our ability to evaluate associations with baseline CD4 count. In addition, this is one of the first studies to examine the impact of ethnicity on CKD in a racially diverse HIV-infected cohort with homogeneous socioeconomic factors including access to health care.

In conclusion, unique features of this cohort, namely younger age, early HIV diagnosis, low prevalence of comorbid diseases, unrestricted access to care, and minimal IDU, may in part explain the low incidence of CKD observed in this cohort. In addition, in this study ethnicity was not
independently associated with the development of incident or progressive CKD. The incidence of CKD was higher in those with lower baseline CD4 count, suggesting that routine HIV screening to identify subjects early in infection and timely introduction of HAART to preserve CD4 counts may reduce the burden of CKD.

**Veterans’ Complex Chronic Illness Requires Personalized Care, Says IOM**

The Journal of the American Medical Association
Rebecca Voelker, MSJ
20 Feb 2013

Chronic multisymptom illness (CMI), a constellation of complex health problems that affects hundreds of thousands of US military veterans, requires personalized care that is most effective when provided by a team of health professionals, according to a recent report.

In the latest of its congressionally mandated reports on veterans' health following their service in the 1991 Persian Gulf War, the Institute of Medicine (IOM) defined CMI as having symptoms lasting 6 months or longer in at least 2 of 6 categories: fatigue, mood and cognition, musculoskeletal, gastrointestinal, respiratory, and neurologic.

Personalized care is needed to treat chronic multisymptom illness, an array of health problems that affects hundreds of thousands of US military veterans, according to a recent report.

Because symptoms can vary greatly, the IOM committee said it couldn't recommend a single therapy or universal treatment program for veterans with CMI. "We reject a one-size-fits-all treatment approach," said committee chair Bernard M. Rosof, MD, chair of the board of directors of Huntington Hospital, Huntington, NY. "Instead, we endorse individualized health care management plans as the best approach for treating this very real, highly diverse condition."

According to the report, between 175 000 and 250 000 Gulf War veterans have CMI and many of the estimated 2.6 million troops deployed to Iraq and Afghanistan have reported CMI symptoms of headache, chronic pain, disrupted sleep, fatigue, and attention and memory problems. The specific cause or causes of CMI probably will never be determined, the report noted.

The IOM committee evaluated evidence for a number of treatment options, including prescription medications and alternative therapies. Their review indicated that some veterans benefit from cognitive behavioral therapy and from medications, including selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors. Aerobic exercise, biofeedback, acupuncture, and St John's wort (a herbal extract
widely used in some countries to treat depression) may be promising approaches, but the committee didn't find convincing evidence of their effectiveness.

Veterans should undergo a comprehensive health examination immediately after leaving active duty, and the results should be available to clinicians within and outside of the Department of Veterans Affairs (VA), the report noted. The IOM also recommended that the VA use its recently developed postdeployment patient-aligned care teams to improve care for CMI. The teams include a project manager, primary care clinicians, nurses, mental health professionals, social workers, and other specialists if needed.

**Topical Paromomycin with or without Gentamicin for Cutaneous Leishmaniasis**

The New England Journal of Medicine
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**Background**

There is a need for a simple and efficacious treatment for cutaneous leishmaniasis with an acceptable side-effect profile.

**Methods**

We conducted a randomized, vehicle-controlled phase 3 trial of topical treatments containing 15% paromomycin, with and without 0.5% gentamicin, for cutaneous leishmaniasis caused by *Leishmania major* in Tunisia. We randomly assigned 375 patients with one to five ulcerative lesions from cutaneous leishmaniasis to receive a cream containing 15% paromomycin–0.5% gentamicin (called WR 279,396), 15% paromomycin alone, or vehicle control (with the same base as the other two creams but containing neither paromomycin nor gentamicin). Each lesion was treated once daily for 20 days. The primary end point was the cure of the index lesion. Cure was defined as at least 50% reduction in the size of the index lesion by 42 days, complete reepithelialization by 98 days, and absence of relapse by the end of the trial (168 days). Any withdrawal from the trial was considered a treatment failure.

**Results**

The rate of cure of the index lesion was 81% (95% confidence interval [CI], 73 to 87) for paromomycin–gentamicin, 82% (95% CI, 74 to 87) for paromomycin alone, and 58% (95% CI, 50 to 67) for vehicle control (P<0.001 for each treatment group vs. the vehicle-control group). Cure of the index lesion was accompanied by cure of all other lesions except in five patients, one in each of the paromomycin groups and three in the vehicle-control group. Mild-to-moderate application-site reactions were more frequent in the paromomycin groups than in the vehicle-control group.
Conclusions

This trial provides evidence of the efficacy of paromomycin–gentamicin and paromomycin alone for ulcerative *L. major* disease. (Funded by the Department of the Army; ClinicalTrials.gov number, NCT00606580.)

Texting Away Malaria: A New Alternative to Directly Observed Therapy

Military Medicine
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February 2013

ABSTRACT

Objective: Operation Onward Liberty is the current U.S. military mentorship program working with the Armed Forces of Liberia, training their national army. Throughout West Africa, and Liberia in particular, malaria remains a serious health concern. This is a critical concern to all U.S. Forces deployed in areas endemic with malaria. In January 2011, a new protocol was instituted among Operation Onward Liberty members using short message service (SMS) technology to ensure 100% daily accountability. Methods: Beginning in January 2011, SMS was used to report completion of daily ingestion of malaria chemoprophylaxis by U.S. Forces in Liberia. Results: Since then, there were no cases of malaria identified by both Binax rapid diagnostic test and thin smear. The previous year (2010) saw 12 cases of malaria identified by both Binax rapid diagnostic test and thin smear. The previous year (2010) saw 12 cases of malaria among U.S. Forces in Liberia (9 during the same 6-month period), with 3 evacuations for malaria, costing an estimated 1.5 million dollars. Conclusions: Although directly observed therapy is still the gold standard of malaria chemoprophylaxis, use of cellular telephone texting technology, or SMS, for communicating ingestion may be the best alternative for reasonable accountability in the deployed setting, especially considering the highly decentralized nature of this and other deployment locations.

INTRODUCTION

Malaria is the second leading cause of death in Sub-Saharan Africa to date, second only to dysentery (usually caused by lack of clean water).1 Numerous attempts have been made to curtail the devastating effects of this disease on the population. Although this disease has wreaked havoc throughout Africa, it is also of special concern to U.S. Forces working in and throughout the African continent. It can be said that Liberia, in 2003, was the sentinel event for a change in malaria prevention by U.S. Forces. In 2003, 80 marines contracted malaria out of 225 deployed (a devastating 35%). During that deployment, marines were relegated to the “buddy system” of daily antimalarial accountability. In the after-action review, pill counts revealed numerous missed doses of daily medications, and was likely the single greatest factor in the 80 marines who contracted the disease.
In 2009, Operation Onward Liberty (OOL) began, as a U.S. military mentorship program, working with the Armed Forces of Liberia, training their national army. As with all African nations, Liberia is no exception to having a high prevalence of malaria. It has an exceedingly high incidence of Plasmodium falciparum (P. falciparum), and some might argue it is among the worst. In 2010 alone, 12 cases of malaria were documented, diagnosed by using a Binax—rapid diagnostic test (RDT) and thin prep smear.

On December 26, 2009, a young construction battalion died after contracting P. falciparum and developing cerebral malaria. Since OOL averages 50 U.S. servicemen during each deployment cycle (about 6 months), the approximate contraction rate for malaria among OOL members was 12% in 2009. Given the cost of medical evacuation (approximately $500,000.00 per evacuation) and potential loss of life, this rate was completely unacceptable, especially since the Swedish military had deployed to Liberia between 2004 and 2006 without a single case of P. falciparum in 1,170 soldiers with over 7,000 person-months (approximately 210,000 person-hours based on the average 30-day month).

METHODS AND MATERIALS

The difficulties of combating malaria in Liberia during military deployments are extensive. First, the environment is highly decentralized. In this deployment, members lived up to 1.5 hours apart and at 3 different locations (times were used because of traffic and road conditions). With a small medical contingent and only 1 physician on station, performing daily directly observed therapy (DOT) was not only impractical but also logistically impossible. Using what was available, we developed a short message service (SMS) program and accountability tracking schedule to ensure daily ingestion of chemoprophylaxis. The entire mission was divided five groups, with four groups of daily medications and a single group of weekly medications. Each medical technician and our two preventative medicine technicians were given a list consisting of approximately ten names, whereas the Chief Medical Officer (CMO) took the list of mefloquine users. Every day, the OOL mentors sent a text message to their list monitor and stated that they took their medication. The technician would then mark off that member, showing that they had taken their chemoprophylaxis for the day. If the member did not text by 5:00 p.m., they then received a reminder text or phone call inquiring about ingestion. This was required on several occasions, but usually in the early stages of the deployment, as most members developed a habit with their medications. The on-site rule was that if a member forgot to take their medication repeatedly and required a reminder, then they were required to present to the clinic at 6:00 a.m. daily for a week and undergo DOT until the member was able to remember to take their medication as directed and contact their list manager. Although this was never needed, it served as a deterrent to missing medications and daily texts. Because the mentors were in a closed user group, there was no additional cost to the mission for these daily text messages and follow-up.

A second difficulty in combating malaria was that the prevailing attitude upon arrival was one of resigned acceptance. On multiple occasions, I was told that it was “not a matter of if, but when you will catch malaria.” People were apparently satisfied with the current status and this was objectively reflected in the previous malaria logs where multiple days of signatures were missing and the general attitude was one of complacency. “Why should I take my meds if I’m gonna catch malaria anyway,” noted one Staff Sergeant. This attitude was the second thing we addressed and in a two-fold manner. Education was the first piece, and malaria was reviewed during each in-processing as service members arrived on station. This consisted of a 3-page educational printout on malaria and a signed acknowledgement of understanding that taking their medications increased the likelihood of avoiding malaria and was a mandatory part of the deployment. In addition to education, a secondary incentive was provided to the entire mission. Two hundred dollars was set aside toward a celebratory party should our group be the first to go an entire
deployment cycle without a single case of malaria diagnosed via RDT or thin smear which were reviewed by the Walter Reed Army Institute of Research (WRAIR). The use of positive reinforcement became infectious when the commanding officer, a marine colonel, matched the initial $200.00, followed by numerous others, eventually creating a large pool of money for an end of deployment party celebrating zero cases of malaria. This was eventually changed to a quarterly event, celebrating 3 months of malaria-free deployment status. The overall morale improvement was most evident in a quote by Corporal Jacob Gateman during our first 3-month festivities, “I know I do not want to be the individual who gets malaria and ruins the chance for another party.” This was likely an additional factor in accomplishing the lack of malaria cases, creating a cultural change that this mission was not only possible, but should be the standard.

All additional preventative measures were continued, but with renewed vigor. Bed nets were still mandatory as before, but with a single random inspection during the deployment cycle to make sure that nets were appropriately placed, tucked in during the day, and free of holes. Uniforms as well as one set of civilian clothes were treated with permethrin (at least 2 per member). During the rainy season, wearing long sleeves and pants were mandatory between sunset and sunrise. Deet was made available throughout the deployment, and each member was given four to five 6 oz tubes at the onset of the deployment.

A member of OOL repeated these “Four Measures” during the weekly “All Hands” meeting. During the meeting, a randomly selected member of the team would stand up and recite the four things being done to combat malaria. This random selection process helped to ensure that everyone memorized the four steps and were cogniscenite of them on a weekly basis.

During the deployment, there were only two instances of failed SMS communication. The first involved a marine forgetting to text that he had taken his medication and then falling asleep. The following morning, he promptly clarified that he had in fact taken his medication but forgot to text his designated medic. The second instance involved an airman who actually missed a dose of medication, leading to a verbal reprimand and reminder that should the behavior continue, DOT would be instituted at 6:00 a.m. in front of the CMO barracks. The exact numbers of sent texts, replies, and reminder texts were not tracked as this was something delegated to the medics and not further accounted for.

RESULTS

Since January 2011, there have been zero cases of malaria identified by either Binax RDT or thin smear, constituting over 7,125 man-hours in theater during each 6-month deployment cycle. Thin smears were evaluated by the physician on station under oil immersion microscopy, with confirmatory read performed by an independent physician at the WRAIR. At the time of this publication, OOL had yet to encounter a single case among U.S. Service members (a total of 21,375 man-hours), suggesting that the above changes are operator independent. This finding is the key for replication in other countries and during other deployments, as well as the civilian population for protective measures.

DISCUSSION

There are numerous and obvious limitations to this study. The first is the integrity of the members stating that they took their medications. As U.S. Military members, there is an expectation of honor and integrity that may not be able to be replicated in the civilian world. However, as seen in the case of the construction battalion who died in 2009, members can lie and say they took their medications when they did not. The expectation is
that troops feel a sense of integrity as well as the need for self-preservation in taking their medications. By constantly stating the threat that malaria posed in the weekly meetings and performing random preventative measure inspections (i.e., bed net checks), it was expected that troops would not only remain honest, but also that the severity of the disease would continue to impress upon them the importance of consuming their chemoprophylaxis. As the physician, I also explained that if side effects from the medications were experienced, members should not hesitate to present to the clinic, but should under no circumstances stop their medications.

There was also the counter-productive possibility of troops feeling enough pressure to avoid malaria that they could possibly avoid seeing the physician for symptoms consistent with malaria. On numerous occasions, when seeing patients for acute gastroenteritis, patients remarked that they did not want to have malaria. Their worry, however, was less about the disease itself and more about "blowing our record." During the weekly meetings where troops were questioned about what we were doing to combat malaria, they were also reminded that early intervention was key to successful treatment and that they should not hesitate to be seen for symptoms. Although Health Insurance Portability and Accountability Act was still enforced, the small number of members on station made illnesses nearly impossible to keep 100% private.

Regarding a second potential limitation, recording individuals (the medics) could have falsified records to the CMO, as well as the CMO falsifying records himself. The honor and integrity part of the military also played a role in this setting, but there was also a fair amount of pressure from the CMO to have 100% daily accountability. Given previous shortfalls in accountability, it was imperative to the OOL mission that our team created a new environment of daily documentation of medication ingestion.

The third consideration is that chemoprophylaxis is not 100% effective in combating malaria and therefore may not perfectly correlate to the drop in cases among U.S. deployed forces. In three randomized placebo-controlled trials, doxycycline was shown to be between 92 and 96% efficacious against P. falciparum and 98% against Plasmodium vivax infections. In another study, Malarone was shown to have a prophylactic effectiveness of 95.8% against malaria.6 Finally, mefloquine has been shown to have an 85 to 94% efficacy against P. falciparum.7 Given these numbers, the simplest conclusion is that inconsistent usage of antimalarials, if not complete lack of ingestion, led to the majority of the previously seen U.S. malaria cases. It should also be noted that the Swedish Forces in Liberia used primarily Malarone and mefloquine as opposed to doxycycline.3 That information, combined with the U.S. Africa Command's recent guideline changes making Malarone the drug of choice to forces deploying in endemic areas, like Liberia, would lend support to the experienced efficacy of Malarone over doxycycline.8 This was also seen in Liberia as none of the 12 patients who contracted malaria were taking Malarone. Although antimalarials are not 100% effective, 90 to 95% prevention is a reasonable goal, if chemoprophylaxis were the sole preventative measure. Since other personal protective measures were enforced, 95 to 100% disease-free state should not only be achievable, but the standard. Therefore, the 88% prevention shown in the previous year of OOL would appear far from that goal, even if chemoprophylaxis were the only means of prevention.

Because of the severity of disease and other compounding factors, there could obviously be no control group (not texting or lacking medications). Human randomized controlled studies in this setting would create a risk to human life that would outweigh any foreseeable benefits, given the limited medical resources in country. Current Air Force guidance on the subject of biomedical research was also taken into account in when forgoing the creation of a control group.9 This could be a useful area of future study. The closest reasonable comparison is a historic one; that of the previous deployment iterations, which did not institute the texting protocol, and yielded a 12% case rate vs. 0% for this most recent iteration.
Because of varied locations, including extensive field operations up-country, there was obviously no way to isolate members to the same locations as the previous iterations. Therefore, the incidence of infected mosquitoes and exposure to these mosquitoes seeking a blood meal could have been very different from location to location.

Seasonal changes could also have played a role in the number of mosquitoes and location of stagnant bodies of water, and therefore disease incidence. Ironically, the period that should have had the highest concentration of cases in the previous iteration had fewer cases comparatively. This could be explained by an increase in vigilance, although the paper records showing missed days of medication would seem to contradict that assertion.

FUTURE PLANS

As noted earlier, there were numerous limitations and few calculations. The majority of the article was undertaken retrospectively, and so exact information concerning the number of texts and necessary reminders were not tracked. This should be an area of future study and is already partially underway at the WRAIR. SMS applications using smartphones and web-based analysis are planned for testing in late 2012 and early 2013. However, this will hopefully be only the tip of the iceberg. There will need to be continued research and innovation using these technologies, with particular consideration for the special operations community and cellular tracking, as well as force strength data that could be acquired via cellular counter intelligence to name a few. As our military forces adapt to current technological advances, it is very important that these applications are explored, vetted, and utilized where and when it is necessary and able.

CONCLUSION

DOT will remain the gold standard of malaria chemoprophylaxis. However, using cellular telephone texting technology, or SMS, for communicating prophylactic ingestion may be the best alternative for reasonable accountability in the deployed setting, especially considering the highly decentralized nature of many deployed locations.
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Abstract

Sarcoidosis patients often have myocardial involvement, however, very few have clinically significant cardiac disease and ventricular tachycardia as the initial presentation is exceedingly rare. We report the case of a middle-aged male with symptomatic but clinically stable ventricular tachycardia. Chest radiograph, computed tomography, and positron emission tomography demonstrated pulmonary and mediastinal abnormalities but no definitive etiology for his arrhythmia. Transthoracic echocardiogram revealed the nonspecific cardiac abnormalities of right ventricular dilation and septal flattening. Cardiac magnetic resonance demonstrated delayed enhancement and akinesia of the right ventricular free and inferior walls—virtually diagnostic of an infiltrative myocardial disease. The diagnosis was then verified with transbronchial biopsy showing noncaseating granulomas consistent with sarcoidosis. In conclusion, this case illustrates an unusual presentation of sarcoidosis and demonstrates how the diagnosis can be made using cardiac magnetic resonance alongside transbronchial biopsy.

Introduction

Sarcoidosis is a multisystem disorder of unknown etiology characterized by the formation of noncaseating granulomas.1 Cardiac involvement is clinically apparent in less than 5% of patients with systemic disease but potentially fatal; historical studies have reported that cardiac involvement accounts for 13 to 25% of deaths from systemic sarcoidosis. Clinical manifestations of cardiac sarcoidosis include conduction abnormalities, syncope, congestive heart failure, and sudden cardiac death. Based on these findings, it is recommended that every patient with systemic sarcoidosis be evaluated for potential cardiac involvement. However, diagnosing cardiac sarcoidosis can be difficult for multiple reasons including its low prevalence, variable presentation, and unproven imaging techniques. Endomyocardial biopsy is often used as a reference standard despite a sensitivity of only 20 to 30% largely because of patchy myocardial infiltration.

Case Presentation

A 34-year-old African–American male without prior cardiac disease presented with a 3-week history of paroxysmal palpitations associated with substernal chest discomfort. Past medical history was notable for tobacco use and hypertension. His only medication was cyclobenzaprine for musculoskeletal pain. Family history was significant for pulmonary sarcoidosis in his mother and 1 maternal aunt.

Resting blood pressure was 103/59 mmHg and heart rate was 160 bpm. Examination of the heart, lungs, and abdomen was unremarkable. A 12-lead electrocardiogram (ECG) revealed monomorphic ventricular tachycardia (VT) (Fig. 1), and he was cardioverted with a procainamide infusion. Initial evaluation as to the etiology of the VT revealed no evidence of a metabolic or drug effect. Chest radiograph (Fig. 2) and computed tomography (CT) demonstrated bilateral upper lobe nodular consolidation, extensive pulmonary scarring in an upper lung zone distribution, and mediastinal and hilar lymphadenopathy (Fig. 3).

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Transthoracic echocardiography revealed normal left ventricular function with an ejection fraction equal to or greater than 65%, mild to moderate right ventricular dilation, and a flattened septum (Fig. 4). Septal flattening was thought to be consistent with right ventricular pressure overload, possibly explained by the pulmonary findings.

Positron emission tomography with CT (PET-CT) demonstrated hypermetabolism within multiple hilar and mediastinal lymph nodes, and the right ventricular free wall (Fig. 5). This was suggestive, but not conclusive, of an infiltrative cardiomyopathy.

Cardiac magnetic resonance (CMR) proved far more revealing. In contrast to the techniques mentioned above, which were unable to accurately demonstrate and localize myocardial involvement, CMR demonstrated transmural delayed enhancement and akinesia of the right ventricular free and inferior walls (Fig. 6). CMR also confirmed the echo and PET-CT findings showing the precise location of many mediastinal and hilar lymph nodes.

Once the CMR results were known cardiac sarcoidosis was strongly suspected. Other considerations included arrhythmogenic right ventricular dysplasia and coronary ischemia. Arrhythmogenic right ventricular dysplasia is a rare genetic cardiomyopathy characterized by fibrofatty infiltration of the myocardium, predominantly of the right ventricle, which can present similarly but is not associated with pulmonary abnormalities. Ischemia was thought to be unlikely with a normal troponin, no evidence of ischemia or infarct on the postcardioversion ECG, and transmural rather than subendocardial myocardial enhancement on CMR.

An electrophysiology study showed a large right ventricular scar with inducible VT (Fig. 7). Catheter ablation was not successful in rendering the VT noninducible. An automatic implantable cardioverter-defibrillator (AICD) was implanted the following day. Final tissue diagnosis was made using transbronchial biopsy guided by CT, CMR, and bronchoscopic ultrasound, which verified noncaseating granulomas (Fig. 8). The diagnosis of cardiac and systemic sarcoidosis was, therefore, confirmed with both radiographic and extracardiac histological proof of this disease.

The patient was treated with corticosteroids and sotalol. In the 3 years since his diagnosis he has suffered from periodic recurrent VT leading to multiple AICD shocks. In addition to corticosteroids, multiple antiarrhythmic and immunosuppressive agents have been tried, including methotrexate and infliximab. Despite best medical management, repeat PET-CT, and nuclear studies show only partial improvement in myocardial sarcoid activity.

Discussion

Sarcoidosis is a multisystem disorder of unknown etiology characterized by the formation of noncaseating granulomas. These granulomas consist of both lymphocytes and phagocytes with the participation of a diverse range of cytokines mediating tissue inflammation and fibrosis. Intrathoracic involvement occurs in more than 90% of patients, but sarcoidosis can also be widespread with systemic manifestations affecting multiple organs including the eye, central nervous system, gastrointestinal tract integument, and kidneys. The heart is another organ that can be affected.
Although 25% of sarcoidosis patients in the United States have myocardial involvement at autopsy, less than 5% have clinically significant cardiac disease. The disease most frequently involves the left ventricle and septum, and is only rarely isolated to the right ventricle as in this case. Despite its low prevalence, cardiac sarcoidosis is often fatal; studies predating the widespread use of AICD devices reported that it accounted for 13 to 25% of deaths from sarcoidosis. In other cases, manifestations include conduction abnormalities, arrhythmia, syncope, and congestive heart failure. Although 23% of patients with cardiac sarcoidosis have VT, this is very rare as the initial manifestation of systemic sarcoidosis. The mechanism of VT is thought to be re-entry through both active inflammatory lesions as well as scarred and fibrotic tissue from old granulomas.

The initial presentation of stable VT because of underlying cardiac sarcoidosis, as seen in this case, is rarely reported, but may be underdiagnosed because of the challenges in its detection. Uusimaa et al established that sarcoidosis can manifest as VT without any detectable systemic findings in a case series of nine such patients. However, in this study eight patients were diagnosed by endomyocardial biopsy and the remaining patient was diagnosed by lymph node biopsy during mediastinoscopy 3 years after their initial presentation.

Here, we extend these findings by suggesting an effective diagnostic strategy using CMR and transbronchial biopsy and avoiding endomyocardial biopsy. In 2006, the most comprehensive guidelines for the diagnosis of cardiac sarcoidosis were updated by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders (Table I). These guidelines were a major step forward and can be very useful clinically, but are not be applicable to every patient. In this case, the guidelines would have failed to identify cardiac sarcoidosis because of the patient's unusual presentation and nonspecific findings on all imaging modalities other than CMR.

Despite these challenges, it is still recommended that every patient with sarcoidosis should be evaluated for cardiac involvement. The diagnosis is difficult because of its rarity, variable presentation, and unproven imaging techniques. Without a gold standard, the most accurate diagnostic strategy likely involves a combination of ECG, imaging, and histological evidence. Generally, all patients should have at least one 12-lead ECG, if not a 24-hour ambulatory ECG. Echocardiography is also often recommended, although the spectrum and significance of echocardiographic findings is not fully known. Some have suggested, as was seen in this patient, that echocardiography may also lack the sensitivity to detect early myocardial involvement.

In the absence of a gold standard, the endomyocardial biopsy is often used as a reference standard despite significant limitations. Although the finding of noncaseating granulomas on biopsy is essentially pathognomonic for cardiac sarcoidosis, the test is not without significant risks, and is also criticized for its relatively low yield. This is largely attributed to patchy infiltration of the myocardium, which decreases the sensitivity to 20 to 30%. Biopsy also carries a risk of cardiac perforation which is theoretically greater in the thin right ventricular free wall. For these reasons as well as overwhelming evidence in support of the diagnosis from PET-CT and CMR findings, a biopsy was not indicated in this case as it would not have changed management.

Of the newer imaging techniques, PET-CT is unique in that it can provide both an indication of disease metabolic activity and measure the extent of myocardial infiltration. However, although small studies have reported PET to have a sensitivity of 85 to 100%, its specificity is much lower and
may be as low as 38.5%. This is due to a similar uptake distribution in patients with dilated cardiomyopathy and in some cases of pulmonary hypertension as well as normal variation.

CMR, another newer modality, is increasingly recognized for its accuracy in the evaluation of cardiac sarcoidosis, as was demonstrated in this case. Its sensitivity and specificity are reported as 75 to 100% and 77 to 78%, respectively. In a prospective trial of sarcoidosis patients by Patel et al, delayed enhancement CMR was proven to be nearly twice as sensitive for cardiac involvement as the consensus criteria in Table I. With these techniques, cardiac sarcoidosis is distinguished from ischemic cardiomyopathy by its lack of restraint to coronary artery distributions and lack of subendocardial predominance. Because of CMR's superlative tissue resolution, it can also serve as a guide to help localize the ideal location for endomyocardial biopsy. If endomyocardial biopsy is to be avoided, as in this case, CMR also has the added benefit of accurately depicting the anatomy which could aid in preprocedural planning for noncardiac tissue biopsy via either mediastinoscopy or bronchoscopy.

An electrophysiology study was performed to further evaluate the electrocardiographic significance of the disease and to potentially eliminate the major focus of VT. Confirmation was made with bronchoscopy and transbronchial biopsy, which demonstrated noncaseating granulomas consistent with sarcoidosis.

Corticosteroids are the first-line therapy in patients with evidence of cardiac sarcoidosis. Although there is still considerable controversy about the optimal dose and duration, they have been shown to halt disease progression and are associated with improved survival. As was illustrated in this case, however, their effects on stopping VT are less conclusive. After corticosteroid therapy, repeat PET-CT, and CMR have both been used successfully to demonstrate suppression of disease activity and reduced tissue infiltration.

Conclusion

Cardiac sarcoidosis is a rare but potentially fatal condition and should be considered in all patients presenting with unexplained arrhythmia. Multiple imaging studies have recently been proposed to evaluate for this condition. Here we report an unusual presentation of cardiac sarcoidosis and show how CMR and transbronchial biopsy can effectively make the diagnosis without the risks associated with endomyocardial biopsy. This case adds further evidence that CMR could be considered the first-line imaging study when cardiac sarcoidosis is strongly suspected.
Our nation's health and wellness trajectory continues in the wrong direction. Nearly 68% of Americans are overweight or obese. Chronic diseases that account for 75% of all direct health care costs are also on the rise; 45% of the U.S. population has at least one chronic medical condition, and of those, at least half have multiple chronic conditions. If current trends continue, by the year 2030, these numbers will skyrocket.

As a nation, we are on an unsustainable cost trajectory. By 2020, U.S. health care costs are estimated to account for 20% of our gross domestic product. Some of the causes for this are unavoidable, such as aging baby boomers. However, we are not doing enough to combat the entirely preventable causes, namely the trifecta of unhealthy behaviors, including inactivity, poor diet, and tobacco/alcohol use. In addition, there is an increasing tendency for our health care system to prioritize and incentivize taking care of the sick rather than keeping people healthy.

Since becoming the Surgeon General of the Navy in November 2011, my priority has been to strategically align Navy Medicine with the priorities of the Secretary of the Navy, Chief of Naval Operations, and Commandant of the Marine Corps. Navy Medicine is fully engaged in executing the operational missions and core capabilities of the Navy and Marine Corps. We do this by maintaining warfighter health readiness, deploying forward, and delivering a continuum of care from the battlefield to the bedside, while also protecting the health of all those entrusted to our care. To ensure the fulfillment of our mission, I have outlined 3 strategic goals for the Navy Medicine enterprise: readiness, value, and jointness.

Transforming our societal focus from health care (a pound of cure) to health (an ounce of prevention) is a strategic imperative. The implications on military readiness are profound. Approximately 30% of potential military candidates ages 17 to 24 do not qualify for military duty because they are overweight; but to sustain our fighting force and successfully execute our missions, our naval forces must be armed with fit, healthy, and ready Sailors and Marines.

Fortunately, we have a way to address this crisis—the Patient-Centered Medical Home (PCMH) model launched at Naval Hospital Pensacola and Walter Reed National Military Medical Center, Bethesda, Maryland (formerly the National Naval Medical Center) in 2008. It is now being implemented throughout the Military Health System (MHS) and carries great promise. It provides the clinical framework we need to meet our strategic objectives in terms of quality of care, impact on costs, population health, and readiness.

One of the most significant benefits of the team-based, collaborative approach is that it allows us to embed within a primary care environment the psychologists, nutritionists, tobacco cessation specialists, mind-body medicine therapists, and health educators our patients need in order to develop and maintain mindful, healthy behaviors—along with the “mental armor,” our active duty military personnel need to increase their operational effectiveness and their resiliency in bouncing back from stressful situations. As we move ahead with this more comprehensive approach to health, we can begin to better address so many of our patients for whom we can find no specific reason for pain and discomfort.

The PCMH model also provides a positive impact on our costs. Early data reporting from the PCMH clinics at Bethesda show reduced visits to the emergency room, lowered pharmacy costs, and significant per beneficiary per year savings and improved Healthcare Effectiveness Data and Information Set metrics, access, and patient satisfaction and trust. These positive impacts on the bottom line can be applied directly to improved
costs or toward the reallocation of resources from reimbursing those who are sick to the population health-based programs that can make and keep our patients healthy.

More significant, however, the PCMH environment allows us to go beyond mere collaboration and to a much more proactive approach to managing our patient populations. It is within the context of the medical home that we can begin to surround our patients with the tools and resources they need to move them from health care to health. To lead vibrant, healthy lives, our patients will need health risk assessments, personal plans for health, live and virtual coaching, and access to a broad array of online and mobile applications, including wireless biometric monitoring devices for our sickest patients. We will also need to link our patients to the social networks and community resources that will reinforce their healthy behaviors.

None of these objectives come easy. Workforce redevelopment will play a critical role in our efforts to be successful. Some patients and providers hold on to the comfort of the personal visit for any and all things; however, the reality of our health crisis is that the workflow of the future will be very different. Because our populations are so unhealthy, there will be fewer personal encounters between patients and their providers in favor of phone, e-mail, or web-based visits by nurses, nutritionists, psychologists, coaches, and others who help address the underlying causes of poor health. Our critical reliance on information technology tools is not just out of desire but necessity. Provider appointments will be reserved for only those patients who truly need a provider to hear, see, or touch directly the patient concern. Fortunately, our patients themselves are yearning for a more “plugged-in/wireless” way to connect to their health providers.

There are challenges in implementing the PCMH model. Change is never easy. Conflicting issues over staff roles on a medical home team, competing objectives between teams and leadership, and institutional inertia in the face of innovation can all present issues that must be worked through and resolved if the transformation from health care to health is to be successful. Because the PCMH concept is different from the primary care we all grew up with, its unique culture must be fostered, nurtured, and championed, and the lessons learned from its implementation shared MHS wide.

The MHS and its population of 9.6 million beneficiaries are positioned uniquely, I believe, to serve as a place where we can pioneer national health care reform efforts. The MHS has the essential ingredients to make this work: an insured population, electronic medical records, potential rewards for health vice health care, and a vertically integrated system that “owns” almost all aspects of care. As a closed system that closely mirrors the U.S. population in general, the MHS can allow health care experts and U.S. policymakers to study the effects of the PCMH model; and our population health efforts as tools for a broader, more concerted, national dialogue on how to improve the health of not just a few, but all, Americans.

And, I might add, with a sense of urgency. Our choices of unhealthy behaviors as a nation are rapidly closing in not only on our fiscal solvency, but also on our ability to thrive as a healthy nation. Health and access to health care are essential pillars for the well-being of our nation as well. The military engagements that have occupied our efforts for so long may be turning the corner, and our first responsibility will always be to the combat
zone; but make no mistake, we must all now deploy to the health care zone. We have no other choice. We need to be healthy, and when danger, disaster, or disease arises, ready.

Enhanced Tracking of Tissue for Transplantation

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The US Food and Drug Administration (FDA) estimates that tissue banks provide 1.5 million tissue grafts annually, often supplying hospitals in several different states or even countries with tissue from a single donor. Tissue allografts have become a vitally important global industry. Nevertheless, tracking mechanisms that exist in other medical contexts have notable deficiencies with respect to tracking tissues. Current tissue tracking practices do not ensure rapid communication through the distribution chain as soon as a problem is discovered, which is crucial for quarantining tissues before they are used. If the tissue has already been implanted, it is often difficult to identify the recipient to provide appropriate medical care.

RISKS POSED BY TISSUES

Millions of patients receive tissues safely each year. However, some illustrative cases will demonstrate the types of risks that might potentially arise, leading to the need to quarantine tissues rapidly or contact tissue recipients.

The risks associated with tissue transplantation and the importance of rapidly communicating such risks were demonstrated by a report describing a 12-year-old boy who contracted hepatitis C from implantation of a cardiopulmonary patch that, along with 43 other tissues, was released owing to a clerical error in reading hepatitis C nucleic acid test results. Once the error was discovered, it took a month to complete the subsequent recall. Tissues from a given donor are often distributed to multiple recipients over a matter of days or weeks, sometimes even months. In the era of instantaneous electronic communication, it ought to be possible to quarantine dangerous tissues as soon as a problem is discovered. However, as the director of the Office of Blood, Organ, and Other Tissue Safety at the Centers for Disease Control and Prevention stated in the aftermath of the case described above, “It's all done the old-fashioned way with phone calls and letters and e-mails.”

In 2006, two patients who underwent cruciate ligament reconstructions developed postsurgical Elizabethkingia meningoseptica infections. Both required additional surgery for joint debridement and aggressive antibiotic therapy. A subsequent investigation traced the transplanted ligaments to a single tissue-processing facility, where it was discovered that over a 6-month period the facility had a 3-fold increase in tissues testing positive for bacterial growth. Cultures taken from drain fixtures in the clean room of the processing facility grew E meningoseptica, a bacterium...
predominately found in water. This prompted an urgent global recall of tissue products involving 750 facilities in Canada, the United States, and Mexico.

Intentional misconduct in the highly lucrative tissue procurement industry has also led to dangerous exposures to patients. From 2002-2005, Biomedical Tissue Services Ltd (BTS) distributed tens of thousands of illegally obtained and improperly processed tissues throughout the world. BTS criminally acquired tissues from cooperative funeral homes in the New Jersey area and produced false death certificates and infectious disease test results, placing thousands of tissue recipients at risk. The FDA ordered the quarantine of all tissues from BTS that had not yet been implanted but estimated that 13,000 patients ultimately received transplants of tissues processed by BTS. Not all hospitals kept records of which tissues were implanted in which patients, so the health effects on recipients is largely unknown.

The FDA responded to the BTS scandal by strengthening the regulations governing tissue procurement. However, within a year another organization supplying improperly obtained and processed tissues, using an almost identical modus operandi, was discovered to be operating in North Carolina, under the name Donor Referral Services (DRS). As in the BTS case, many patients who received tissues from DRS could not be identified because of inadequate tracking at the hospital level.

REGULATORY OVERSIGHT OF TISSUES

The FDA is the federal agency responsible for regulating human cells, tissues, and cellular and tissue-based products (HCT/Ps) in the United States. Tissue banks are required under 21 CFR 1271.290 to track tissues from the donor to the consignee or final disposition. However, the FDA does not consider hospitals to be covered by the regulations and does not regulate the tracking activities of hospitals.6 Tissue suppliers generally provide information cards for hospitals to complete and return when tissues are implanted. The degree of cooperation varies among hospitals, however, as demonstrated by the BTS and DRS cases.

The FDA strengthened its regulations after the BTS scandal but did not attempt to extend the tissue-tracking regulations to include hospitals. When the DRS scandal came to light less than a year later, the Department of Health and Human Services convened a human tissue task force (HTTF) to reevaluate the scheme for regulating HCT/Ps.7 The HTTF report, issued in 2007, noted that “21 CFR 1271.290 requires tracking to the consignee or final disposition, but not to the patient.” The report recommended developing a plan for tracking tissues all the way to the recipient but stated that accomplishing this goal “would involve an examination of legal authority and current practices.”

Organizations that voluntarily set standards have some ability to enforce those standards, but only among their members. The American Association of Tissue Banks (AATB), AABB (formerly American Association of Blood Banks), and The Joint Commission have promulgated standards for tracking tissues from donor to recipient. However, even the most rigorous adherence to good processing and tracking practices by the vast majority of accredited tissue suppliers will not prevent events such as those described above. To ensure traceability, the FDA should mandate that hospitals complete the final link in the process. If the FDA does not possess the legal authority to do so, appropriate legislation is needed to close the gap.

CONCLUSIONS
Several changes can improve patient safety. First, a standardized electronic tracking system like the ISBT-128 system already used in blood banking could be adopted by the tissue banking industry. This would allow tissues to be tracked almost instantaneously from the donor to the patient. Such a system will enhance the ability to recall at-risk tissues prior to implantation. The AATB and AABB have been working to implement ISBT-128 tracking among their memberships. Hospitals and clinics can contribute to that effort by making electronic tracking a component of their qualification process for suppliers.

Most hospitals and clinics currently rely on their operating rooms to receive and store tissue and to communicate final disposition back to tissue banks, frequently via postcards. To the extent possible, tissue management could instead be placed under the responsibility of blood banking departments, which have the training and technical expertise to manage ISBT-128 labeling, proper storage protocols, and product tracking. Surgical nurses are trained in surgical nursing; they should not be asked to adopt an entirely different kind of expertise when it already exists in the blood bank.

The FDA, with the support of the medical community, must work toward correcting the gap in 21 CFR 1271.290 to mandate tracking tissue from procurement to implantation. Too much time has passed since the HTTF report was issued in 2007, and patients continue to be at risk. Instead of relying on voluntary tissue tracking by hospitals, the FDA needs to hold hospitals accountable by designing and enforcing regulations similar to those that have existed for many years for blood banking.

Examining Selected Patient Outcomes and Staff Satisfaction in a Primary Care Clinic at a Military Treatment Facility After Implementation of the Patient-Centered Medical Home

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Abstract

Background: The patient-centered medical home (PCMH) model is a holistic multidisciplinary approach to providing care in the primary care setting. Provider-led teams engage the patient and family in their own health care plan. It is linked to improve continuity of care and enhance access. Objective: This article describes comparison outcomes in access to care, emergency department (ED) utilization, and population health management 2 fiscal years before and after implementation of the PCMH. Staff satisfaction was measured after implementation. Design: A mixed study design approach was elected. De-identified aggregate data were mined from the Command's Business Report portal, from the pay-for-performance-based “Get to Goal” report, and through an anonymous voluntary questionnaire survey providing both qualitative and quantitative data interpretation. Result: Access to care increased by 7%, ED utilization decreased by 75.3%, and population health/Healthcare Effectiveness
Data and Information Set (HEDIS) measures improved overall. Seventy-five percent of the staff who volunteered to be surveyed was satisfied with the PCMH. Conclusion: After 2 years of implementation, the PCMH was associated with improvement in access to care, reduction of ED visits, improvement in population health/HEDIS measures, and a high degree of staff satisfaction.

Introduction

The U.S. health care system has been described as a nonintegrated entity with variable performance and largely unmeasured outcomes. Two Institute of Medicine (IOM) landmark articles, “To Err is Human” (1999) and “Crossing the Quality Chasm” (2001), addressed the deficiencies within the health care system. In “To Err is Human,” the IOM estimated that 98,000 people die in hospitals because of avoidable medical errors. This translated to over approximately $29 billion in lost income, loss of household productivity, and personal disabilities. Moreover, the errors generated a lack of trust and decreased patient satisfaction. They also produced a loss of morale and great frustration among health care professionals.

Similarly, the IOM's report “Crossing the Quality Chasm: A New Health System for the 21st Century,” reiterated inconsistencies in the U.S. health care system and the disparity of providing high-quality care to its people. Contributing factors cited include a major gap between the rapid growth of technology without the concurrent ability to rapidly translate and apply this knowledge, an increase in population with chronic diseases, and a complexity in the health care system that is generally focused on acute episodic care. Compounding these factors is the isolating practice of physicians in managing the health care needs of their patients. As a result, care is fragmented. The report “Crossing the Quality Chasm” puts forth the policies of safety, patient-centered care, timeliness, and efficient and equitable care for the delivery of holistic care.

The patient-centered medical home (PCMH) model embraces the strategies set forth by the IOM and offers a promising model for health care delivery in the United States. It facilitates holistic health care among patients, families, and the health care team. The concept of “medical home” was developed in 1967 by the American Academy of Pediatrics to describe a primary source of medical information for a patient. Eventually, the term was expanded to include accessible, comprehensive, coordinated, family-centered care, with a list of 37 specific activities for the operation of a medical home. Today several definitions of the medical home can be found. The Agency for Healthcare and Research Quality (AHRQ) has defined it as a model that delivers the key functions of primary health care. The medical home emphasizes five components: patient-centeredness, comprehensive care, coordinated care, excellent access, and systems-based approach to quality and safety. The core principles agreed on by the American Academy of Family Physicians, the American Academy of Pediatrics, the American College of Physicians, and the American Osteopathic Association remain true for the model:

(1) Personal Physician: Patient and family (as indicated) establish an ongoing relationship with the personal physician who provides continuous and comprehensive care.
(2) Physician-Directed Medical Practice: The personal physician leads the health care team in taking responsibility for the continuous care of the patient/family.
(3) Whole Person Orientation: The personal physician cares for the patient/family throughout the life span and wellness–illness continuum.
(4) Coordination/Integration of Care: Throughout the health care system, management of care is facilitated by registries, information technology, health information exchange, and other means to ensure culturally and linguistically appropriate care for the right patient/family at the right time and place.

(5) Quality and Safety: Evidence-based medicine, accountability for continuous quality improvement, active participation of the patient in his or her care, appropriate use of information technology, and surveillance by appropriate nongovernmental agency are used to show the capability to provide patient-centered care.

(6) Enhanced Access: Care is available when needed, with options for communication among patients, personal physician, and staff.

(7) Payment Reform: Appropriate reimbursement is provided for the benefit of a PCMH.

The National Committee for Quality Assurance (NCQA) also supports these principles and upholds that the medical home strengthens a long-term, coordinated care between physicians and their patients. In addition, the Joint Commission has recently adopted standards that recognize nurse-led clinics as “primary care medical homes.”

Significance and Aims

Within the Bureau of Naval Medicine and Surgery, the first pilot project of the PCMH began in June 2008 at the National Naval Medical Center, Bethesda, Maryland. By calendar year 2010, additional medical homes were implemented in several military treatment facilities (MTFs) across the enterprise. In September 2009, the Office of the Assistant Secretary of Defense sent out a policy memorandum supporting the PCMH as the model of care for all MTFs. The Office of the Medical Home Program Management at the Bureau of Medicine and Surgery is charged with providing guidance in the implementation and expectations of the “Medical Home Port” (MHP), the Navy’s PCMH model, throughout Navy Medicine. The Deputy Chief of Bureau of Medicine provides a liaison to the NCQA to facilitate the NCQA onsite evaluation of MHPs’ compliance with PCMH standards.

Currently, no aggregate data and impact of the selected variables for this project have been reported before and after implementation of the PCMH in a primary care clinic. The focus of this study was to examine access to care, emergency department (ED) utilization during clinic hours, population health/Healthcare Effectiveness Data and Information Set (HEDIS) measures, and staff satisfaction 2 fiscal years after implementation of the PCMH in a primary care clinic at an MTF. In keeping with the business goals as articulated by the department head for the primary care clinic in this project, the outcomes sought were an increase in access to care by 75% or greater, a decrease in ED utilization during clinic hours by 50%, improvement in all population health measures, and a staff satisfaction of 50% or greater.

Relevant Literature

Becoming a PCMH requires a transformation in practice and roles. Lessons learned from the National Demonstration project on practice transformation of a PCMH included redesigning of practice, new scheduling and access management, new coordination, strategies for patient engagement, use of information technology, and many more to address all components of the PCMH. It is much more than an incremental
application of the model. It is a developmental process whereby changes in one component automatically affect the rest. In addition, a coordinated team approach is necessary to maximize patient outcomes and increase patient satisfaction.

Access and continuity of care are essential and valued factors in primary care. The cross-sectional analysis of 15,341 patients who participated in the national online survey DrScore indicated that patients were more satisfied when they see the same provider on return visits (p < 0.05). Continuity of care fosters a therapeutic relationship especially when access is not an issue and care is well coordinated. Such an accomplishment is significant in terms of efficiency, quality of care, patient satisfaction, and overall evolution of the PCMH. The critical review of Saultz and Albedaiwi also supported the forming of strong interpersonal relationships that improve continuity of care and patient satisfaction. Similarly, the findings from the cross-sectional survey of 21,689 patients associated continuity of care with higher patient satisfaction. In addition, the perception of safety is increased especially in certain older populations.

Improving access to primary care to decrease ED overcrowding is a major focus of the PCMH. Patients habitually use the ED as a safety net due to unavailability of appointments in primary care. Such nonurgent visits to the ED continue to increase the cost of health care. In 2006, the cross-sectional study of Chin et al16 found that nonurgent ED visits were mostly attributed to system design and structure. Changes such as extended clinic hours could allow such visits to be conducted in primary care. Similarly, Pitt et al17 and Rust et al18 noted that improving access to care would decrease the overutilization of the ED for nonurgent visits.

A fundamental aspect of the PCMH is care coordination. Care coordination facilitates the operation of the medical home. It is especially useful for chronic disease management and monitoring of population health/HEDIS measures. The study of Cooley et al19 supported the effectiveness of the medical home in children with chronic diseases. They identified 43 primary care practices in five states including the District of Columbia. Their focus was on children with chronic conditions (the six chronic conditions included in their study were asthma, diabetes, cerebral palsy, epilepsy, attention-deficit/hyperactivity disorder, and autism). They measured the effectiveness of the PCMH using the medical home index (MHI). They found that fewer children were hospitalized and there were less ED visits for those organizations with a high MHI. The MHI is a pediatric and adult validated self-assessment and classification tool used for translating the broad indicators of the medical home into tangible behaviors and processes of care. The data from the 2005–2006 National Survey of Children with asthma found out that 49.9% of asthmatics had a medical home and as a result had fewer ED visits (incidence rate ratio = 0.93, 95% CI = 0.89–0.97). This finding calls for further exploration of strategies to improve use of access for all children with chronic needs. Success of the PCMH is further validated by the National Demonstration Project intervention in transforming family practices into the PCMH. The adoption of the model improved access (standardized beta [SB] = 0.32, p = 0.44), prevention (SB = 0.42, p = 0.001), and chronic disease scores (SB = 0.25, p = 0.08). The observational cohort study of Stewart et al affirmed the association between patient-centered communication and overall patient-centered practice to improve health outcomes while decreasing diagnostic tests and referrals.

Methods

Design
A mixed study design approach was selected. Data were mined from the Command's Business Report portal, the Pay-for-Performance-Based “Get To Goal” report, and through an anonymous voluntary questionnaire survey providing both descriptive qualitative and quantitative data interpretation.

Sample and Participants
The aggregate clinic database of 13,000 patients based on the average enrollment capacity within the time frame of this project and the clinic's 36 staff participants in the voluntary and anonymous survey provided a convenience sample for descriptive quantitative and qualitative data interpretation.

Data Collection
De-identified data were mined for 2 fiscal years (2007 and 2008) before implementation of the PCMH model in 2009 and for fiscal years 2010 and 2011 after implementation of the model from the Command's Business Report portal. Population health/HEDIS data were obtained from the Performance Based Budget “Get To Goal” report, which is a command-wide report for all the branch health clinics with their population health/HEDIS performance. It consists of the score for each indicator, the performance percentile, and the target score to reach respective benchmarks. Staff satisfaction was obtained through an anonymous and volunteer survey questionnaire in the fall of 2011.

This study was approved by the clinic's overarching institutional review board and was conducted in compliance with all applicable federal regulations governing the protection of human subjects in research.

Data Analysis
Data analysis was both quantitative and qualitative. The Stata Data Analysis and Statistical software, version 12.024 was used to provide descriptive analyses using the 2-sample t-test and analysis of variance (ANOVA). The two-sample-t-test is a statistical technique that tests the difference between two population means, usually to determine if they are equal. This technique was used for the analyses of the HEDIS measure. ANOVA is a statistical technique used to evaluate the contribution of categorical factors to variation in the mean of a continuous outcome variable. In one-way ANOVA, the effect of a single factor on a single response variable is evaluated. Access to care and ED utilization during clinic hours were evaluated using ANOVA. Missing data in each variable were eliminated. Quantitative and content analysis of the staff satisfaction survey was also conducted. A conceptual approach was used for the content analysis. Coding was conducted for frequency of a thematic concept and themes were recorded the same even when they appeared in different forms. Ambiguous responses were eliminated.

Results

Access to Care
The access-to-care report displays the compliance to the Department of Defense's access-to-care standards for booking appointments based on acuity. The 4 access-to-care categories—such as “acute,” booking within 24 hours; “well,” booking within 28 days; “routine,” booking within 7 days; and “procedures,” booking within 28 days—were evaluated for this project. The “routine” access to care was discontinued in the last quarter of
fiscal year 2011. This was a major contributor to the missing data in this analysis. The target for each category was 90%. Tables I and II show the pre- and post-descriptive statistics for overall clinic access-to-care for each category.

In the post-descriptive analysis by teams, Team One shows a nonsignificant mean decrease of 90.99 for “acute” visits and a mean increase of 99.78 for “well” visits. “Routine” and “procedure” visits had a significant decrease of 74.7 and 88.74, respectively. Team Two had a mean increase in all categories: “acute” (92.27), “well” (99.96), “routine” (94.24), and “procedures” (99.44). Team Three had a nonsignificant increase for “acute” (91.72), and a significant increase for “well” (99.84), “routine” (91.06), and “procedure” (99.47). In Team Four, there was a significant decrease in “acute” (80.24), “routine” (47.88), and “procedures” (76.88), but a significant increase for “well” (100). The overall ANOVA for each access-to-care category indicated that the “acute” category had no significant differences (pre-p value = 0.65, post-p value = 0.90). However, the one-way ANOVA between teams showed a significant difference (p = 0.01). “Well” had a significant difference pre to post, but not in teams (pre-p value = 0.00, post-p value = 0.99); its one-way ANOVA between teams showed no significance (p value = 0.38). Pre- to post-p values for “routine” were 0.00 to 0.03, respectively. The p value for the one-way ANOVA between teams was significant at 0.00. “Procedure” had no significant difference in any (pre-p value = 0.89, post-p value = 0.19), and its one-way ANOVA between teams showed no significance (0.09).

ED Utilization During Clinic Hours
This variable represents the total number of nonacute (i.e., patients who do not need to be seen within 24 hours) patients seen in the ED during clinic hours. The mean utilization pre-PCMH was 150.3, with a standard deviation of 26.99. Post-PCMH, there was a significant drop in each team (Fig. 1). The means for Teams One, Two, Three, and Four were 46.5, 53.66, 36, and 2.05, respectively. The one-way ANOVA (Table III) showed a significant difference between pre-PCMH and teams (p < 0.0000), but no significant difference between teams (p = 0.760) (Table IV).

Population Health/HEDIS Measures
The HEDIS is a set of criteria that the Military Health System Population Health Portal uses to benchmark medical treatment facilities and Managed Care Support Contractors. A comprehensive benchmarking measurement is provided for the clinical management of asthma and diabetes and for the screening for breast cancer, cervical cancer, and colorectal cancer. Overall, the two-sample t-tests with equal variances for each of these measures showed that there was a nonsignificant decrease in the measurement for asthma by 1.8. In the diabetic category, there was an increase by 3.5 for ages 18 to 75 years with A1C in 12 months; A1C ≤ 9%, increased by 4.8; and LDL ≤ 100 mg/dl, increased by 9.5. Breast cancer screening showed an increase by 1.4, cervical cancer screening by 1.0, and colorectal cancer screening by 9.8. The reported p value for all of the HEDIS measures was less than 0.001 (p < 0.001).

Staff Satisfaction
Overall, staff members felt a strong connection with their team and the patients and had a deep feeling of ownership in the process and a fulfillment in their roles. The Staff Satisfaction Survey is provided in the Appendix. High-functioning care teams will be critical to future patient- and family-centered care. Figure 2 represents the response from the staff satisfaction survey. The content analysis of the survey showed that 36% of the staff desired improvement in resources such as personnel, equipment (especially computers) availability, and space utilization; 25% wanted improvement in overall efficiency and teamwork; and 15% wanted improvement in access.
Interpretation of Findings

Overall, access to care showed a nonsignificant 2% decrease in the “acute” category and a 14% increase in “well”; there was a significant difference in pre to post but not among the teams. There was a 25% increase for “routine,” with a large significance from pre- to post-PCMH (65.50 to 81.96), and varying increased significance in Teams One to Three and a decrease for Team Four. There was a 3% reduction for “procedures,” without any pre to post or team significance. Overall access to care increased by 7%. A significant reduction was found in non-urgent emergency room visits post-PCMH; Teams Three and Four showed the most reduction. However, there was no significance in the number of decrease visits between the teams. As a whole, ED utilization during clinic hours, was reduced by 75.3%, exceeding the desirable outcome of 50%.

The HEDIS measures show much improvement, with only one measurement, asthma, with a nonsignificant decrease. Diabetes ages 18 to 75 years with A1C in 12 months, A1C ≤ 9%, and LDL ≤ 100 mg/dl all had a significant increase post-PCMH. Cervical cancer and colorectal cancer screening also increased substantially, and although not significant, there was an increase for breast cancer screening. The staff satisfaction survey showed 75% of the staff was satisfied with the PCMH.

Limitations to Findings

There are several limitations to this study. First, the variables for this project were selected and do not represent all the attributes of the PCMH. Data at the time of collection were missing, and an inconsistency existed in the number of observations across and within variables. The use of secondary data raises the possibility of data error, since secondary datasets usually contain missing and unusual values. Such datasets may also limit data interpretation and understanding. The inconsistent composition of Team Four and its lack of a consistent panel of patients played a significant role in data analyses and interpretation. Transiency of the patient population and lag time for updated population health/HEDIS metrics were not factored into the analyses. Also, the population health database for the clinic is internally known to be made up of patients who have TRICARE Plus or some other insurance plan and are, therefore, not seen at the assigned primary care clinic. As internally acknowledged, a mechanism has not yet been identified to connect with these patients to update or conduct preventive health measures. This study did not evaluate the clinic’s activities pre- and post-PCMH, and hence, offers no additional insight for reasons for improvements or lack thereof for the selected variables. It only made a comparison of the data of the selected outcomes that are mentioned, pre- and post-PCMH. An opportunity exists for future studies to elaborate on these findings. In addition, these inferences were based on a 24-month postobservation. Given the several components and extensive changes associated with the implementation of the PCMH model, more time for ongoing execution and adaptation to the change could have been necessary before undergoing evaluation.

Discussion
Access and continuity of care are major components to the success of the PCMH. Access can influence continuity, and with continuity comes decreased ED visits and improved proactive population health management, as in the HEDIS measures. Based on the findings of this project, assessment and development of a road map to further improve access will be necessary to fully achieve the goals of the medical home. Access can be further improved through creative template management, such as group visits and open access scheduling. The NCQA principles support open access and expanded hours to improve access to care. Sufficient support staff, equipment, and space utilization warrants assessment and appropriate allocation of these resources. For instance, the current system of built-in computers in patients’ rooms can be converted to computers on wheels. In light of the rapid and frequent turnover of military staff, a robust civilian staff is necessary to serve as an anchor for a sustainable medical home.

The findings of this study have added to the body of evidence supporting the PCMH as a health care delivery model that improves the quality of patient care. The primary care setting, to include the pivotal role of the advanced nurse practitioner, is especially suited for the medical home. Given the support and resources, a high degree of patient care, staff satisfaction, and NCQA recognition can be achieved.

Evidence can influence practice, and, as such, further evaluation to improve the PCMH could be undertaken in the areas of quality of care, cost, and patient satisfaction. A mock evaluation using the NCQA criteria would be helpful in ascertaining medical home status and actions needed to achieve the highest, Level 3, recognition by the NCQA.

Conclusion

Two years after implementation, the PCMH was associated with improvement to access to care, reduction of ED visits, and improvement in population health/HEDIS measures. Although prestatisfaction data were not determined, the postsatisfaction survey showed a high degree of staff satisfaction. The PCMH is still evolving. Synergy among all the essential components is necessary to achieve the transformation for a better primary care delivery system. Based on this evidence-based project, and given the motivation of the staff and key components in place, the PCMH, indeed, promises improved access and quality of patient services in primary care.

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Impact of a Patient-Centered Medical Home on Access, Quality, and Cost

Military Medicine
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Abstract

Context: Patient-centered medical homes (PCMHs) are intended to actively provide effective care by physician-led teams, where patients take a leading role and responsibility. Objective: To determine whether the Walter Reed PCMH has reduced costs while at least maintaining if not improving access to and quality of care, and to determine whether access, quality, and cost impacts differ by chronic condition status. Design, setting, and patients: This study conducted a retrospective analysis using a patient-level utilization database to determine the impact of the Walter Reed PCMH on utilization and cost metrics, and a survey of enrollees in the Walter Reed PCMH to address access to care and quality of care. Outcome measures: Inpatient and outpatient utilization, per member per quarter costs, Healthcare Effectiveness Data and Information Set metrics, and composite measures for access, patient satisfaction, provider communication, and customer service are included. Results: Costs were 11% lower for those with chronic conditions compared to 7% lower for those without. Since treating patients with chronic conditions is 4 times more costly than treating patients without such conditions, the vast majority of dollar savings are attributable to chronic care. Conclusions: Results suggest focusing first on patients with chronic conditions given the greater potential for early gains.

Introduction

The dual mission of the U.S. Military Health System (MHS) is to provide medical support for military operations and to care for 9.6 million Department of Defense (DoD) beneficiaries. Given the fact that over 17% of enlisted personnel and 49% of officers complete a 20-year military career, and as a result incur lifetime health care benefits, the MHS has a vested interest in its beneficiaries' long-term health. Furthermore, a large number of children from military families go on to serve their own military careers, creating a cradle-to-grave health interest for the MHS. Thus, the MHS has been extremely interested in a primary care delivery model that directly promotes improved access to care, population health, military readiness, and reduced health care costs.

The patient-centered medical home (PCMH) concept is “an approach to providing comprehensive primary care [in] a health care setting that facilitates partnerships between individual patients, the personal [provider and the medical home team], and when appropriate, the patient's family.” Unlike traditional care, the PCMH model uses a physician-led team approach that focuses on providing more patient-centric care, proactively addressing patients' needs by effectively utilizing other team members such as nurse practitioners and physician assistants, registered nurses, licensed practical nurses, and administrative assistants to perform at a level commensurate with their professional expertise. The concept of the “right patient at the right place and right time” is vital to the appropriate utilization of health care services across a broad spectrum of patient needs and interventions. Instead of relying on face-to-face visits, the medical home team and patients also interact virtually to manage chronic conditions, administer health risk assessments, provide preventive care management, and co-ordinate care. The provision of many of these services virtually allows providers to use appointments to focus on managing those patients with complex and acute care needs.

Multiple studies have shown that both continuity and longevity of patient–provider relationships can improve preventive care, reduce hospitalizations, and reduce health care costs. Similarly, several studies suggest that optimal case management can improve patient outcomes, enhance provider productivity, and be cost effective. Although the PCMH delivery model has a number of innovations that are widely expected to
optimize population health indicators and enhance patient experience, previous reports have shown mixed results on the issue of overall costs. Milstein and Gilbertson10 identified four PCMHs whose patients incurred 15% to 20% less costs than peer sites. Similarly, studies have shown that Community Care of North Carolina's PCMH program resulted in a reduction in per member per month cost by 17% in 2004 and by 11% in 2007. Meanwhile, a Geisinger PCMH pilot at two sites showed a 7% cost reduction after 1 year, but a later study at 11 sites did not show a statistically significant reduction. Moreover, results at a PCMH demonstration at the Group Health Cooperative showed no statistically significant cost differences after 1 year, even though emergency room (ER) visits decreased by 29%.

The variability of the outcomes is not surprising given that the PCMH is not a single, well-developed model of care but rather a set of guiding principles and that each patient population, organizational structure, and culture are unique, and may deserve unique work flow processes and team make up. The specific design and implementation process must not only follow these principles but also be well thought out and executable. Other possible contributing factors of variability include the differing reimbursement systems and the population settings in which the care was delivered (hospital vs. ambulatory practice). In addition, when the principles are applied in isolation, there are often unintended consequences that occur elsewhere in the system of care that may result in clinically appropriate cost increases (such as increased utilization of preventive care services). This makes a successful solution in one system difficult to generalize without broader consistency in the reimbursement model and basic functional attributes of the system of care.

The literature provides an array of studies that evaluate the effectiveness of a subset of the expected PCMH impacts, such as cost or hospitalizations, but lacks a refined analysis of how the new delivery model fared among populations with and without chronic conditions. This study attempts to close this gap by examining the prolonged impact of the Walter Reed National Military Medical Center (WRNMMC) PCMH (formerly the National Naval Medical Center PCMH) on its health care access, quality metrics such as patient satisfaction and Healthcare Effectiveness Data and Information Set (HEDIS), and cost data. Furthermore, this study also analyzed the effect of the PCMH model on patients with and without chronic conditions. This is important because a focus of the PCMH model is to effectively manage patients with chronic diseases and to prevent chronic diseases from manifesting later in those currently without such conditions.

Methods

We conducted this comprehensive analysis of the Walter Reed PCMH (WR PCMH) using a patient-level utilization database and a patient survey. Table I shows the metrics we used for access, quality, and cost, as well as the data source for these metrics. We derived these metrics from two data sources. The access metrics and most of the quality metrics come from a patient satisfaction survey. This survey enabled us to assess patients’ perceptions of access and quality. The remaining quality metrics (HEDIS and primary care manager [PCM] continuity) and the cost and utilization metrics come from a patient-level utilization database. For access, quality, and cost metrics, we designed our approach to facilitate an analysis of PCMH impacts for patients with and without chronic conditions. Given the emphasis of the PCMH model on managing and preventing chronic diseases from manifesting, this is a critical distinction. The following sections discuss the methods behind each of these data sources.

Cost (and Utilization) Methods
We used a differences-in-differences approach to conduct the utilization analysis for a pre–post comparison of the Walter Reed PCMH against itself while controlling for trends at comparison sites. The clinic began its transition to a PCMH starting June 2008 and completed its transition in January 2009. Accordingly, we used six quarters of patient-level utilization data before and after the transition period as the basis of the pre–post analysis. For comparison sites, we used enrollees of the internal medicine clinics at the Navy's medical centers in Portsmouth, Virginia and San Diego, California; as well as the Navy's teaching hospital in Pensacola, Florida. The similarities of these sites in mission, graduate medical education, and patient demographics minimize self-selection and comparison problems related to patient equivalence, practice equivalence, and external factors that can be problematic in evaluations.

Unlike prior research that measures the impact of PCMH on utilization using a multivariate regression methodology, we used a two-step regression methodology. Multivariate regression is econometrically problematic because the distribution of the dependent variable—in this case, utilization—is highly skewed and has a heavy weight on zero (no utilization). Such data do not satisfy the assumptions of normality, homoscedasticity, or independence that multivariate regression requires. With sufficient data, this approach will provide unbiased estimates, but the standard errors may be too small, thus overestimating the significance.

A two-step model, in which the first equation estimates the probability of use of a particular health care service and the second equation estimates the amount of use for users, overcomes these limitations. Not only is this approach econometrically sound, but it also provides additional information that the standard multivariate regression approach cannot. For example, multivariate regression may provide an estimate showing reductions in ER services, but it does not provide information about whether fewer patients are presenting at the ER (i.e., the probability of use) or whether those presenting at the ER are using less ER care (i.e., the amount of ER use for ER users) is the reason for reduced ER utilization overall. The two-step methodology allows us to answer these questions. Table I shows descriptive statistics for the data used in this analysis.

Access and Quality Methods

To estimate the impact of the Walter Reed PCMH on access and quality, we conducted a patient survey to compare Walter Reed's PCMH enrollees to enrollees in its traditional internal medicine clinic. The patient survey was designed to assess enrollees' satisfaction with access to their PCM and clinic staff, PCM communication, and care co-ordination. We drew questions from several existing surveys, most prominently from the Consumer Assessment of Healthcare Plans and Services survey, Clinicians and Groups; the Insignia Health Patient Activation Measure; and the Primary Care Assessment Survey (PCAS). The survey instrument was developed in consultation with providers and researchers at Walter Reed, the Uniformed Services University, and the Center for Naval Analyses. The survey instrument and protocol were reviewed and approved by the Walter Reed Institutional Review Board with secondary reviews by TRICARE Management Activity and the Defense Manpower Data Center Survey Office.

We administered the survey via a mail invitation to complete the survey either online or by mail. In total, 4,090 completed surveys were received for a 39% response rate in both the medical home and the comparison clinic. This response rate is in line with the 40% response rate among the
DoD population per the 2011 Health Care Survey of DoD Beneficiaries. More specifically, our response rates for subpopulations such as active duty at 16% were in line with the 2011 Health Care Survey of DoD Beneficiaries. We also had varying response rates by chronic condition status (47% for those with a chronic condition compared to 32% for those without a chronic condition) and by age (71% for those 65 and older compared to 28% for those under 65). The survey results were weighted to account for these differing response rates so that the results better reflect the Walter Reed PCMH enrollee population. We weighted the survey results to account for differences in selection and nonresponse; Specifically, the weights correct for such differences in gender, age, and beneficiary type so that the weighted survey responses reflect the population.

As noted in Table I, all quality methods except the HEDIS measures and PCM continuity are based on the patient survey. For the HEDIS measures and PCM continuity, we relied on the patient-level utilization database.

Results

Cost and Utilization

We first present the results for the impact of the Walter Reed PCMH on utilization and cost (Fig. 1). The results show that a statistically higher percentage of Walter Reed PCMH enrollees had some primary care use (i.e., the probability of having some primary care utilization increased). In addition, the amount of primary care services these enrollees received was statistically higher than the comparison sites (21%). This is consistent with the idea that PCMHs provide more comprehensive care to reduce the amount of more costly specialty, inpatient, and ER care. Note that our primary care measure is encounters not just in-office visits. Encounters include in-house visits and virtual care, including secure e-mail and telephone consultations. Although the number of primary care encounters has increased, the composition has changed as well. For example, before PCMH implementation, telephone consultations accounted for 16% of encounters, but after implementation, this figure was 24%. For the comparison clinics, this trend was either flat or reversed. These trends are consistent with the notion that more of the care occurs in the PCMH. The question, then, is whether this increase in primary care is offset by utilization and cost reductions elsewhere in the system.

The results show that ER visits decreased 6.8% for WR PCMH enrollees because of a reduction in the probability of using the ER (i.e., the likelihood of having any ER care). For pharmacy and ancillary costs, we observe decreases in both the probability of use and the amount of use. Combining all forms of utilization, the results show that costs for Walter Reed PCMH enrollees are 9% less overall.

We conducted this same analysis on the strata of those with and without chronic conditions. For those without chronic conditions, there is no significant impact of the Walter Reed PCMH on inpatient utilization and ER visits and no substantial impact on primary care encounters. Conversely, there are significant and substantial impacts on inpatient days, ER visits, and primary care for enrollees with chronic conditions. These results are logical in that relatively healthier patients are infrequent users of inpatient and ER services. Interestingly, the results were mixed for inpatient care, with an overall 4% reduction in inpatient admissions and a 19% increase in the number of inpatient days. These results are consistent with the expected decrease in admissions for healthier patients with conditions that are either prevented or caught early, so they never progress to require an inpatient admission.
The results show that the Walter Reed PCMH is associated with an increase in specialty care utilization overall (2%). In concept, PCMH models should lead to less utilization of specialty care in the long run. Whether this is true and when it might occur are not known. Although these questions remain to be answered, a continued evaluation of the Group Health PCMH demonstration showed an increase in specialty care visits with PCMH patients, but that the magnitude of the specialty care increase declined from 6% after 12 months to 3% after 21 months. Perhaps, specialty care will also decrease at some point, but it clearly does not seem to happen immediately. Adding to this literature, our analysis shows that specialty care encounters increased for enrollees without chronic conditions (15%) and decreased for those with chronic conditions (3%). It is an open question why we observe this pattern, but one possibility is that the Walter Reed PCMH is driving some nonchronic patients to specialty care as a matter of prevention, and bringing some of the complex patients' care back from specialty care as it takes more active management of patients with chronic conditions and works with patients to teach them how to better manage their conditions. An analysis of only the overall population can easily mask the opposite impacts we find when analyzing chronic condition status.

As for specialty care costs, the results show cost improvements for both those with (11%) and those without (7%) chronic conditions, or $83 and $13 reductions per quarter, respectively. This reminds us that since treating enrollees with chronic conditions costs four times more than treating enrollees without chronic conditions, there may be substantially greater impact to trim health care costs when focusing PCMH initiatives on this very same population and preventing healthy enrollees from falling into that category. Note that we also analyzed subpopulations with a specific chronic condition, such as diabetes, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, coronary artery disease, and mental health, and found that the overall pattern we observed for those with a chronic condition holds for all of these subgroups.

Access and Quality
The HEDIS measures are an important quality indicator. In looking at the HEDIS metrics for the Walter Reed PCMH, it is the case that they have improved postimplementation relative to preimplementation of the PCMH. This is true for multiple metrics such as annual hemoglobin A1c (HbA1c) testing with values greater than 9.0; low-density lipoprotein-cholesterol (LDL-C) values less than 100 mg/dL; asthmatics with appropriately prescribed medication; and screening rates for mammography and colorectal cancer. At the same time, we observed that the HEDIS metrics also improved at the comparison sites. These improvements are likely because of the influence of pay-for-performance programs in the MHS; hence, we cannot conclude that the improved HEDIS metrics at Walter Reed PCMH were necessarily because of the implementation of the PCMH model of care. However, we can conclude that the PCMH model has been successful in improving cost and utilization metrics while improving the HEDIS metrics at the same time (Table II). In other words, our results show that the Walter Reed PCMH has been able to reduce costs while at least maintaining the HEDIS levels.

Another quality indicator for a PCMH model of care is PCM continuity, since it is a process or approach that PCMHs use to achieve desired outcomes. As such, understanding the degree to which the Walter Reed PCMH has been successful in increasing its PCM continuity is indicative of its ability to affect change. When looking at PCM continuity, we observed that it rose following PCMH implementation, but that it has been extremely difficult to keep PCM continuity at a high level. PCM continuity is highly sensitive to outside influences such as deployments of
providers, permanent changes of station (military orders to change location), Family Medical Leave Act absences of providers, and the merger of the National Naval Medical Center and the Walter Reed Army Medical Center during the postimplementation period.

We now turn to the results for the access and quality metrics, such as patient satisfaction, PCM communication, trust, customer service, and patient activation, that we estimated through the patient survey (Table III).

For access, the composite access measure is significantly higher for the Walter Reed PCMH relative to the comparison sites. Similarly, Walter Reed PCMH enrollees are more satisfied overall, are more likely to have high PCM ratings, have a higher level of satisfaction with the office staff (customer satisfaction), and are more likely to have the highest level of patient activation. There are also statistically significant differences between the PCMH and its comparison sites for communication and trust. Overall, the results of these composite measures indicate that the Walter Reed PCMH has improved access and quality while reducing costs. Furthermore, these differences exist for patients with and without chronic conditions alike. The magnitudes of these differences are fairly consistent by chronic status, but the significance is generally greater for patients with chronic conditions.

We wanted to understand how the Walter Reed PCMH could improve patients’ perceptions of access and quality. Accordingly, we analyzed the factors associated with higher satisfaction. We found that the odds ratios (ORs) for being satisfied were 2.10 (confidence interval [CI]: 1.40–3.16) and 1.88 (CI: 1.16–3.04) for those who perceived a high level of access and provider communication, respectively. That information alone does not indicate how the clinic can improve access and communication, so we then analyzed the drivers of access and communication to see which factors are most highly correlated with access and communication. The results show that the biggest drivers of access are ease of scheduling appointments (OR: 4.60; CI: 3.01–7.03), ability to get a routine care appointment (OR: 4.42; CI: 3.16–6.17), and ability to get an urgent care appointment (OR: 3.74; CI: 2.53–5.54). In comparison, the time spent waiting to see the PCM is a relatively minor factor. Similarly, the analysis of communication drivers shows that the two most important drivers are whether the PCM listens carefully (OR: 13.47; CI: 6.39–28.39) and provides complete and accurate information (OR: 12.89; CI: 5.21–31.86). These results indicate clear directions for improvement in individual PCMHs.

Limitations
This study, of course, is not without limitations. Among the challenges we faced in analyzing the impacts of the WRNMMC PCMH on access, quality, and cost was the substantial churn and disruption caused by the merger of the National Naval Medical Center and Walter Reed. Although the actual merger did not occur until September 2011 (after the period of our data), all of the premerger work to prepare for integrating clinics and the construction to accommodate the merger no doubt impacted the PCMH teams and patients.

Another challenge with this evaluation was to identify comparison clinics that were not PCMHs. The Walter Reed PCMH was the first PCMH in the MHS; but since it started, all primary clinics have transitioned to or are in the process of transitioning to PCMHs. Although the comparison sites we selected were not PCMHs during the most of the analysis period, they were nonetheless planning for and beginning the process of transitioning to PCMHs. We see this as less of a limitation if one presumes that transitioning to a PCMH would have made the comparison sites more effective in addressing access, quality, and cost, thus making these sites more robust comparisons.
Discussion

The U.S. health care system is undergoing a period of rapid change as the provisions of the Patient Protection and Affordable Care Act are implemented. Beyond this, cost pressures are driving the need to arrest cost growth and put it on a sustainable path. Also, numerous studies and reports link health care costs and cost growth to chronic conditions, most of which are a result of patients’ poor health choices and lifestyles.

The results for the WRNMMC PCMH suggest that if other PCMHs are similarly effective that the PCMH model is a good first step to address these trends and challenges. Our results show that the Walter Reed PCMH has been successful in the short term by reducing costs while improving access, quality, and patient satisfaction. These findings were consistent across the study population but were greatly amplified for patients with chronic conditions. Consequently, if our nation’s current health care systems cannot afford to be all things to all people, our results suggest starting with those patients suffering from chronic conditions. Furthermore, the rationale in the literature is also compelling: “78% of health spending is devoted to people with chronic conditions. Quality medical care for people with chronic conditions requires a new orientation toward prevention of chronic disease and provision of ongoing care and care management to maintain health status and functioning.”

Although our study and the literature generally show desirable results for medical homes, there are exceptions. This suggests that PCMHs have value, but successful implementation is not guaranteed, and not all care models can be easily generalized without careful considerations of patient demographics and needs as well as system limitations and unique characteristics of both. The implementation and execution of any PCMH must be actively managed and evolve with changing needs and trends. The entrenched systems and attitudes inherent in health care add an additional layer of complexity that necessitates an analysis of the overarching organizational culture and subcultures that will have to adapt to the PCMH model (K. Dorrance, P. Grundy, J. LaRochelle, S. Lynch, F. Mael, S. Ramchandani, unpublished data, 2012). Moreover, although the results are positive, we emphasize that they are only near-term results—1.5 years postimplementation.

Although PCMH is a good first step, we must address the root cause of the current health care crisis—poor health behaviors and individual lack of responsibility for lifestyle choices. The true test for PCMH success is whether it will have an impact on the rate at which patients develop chronic conditions and not just on treating chronic conditions in a more cost-effective way. The PCMH must also facilitate patient activation and responsibility for health behaviors that can ultimately reverse many of the chronic conditions. This cannot be understated; the long-term success of health care transformation and our ability to rescue the American health care system relies on the reduction of the ever-increasing burden of chronic (preventable) disease. Without such a shift from health care to health, we simply delay the demise of the American health care system. Whether PCMHs are successful in changing patient behavior and lifestyle choices over the long run still needs to be shown, and the addition of these efforts in future studies must not be ignored.

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The Patient-Centered Medical Home: A Case Study in Transforming the Military Health System
Military Medicine
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Abstract

This case study describes the Military Health System's (MHS) patient-centered medical home (PCMH) initiative and how it is being delivered across the MHS by the Army, Navy, and Air Force. The MHS, an integrated delivery model that includes both military treatment facilities and civilian providers and health care institutions, is transforming its primary care platforms from the traditional acute, episodic system to the PCMH model of care to maximize patient experience, satisfaction, health care quality, and readiness and to control cost growth. Preliminary performance measures are analyzed to assess the impact of PCMH implementation on the core primary care processes of the MHS. This study also discusses lessons learned and recommendations for improving health care performance through the PCMH care model.

Introduction

The purpose of this case study is to describe the implementation of the Military Health System's (MHS) patient-centered medical home (PCMH) initiative and how it is transforming the primary care delivery system into a more integrated and comprehensive model. The overall goal of the PCMH system is to better deliver high-quality, accessible, and cost-efficient health care for MHS beneficiaries.

The PCMH model is based on the premise that a strong primary care foundation for each beneficiary is required to maximize health care quality, optimize patient activation, and lower overall costs. Primary care practices are provider-led and supported by a highly efficient and collaborative practice team, empowered to operate at the top of their respective skill sets using evidence-based medicine and decision support technology. This transformative model of care has the potential to improve the health care experience by providing continuity of care, proactive population-based health management, preventive and wellness services, and support for patient self-management. Patient self-management should be enhanced by improving communication between the patient, the health care provider, and the health care team. The PCMH approach may also be better suited to activate patients to be partners in their health care while also building trust between the patients and their providers.

Impetus for PCMH Initiative

The PCMH concept of care was introduced by the American Academy of Pediatrics in 1967 and later adopted in 2002 by the Family Medicine specialty as part of its "Future of Family Medicine" project. In response to numerous health care stressors, including cost growth, the joint principles of the PCMH were published by the American Academy of Family Physicians, American Academy of Pediatrics, American College of Physicians, and the American Osteopathic Association in 2007.
The concept of the PCMH is still in its formative phase. Although the model has been adopted by several large third-party payers, employers, and health plans, studies are identifying challenges to changing the current structure and process of providing primary care. For example, research suggests that the development of the PCMH requires transformation of the organization's patterns and processes. Geisinger Health Plan's Advanced Medical Home identified that a fundamental redesign (such as a PCMH) results in new tasks and relationships for every team member. Although the transformation to a successful PCMH can be problematic, several critical success factors for PCMH initiatives have been identified including ensuring timely access to acute care, changing practice patterns, offering after-hours care, setting clear expectations for performance, and enhancing communication with patients. There is still uncertainty regarding which structural and process elements of the PCMH concept (e.g., increased staff, after-hours access, more effective communication) impact clinical and financial performance and by how much. The implications of identifying which aspects of PCMH implementation provide the greatest return and value on investment are important because of the relative expense of each aspect of PCMH implementation. In addition, even if the PCMH model was in its ideal and proven state, it would still need to evolve with changes in the health care environment. This evolution recognizes that each PCMH should be unique to each clinical environment because of its unique physical layout, patient population, available resources, local and regional culture, and geographical location.

Just as the nation has been grappling with increasing health care costs, the MHS has also experienced substantial increases over the last decade. Reasons for this cost growth include (1) increase of approximately 400,000 beneficiaries since 2007, (2) expansion of entitlements to include TRICARE for Life (which made TRICARE the second payer to Medicare for the over-65 beneficiaries) and coverage for military reservists, (3) higher utilization rates of civilian providers and health care institutions (designated as the purchased care sector) for emergency and specialty care, (4) 70% increase in active duty service members' outpatient purchased care, and (5) medical inflation rate far in excess of the general inflation rate. In addition, over the past 3 years, patient satisfaction in military treatment facilities (MTFs) has remained relatively flat at 77% while beneficiaries seen in the purchased care sector have reported a satisfaction rate of 87%. Major complaints of beneficiaries include their inability to get appointments, difficulty in obtaining specialty care, waiting an unacceptable length of time in clinics, and lack of parking support. More importantly, only about 50% of the users of MTFs believe they have a "personal" doctor. Beneficiaries also rate the MHS below national averages in doctor's communication and overall satisfaction with health care. Finally, although measures of quality demonstrate that the MHS compares well with civilian institutions, there is an opportunity for improvement in other areas. To address these system challenges, MHS leadership initiated a PCMH pilot to explore its impact on reducing cost and increasing satisfaction and, ultimately, positively impacting the MHS' Quadruple Aim (Fig. 1).

MHS Implementation of PCMH Initiative

The initial planning and testing of the PCMH concept began in 2007 at the National Naval Medical Center (now the Walter Reed National Military Medical Center [WRNMMC]) and, in 2008, at Edwards Air Force Base and Ellsworth Air Force Base. In September 2009, the Office of the Assistant Secretary of Defense (Health Affairs) directed MHS-wide PCMH implementation. This action establishes the PCMH as the foundation...
for refocusing the MHS’ primary health care delivery model within the MHS. Primary Care specialties include Family Medicine, Internal Medicine, Pediatrics, Undersea Medicine, and Flight Medicine.

Although the Army, Navy, and Air Force are authorized to implement the PCMH model of care somewhat differently in accordance with their service-specific policies, the overall MHS PCMH concepts of care, requirements, and performance measures are the same. Service implementation allows service-specific branding; the Army’s PCMH is the “Army Home” and the Navy’s is the “Navy Medical Homeport.” Although the Air Force PCMH was originally known as the “Family Health Initiative,” it is now referred to as the “Air Force Patient-Centered Medical Home.”

In December 2009, to drive continuous process improvement, to measure its implementation of the concept of care by an objective outside body, and to demonstrate the commitment to the PCMH model of care to beneficiaries, MHS leadership approved the use of a standard assessment methodology, that is, the National Committee for Quality Assurance (NCQA) Standards. These NCQA standards describe the key characteristics required for a practice to qualify as a medical home. Starting in 2011, 48 MHS primary care practices were selected to seek NCQA recognition for the first time. By 2016, the MHS’ goal is for all MTFs’ primary care practices to have achieved NCQA recognition as level 2 or level 3 PCMHs.

Performance Measures

As previously noted, the PCMH initiative is aligned with the MHS Quadruple Aim. Accordingly, success for this initiative will be determined using the following measures, which support the Quadruple Aim:

— Optimize access to care
— Primary care third available appointment (routine/acute)
— Getting timely care
— Potential recapturable primary care workload for MTF enrollees
— Promote patient-centeredness
— Percent visits where MTF enrollees see their Primary Care Manager (PCM)
— Health care satisfaction
— Manage health care costs
— Annual cost per equivalent life (per member per month)
— Enrollee utilization of emergency services
— Hospital readmission rate
— Develop our people: primary care staff satisfaction
— Patient satisfaction
— Getting timely care
— Overall satisfaction with health care
Design of PCMH Model

Although the MHS is composed of 9.7 million beneficiaries, the MHS leadership chose to focus its initial PCMH implementation efforts on the approximately 3.7 million TRICARE Prime and TRICARE Plus beneficiaries enrolled to MTFs. These enrollees include active duty service members, active duty family members, retirees and their family members, and a limited number of Medicare-eligible beneficiaries.

By 2011, there were 180 Army, 107 Navy, and 140 Air Force PCMH practices in operation or in development. These practices were established consistent with the 7 core principles of the PCMH as defined by the Patient-Centered Primary Care Collaborative. However, it was necessary to adapt them to fit military-unique policies and procedures. Specifically, the core principles within the MHS are the following:

— Personal physician is defined as a provider (i.e., physician, nurse practitioner, or physician assistant) who is assigned as the “Primary Care Manager by Name.”
— Physician-directed medical practice is a team of military or civilian health care professionals (i.e., physician, nurse practitioner, physician assistant, independent duty corpsman, medical technician, and support staff) under the leadership of a primary care physician as team leader.
— Whole person orientation is the expectation of the active and retired military service members that all aspects of care will be comprehensively addressed for themselves and their family members.
— Care is coordinated or integrated as an established part of the TRICARE medical benefit, and all military beneficiaries are entitled to comprehensive, coordinated, and accessible primary care.
— Quality and safety are embraced by the MHS’ evidenced-based model of care, which includes an evidence-driven medical benefit, an extensive Department of Defense/Veterans Affairs Clinical Practice Guidelines Program, comprehensive Healthcare Effectiveness Data and Information Set (HEDIS) and ORYX reporting and monitoring, and a sophisticated patient safety program.
— Enhanced access is formally established within the MHS by access standards for primary care including acute, routine, and wellness visits.
— Payment recognizes added value is the principle that remains a challenge due to the nature of the MHS’ federal funding and financial incentives related to pay-for-performance.

Each practice consists of one or more physicians, and the design of the PCMH practices focuses on ensuring accountability for their entire patient population and all of the patients’ health care needs including acute care, chronic care, preventive services, and end-of-life care. As reflected in Figure 2, the practices adopt the concept of patient-centeredness, which includes allowing free choice of provider, ensuring prompt appointments, and reducing wait times. As noted earlier, each service has implemented the PCMH initiative based on its service-specific needs. This is consistent with successful civilian PCMH practices, which recognize that no single model fits all practices because each practice must specifically address the needs of its patient population (Presentation by the American College of Healthcare Executives [ACHE] Fund for Innovation. Accountable Care and Medical Homes: Steps to Creating Value-Based Healthcare. October 11, 2011, San Francisco, CA). For example, the Air Force model defines staffing for each type of practice by showing ratios by team member type, such as family practice physician, extenders
(physician assistant or family nurse practitioner), registered nurse, and medical technician support. Based on enrollment, individual teams earn additional team members such as administrative staff, disease managers, and other key members of the health care practice. To be considered as an MHS PCMH, a current or developing primary care practice may be recognized as a level 2 or level 3 NCQA PCMH. Alternatively, the practice must include all of the following criteria:

- Enrollment Capacity Modeling: The practice has accomplished enrollment capacity modeling using service methodology and reviewing, at minimum, practice needs and characteristics.
- Demand Management: The practice has analyzed and modified its template utilization of appointment types. At minimum, the practice has analyzed demand and ensures appropriate access to meet demand and access standards as measured by the metric entitled third next available appointment.
- Team-Based Practice: The practice has transformed itself into collaborative teams working at the top of their respective licenses with identified roles for nurse, technicians, etc., to accomplish population-based health management.
- Staffing Evaluations: The practice has reviewed its population needs, compared staffing to existing staffing resources, and, based on service-specific standards, is taking corrective action to resolve the gaps.
- Standard Position Descriptions: The practice has identified standard business rules for staff to allow them to practice with the greatest amount of autonomy at the top of their license.
- Co-location of Practices/Team: The team members are located in a way to optimize collaboration and communication improving efficiency within the team.
- Continuous Process Improvement: The practice accomplishes daily huddles as well as periodic “Big Team” huddles to identify and plan opportunities for process improvement.
- Continuous Quality Improvement: The practice regularly reviews the following metrics and identifies areas and methods for improvement: access, satisfaction, quality, HEDIS, readiness, and emergency room utilization.

Implementation Results

The goal is for 1.25 million beneficiaries to receive care at an MTF PCMH practice by December 2012 and 2.5 million beneficiaries by December 2013. As of January 2012, an estimated 2.28 million beneficiaries enrolled to MTFs were receiving care in PCMH practices. By service, the enrollment was Army 900,000; Navy 573,228; and Air Force 808,641. The number of beneficiaries in recognized PCMH practices reflected the rapid expansion of PCMH implementation across the MHS. Finally, as of January 2012, 44 MHS PCMH practices were officially recognized as PCMHs by NCQA; 93% of these practices were recognized as level 3 PCMHs, NCQA's highest recognized level. The goal remains to have all PCMHs seek recognition from NCQA.

Preliminary results suggest that the PCMH positively impacts MHS performance. For example, at the WRNMMC, there has been a 19% improvement in PCM continuity compared to its respective non-PCMH peer group. At Edwards Air Force Base, there was a 10% improvement in PCM continuity as compared to the non-PCMH peer group. Edwards AFB enrollees also experienced an 8% higher level of overall satisfaction.

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with their health care. Additionally, at WRNMMC, there was a dramatic annual decrease of 39% in emergency room utilization. Similar results are seen when reviewing the performance results at some of the MHS’ more mature PCMHs. For example, the top performing PCMHs exceed current MHS goals by approximately 25%. Continued performance in key PCMH measures is expected to improve with the MHS emphasis on identification of best practice tools and techniques, adequate resourcing, business intelligence capabilities, information transparency, and alignment of policies in support of PCMH.

Lessons Learned and Recommendations

As described earlier, there are many positive aspects of the PCMH model. But, there are also a number of lessons, noted below, that the MHS PCMH implementation has revealed. If addressed by the following recommendations, these lessons should help ensure successful implementation of future PCMHs.

The first lesson is that significant cultural changes will be required. Medical homes require providers to sacrifice their autonomy, integrate with other health care professionals, and leverage both health technology and up-to-date clinical evidence (Fig. 3). Therefore, it is recommended that the overarching organizational culture, and the distinct clinic-specific and occupation-specific subcultures need to be understood and addressed. Specifically, without understanding how these cultures compete and collide with one another and shape their members' values and expectations, successful cultural change may not occur (Dorrance K, Grundy P, LaRochelle J, Lynch S, Mael F, Ramchandani S: Protecting the culture of a patient-centered medical home, unpublished manuscript, 2012). In addition, patients will need to take ownership of their health and actively participate in the delivery of their health care. Feedback from the existing semiannual primary care staff satisfaction survey must be reviewed to identify trends in staff perceptions and allow leadership intervention to prevent staff discontent. Also, individual MTFs will have to embrace a culture of change and continuous improvement throughout their respective organizations.

The second lesson is that PCMH performance measures must be monitored, and acted upon, by team members. Essential to a team's ability to monitor performance is the need for transparent, reliable, replicable, and accurate information. Therefore, it is recommended that more granular workload data as well as the management information necessary to optimize the PCMH concept should be provided to leadership. For example, implementing the 4th level Medical Expense & Performance Reporting System (MEPRS) element should provide meaningful and actionable management information. In addition, to optimize the acquisition, analysis, and application of these data, leadership should consider building an environment that encourages information technology (IT) and PCMH team innovation.

Another lesson is that PCMH team composition should vary based on the needs of the patient population. For example, more embedded behavioral health team members may be required if the population health data review shows a demonstrated need. Similarly, if a patient population has a larger than normal percentage of chronically ill patients, additional disease management, integrated health services including nutrition and exercise, health education, and mind–body medicine and pharmacy (at the point of care), and other intervention specialties may be required to maximize the patients' health. Finally, given that the MHS is a military organization, team staffing must be designed to accommodate active duty staff deployments and special duty as well as staff and beneficiary change of station cycles, discharges, and retirements. Because of
these considerations, it is recommended that staffing review is conducted on an annual basis (MedXellence: USU Executive Skills Training Course. Critical Decision Making for Medical Executives: Keys to Improving Healthcare Delivery. Patient-Centered Care. CDR Dorrance, September 19, 2011).

A fourth lesson is that productivity in a PCMH may not be similar to other clinics because of the type and expectations of patients and organizational demands. As a result, it is recommended that consideration be given to compensate or otherwise reward the PCMH team for increased productivity for caring for high-risk patients and providing after-hours services (Presentation by the ACHE Fund for Innovation. Accountable Care and Medical Homes: Steps to Creating Value-Based Healthcare. October 11, 2011, San Francisco). Consideration also should be given to the weight assigned to the existing MHS metric regarding team continuity. This metric indicates whether team turnover is adversely affecting PCMH productivity.

A similar lesson is that an incentivized payment system may enhance the achievement of higher levels of health care quality and outcomes. This is in contrast to the current system that reimburses for individual episodes of care and volume output of services. In addition, it appears that current national legislation and policies may drive the health care system toward developing Accountable Care Organizations (ACOs) or similar organizational arrangements. Therefore, it is recommended that the MHS consider aligning incentives to become an ACO. This alignment might contribute to reducing unnecessary cost, controlling inflation, and improving beneficiary health (Presentation by the ACHE Fund for Innovation. Accountable Care and Medical Homes: Steps to Creating Value-Based Healthcare. October 11, 2011, San Francisco).

Another lesson is that patient surveys have demonstrated that current information dissemination mechanisms are not adequate to ensure the level of communication necessary to achieve optimal results. Therefore, it is recommended that communications be enhanced by implementing PCMH campaigns to provide current information to key stakeholders.9 In addition, technology should be leveraged by incorporating state-of-the-art secure messaging, identifying IT capability gaps, optimizing clinic workflow patterns, and establishing a MHS Portal link.

A seventh lesson is that there is uncertainty regarding whether the PCMH model of care influences graduate medical education (GME) and clinical competency. As a result, one recommendation is to analyze the change in the health status of beneficiaries enrolled in the PCMH. This analysis may result in a different mix of beneficiaries to ensure that providers-in-training have a broad population of patients.10 Another recommendation is to conduct a population health review relative to the location of GME programs, which may suggest a redistribution of provider assets to locations where they can most positively impact performance across the MHS.

Another lesson, reinforced by the private sector’s experience, is that the performance of the PCMH may be enhanced by establishing a care coordinator role within each team. Therefore, it is recommended that a registered nurse be designated as the care coordinator with the responsibility to meet each patient to review the patient's care plan (which was originally developed jointly by the primary care physician and the patient). At the same meeting, the care coordinator would review the patient's current social and economic determinants of health and then coordinate with other team members, for example, social worker or pharmacist, to recommend care plan changes to the primary care provider.

It was also learned that the physical layout of the clinical teams' clinic is crucial to the success of the PCMH. Therefore, it is recommended that innovative and site-specific clinic design be considered before implementing a PCMH. For example, Naval Hospital Pensacola demonstrated that the concept that "templated" examination rooms increased efficiency. This concept meant that all practice teams were co-located in the same area, such as treatment hallways, and ensured that each exam room was set up identically.

The final lesson is that there is an opportunity for the PCMH to increase the attention on populations at risk of developing chronic conditions. Given that poor health behaviors are the primary drivers of health care costs, it is recommended that the PCMH be the focus point for aggressively seeking primary prevention through behavior modification. The PCMH should implement a primary prevention program with the use of motivational interviewing, health coaches, and IT systems to identify and stratify at-risk patients.

Conclusion

Preliminary MHS outcome measures, as well as recent private sector studies, suggest that the PCMH initiative has the potential to address some of the inadequacies of the current MHS health care system. It is a balanced approach that addresses military readiness, population health outcomes, and patient experience of care while also reducing per capita cost. The result may be the transformation of the military's health care delivery system to better meet the needs of its beneficiaries.

The Patient-Centered Medical Home: A Systematic Review

Annals of Internal Medicine
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Background: The patient-centered medical home (PCMH) describes mechanisms for organizing primary care to provide high-quality care across the full range of individuals' health care needs. It is being widely implemented by provider organizations and third-party payers.

Purpose: To describe approaches for PCMH implementation and summarize evidence for effects on patient and staff experiences, process of care, and clinical and economic outcomes.

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Data Sources: PubMed (through 6 December 2011), Cumulative Index to Nursing & Allied Health Literature, and the Cochrane Database of Systematic Reviews (through 29 June 2012).

Study Selection: English-language trials and longitudinal observational studies that met criteria for the PCMH, as defined by the Agency for Healthcare Research and Quality, and included populations with multiple conditions.

Data Extraction: Information on study design, populations, interventions, comparators, financial models, implementation methods, outcomes, and risk of bias were abstracted by 1 investigator and verified by another.

Data Synthesis: In 19 comparative studies, PCMH interventions had a small positive effect on patient experiences and small to moderate positive effects on the delivery of preventive care services (moderate strength of evidence). Staff experiences were also improved by a small to moderate degree (low strength of evidence). Evidence suggested a reduction in emergency department visits (risk ratio [RR], 0.81 [95% CI, 0.67 to 0.98]) but not in hospital admissions (RR, 0.96 [CI, 0.84 to 1.10]) in older adults (low strength of evidence). There was no evidence for overall cost savings.

Limitation: Systematic review is challenging because of a lack of consistent definitions and nomenclature for PCMH.

Conclusion: The PCMH holds promise for improving the experiences of patients and staff and potentially for improving care processes, but current evidence is insufficient to determine effects on clinical and most economic outcomes.

The United States spends a greater proportion of its gross domestic product on health care than any other country in the world yet often fails to provide high-quality and efficient care. At the same time, satisfaction among primary care physicians has waned amid the increasing demands of office-based practice. There has been growing concern that current models of primary care will not be sustainable for meeting the health care needs of the population.

The patient-centered medical home (PCMH) is a model of primary care transformation that seeks to meet the health care needs of patients and to improve patient and staff experiences, outcomes, safety, and system efficiency. The term “medical home” was first used by the American Academy of Pediatrics in 1967 to describe the concept of a single centralized source of care and medical record for children with special health care needs. Building on other widely promulgated efforts, such as the chronic care model, the current concept of PCMH has been greatly expanded and is based on 40 years of previous efforts to redesign primary care to provide the highest quality of care possible.

As defined by physician and consumer groups, the core principles of the PCMH are the following: wide-ranging, team-based care; patient-centered orientation toward the whole person; care that is coordinated across all elements of the health care system and the patient's community; enhanced access to care that uses alternative methods of communication; and a systems-based approach to quality and safety. Although these principles are frequently cited in relation to PCMH, it should be recognized that specific PCMH definitions vary widely, reflecting the rapid expansion of the use of PCMH concepts in the past decade. This review was conducted as part of the Agency for Healthcare Quality and
Research’s (AHRQ's) “Closing the Quality Gap: Revisiting the State of the Science” series and sought to describe how studies conducted to date have implemented PCMH and to evaluate the current evidence of the effect of PCMH interventions on patient, staff, and economic outcomes.

Methods

A technical report that details our methods and results for all 4 original research questions is available at www.ahrq.gov. Topics for the “Closing the Quality Gap” series were solicited from the portfolio leads at AHRQ. Investigators at the Duke Evidence-based Practice Center refined the research questions through discussions with the Stanford Evidence-based Practice Center, which coordinated the series, and with representatives of AHRQ. A panel of experts knowledgeable in PCMH principles provided input during the protocol development process.

Research Questions

The present review addresses 3 of the 4 research questions included in the original AHRQ evidence report (omitting a horizon scan of ongoing research). We sought to describe PCMH interventions that have been studied in the peer-reviewed literature and the effectiveness of PCMH in studies that included a comparison group. Specifically, we addressed the following questions:

1. In published, primary care–based evaluations of comprehensive PCMH interventions, what individual PCMH components have been implemented?

2. In published, primary care–based evaluations of comprehensive PCMH interventions, what financial models and implementation strategies have been used to support uptake?

3. In published, primary care–based evaluations of comprehensive PCMH interventions, what are the effects of the PCMH on patient and staff experiences, process of care, clinical outcomes, and economic outcomes?

Definition of PCMH

We created an operational definition of a PCMH intervention based on the AHRQ's definition of PCMH. To be considered a PCMH intervention required the following: 1) team-based care, 2) having at least 2 of 4 elements focused on how to improve the entire organization of care (enhanced access, coordinated care, comprehensiveness, systems-based approach to improving quality and safety), 3) a sustained partnership, and 4) having an intervention that involves structural changes to the traditional practice. Interventions that did not use the term “medical home” but that met this definition were categorized as “functional PCMH” interventions.

Data Sources and Searches

We searched PubMed, Cumulative Index to Nursing & Allied Health Literature, and the Cochrane Database of Systematic Reviews. Our search strategy used the National Library of Medicine's Medical Subject Headings keyword nomenclature and text words for the medical home and...
related concepts and for eligible study designs. We included studies published in English and indexed from database inception through 29 June 2012. We supplemented these electronic searches with a manual search of citations from a set of key primary and review articles.

**Study Selection**

To be included in the review, studies had to 1) be peer-reviewed; 2) have interventions that met the preceding PCMH definition; 3) have interventions delivered to patient populations representing multiple diseases (that is, no single-disease care management studies); 4) be conducted among adult or child primary care patients; 5) have follow-up of at least 6 months; and 6) be a randomized, controlled trial or an observational study. Studies describing PCMH interventions in the published literature did not require a comparison group. However, studies examining the effectiveness of PCMH were required to have such a group.

Two investigators independently reviewed each title and abstract for potential relevance to the research questions; articles included by either investigator underwent full-text screening. At the full-text screening stage, 2 investigators independently reviewed the full text of each article for inclusion. Disagreements were resolved through review and discussion among investigators.

**Data Extraction and Quality Assessment**

One researcher abstracted the data, and a second over-read the abstracted data to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus could not be reached by the first 2 investigators. To aid in reproducibility and standardization of data collection, researchers received data abstraction instructions directly on each form created specifically for this project within the DistillerSR software program (Evidence Partners, Manotick, Ontario, Canada). Abstraction forms were pilot-tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility across abstractors. Data abstraction forms included information on study design, study population, interventions, comparators, financial models, implementation methods, study outcomes, and study quality. Results of interest examined for PCMH effectiveness included patient experiences, staff experiences, process of care, clinical outcomes, and economic outcomes.

We evaluated the quality/risk of bias of individual studies addressing the effectiveness question by using the approach described in AHRQ's "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (hereafter called the "Methods Guide") by applying predefined criteria for methodological quality and adequacy of reporting for each study type to arrive at a summary judgment of the study's quality (good, fair, or poor).

**Data Synthesis and Analysis**

Studies were categorized into those that explicitly tested the PCMH model and those that met our functional definition for PCMH but did not use the terms “PCMH” or “medical home”; we refer to the latter as “functional PCMH” studies. Outcomes described below were broadly categorized as relating to the following: 1) the quality of both patient and staff experiences with care, 2) clinical quality (that is, provision of evidence-based care and health outcomes), or 3) the economic effect of PCMH initiatives. Because of the wide variability in recommended measures for evaluating
PCMH, we analyzed outcomes that were reported across studies, focusing on those collected by using validated instruments or methods. With the exception of inpatient and emergency department utilization, studies were too heterogeneous in design and in outcomes reporting for quantitative syntheses. We used a random-effects model using the DerSimonian–Laird method to compute summary estimates of effect for hospitalizations and emergency department visits for the subset of studies that used randomized, controlled trial designs. Summary estimates were calculated by using Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, New Jersey) and are reported as summary risk ratios (RRs).

For other outcomes, the study populations, designs, and outcomes were too variable for quantitative analysis. We computed effect sizes, represented as the standardized mean difference (SMD, a summary statistic that uses a common scale), to aid in interpretation of the qualitative synthesis. The SMD is useful when studies assess the same outcome but with different measures or scales. The SMDs were calculated for each study by using the Hedges g (which corrects for small sample sizes) by subtracting (at posttest) the average score of the control group from the average score of the experimental group and dividing the result by the pooled standard deviations of the experimental and control groups. Beneficial effects are presented as positive effect sizes.

The strength of evidence for the highest-priority effectiveness outcomes was assessed by using the approach described in the Methods Guide. In brief, the Methods Guide recommends assessment of 4 domains: risk of bias, consistency, directness, and precision. Additional domains are to be used when appropriate: coherence, dose–response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively and a summary rating was assigned, after discussion by 2 reviewers, as “high,” “moderate,” or “low” strength of evidence. In some cases, such ratings were impossible or imprudent to make (for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn). In these situations, a grade of “insufficient” was assigned.

Role of the Funding Source

Funding was provided by AHRQ. Representatives of the funding source provided technical assistance during the conduct of the review and commented on draft versions of the full technical report. The funding source did not, however, directly participate in the literature search; determination of study eligibility criteria; data analysis; or interpretation, or preparation, review, or approval of the manuscript for publication. The AHRQ granted copyright assertion.

Results

Study Selection

We identified 5731 citations from all sources. After applying inclusion and exclusion criteria at the title-and-abstract level, 768 full-text articles were retrieved and screened. Of these, 708 were excluded at the full-text screening stage, leaving 60 articles representing 31 unique peer-reviewed studies. Nineteen studies were comparative studies of the effects of PCMH; these 19, plus 12 noncomparative studies, described aspects of studied PCMH interventions. With 1 exception, all studies were rated as being of good or fair quality.

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Implemented PCMH Components

The PCMH interventions tended to involve comprehensive changes in the delivery of primary care, with 24 of 31 studies describing interventions that included all 7 major PCMH components. However, studies varied greatly in the number and types of specific approaches used to implement these core components; overall, 51 different strategies or approaches were used. The PCMH studies used more strategies than did functional PCMH studies. Most studies addressed chronic illness, preventive care needs, and acute care needs; used multidisciplinary teams that included a designated primary care provider and defined roles (such as who manages specific aspects of care); and coordinated care transitions (for example, follow-up of patients who have been hospitalized). Three quarters reported adding new staff (such as a case manager). All but 4 studies used strategies to enhance access, such as home or telephone visits, but no single strategy was used in most studies. Identifying high-risk patients and using evidence-based clinical guidelines, performance monitoring, and electronic health records were the most commonly used approaches to improving quality and safety.

Financial and Implementation Strategies

Implementation of PCMH requires significant restructuring for most primary care practices. Recognizing the increased range of services required, some definitions of the medical home include a financial component, but this was not a requirement for inclusion in our review. Among the 31 included studies, only 13 described aspects of their financial model, including fewer than half of the studies specifically designed to test PCMH. These studies used a variety of methods to fund PCMH implementation, including receipt of external study funding, capitation payments, enhanced fee-for-service, or a hybrid approach. Although not a PCMH-specific financial mechanism, it should be noted that most studies were conducted in integrated delivery systems, such as staff- or group-model HMOs, led by payer organizations, or conducted outside the United States. Little information is available on financial models for using PCMH principles in independent fee-for-service primary care practices.

Although it is likely that both organizational learning and implementation strategies are necessary for implementation of complex interventions, we recognize that these concepts can overlap substantially. The most commonly used organizational learning strategy, applied in most studies (n = 19 of 24 studies reporting information on learning strategies), was a formal learning collaborative or collaborative program planning forums for practice team members to learn about PCMH or its components. For implementation, more than half of 20 studies reporting information on implementation strategies used audit and feedback, usually involving quality improvement methods. The largest trial found that facilitated PCMH was associated with better staff experience than nonfacilitated PCMH; facilitation was qualitatively shown to be important for PCMH implementation. This suggests that the effect of PCMH on practices may go beyond simply having the identified elements in place. The process of facilitation may also represent an important part of the process for making PCMH successful.

Effects of PCMH Interventions

Only 7 studies explicitly evaluated PCMH; an additional 12 studies evaluated functional PCMH interventions. Studies included both observational designs (n = 10) and randomized, controlled trials (n = 9). Older adults in the United States with multiple chronic conditions were the most commonly studied population (primary focus of 10 of the 19 studies). Most studies were conducted in integrated health care systems (10 of 19
studies). Studies varied widely in the range of outcomes reported and the specific measures used. With the exception of 1 study that examined facilitated versus nonfacilitated PCMH implementation, all studies compared PCMH interventions to usual care.

For most outcomes, the small number of studies conducted among children precluded formal comparison with studies conducted in adults. However, results in these 2 populations were similar.

**Patient and Staff Experiences**

Patient-centered medical homes have the goal of improving the experience of the key partners in health care: patients and staff. In this domain, evidence suggests short-term (with 3 exceptions, 2 years or less) benefits of PCMH for both patient and staff experience. Moderate-strength evidence indicates that interventions meeting PCMH criteria are associated with small improvements in patient experiences, on both overall measures of patient satisfaction and measures of patient-reported or patient-perceived level of care coordination. These studies included a variety of patient populations, indicating broad applicability of this finding. Although less compelling than evidence related to patient experiences, some studies (low strength of evidence) support the hypothesis that primary care staff may be more satisfied in PCMH practices. Two of these were PCMH studies, and 1 evaluated a functional PCMH intervention. Two of the 3 studies were conducted in an older adult population; none was conducted in pediatric practices. Overall, relatively few practices and few clinicians have been involved in these studies, and these practices may not be representative of the wider primary care practices in the United States.

**Clinical Quality**

Clinical quality can be considered to encompass both the provision of evidence-based care processes and the resulting health outcomes. We categorized process-of-care outcomes into preventive services and chronic illness care services. Prioritization was given to generally accepted, guideline-recommended care processes. Our summary of clinical outcomes is divided into biophysical markers (3 studies), patient-reported health status (4 studies), and mortality (2 studies).

Evidence suggests that PCMH may improve care processes, especially for preventive services. This is based on a combination of moderate evidence of an effect for prevention services and insufficient evidence to evaluate effects on care for patients with chronic illness. Although results are mixed in terms of whether differences are statistically significant, the point estimates for all but 2 of the process-of-care comparisons are in the direction of the intervention. A lack of power may account for the lack of statistical significance for at least some of the differences. Although there is a possibility that PCMH may lead to more appropriate care, more research is needed to examine this possibility, especially in relation to chronic illness care.

Insufficient evidence is available to determine the effect of PCMH implementation on clinical outcomes. Only 1 of the studies had a stated goal of testing PCMH, and that study compared facilitated PCMH against nonfacilitated implementation. Most studies were conducted in an older adult population; none were conducted among children. Only 2 observational studies reported effects on biophysical markers, finding a higher rate of improved hemoglobin A1c and low-density lipoprotein cholesterol values in intervention patients in 1 study and no difference in composite diabetes and coronary artery disease outcomes in another. Four studies examined effects on patient-reported health status. None of the 3 randomized,
controlled trials found a statistically significant benefit on health status, but the single observational study found a lower rate of functional decline (31% vs. 49% of patients) at 1-year follow-up in older adults receiving functional PCMH care. In the older adult population, limited data show that PCMH may have a positive effect on mortality. A single good-quality observational study found a mortality benefit at 1 year that was no longer significant at 2 years. Two other studies (1 RCT, 1 observational) had non–statistically significant findings also in the direction of lower mortality, pointing to the potential benefit of continuing to examine intensive PCMH-type interventions targeting frail seniors and the effect on mortality.

Economic Effects

The most studied potential effect of PCMH involves the hypothesis that PCMH interventions will reduce health care utilization and costs. Our summary of economic outcomes is divided into differences in inpatient utilization, emergency department utilization, and total costs. There is a low strength of evidence that PCMH does not lead to uniformly lower utilization of 2 areas hypothesized to be affected: inpatient and emergency department utilization. Moreover, total costs were not consistently decreased in the reviewed studies. The 5 randomized, controlled trials of functional PCMH interventions did not find a statistically significant effect on inpatient utilization (combined RR, 0.98 [95% CI, 0.86 to 1.12]). Three of these trials reported on emergency department utilization, finding no effect (combined RR, 0.93 [CI, 0.72 to 1.20]), but the CI was wide. However, a subgroup analysis of the 2 trials among older adults pointed to the possibility of an association with lower emergency department utilization (combined RR, 0.81 [CI, 0.67 to 0.98]). In contrast to the trial results, 3 observational studies (1 each in a general adult population, older adults, and children) found small to moderately decreased inpatient and emergency department utilization. With the exception of 1 subanalysis, no studies, including the 3 observational studies showing lower inpatient and emergency department utilization, reported statistically significant cost savings among PCMH patients during 6 to 24 months of follow-up. In fact, when program costs were considered, 1 good-quality trial and 1 fair-quality observational study reported greater total costs among PCMH intervention patients. Despite these findings, 1 study, a subgroup analysis of expected cost differences among patients enrolled in the PCMH clinics of the Geisinger Health System, indicates that savings may occur with lengthy exposure to the PCMH system of greater than 1 year. This hypothesis may be taken up by future work in PCMH.

Discussion

Although few studies have evaluated the effects of the PCMH, a moderately well-developed series of randomized, controlled trials and observational studies have tested interventions meeting the functional definition of the medical home. Moderately strong evidence suggests that the medical home has a small positive effect on patient experiences and small to moderate positive effects on preventive care services. Staff experiences are also improved by a small to moderate degree (low strength of evidence), but no study reported effects on staff retention. Current evidence is insufficient to determine effects on clinical and most economic outcomes. Given the relatively small number of studies directly evaluating the medical home and the evolving approaches to designing and implementing the medical home model, these findings should be considered preliminary.

It is not surprising that the approaches to implementing the various components of PCMH varied widely. Interventions explicitly developed from the PCMH model used more approaches than those simply meeting our operational definition of “functional PCMH.” As the evidence base expands, analyses of the relative effect of PCMH components will be important for clarifying the key approaches and could inform certifying agencies'
criteria for medical home practices. Clinical practices and policymakers also need better information on the financial context and implementation strategies required for successful spread and sustainability of the PCMH model. Fewer than half of the studies included in this report described any new payment model, such as enhanced fee-for-service or additional per-member, per-month payments to PCMH practices. Further, there were no data on direct financial consequences to the practice implementing PCMH. This information—possibly through the mechanism of detailed case studies—could inform implementation efforts and the design of enhanced payment mechanisms for medical home practices.

Our review identified important gaps in currently available evidence on the effects of PCMH. Most studies evaluated effects in older adults with multiple chronic illnesses; few studies were conducted in pediatric or general adult primary care populations. Effects on quality indicators for chronic illness care and on clinical outcomes are uncertain. These are among the most important outcomes to patients, clinicians, and policymakers. Other gaps in evidence include the absence of data on staff retention and unintended consequences. If the improvements in staff experiences translate into improved staff retention and greater attractiveness of primary care practice, then PCMH would have met 1 of its goals. The potential for unanticipated consequences has not received much attention in the literature and was not evaluated in any of our included studies.

A horizon scan conducted for this review (results reported in AHRQ evidence-synthesis report) identified 31 ongoing PCMH studies that are broadly representative of the U.S. health care system, both in geography and in the complexity of private and public health care payers and delivery networks. Many of these studies are being done in cooperation with payer organizations, and most are expected to be completed in the next 2 years. As a result, the evidence base related to PCMH will soon be greatly expanded. We encourage investigators to report the interventions in detail (that is, specific tasks, roles, and activities; detail on study setting; information on how the program is financed; and detail on how the team encouraged implementation), adjust for clustering when appropriate, report meaningful quality indicators for chronic illness (both processes and clinical outcomes), and provide data on the effect of PCMH on staff (including both survey data and staff turnover). We also encourage long-term follow-up of results. Outcomes examined in this report rarely had follow-up periods longer than 2 years. For certain outcomes, data from the electronic health record may provide the ability to examine long-term outcomes after the conclusion of formal funded studies.

Our review has important limitations. The PCMH is a model of care with considerable flexibility, not a narrowly defined intervention or manualized protocol. There is no standard nomenclature for components of the PCMH model. Further, various professional and patient organizations have proposed multiple definitions of the PCMH model. We developed an operational definition derived from the AHRQ definition of the medical home, which does not require an enhanced payment model. Because we used this definition, our review was more inclusive of studies that tested the critical principles that embody the Institute of Medicine concept of patient-centered care. However, greater inclusivity came with the trade-off of greater variability in study interventions. Although our search of ClinicalTrials.gov and other research databases did not suggest completed but unpublished studies, publication and selective outcomes reporting remain possible and could bias results. Related to this issue is the fact that PCMH models may be evaluated by organizations that do not routinely produce publications for peer review (such as consulting firms). Such results would then not be reflected in an analysis such as ours. Finally, heterogeneity in study designs, populations, and outcomes meant that standard quantitative summary methods were generally not possible.
The PCMH model is being widely implemented in various health care systems and includes key principles that are encouraged in the Affordable Care Act and required for recognition as an Accountable Care Organization. Despite this impetus for implementation and agreement on broad concepts, such as enhancing team-based care and patient access, the exact approaches to PCMH implementation vary broadly. This review indicated that PCMH is a conceptually sound approach to organizing patient care and appears to hold promise, especially for improving the experiences of patients and staff involved in the health care system. Evidence points to the possibility of improved care processes; however, ongoing and future studies are needed to determine whether these improvements translate into improved clinical outcomes or economic benefit. Although implementing the PCMH principles is something to be considered by organizations seeking to enhance patient experience and quality of care, no menu is yet available for specific actions that are most likely to enhance benefits to patients, staff, and organizations.

Leveraging the Military Health System as a Laboratory for Health Care Reform

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Abstract

The Patient Protection and Affordable Care Act recently passed into law is poised to profoundly affect the provision of medical care in the United States. In today's environment, the foundation for most ongoing comparative effectiveness research is financial claims data. However, there is an alternative that possesses much richer data. That alternative, uniquely positioned to serve as a test system for national health reform efforts, is the Department of Defense Military Health System. This article describes how to leverage the Military Health System and provide effective solutions to current health care reform challenges in the United States.

Introduction

The Patient Protection and Affordable Care Act (PPACA) recently passed into law under the Obama Administration is poised to profoundly affect the provision of medical care in the United States. Less certain, however, is whether these reform efforts will produce significant, lasting, and positive changes to the outcomes and the costs of medical care.

Requirements of the PPACA emphasize the importance of ongoing comparative effectiveness research (CER) by establishing the private, nonprofit Patient-Centered Outcomes Research Institute (PCORI). The PCORI is charged with spearheading efforts to prioritize and fund CER efforts with the input of multiple stakeholders, including clinicians, patients, researchers, insurers, and manufacturers. Among the duties of the
PCORI will be to (1) develop an objective research agenda, (2) articulate CER methodological standards, and (3) contract with qualified individuals or groups to conduct research. A widely accepted view of CER is that it should provide evidence for the effects of medical care (i.e., treatments, processes, and technologies) in “real-world” or usual care settings.1

Finding real-world systems in which to quickly and effectively initiate the reforms outlined in the PPACA and enable accurate measurement of the resulting outcomes will be among the first challenges the PCORI will need to overcome. In today's environment, financial claims data and pharmacy prescribing activities are the foundation for most CER. However, there is an alternative to claims data, one which possesses much richer data via an active electronic health record (EHR) system. That alternative, which is uniquely positioned to serve as a test system for national health reform efforts, is the United States Department of Defense Military Health System (MHS). The MHS serves a broad patient population similar to those served in private sectors and is the largest global health system in the world. Our aim in this article is to describe how to leverage the MHS and provide effective solutions to current health care reform challenges in the United States.

The Military Health System: History and Current Mission

The MHS is a comprehensive medical network within the U.S. Department of Defense (DoD) that provides health care to all U.S. military personnel, their dependents, and selected retirees.2 During the First and Second World Wars, medical care was applied primarily on the battlefield and in larger combat theaters to meet the evolving demands of war. Subsequently, significant changes in the organization and structure of the MHS brought increasingly greater medical capacity into the military.

Following World War II, the Department of War and Department of the Navy were reorganized under a single Department of Defense. Efforts to integrate and coordinate the Army, Air Force, and Navy systems were undertaken. In 1956, Congress passed the Dependents Medical Care Act to address the needs of military dependents; 10 years later Congress passed the Military Medical Benefits Amendments, which led to the creation of the program known as the Civilian Health and Medical Program of the Uniformed Services (CHAMPUS). A number of managed care features were integrated in the CHAMPUS program in the late 1980s, including beneficiary choice of providers and higher-cost shares and deductibles. In the late 1990s, the MHS implemented a nationwide managed care program known as TRICARE, which coordinated health care services for all DoD beneficiaries around the world. Through TRICARE, the MHS combines the health care resources of military treatment facilities and clinics with a supplementary network of private sector health care professionals, institutions, pharmacies, and suppliers to ensure access to high-quality health care services for all eligible participants.

Today, the MHS mission is to (1) improve the population health of its beneficiaries; (2) enhance the patient experience of care (including quality, accessibility, and reliability); (3) reduce (or at least control) the per capita cost of care; and (4) ensure medical readiness of the total military force.3 It serves an active beneficiary population of 9.6 million service members, veterans, and family members2 with 130,000 medical professionals, 65 hospitals, and 411 health clinics spread around the globe. The MHS has an annual budget of nearly $50 billion, and its medical providers record almost 225,000 outpatient visits each day,4 or approximately 8.5 annual outpatient visits per 1000 beneficiaries (2009 data). In addition, the
combined network provides nearly 3.5 million inpatient days of care annually, roughly 3.6 inpatient days of care per 1000 beneficiaries each year. Further, more than 2,300 babies are born in military treatment facilities and TRICARE network facilities each week.

MHS Patient Population

The population served by the MHS is very similar to the overall U.S. population (Table I). The age distribution of the MHS reflects that of the U.S. population, with the exception of 35- to 44-year olds, who are slightly underrepresented, and 65+ year olds, who are slightly overrepresented in the MHS population. The gender distribution and the proportion of married and unmarried individuals are also comparable in both groups. Similarly, the MHS population roughly parallels the U.S. general population in terms of the occurrence of common conditions and overall health (Table II). For example, the prevalence estimates of coronary heart disease and hypertension are fairly consistent between the two populations. Available estimates for other common medical conditions are somewhat lower for the MHS population; however, these estimates may be more reflective of differences in criteria definitions and/or epidemiological methods used for reporting than they are of true differences between these populations. Viewed broadly, though, these findings show that the population served by the MHS represents a cross section of the U.S. population. As a result, programs, processes, and policies for health care reform that are successfully implemented in the MHS are likely to have strong potential for being successfully implemented on the national stage.

MHS Care Quality

In addition to serving a cross-sectional patient population, MHS care quality is on par with that of private health maintenance organizations (HMOs) in the United States, as showed by comparing National Committee for Quality Assurance Health Plan Employer Data and Information Set (HEDIS) standardized scores for clinical quality performance in MHS and HMO settings (Table III). Arguably, these statistics suggest that care delivery in the MHS has enjoyed successes similar to those in private sector systems and, at the same time, faces similar quality challenges.

Leveraging the MHS to Initiate and Evaluate Critical Health Care Reforms

Given its role as an integrated health care payor, provider, and employer of its beneficiaries, the MHS is uniquely positioned to serve as a “laboratory” for national health reform efforts. Its patient population and delivery systems strongly mirror those found across private sector health systems in the United States, and its size would elucidate realistic obstacles during transformation efforts. Given the geographic diversity of its patient population, the MHS would also offer a unique opportunity for comparing its health care metrics with those of other systems. Some of the MHS’ specific advantages include:

The MHS is a closed, continuous system. The MHS has a closed, but representative population of individuals who have the potential to be followed throughout their lives. Besides active military personnel, beneficiaries in the MHS include dependents (children, spouses, and parents), retirees, and others authorized by statute or civilian emergency. Dependent children are currently eligible to remain in the MHS until the age of 21 (or 23, if they are enrolled in school). Members who choose to leave the military and work in the private sector may receive care through another...
primary health system; however, in many of these cases DoD insurance is used as supplemental form of coverage. Upon retirement, certain DoD members are eligible for care in the Veteran Health Administration system. This continuity of coverage may be particularly attractive to researchers, as it allows large patient populations to be tracked longitudinally as migration inevitably occurs.

The MHS has a centralized structure. The centralized structure of the MHS offers two principle advantages over private sector health systems. First, the MHS can mandate and implement system-wide changes and processes faster than similar modifications in the technically and organizationally diverse private sector. Second, the centralized authority of the MHS can facilitate the definition and operationalization of standardized metrics in the areas of health care cost, quality, access, and satisfaction. Thus, implementing and evaluating health care reforms in the MHS may prove advantageous for researchers who wish to design, execute, and/or evaluate specific improvements, or who seek stronger evidence with which to advocate for the nationwide adoption of initiatives that so far have only small-scale successes to their credit.

The MHS has a well-developed, integrated EHR and existing database of patient experience. All clinical, financial, and administrative data related to primary, specialty, and subspecialty care, in both the inpatient and outpatient settings, are captured in an EHR and subsequent health systems. The EHR also captures a large portion of the data resulting from care purchased in the civilian setting (outsourced) for DoD beneficiaries. These data remain in the MHS and are archived; to date, there are approximately 30 billion archived medical records and 5 billion active medical records in existing databases. The investment required to develop, implement, and populate EHR systems that do not otherwise exist may be a barrier to appropriate evaluation of private sector reforms.

The MHS uses state-of-the-art medical informatics tools. The MHS uses the Population Health Navigator (PHN) system, a Web-based, medical informatics tool used by military treatment facilities to assist in population health and process improvement efforts. The PHN system allows personnel to assess data quality, enrollment management, demand forecasting, utilization of services, and the quality of health care provided to beneficiary populations. It also serves as the centralized data source for reporting an individual military treatment facility's clinical performance as compared to civilian care treatment facilities. The PHN transforms health care data into actionable information and identifies enrollees in need of clinical preventive, disease management, or case management services. PHN delivers both corporate-level (i.e., HEDIS) metrics and patient-level information to compare health care quality.

The MHS has its own medical education programs. The DoD has its own medical school, postgraduate training programs, and contains a civilian equivalent of a medical vocational training center. Because of its centralized nature, the MHS can, with relative speed, restructure its training pipelines (physician, nursing, and medic/corpsman education programs) to promote large-scale transformation efforts. In addition, one can evaluate the impact of variations in medical education and training on care processes, costs, and quality improvement. This capacity to adapt training, develop curricula, and provide continuing education to meet the needs of new care models would, at best, be quite fragmented in the private sector.

The MHS is a budgeted system. Another distinct advantage of the MHS is its closed, budgeted system. Most private sector insurers and health care delivery organizations operate based on a productivity reimbursement model that is tied to Medicare payment schemes. As a result, the
private sector is limited in implementing drastic change, especially when the potential financial values of transformations have not been fully defined. In contrast, the budget-based system of the MHS allows it to be more responsive to experimentation, thereby producing more rapid measurement and reporting of results.

Limitations of the MHS for Evaluating Health Care Reforms

The MHS is not based on a productivity reimbursement model. Although it can be advantageous for research purposes and practice transformation, a potential limitation of the MHS is that its closed, budgeted system may pose challenges when evaluating payment reform. This limitation may, in fact, be an advantage when evaluating treatment effectiveness in facilities or systems unencumbered by relative value unit productivity incentives.

Another potential limitation is that programmatic changes to medical education and training curricula may be possible and work well within the MHS, but may not readily translate to other programs. Outside the MHS, programmatic changes might need to affect the entire medical education system. Furthermore, educational initiatives that successfully improve the practice model, clinical behaviors, or outcomes of care within the MHS may not be readily adopted by providers within the larger health care system, who likely received different training. Despite this limitation, research within the MHS may prove valuable and lead to educational improvements in other training programs.

Conclusion

We believe the MHS is well suited for testing the comparative effectiveness of medical treatments, procedures, processes, educational approaches, initiatives, and health policy alternatives. The MHS' large and diverse patient population (placed around the globe) is a more representative demographic than most individual, private sector health systems that are typically regional. Furthermore, the standard of care provided in the MHS is reflective and consistent with the care quality provided nationally. These points, coupled with the centralized structure of the MHS, its closed budget system, state-of-the-art medical informatics tools, and medical education programs, suggest that the MHS may serve as an ideal laboratory for both implementing and evaluating health care reforms. Together, these features allow the MHS to provide an environment that can rapidly implement, adapt to, and evaluate the benefits of disparate health care delivery models and innovations.
Abstract

Objective: This study describes and categorizes the cultural frictions and conflicts within a successfully implemented Internal Medicine Patient-Centered Medical Home (PCMH) clinic at the National Naval Medical Center, and provides lessons learned for combating these concerns. Methods: A semistructured interview protocol was developed, focusing on unique tenets of the PCMH, benefits of the model, and perceived obstacles to practicing medicine within this delivery system. The interviews included questions regarding efforts to foster team cohesion and impediments within the PCMH, as well as unique influences of the larger organization and the patient population, and lingering concerns about threats to the PCMH's viability. Key Results: Cultural tensions were revealed in four areas: perceived competing values within PCMH, individual resistance to PCMH values, within-team conflicts threatening the acculturation of PCMH values, and threats to the culture from external stakeholders. Conclusions: Recommendations for addressing these areas include values clarification and empowerment, training for socialization, realistic job previews, selective personnel retention, team building and conflict resolution mechanisms, and increased senior managerial support.

Background

The Patient-Centered Medical Home (PCMH) is a much heralded health care delivery model that aims to redefine primary care. It has begun to show exceptional results in improving patient satisfaction, reducing emergency room visits, and increasing the efficiency of referral services. However, the implementation of the PCMH involves a patient-centered culture shift that can be difficult to embrace by many health care workers. Resistance is most notable among professionals and leaders who are comfortable with the status quo or who fear the unknown. Although resistance to change is to be expected with any innovative model, cultural issues within the context of PCMH implementation remain to be explored and answered.

The Importance of Culture

Organizational culture has been defined as a set of values, beliefs, and ways of thinking that are embraced by the members of an organization. Examples include the relative emphasis an organization places on quality versus speed of service, the acceptability of admitting mistakes versus concealing them, or the value of cooperativeness versus competitiveness. The quality of an organizational culture has been shown to have significant implications for employee satisfaction, organizational citizenship behaviors, objective performance criteria, and consistent attendance in a range of different health care organizations.

The Difficulty of Culture Transformation

Transforming the culture of any business can be a wrenching experience that cannot be assumed to be permanent. There is ample evidence that people's values and beliefs can be changed significantly enough to achieve and maintain cultural transformation. However, under duress, stakeholders often retreat into their old cultural norms. Thus, it is especially important to attend to cultural issues even after new procedures and policies have been put into place.

Multiple Clashing Cultures and Identities
In large organizations, members of departments or units develop distinctive subcultures that exist alongside the overarching organizational culture. In addition, occupations (e.g., providers, nurses, accountants) develop distinct cultures over time that may shape the values and expectations of their members in addition to the cultures of their work organizations. For example, hospital management may stress fiscal responsibility and efficiency, whereas medical staff may wish to emphasize the need for greater resources to elevate the quality of care. These subcultures may compete and collide with one another and with organizational and clinic-specific cultures, leaving ambivalent members to struggle with unclear identities, ambiguous roles, and vacillating allegiances and expectations. Hospitals that can better resolve conflicting values and combine productivity with staff empowerment have more committed and satisfied staff.

The current study describes how a successful Internal Medicine PCMH clinic embedded within a larger medical center addressed cultural challenges while implementing a PCMH model of care. We examine the perceptions and values of those involved in the PCMH practice and how their values contrast and at times appear to conflict with the organization's values. We also recommend a range of interventions that could aid in avoiding cultural artifacts potentially derailing PCMH implementation and maintenance efforts.

Design and Approach

This study was designed and subsequently approved by the chair of the National Naval Medical Center Institutional Review Board as a quality improvement initiative intended to discover cultural barriers that prevented medical home implementation. The study was conducted in an Internal Medicine PCMH clinic within a large military medical center. The PCMH consisted of four teams, each of which had nine staff including two physicians, a nurse practitioner or physician assistant, a registered nurse (RN), three licensed practical nurses (two civilians and one corpsman), and two administrative assistants. The four teams were established sequentially throughout 2008 and 2009 to prevent large-scale disruption of clinical functions. Thus, the duration of their status as functioning PCMH teams ranged from 6 to 22 months. In-person interviews were conducted with 30 members of the clinic's four teams using the questions in the Appendix, including nine physician and nonphysician providers, four RNs, five licensed practical nurses, five corpsmen, and seven administrative assistants.

An additional 17 subject matter experts, including members of the clinic management staff, medical center leaders, and outside PCMH and primary care innovators, were interviewed by phone. We define the subject matter expert for this study as someone who was involved in the development of this PCMH, someone who had written on or studied the phenomenon of PCMH in this context, or someone who was involved in the management of the PCMH as part of his/her broader management responsibilities at the medical center.

All interviews were conducted by professionals with backgrounds in organizational behavior and culture, who were external to the clinic and the military. The questions focused on perceptions of the unique tenets of PCMH, the benefits of converting to PCMH practice, and of efforts to foster team cohesion. The questions also addressed perceived obstacles to providing care based on PCMH values, the influences of other stakeholders such as the medical center and the patient population, and lingering concerns about threats to the PCMH's viability. An iterative process was used, whereby insights of early interviewees were used as probes for later interviews to determine how widespread a specific perception was within or across professions and teams. The data were analyzed using an inductive approach akin to grounded theory and concerns were categorized.
along a spectrum of potential sources of cultural conflict and constraint. Thorough reading of the transcripts led to a grouping of concerns along a micro–macro continuum from intrapersonal concerns to within-team conflicts through issues involving external stakeholders. These concerns were first categorized by the lead interviewer and then reviewed and refined by other lead authors.

Results

The participants described many real advantages of adopting the PCMH model and very few expressed a desire to return to a more provider-centric model. These advantages included that their work style was more patient-centered and responsive to patient needs and preferences, that they felt more continuity in their work, that there was better integration of staff and support staff, that specific additional resources or processes made available were valuable, and that the values of PCMH made work more meaningful for employees. On the sole empirical question on the interview, "How happy are you with your changed role, the team, and the PCMH idea in general now," the average score on a scale of 1 to 10 was 7.2, with team scores ranging from 8.2 to 6 and individual scores ranging from 9.9 to 3.5.

However, the participants identified numerous issues that could be attributed to cultural conflicts. They expressed fear that these cultural influences could compromise their PCMH efforts and force their clinic back toward traditional medical practice.

Perceived Tensions and Contradictions Between Potentially Competing PCMH Values

In theory, the basic tenets of PCMH should work together seamlessly. In practice, many PCMH staff members saw tension between two core values espoused in their PCMH: continuity of care, defined as a patient being seen by the same PCMH team, preferably by the same physician on that team, and enhanced access to care, defined as an ability to rapidly address a patient's acute care needs by the PCMH, often with a same-day appointment.

Disagreements and misunderstandings among the various PCMH subcultures (management, staff, and patients) as to whether enhanced access was meant to increase access for the acutely ill or was also designed to provide for convenience-driven visits led to different stakeholders placing varying degrees of emphasis on continuity or enhanced access to care.

Another source of concern was some staff members' perception that the clinic's desire to provide a more integrated PCMH care model was slow in coming. Although there was improved monitoring of those with chronic health issues, there was insufficient time or structure for truly preventive and proactive efforts with the "not yet sick." These staff members wanted a bolder and expansive version of PCMH that involved confronting patients to take responsibility for preventive behaviors and changing their lifestyles.

Pre-Existing Occupational/Professional Values Perceived as Conflicting With PCMH Values

Some team members, primarily physicians, were seen by other staff members as resisting the PCMH culture in favor of behaviors or perspectives to which they were accustomed. Some doctors were reluctant to cede autonomy and work as team members by sharing patients, office space, and examination rooms. Given their fee for service reimbursement while working in the private sector, some were accustomed to being more
provider and/or practice centered rather than patient centered. In general, the amount of effort expended on socializing and inculcating physicians into the values and culture of PCMH varied widely, depending, in part, on when they had entered the clinic. Some providers also expressed concern about missing career-related activities they deemed necessary for their craft, such as morning report and grand rounds. Although they may have felt that their PCMH work was gratifying, they were still embedded in their occupational cultures. Therefore, they feared that by missing out on those professional activities, they would fall behind their medical peers elsewhere with whom they identified.

Conflicts Between Different Professionals' Opposing Assumptions That Undermine Maintenance of a Unified PCMH Culture
A medical home team by definition is composed of members of different professions, each of which has its own cultural norms and presumptions about their roles with respect to the other professions. These presumptions may often clash with the desired egalitarianism of the PCMH or with the cultural expectations of the other professions. We found tensions on most teams between different professions regarding the overlap of their roles, the relative work-load for each profession, and the perceived competency of other professional groups.

Although great effort had been put into developing and maintaining esprit de corps and cohesion within and across the first two teams, an overarching concern was that the effort had not been sustained with the newer teams that were formed. A few new staff members were not properly socialized into teams or PCMH clinic norms and expectations. Recent team-building efforts were seen as lacking longstanding benefit, in part because they did not address core PCMH values or group frictions. A common perception was that there were few opportunities for staff to get to know each other personally, and limited mechanisms for resolving conflicts. The staff and management, although admittedly very busy and often shorthanded, lamented the difficulty of maintaining the cohesion and core values that would have aided progress.

Perceived Conflicts Between the Desired PCMH Culture and the Influences and Expectations of the Stakeholders in the Larger Culture
Numerous stakeholders in the system, such as patients, other primary care clinics, specialty clinics, and ancillary services, had preferences about issues such as scheduling and enhanced access that were seen as conflicting with the PCMH's preferred ways of providing care. However, the greatest source of provider and RN concern was the medical center's senior management. PCMH staff saw management as advancing priorities that diverged from the tenets of PCMH. They also saw management as over-reactive to complaints from patients or other sources, leading to micromanagement, unexplained edicts and policy changes. These intrusions were symptomatic of underlying concerns about management's commitment to PCMH. Although management publicly and enthusiastically advocated for PCMH, they had competing business concerns as well. PCMH staff interpreted their lack of visibility in the clinic, their micromanaging, and their policy changes as possible indications that management was not convinced of the long-term viability of the PCMH concept. This led to a palpable concern that the PCMH would be allowed to revert back to a more traditional practice model.

Discussion

Our study was able to describe a series of cultural conflicts related to the transformation and maintenance of a successful Internal Medicine PCMH practice embedded in a large medical center. Despite receiving positive feedback from patients and staff (feedback from patients was received via
a general customer satisfaction questionnaire circulated by the Navy Bureau of Medicine and Surgery), the clash of various cultural assumptions made maintaining this new culture challenging. The staff expressed fears of cultural erosion and reverting back to non-PCMH patterns.

In retrospect, a number of factors may have contributed to these concerns: first, the teams differed in their training and socialization, with the earlier teams having undergone longer preparatory value clarification and team-building efforts. For example, earlier teams received specific training provided by an organization development specialist with expertise in workplace team building, individualized personality assessments using the Myers–Briggs Type Indicator, and detailed presentations on PCMH concepts and their individual roles within the PCMH. Later teams received training on PCMH and their roles, but did not receive team-building training and did not use Myers–Briggs. In addition, each team experienced turnover, such that no team remained entirely intact from the point of its inception to the time of the study.

Second, some providers in later teams did not join the PCMH voluntarily and may have continued to identify predominantly with external peers rather than with the PCMH. Perceptions of shared cultural norms will tend to strengthen identification, whereas dissonance between the values of the individual and culture can lead to alienation, retreat, and diminished identification, in turn tempering the positive work outcomes associated with identification.

Third, the PCMH had been spearheaded by a passionate leadership team within the clinic rather than by senior management. The internal leadership team was responsible for transforming the culture, socializing the earliest teams into PCMH values, and advocating for the PCMH. When these leaders departed or deployed, their replacements needed to focus on the maintenance of a fully operational clinic. They did not have the wherewithal to expend comparable effort on protecting the hard-fought culture changes in the PCMH as their predecessors had spent on creating the culture. Suddenly, the lack of visibility of upper management within the clinic became a concern to the staff, who worried that management would allow the clinic to revert back into a traditional practice model.

Thus, turnover of staff and key change agents may have contributed to the expressed concerns. They also may have exacerbated occupational and interpersonal fissures that led individuals back to previously held preferences that were in conflict with the new PCMH culture. As is typical with cultural change, opponents who remained silent during implementation tended to emerge and push back when exhaustion or complacency set in.

Recommendations

The identified areas of competing values, categorized according to the aforementioned four dimensions, have the potential to exist within most medical environments. We suggest that each be addressed in the following ways.

Alleviating the Perception of Competing Values Within PCMH

Values Clarification
Perceived contradictions or competitions between values need to be addressed by the PCMH's management, and the parameters of adopted policies need to be clarified so that contradictions cease to exist. Core PCMH values need to be stated, reiterated, and communicated effectively to staff through multiple media sources. In the current study, various parties expanded the concept of enhanced access for acute care into open access for convenience visits, thereby confusing the true intent and philosophy of PCMH, and leaving some staff and patients bewildered. In response, the clinic decided to send letters to patients reasserting what enhanced care did and did not mean. That message was to be reiterated in town hall meetings and on the video screen in the clinic waiting room. In another example, those staff who felt that the whole person was not being considered and that integrated care was not being achieved needed to be challenged to share in the effort to add more services (and more demands) to the clinic's offerings.

Empowerment
Empowering the teams to make decisions about processes and working out ways to balance their seemingly competing demands increases a sense of ownership and reduces the finger pointing that characterizes disengaged, dysfunctional teams. Such high-performance cultures are characterized by involved and empowered employees.

Aligning Professionals' Values With PCMH Values

Realistic Job Preview
An important component of selection and orientation that can help ascertain those who may be a poor fit for the PCMH is a realistic job preview. In this way, a new candidate understands the relatively egalitarian, organic form of a PCMH team and the expectations associated with team membership.

Personnel Appraisal Systems
Evaluation of PCMH team members should be done with explicit inclusion of team-oriented and PCMH-oriented behavioral criteria to reinforce the importance of playing one's role within the team concept. Those demonstrating organizational citizenship behaviors that support the PCMH fabric should be recognized accordingly. Organizations with well-established evaluation processes and procedures based on previously established cultural norms must be adapted to meet the new cultural norms of the PCMH.

Training and Socialization
Formal methods such as training, mentoring, and acculturating are useful to inculcate new PCMH members with both an understanding of the rationale for and advantages of PCMH, and a demonstration of how goals are accomplished within the PCMH and with other parts of the organization. The PCMH team members are important resources for identifying and imparting the content during socialization and acculturation. The goal is to develop a more homogeneous culture that will persist even under duress among individuals willing to embody PCMH values regardless of their distinct cultural background.

Selective Retention
If a professional cannot commit to the PCMH values and environment, it can be disruptive to maintain a transformed culture, especially if an individual is influential and vocal. When presented with the necessity of adopting shared norms, some will opt to leave, whereas others may need to be forced to choose between adapting or leaving. For the long term, we believe that patient-centered training beginning in medical school and continuing as an embedded part of graduate medical education programs will be needed to build a generation of physicians steeped in the PCMH culture.

Alleviating Within-Team Conflicts

Team Building
Conflict can be pre-empted by team-building activities. Formal and informal events are useful to help staff relate better to one another, especially across professions. However, it is not enough to build positive relations between individual clinic members. Team-building efforts, such as exercises surrounding relevant group processes, should focus on the shared mission of the PCMH clinic, and thereby build support for the core values that must persevere under duress of change.

Conflict Resolution
Better mechanisms for dispute resolution are needed. In the current study, within-team managerial structures were loosely defined by design, and the clinic had limited mechanisms for resolving interpersonal conflicts, even among those working together closely on a daily basis. Professional, ethnic, and personality differences often exacerbated problems. There was a need for enhanced means of conflict resolution, in particular between providers and other staff on the PCMH teams. Providers generally receive little leadership training specifically geared to working in a team environment or serving as team leaders, and we believe it will be important for future generations leading PCMH teams to be trained and adept at team membership and leadership and conflict resolution.

Alleviating Conflicts With External Stakeholders That Threaten PCMH Processes and Values

Managerial Support
Clearer evidence of support and personal investment in the success of PCMH from organizational management31 is necessary for successful maintenance of cultural change, and it must be unequivocal. At a minimum, there must be a champion of PCMH within the executive suite who can clearly communicate support to the PCMH teams. In the current study, PCMH staff was unsure of continued organizational support. To allay staff fears in such cases, it may fall to PCMH clinic management to encourage senior management to demonstrate and reiterate top-level support.

Build Alliances
To overcome stakeholder resistance in other areas, it is necessary to build alliances with those stakeholders in areas of shared values. When a PCMH clinic is chosen as a demonstration project, there is a greater possibility that other units will be resentful of the clinic's presumed preference and/or superiority. It is important for PCMH teams to realize that even if they wish to be an island, as long as they are interdependent, they need to
expend effort maintaining positive and respectful relations with interdependent entities. The effort should be to concurrently move toward greater autonomy as much as possible31 to maintain the integrity of PCMH’s goals.

Conclusion

Medical Home shows great promise; however, even if the cultural transition is handled well, it cannot be assumed that it will remain an unchallenged norm. Rather, a new culture is a dynamic and fragile entity16 that has to be supported, led, and invigorated on a regular basis. The key period of establishing a new culture is not at the onset of transformation, when behaviors, procedures, and policies need to be changed. Rather, the key alterations in norms and shared values come at the end of the transformational process, when new behavioral patterns need to become normative and employees need to be strengthened against backsliding into old, nonproductive ways. Implementing PCMH brings with it remarkable new challenges and dramatic change in the culture of care. Those who wish to pursue this endeavor must pay particular attention to and understand their organization's current culture and the intended future culture to successfully implement and institutionalize the PCMH model.

A Pilot Study Describing Knowledge and Practices in the Health Care of Men Who Have Sex With Men by U.S. Air Force Primary Care Providers

Military Medicine
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February 2013

ABSTRACT

Background: The Centers for Disease Control and Prevention (CDC) recommends annual sexually transmitted infection (STI) screening in men who have sex with men (MSM) that is unique to this patient population. The goal of this study is to establish whether U.S. Air Force (USAF) providers are familiar with these guidelines and determine if USAF providers offer these tests appropriately. Methods: A survey designed to determine primary care provider knowledge and practices in MSM health care was disseminated via e-mail to 124 primary care providers at 3 separate USAF medical facilities in Northern California from September 15 to 30, 2011. Findings: There was a 46% response rate. 15% of respondents correctly identified all CDC-recommended STI screens. 42% stated that they did not know the CDC screening guidelines. 51% did not screen male patients for MSM activity in the past year. 81% of respondents had not offered the full complement of MSM STI screening in the past year. Conclusion: The majority of USAF primary care providers surveyed were not familiar with CDC-recommended annual screening tests for STIs in MSM, and they did not screen for MSM activity or offer MSM STI screening tests regularly. Further studies across the Department of Defense are needed to corroborate the findings of this study.
INTRODUCTION

According to current population studies, between 2.8 and 9.2% of American men identify themselves as gay, with some 15.8% of men reporting having had some same sex activity since puberty. There continues to be a higher rate of unsafe sexual behaviors among men who have sex with men (MSM) and correspondingly higher rates of sexually transmitted infection (STIs) in this population. Owing to increased STI rates in MSM, the Centers for Disease Control and Prevention (CDC) has recommended annual testing for human immunodeficiency virus, syphilis, gonorrhea, and chlamydia in this population, with additional testing for pharyngeal gonorrhea in men with oral-genital exposure, and rectal gonorrhea and chlamydia screening in men having receptive anal intercourse.

Previously, military medical providers could not ask military members about same sex activity because of policies barring homosexual behavior. However, in 2010, before the full repeal of Don't Ask Don't Tell (DADT), an Air Force policy letter was circulated among Air Force health care providers, which essentially made an exception to DADT policies when pertinent to patient care. Since this change in policy in 2010 and the subsequent full repeal of DADT in 2011, there have been no studies describing military provider knowledge of CDC guidelines for MSM patients, nor have there been any study describing military provider practices with regard to this population.

METHODS

In an effort to further investigate military provider knowledge and practices in MSM health care, our group developed an online questionnaire to distribute to Air Force primary care providers. Questions were designed to determine provider knowledge of CDC guidelines for STI screening in MSM patients and to establish provider practices in MSM patient care. To internally validate the survey, 2 separate focus groups were held. The initial focus group consisted of 5 Air Force graduating third year family medicine residents who would not be participating in the study. The second focus group consisted of 2 Air Force staff family medicine physicians, an Air Force staff internal medicine physician, and an Air Force nurse practitioner, all of whom were not part of the survey population.

The survey was disseminated to 3 separate Air Force medical treatment facilities in Northern California after full institutional review board approval at David Grant U.S. Air Force Medical Center and support from respective treatment facility medical directors. The study population consisted of 124 primary care physicians, nurse practitioners, and physician assistants in internal medicine, family medicine, primary care, and flight medicine. Rosters from hospital commanders were used to collect e-mail addresses for providers. E-mails were then sent with links to surveys. SurveyMonkey was used for survey collection and assistance in final analysis.

The survey was open for responses from September 15, 2011 to September 30, 2011. After initial distribution to study sites via e-mail, an additional reminder was sent at the midpoint of the study to elicit more responses. Responses were completely confidential.

STATISTICAL ANALYSIS

Descriptive statistics were computed for each item in the survey, including means, SDs, and percentages.
**RESULTS**

Sixty-five of 124 primary care providers responded to the survey (46% response rate). Six surveys were excluded from final analysis. Five of the excluded surveys were from respondents outside of the target population (four pediatricians, one medical technician). One survey was incomplete. Excluded surveys did not have a statistically significant impact on final results.

Twenty-five respondents (42%) reported that they did not know CDC-recommended annual screening tests for MSM. Nine respondents (15%) identified all 7 CDC-recommended STI screening tests for MSM patients. These 9 respondents also erroneously included other tests not recommended to be obtained annually by the CDC. Fifty-one respondents (86%) were aware that MSM patients had a different risk for developing STIs than men who have sex only with women. Forty-three respondents (73%) were aware that screening guidelines for MSM were different than men who have sex only with women.

Thirty respondents (51%) stated that they had not asked any of their patients whether they had participated in MSM activity in the past year, despite Department of Defense (DoD) directive allowing such questions since April 2010. In general, respondents were aware of this policy as 50 respondents (85%) were aware that they were not prohibited from enquiring about same sex activity in active duty personnel.

Forty-eight respondents (81%) had not offered the full complement of MSM STI screens in the past year. Fifty-five respondents (93%) had not offered oropharyngeal gonorrhea testing to any patient in the past year. Fifty-four respondents (92%) had not offered rectal chlamydia/gonorrhea testing in the past year.

Twenty-three respondents (39%) stated that they had never received training in the medical care of MSM. Forty-nine respondents (83%) stated that they did not receive any directive from the military regarding protocol for screening and documentation of MSM activity in a medical setting.

Providers with prior training of any kind in the care of MSM patients were more likely to correctly identify all 7 of the CDC-recommended STI screening tests ($p = 0.04$). The only factor associated with increased likelihood of providers offering STI screening to MSM patients was if the provider reported caring for 1 or more MSM in the past year ($p = <0.01$).

**DISCUSSION**

The health care repercussions of the DADT policy on lesbian, gay, bisexual (LGB), and MSM service members was a longtime concern for many in the medical community and led the American Medical Association to urge a repeal in 2009. DADT policies prevented military personnel from utilizing their own health care facilities, and there were serious concerns that active duty LGB and MSM also posed a health threat to surrounding LGB, transgender (LGBT) communities because of undiagnosed and untreated infections.
We are optimistic that the repeal of DADT may lead to improved care for all military members. Encouragingly, survey respondents generally were aware that MSM had significantly different risks for developing STIs when compared to men who have sex only with women. Furthermore, most respondents were aware that MSM have different STI screening guidelines than men who have sex only with women. However, within our study population, there was a concerning lack of knowledge regarding specific MSM STI screening guidelines as evidenced by 85% of respondents not correctly identifying CDC-recommended STI screening tests. We suspect that poor knowledge of MSM STI screening guidelines within our study population is multifactorial. During DADT, it is likely that MSM screening guidelines were not stressed among providers in military postgraduate training and in-service education. Future training aimed at increasing awareness of MSM STI screening guidelines could significantly improve provider knowledge of CDC recommendations and hopefully lead to increased detection and treatment of STIs among MSM personnel.

Of equal concern was the irregular screening for MSM activity noted in our study population. Thirty respondents, or roughly half of the providers surveyed, were not routinely screening male patients for MSM activity despite DoD directives allowing such questions for over 12 months before dissemination of this survey. Providers generally were aware that under current policies, questions regarding same sex activity were permitted; 50 respondents (85%) knew that they were allowed to inquire about same sex practices among active duty personnel. It is possible that prior policies may have led many providers to avoid asking questions regarding same sex activity because of fears of negative repercussions for patients and providers themselves. In addition, many providers may have been reluctant to ask patients about same sex activity out of concerns for offending and alienating some patients. Finally, a lack of clear guidance from the DoD regarding the process for screening and documentation of MSM activity could have played a role in decreased screening observed in our population. Forty-nine respondents (83%) still felt that they had not received sufficient directive from the DoD regarding screening and documentation processes for MSM behavior. Additional Air Force and DoD clarification of the protocol for screening and documentation of same sex activity in the medical record may facilitate increased screening for MSM activity in the future. Training in taking a complete sexual history may also aid in identifying MSM patients who may benefit from CDC-recommended STI screening. Education in cultural competency and a willingness to use neutral and welcoming language that invites disclosure of sexual practices will also be crucial. Other possible avenues to increase screening could include the addition of MSM screening on clinic intake forms or on annual health assessments administered by the DoD such as the Periodic Health Assessment conducted by the Air Force.

These results are limited by the relatively small sample of 65 providers in three geographically co-located Air Force medical facilities. The sample size is too small to report stratified analysis such as Doctor of Medicine (MD)/Doctor of Osteopathic medicine (DO) vs. allied health professional, staff vs. resident, or by years of practice. Despite attempts to design neutral questions, the results of this study may have been affected by response bias. Furthermore, it is possible that bias because of self-selection may have occurred as providers with strong feelings regarding this topic may not have responded. Future research is needed to determine if the findings of this study are reflective of the entire DoD medical community. Subsequent studies that include vaccine recommendations for MSM as well as non-MSM STI care would also be very useful to the military medical community.

It is unclear if the knowledge gap found within our population is unique to military institutions. There is concern in the civilian sector that MSM STI guidelines are not well publicized and that wider dissemination of MSM STI screening guidelines is needed to support clinicians. Recent studies have also highlighted the lack of LGBT and MSM curriculum in medical schools and postgraduate training. These issues represent problems that
the entire medical community faces. Though further studies are needed, we suspect that the shortcomings highlighted in our study are closely mirrored in the civilian sector.

Future training for both military and civilian primary care providers will be imperative in ensuring that MSM patients get appropriate medical care. Obedin-Maliver et al highlighted that a strategy for increasing LGBT content in medical schools was to have faculty who were willing to teach such topics, though this could prove difficult in settings where homophobia persist, including the military. In such environments, online learning modules such as those available in the University of California, San Francisco LGBT resource center and the Fenway Institute may prove useful.

Though this study focuses on provider knowledge, patient perspective will also need to be taken into account to ensure full disclosure at office visits. Openness, discretion, confidentiality, and cultural competency should be fostered to ensure that patients feel safe when discussing MSM behavior in the future. Military MSM informally polled by one of our authors generally report they are reluctant to volunteer their MSM behaviors or risk factors to military doctors but would be willing to answer honestly if asked directly. Despite the fact that the military has made great strides with the repeal of DADT, it is likely that more still needs to be done to ensure that MSM patients receive appropriate care at all DoD medical facilities.

Increasing Educational Indebtedness Influences Medical Students to Pursue Specialization: A Military Recruitment Potential?

Military Medicine
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February 2013

ABSTRACT

Background: Cost of medical education and student indebtedness has increased dramatically. This study surveyed medical students on educational debt, educational costs, and whether indebtedness influenced career choice. Responses should impact (1) Department of Defense (DoD) recruitment of physicians and (2) future of primary care. Method: The authors surveyed 188 incoming medical students (University of Medicine and Dentistry of New Jersey – New Jersey Medical School, Class of 2012) concerning educational indebtedness, perceptions about educational costs, and plans regarding loan repayment. Data were analyzed and expressed as mean ± standard error. Results: Students with loans anticipated their medical educational costs to be $155,993. 62% felt costs were “exorbitant,” and 28% “appropriate.” 64% planned to specialize, whereas only 9% chose primary care. 28% of students planning specialization said income potential influenced their decision. 70% of students said cost was a factor in choosing New Jersey Medical School over a more expensive school. Students anticipated taking about 10 years to repay loans. Conclusions: As medical educational costs and student indebtedness rise, students are choosing less costly education and career
paths with higher potential future earnings. These trends will negatively impact health care availability, accessibility, and cost. DoD programs to provide financial assistance in exchange for military service are not well publicized. These findings should increase DoD recruitment opportunities.

INTRODUCTION

The cost of medical education has increased annually. In 2009, the Association of American Medical Colleges estimated that 29% of medical students graduated with indebtedness of $200,000 or more. Medical educational indebtedness has grown at a rate disproportionately higher than that of compensation for physicians. Grants and scholarships have helped offset this debt, but are limited in availability and amount. Thus, students increasingly rely on loans to finance their medical education.

Following medical school graduation, loan repayment becomes a challenge. A survey of academic surgeons indicated that many felt educational indebtedness negatively impacted academic productivity, career choices, and quality of life. Strategies to reduce this financial burden, either during or after medical school have emerged. They include loan deferment during residency, or selecting a state versus private school. Department of Defense (DoD) loan repayment programs and exchanging years of service for loan repayment have been less commonly selected options. Many students have selected graduate medical training in specialties with maximal financial remuneration.

There are multiple factors that influence medical students' career choices, including lifestyle, specialty interest, role models, etc.; but does greater financial reward influence career choices of medical students and if so, is this in any way a consequence of the increasing amounts of educational indebtedness? This question has been addressed, but results are controversial. Currently, a greater percentage of U.S. graduates have sought specialty residency positions, as opposed to those in primary care, leading some to conclude that higher income potential may influence this decision.

Our study is designed to identify the anticipated amount of educational indebtedness among current medical students, to define their perceptions of educational costs, and to examine their strategies for loan repayment after graduation. To address these questions, we have queried incoming medical students regarding (1) their educational financial plan, (2) their anticipated indebtedness, (3) their strategies for loan repayment, and (4) whether choice of specialty training is influenced by indebtedness. The role of recruitment for DoD medical manpower also will be assessed. Answers to these questions should be incorporated in the ongoing debates concerning our nation's health care reform plans and recruitment of physicians for our armed forces.

METHODS

188 first year medical students (New Jersey Medical School [NJMS], Class of 2012) were surveyed using a questionnaire. The survey instrument consisted of 26 questions, including demographics and attitudes toward educational indebtedness and military service. All questionnaires were collected immediately at the conclusion of the session and proctors verified independent answers. Data were collated and values expressed as percentages or as mean ± standard error.

RESULTS

February 2013
188 students completed the questionnaire. Their mean age was 23.2 ± 2.6 years. 60% of the class was male. New Jersey was the home state for 94% of students. 43% of students were Caucasian, 37% Asian, 8% African American, 8% Hispanic, and the remaining 4% selected “other” or had no response. 98% of students were single/not married. 99% had no children. One couple had one child. 23% of students had a career before entering medical school. 84% had taken out student loans.

43% of students had college educational loans. Mean undergraduate indebtedness of those with loans was $34,989 ± 2,637. Half of the class graduated from a private college. Of those students who had outstanding college loans, 77% said they would repay those loans with future earnings as physicians. Students anticipated an average of 5.2 years after graduation to repay their college educational loans.

87% of the class (164 students) financed their medical education with loans: the average loan was $42,859 ± 3,110 for the first year. Students estimated that their medical school education would cost them an average of $155,993 ± 4,649. Of those who had loans for medical school tuition, 94% indicated that they planned to repay those loans with future earnings as a physician. A majority (78%) did not feel that the responsibility to repay their educational loans would impact their future decisions to marry or to have children. One-quarter (41 students) of those with loans stated that they would consider military service to help repay their loans.

When queried about the cost of medical education, 61% of students felt that the cost was “exorbitant,” 29% felt it was “appropriate,” and 10% had no opinion. 22% of students said that the cost of medical education was “more than what I expected,” whereas 72% said the cost was what they expected. 70% of students reported that the cost of education was a factor when choosing NJMS over a more expensive private school. Students expected it would take them an average of 10.4 ± 0.6 years, after training, to repay their medical student loans.

The majority of students (59%) in our survey believed that income potential did not play a role in their decision to choose medicine as a career. Moreover, 54% of students felt that physicians were adequately compensated for the care they provided to patients. Nonetheless, when queried concerning motivation to become a physician, almost one-third of students indicated earning potential was a motivating factor. 24% reported that physician family members were a motivating factor. 64% of students planned on becoming specialist providers, whereas only 9% of students intended to become primary care physicians. Of those planning to become specialists, most (53%) said income potential did not play a role in their decision.

Finally, when asked how best to change the system, 23% of students felt medical school tuition should be decreased, 16% felt there should be more government subsidies available for education, and 14% thought more scholarships should be made available. 10% of students stated regulation of Health Maintenance Organizations (HMOs) would be beneficial, and 10% stated universal health care would be helpful in “changing the system.”

DISCUSSION

Several impending challenges to the health care system in the United States are at the forefront of discussions today. Most important is the anticipated future shortage of physicians to provide the necessary health care which ultimately will be required for the increasing patient population in our country. As a factor in this debate, one must consider the difficulties of recruiting and retaining students in our medical educational system.
Their career choices and the factors that influence those choices will have a significant impact on the quantity and quality of health care delivered to us in the future. The question is: Does the rising cost of medical education play a role in medical students' decision making regarding career and specialty choice?

Many medical students are making educational and career choices designed to decrease the postgraduation financial burden. Educational debt will represent a significant percentage of total indebtedness (housing, automobile, credit card, etc.) for students after they graduate. The consequences of this debt are unknown to our knowledge. High tuition cost deters some of our brightest students from applying to medical school, and is the number one deterrent of minority application to medical school. If the same student applied to business school or law school, he or she would find that the time commitment was less, the earning potential probably comparable, and the number of years invested in education and training before starting a first job was significantly less than that for medical school. In addition to deterring some students from pursuing careers in medicine, the deep indebtedness that results from medical education has long-lasting effects after graduation.

During residency training, when work hours are long and income relatively low, indebtedness, because of interest on loans, continues to increase. After residency, additional loans, for home mortgage or business, add to total burden. As a consequence, students must develop strategies early in their careers for loan repayment. Military service in exchange for loan repayment is one option that a quarter (41) of those with loans in the NJMS 2012 class considered. Over the past 5 years, an average of 9 students per year (less than 5% of the class) have taken advantage of the Health Professions Scholarship Program (HPSP). All three armed forces (Army, Navy, and Air Force) and the National Health Service were represented. The Army predominated at 49%. Most of the students in our study chose to attend a less expensive state medical school over a more costly private school. Lastly, a majority of students (64%) said they planned to become specialist providers, a path associated with higher incomes. Although 53% said income potential did not play a role in this decision, it is striking that despite the constant emphasis on primary care in medical school curricula, only 9% of the first-year medical students planned to pursue this career!

A shortage of primary care physicians has been identified as a major problem in our health care delivery system in several reports. Less enthusiasm by medical students for primary care, the "gatekeepers" of our health care system, is a threat to this country's best interests. Students seek residencies in specialties known to be especially remunerative to help pay for their education. Lower income, less "controllable lifestyle," and increasing job demands all play a role in the declining interest of medical students in pursuing primary care as a career. Already there is a shortage of primary care providers in many parts of the country, and access to health care has been impeded further by Medicare reductions in remuneration to physicians. If these trends continue, the increasing costs of medical education will have an increasingly negative impact on the future of health care availability, accessibility, and cost.

How can we decrease medical educational costs? In our study, students offered such solutions as tuition decrease, government subsidies and scholarships for education, more regulation of HMOs, and developing a universal health care program. Additionally, exposure to programs such as the Reserve Officers' Training Corps (ROTC) and HPSP should be introduced to high school and college students much earlier, as options to defray future medical educational costs. In August 2012, personal communication with three local high schools in proximity to NJMS (Science Park High School in Newark, New Jersey; West Orange High School in West Orange, New Jersey; and Columbia High School in South Orange, New
Jersey) confirmed that there is no military or DoD presence at student advisory meetings. The Vice Principal of Science Park High School (Ms. Julia Jackson), a magnet school in Newark, revealed that they had never hosted on-site recruitment of students by military officers.

Would this influence more students to pursue careers in primary care? Certainly, income level, interest in the field, and "lifestyle" are the most important factors that determine students' career choices. A solution to the shortage of primary care providers would be, to increase incomes and incentives offered to these physicians. If they received comparable incomes to specialist providers, this would shift the pattern of career choice among medical students, influencing more to follow their interests. To promote this change, politicians would need to be educated concerning need for primary care physicians, and medical school leaders would need to develop plans to recruit and retain qualified students into this field. Perhaps government subsidies could be given to students who commit to careers in primary care. Programs which reward primary care givers who practice in underserved areas could be developed and instituted, in hopes that these caregivers would find their experiences sufficiently rewarding that they commit to such careers long term. Lastly, DoD programs such as the HPSP and Health Professionals Loan Repayment Program should be publicized and promoted during high school and college versus medical school, as an option to keep incurred educational costs low.

CONCLUSIONS

As medical educational costs and student indebtedness continue to rise, many medical students are making educational and career choices designed to ameliorate this financial burden. Medical students in this study were found to have chosen a medical school education that was less costly and career paths with maximal future earnings. These trends will impact the future of health care availability, accessibility, and cost. Primary care will suffer disproportionately. Solutions to these problems greatly favor alternatives such as recruitment and retention of future physicians in military medicine.

BACK TO TOP

**Nutrition and Fitness**

**The Association Between Physical Fitness and Dementia**

Annals of Internal Medicine
5 Feb 2013

What is the problem and what is known about it so far?
Dementia is the progressive loss of memory and thinking that usually affects older adults. People who are healthier and more physically fit seem to be less likely to develop dementia. However, that could be because dementia causes people to be less active and physically fit. If researchers
could demonstrate an association between physical fitness earlier in life and dementia later in life, it may suggest that working toward becoming and staying physically fit at younger ages could prevent dementia later in life.

Why did the researchers do this particular study?
To assess the association between objectively measured physical fitness and dementia.

Who was studied?
19,458 healthy middle-aged people who had a treadmill exercise test as part of a preventive health clinic visit.

How was the study done?
The researchers divided the participants into those who were most and least fit, defined as the amount of time people ran on a treadmill. They then followed the participants for many years, beyond the time they reached age 65 years, to see who went on to develop dementia. The researchers then compared the number of people who had dementia among the most and least fit.

What did the researchers find?
The most fit study participants were much less likely to develop dementia than those who were the least fit.

What were the limitations of the study?
The findings may be influenced by other healthy behaviors, such as healthy eating, that are common among physically fit people. The findings of association between fitness and dementia do not suggest a specific level of physical fitness that people can achieve to prevent dementia. Participants were generally healthy and white, and the findings may not apply to other groups.

What are the implications of the study?
Physical fitness in middle age seems to be associated with a lower chance of developing dementia after age 65 years. Although the findings do not prove that fitness prevents dementia, they provide yet another reason to become or stay physically fit in middle age.

BACK TO TOP

**Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial**

The Lancet
Claudia Paula Heidegger MD; Prof Mette M Berger MD; Séverine Graf BSc; Walter Zingg MD; Patrice Darmon MD; Prof Michael C Costanza PhD; Ronan Thibault MD; Prof Claude Pichard MD
Background

Enteral nutrition (EN) is recommended for patients in the intensive-care unit (ICU), but it does not consistently achieve nutritional goals. We assessed whether delivery of 100% of the energy target from days 4 to 8 in the ICU with EN plus supplemental parenteral nutrition (SPN) could optimise clinical outcome.

Methods

This randomised controlled trial was undertaken in two centres in Switzerland. We enrolled patients on day 3 of admission to the ICU who had received less than 60% of their energy target from EN, were expected to stay for longer than 5 days, and to survive for longer than 7 days. We calculated energy targets with indirect calorimetry on day 3, or if not possible, set targets as 25 and 30 kcal per kg of ideal bodyweight a day for women and men, respectively. Patients were randomly assigned (1:1) by a computer-generated randomisation sequence to receive EN or SPN. The primary outcome was occurrence of nosocomial infection after cessation of intervention (day 8), measured until end of follow-up (day 28), analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00802503.

Findings

We randomly assigned 153 patients to SPN and 152 to EN. 30 patients discontinued before the study end. Mean energy delivery between day 4 and 8 was 28 kcal/kg per day (SD 5) for the SPN group (103% [SD 18%] of energy target), compared with 20 kcal/kg per day (7) for the EN group (77% [27%]). Between days 9 and 28, 41 (27%) of 153 patients in the SPN group had a nosocomial infection compared with 58 (38%) of 152 patients in the EN group (hazard ratio 0.65, 95% CI 0.43—0.97; p=0.0338), and the SPN group had a lower mean number of nosocomial infections per patient (−0.42 [−0.79 to −0.05]; p=0.0248).

Interpretation

Individually optimised energy supplementation with SPN starting 4 days after ICU admission could reduce nosocomial infections and should be considered as a strategy to improve clinical outcome in patients in the ICU for whom EN is insufficient.

Funding

Nutritional support for patients in the intensive-care unit (ICU) is part of standard care. When the gastrointestinal tract is functioning, guidelines recommend early initiation of enteral nutrition (EN). However, findings have shown that EN alone frequently results in insufficient energy and protein intakes leading to underfeeding, which causes complications. Even in stable patients in the ICU, early initiation of EN is associated with a high incidence of gastrointestinal intolerance, and potentially serious adverse events, such as bronchoaspiration with an increased risk of pneumonia.

Results of meta-analyses show that parenteral nutrition (PN) is not associated with excess mortality compared with EN. However, the optimum timing of PN initiation is controversial. We previously proposed an algorithm using the supplemental PN (SPN) approach (EN combined with PN when EN alone is insufficient), which aims to optimise clinical outcome by providing patients with their full energy target from day 4 after admission to the ICU. However, the combination of PN with EN can cause overfeeding, leading to increased risk of infection, metabolic disturbances such as hyperglycaemia, liver dysfunction, and extended time on mechanical ventilation. Therefore both underfeeding and overfeeding carry risks of infectious complications and can delay weaning from mechanical ventilation.

We aimed to test the hypothesis that individually optimised energy provision by SPN for 5 days after day 3 of ICU admission could improve clinical outcome in severely ill patients in the ICU for whom EN alone is insufficient.

Methods

Trial design and patients

This two-centre, randomised, controlled, intervention trial took place in the mixed medical and surgical ICUs of two tertiary care hospitals in Switzerland: Geneva University Hospital and Lausanne University Hospital. After trial approval by both institutional ethics committees, we recruited adult patients 3 days after they had been admitted to the ICU. Written informed consent was obtained from the patients or their next of kin. Eligible patients were those who had received less than 60% of their energy target from EN at day 3 after admission to the ICU, were expected to stay for more than 5 days, expected to survive for more than 7 days, and had a functional gastrointestinal tract. We excluded those who were receiving PN, had persistent gastrointestinal dysfunction and ileus, were pregnant, refused to consent, or had been readmitted to the ICU after previous randomisation.

Randomisation and masking

On day 3, consecutive patients were randomly assigned (1:1) to receive EN with SPN, or to continue with EN alone. The pharmacies of both hospitals generated the allocation schedule with a computer-generated randomisation sequence stratified by sex, admission category (surgery or medicine), and subsequent block size of four for SPN or EN. Allocation concealment was achieved with sequentially numbered, sealed, opaque envelopes. The daily on-duty investigator told the physician in charge of the eligible patient which treatment had been assigned. Care providers and patients were not masked; however, the investigators who established caloric goals were not directly involved in patient care. The senior site
investigator from each university hospital prospectively obtained information about infectious episodes in study patients from the other centre, and was unaware of the treatment groups assigned to patients. Statisticians were masked to group allocation.

Procedures

At ICU admission (day 1) the nutritional target was set for all admitted patients at 25 kcal per kg of ideal bodyweight a day for women and 30 kcal per kg of ideal bodyweight a day for men, and anamnetic bodyweight was used for patients with a body-mass index of 20 kg/m² or lower. Protein administration was set to 1.2 g per kg of ideal bodyweight a day. From day 1, all patients in the ICU who were unable to eat orally were given EN (20—30 mL/h up to a maximum of 150 mL/h). EN was administered continuously by the primary care team according to routine protocols, including the following items: semi-recumbent positioning, preferred use of nasogastric tubes, and the use of prokinetic agents if necessary (gastric residual volume ≥300 mL). EN products consisted of polymeric, fibre-enriched formulas, routinely prescribed in both hospitals, containing 1.05—1.62 kcal/mL of energy (18% proteins, 29% lipids [8% medium-chain triglycerides], 53% carbohydrates).

We assessed baseline characteristics at ICU admission (day 1) for all admitted patients. We measured severity of illness with the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Simplified Acute Physiology II (SAPS II) scores. On day 3 of ICU admission, after randomisation took place, we used indirect calorimetry (Deltatrac II metabolic monitor, Datex-Ohmeda, Finland) to adjust the energy target to be delivered from day 4 for all study patients. On day 4, SPN was administered by central or peripheral catheter for 5 days. PN formulas consisted of 0.62—1.37 kcal/mL of energy (20% proteins, 29% lipids [15% medium-chain triglycerides], and 51% carbohydrates). EN and PN formulas came from four different manufacturers. The complete (100%) achievement of the energy target in those assigned to receive SPN was verified twice daily.

Trial design

The black solid line shows the potential progression of EN in all patients before inclusion into the trial (day 3), and the blue line shows the potential energy provision for patients remaining on EN only. The red line shows the energy delivery in patients on EN with SPN during the intervention period (days 4—8), resulting in the potential prescription of 100% of the energy target (determined by indirect calorimetry, 3 days after admission in the ICU). EN=enteral nutrition. ICU=intensive-care unit. SPN=supplemental parenteral nutrition.

Continuous intravenous insulin therapy to maintain blood glucose at lower than 8.5 mmol/L was provided according to clinical protocols, and we checked arterial blood glucose frequently (as recommended and depending on the clinical situation, but at least four times a day). Hyperglycaemia was defined as a blood glucose concentration higher than 10 mmol/L, and hypoglycaemia as lower than 4 mmol/L. Trace elements, minerals, and vitamins were administered to both treatment groups daily as recommended by European guidelines. Immune-enhancing enteral formula, intravenous glutamine, and omega-3 fatty acids were not administered during the trial period.

We recorded daily and cumulative energy balances from day 1 until day 8, and obtained data for follow-up variables from day 4 to day 28. Both groups continued to receive EN during follow-up, as needed. We included energy from nutritional products and from non-nutritional fluids (glucose...
for drug dilution, lipid from propofol) in the calculation of energy balances. A different patient computerised information data management system was used at each hospital (CliniSoft 6.2, General Electric, in Geneva; Metavision 5.45, iMDsoft, in Lausanne).

Trial endpoints

The primary endpoint was the occurrence of nosocomial infections after day 8 until day 28. Infections were defined according to definitions from the Centers for Disease Control and Prevention. Five infection categories were defined: pneumonia (ventilator or non-ventilator-associated pneumonia, and other lower respiratory tract infections); bloodstream infection (laboratory-confirmed bloodstream infections and clinical sepsis); urogenital infection (device-associated or non-device-associated urinary tract and genital infections); abdominal infection (intra-abdominal infections); and other infection (skin, bone, and soft tissue infections; ear, nose, and throat infections; upper respiratory and intrathoracic infections).

The main secondary endpoints were the number of antibiotic days (defined as days from day 1 to day 28 during which a patient received at least one dose of antibiotics) for nosocomial infection and number of antibiotic-free days (days during which a patient did not receive antibiotics; if a patient died, antibiotic-free days were censored at death). Antibiotics were given to treat infection and as a prophylaxis.

Other secondary endpoints were duration of invasive and non-invasive mechanical ventilation, length of stay in the ICU and hospital until day 28, mortality in the ICU, general mortality, duration of renal replacement therapy, glycaemia (crude blood glucose concentration and area under the curve [AUC]), phosphataemia, concentration of C-reactive protein, liver test results, and drug administration (insulin, steroids, and antifungal agents).

Statistical analysis

We based sample size calculations on an assumed overall infection rate of 50% in the targeted patient population, on the basis of results from our previous study, which showed an incidence of 57% of nosocomial infections in patients admitted to the ICU for more than 5 days. We postulated that full coverage of energy needs might decrease the infection rate by 33%. To detect such an effect with a statistical power level of 80%, 148 patients had to be included in each group. The intention-to-treat analysis included all patients randomly assigned to the intervention (SPN) group or control (EN) group; the per-protocol analysis included only patients who fully completed the 5-day intervention in the ICU. Variable summaries are shown as frequency, proportion, mean (SD), or median (IQR) as appropriate. We used the Q—Q plot to assess whether continuous data were normally distributed. We did descriptive analyses with the χ² or Fisher's exact tests for categorical variables, and the Student's t test or Mann-Whitney-Wilcoxon test for continuous variables when appropriate. We used Cox proportional hazards ratios in univariable and adjusted multivariable models to compare between-group differences in the primary outcome. We selected variables for the adjusted multivariable analysis if their p value was 0-20 or lower in the univariable analysis and according to their clinical relevance. We included the following variables: SAPS II score, hospital (Geneva vs Lausanne), admission category (surgery vs medicine), antibiotic use, and mechanical ventilation before day 9. We generated survival analysis curves during 28-day follow-up using the Kaplan-Meier method. We checked proportional hazards assumptions with a test based on Schoenfeld residuals. We calculated Harrell's C index from the multivariable model to establish the concordance between estimated
and observed values. We also analysed the between-group difference in the number of nosocomial infections with a multivariable Poisson regression model because the mean and the variance were equal adjusted for covariates.

We used multivariable negative binomial regression models to analyse the number of antibiotic days for nosocomial infections, because this outcome had an overdispersion in the Poisson model. The negative binomial model included SAPS II, hospital, and admission category as covariates. We also analysed time on mechanical ventilation with a multivariable negative binomial regression model adjusted for covariates and controlled for length of ICU stay. We did subgroup analyses for time on mechanical ventilation of infected and non-infected patients during follow-up. We analysed mortality using the Cox proportional hazards models. The length of stay, antibiotic days, and antibiotic free-days were tested with multivariable linear regression models adjusted for covariates. In case of suspicion of heteroscedasticity (unequal variances), we used Eicker-Huber-White standard errors.

We used Stata 12.0 software for all statistical analyses and set statistical significance to \( \alpha = 0.05 \). We used the false discovery rate controlling method (the Benjamini-Hochberg procedure) to correct for multiple comparisons.

The protocol is registered with ClinicalTrials.gov, number NCT00802503.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We enrolled 305 patients between December, 2008, and December, 2010, 153 of whom were assigned to receive SPN, and 152 to EN only. All patients received their allocated nutritional protocol, although 20 in the SPN group and ten in the EN group discontinued the study, mostly because of protocol violation.

Trial profile

*We considered the protocol to be violated if the proportion of the energy target delivered by EN was more than 60% after inclusion on day 3, or if the patient stayed in the ICU for less than 5 days, or died before day 9.

Demographic and clinical characteristics of the trial groups were similar at randomisation. On day 4, the mean cumulative deficit of all patients was \(-3999 \text{ kcal (SD 1293)}\) on the basis of predictive equations (\(-4064 [1322]\) in the SPN group vs \(-3880 [1332]\) in the EN group). The target was measured by indirect calorimetry in 198 (65%) of 305 patients, resulting in reduced targets in both groups: SPN \(-42 \text{ kcal (p=0.2545)}\); EN \(-89 \text{ kcal (p=0.0155)}\); overall \(-66 \text{ kcal (p=0.0110)}\). Mean energy delivery between day 4 and day 8 was 28 kcal/kg per day (SD 5) in the SPN group and 20 kcal/kg per day (7) in the EN group (103% [18%] of energy target in the SPN group vs 77% [27%] in the EN group; \(p<0.0001\)). The mean
cumulative energy balance during the intervention period was 124 kcal (1589) in the SPN group versus −2317 kcal (2657) in the EN group (p<0.0001). Mean protein delivery between day 4 and day 8 was 1·2 g/kg per day (0·2) for the SPN group and 0·8 g/kg per day (0·3) for the EN group (100% [16%] vs 71% [27%]; p<0.0001).

Energy delivery

Energy (nutritional products and non-nutritional fluids) expressed in percentage (%) of energy target according to method of delivery: enteral route (A), parenteral route (B), or a combination of both routes (C) in the intention-to-treat patients. Horizontal lines within the boxes show the median, and the boxes show IQR. EN=enteral nutrition. ICU=intensive-care unit. SPN=supplemental parenteral nutrition.

The adjusted probability of nosocomial infection between days 9 and 28 was significantly lower in the SPN group than in the EN group (41 [27%] of 153 patients in the SPN group had a nosocomial infection during follow-up compared with 58 [38%] of 152 patients in the EN group; hazard ratio 0·65 [95% CI 0·43—0·97]; p=0·0338) The Poisson regression model analysis also showed a significant reduction in the number of nosocomial infections in the SPN group compared with the EN group (−0·42, 95% CI −0·79 to −0·05; p=0·0248) during the 28-day follow-up.

Univariable and multivariable Cox regression model for first nosocomial infection during follow-up (primary endpoint)

We noted no increase in the number of bloodstream infections in the SPN group, nor a difference in the distribution of nosocomial infections, during intervention (days 4—8) and follow-up (days 9—28)

During follow-up, the mean number of antibiotics days was significantly lower in the SPN group than in the EN group, and the mean number of antibiotic-free days was higher in the SPN group.

Secondary outcomes during follow-up and throughout duration of study

Time on mechanical ventilation during the entire study and during follow-up only was similar in both groups, but was significantly reduced in patients without nosocomial infections. The mean lengths of stay in the ICU and hospital, frequency of hypoglycaemia and hyperglycaemia, and renal replacement therapy requirement (data not shown) did not significantly differ between groups. ICU and general mortality at day 28 was similar in both groups. During the intervention period, glycaemic AUC measurements and the amount of insulin did not differ between groups (data not shown). Throughout the study, 21 911 blood glucose measurements were taken (11 305 during intervention). More short episodes of hyperglycaemia occurred in patients given SPN than in patients given EN, but the AUC did not increase during the intervention period (mean blood glucose concentration 1100 mmol/L [SD 282] in the EN group vs 1092 mmol/L [264] in the SPN group). Daily insulin requirements did not differ between the groups, and episodes of hypophosphataemia and hyperphosphataemia were equally distributed between groups (data not shown). By day 8, aspartate aminotransferase and alanine aminotransferase plasma concentrations were similar in both groups (data not shown), but alkaline phosphatase concentrations were lower in the SPN group than in the EN group (2·01 μkat/L in SPN group vs 2·75 μkat/L in EN group; p=0·0131). Mean C-reactive protein concentrations did not differ significantly between groups in the intention-to-treat analysis (data not shown), but did decrease significantly more in the SPN group than in the EN group after day 8 according to the per-protocol analysis (decrease of 959·54
nmol/L in SPN group vs 667·44 nmol/L in EN group; p=0·0180). The use of prokinetic agents did not differ between the SPN and the EN groups (data not shown).

Discussion

Findings from this trial suggest the clinical usefulness of complementing the energy delivery of insufficient EN with a parenteral booster between day 4 and day 8 after ICU admission. The provision of close to 100% of energy requirements reduced the risk of development of nosocomial infections, the number of antibiotic days, and the duration of mechanical ventilation in patients without nosocomial infections up to day 28.

This trial is one of the first studies to show that a combined feeding strategy with exact provision of energy needs is beneficial. Malnutrition and underfeeding are associated with poor outcome in patients in the ICU, especially infectious complications, but the optimum timing of parenteral intervention is controversial because septic complications have been associated with this approach. In patients with an infection, mortality rate is higher with the use of early PN alone, or combined PN with EN, than with EN alone. Furthermore, results of the Tight Calorie Control Study (TICACOS), showed that EN supplemented with PN with an energy target determined by repeated indirect calorimetry measurements, adjusted from the first day of ICU admission, led to lower hospital discharge mortality than did EN supplemented with PN with targets not calculated by calorimetry, but was associated with more infections and a longer time on mechanical ventilation than was the control group.

Panel

Research in context

Systematic review

We searched online bibliographic databases (PubMed), personal files, and relevant reference lists with the search terms “parenteral nutrition”, “enteral nutrition”, “critically ill” and “clinical outcome”, restricting our search to articles published in English between January, 1990, and July, 2012. The meta-analysis by Simpson and colleagues was the first to show that parenteral nutrition (PN) improves overall clinical outcome in patients in the intensive-care unit (ICU), although PN did increase the infection rate. Villet and colleagues and Dvir and colleagues showed that nutritional deficits resulting from insufficient enteral nutrition (EN) were closely associated with an increased number of complications, mostly infections, in these patients. Our group previously presented a nutritional algorithm for this critically ill population, with the objective of providing 100% of the energy target from day 4 after ICU admission by supplementing EN with PN.

Two other studies explored the same hypothesis with conflicting results. The Tight Calorie Control Study (TICACOS), a prospective randomised controlled study, assessed the effects of precisely calculated daily energy needs in mechanically ventilated patients in the ICU. Patients were randomly assigned either to target energy delivery, calculated by indirect calorimetry, adding PN to EN when necessary, or to routine nutritional support (25 kcal/kg per day). A non-significant decrease in post-ICU mortality was reported in patients fed according to indirect calorimetry, despite more infections and a longer duration on mechanical ventilation; of note, non-nutritional energy delivery was not incorporated into the
prescription, causing overfeeding. The large, prospective, Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) trial, randomised patients to early (day 2 with glucose from day 0) versus late (day 8) PN after ICU admission, and concluded that early PN was harmful (more complications, including infections), although tight glycaemic protocol was provided for all patients.

Interpretation

Our study is the first randomised controlled trial to show that optimisation of the energy target by supplemental PN (SPN) in critically ill patients for whom EN is insufficient is associated with reduced nosocomial infections, antibiotic use, and shorter duration of mechanical ventilation. The initiation of PN on day 4 after admission, the careful adjustment of the energy supply to avoid excessive energy delivery, and close metabolic monitoring contributed to the favourable outcome and allowed good glycaemic control. The difference in outcomes between our SPN study and both TICACOS and EPaNIC could be attributed to a slight but systematic overfeeding in both trials’ intervention groups, and to the inclusion in the EPaNIC trial of patients without a firm indication for nutritional therapy or PN (ie, very short ICU stay not allowing EN intolerance detection, 61% elective heart surgery, 58% stayed ≤5 days). Furthermore, an early hypertonic glucose load during the acute phase in the early PN group, and overfeeding due to the absence of indirect calorimetry, contributed to the increased rate of infections in EPaNIC.

Our findings provide evidence that individually optimised energy supplementation with SPN starting 4 days after admission should be considered as a strategy to improve clinical outcome in patients in the ICU with insufficient EN.

By contrast, findings from other studies have shown that the optimisation of EN within 24—48 h of ICU admission reduces infectious complications and mortality. In parallel to the lower infection rate in the SPN group, we also noted lower C-reactive protein concentrations in the SPN group than in the EN group, reflecting the reduced number of infectious complications. Results of our trial further reinforce the importance of energy provision by showing that delivery of near 100% of energy supply with an SPN approach can effectively decrease infections and antibiotic use.

Three factors might explain the between-group difference in the number of infectious complications in our trial: the trial protocol, in particular the initiation on day 4 of SPN; careful adjustment of energy supply, which avoided excessive energy delivery (ie, overfeeding) in the SPN group; and metabolic monitoring. Contrary to previous studies that started PN early after admission to the ICU, we delayed PN until 4 days after ICU admission, allowing EN to progress sufficiently so as to limit the amount of PN needed. Moreover, by allowing advancement of EN delivery during the first 3 days, no attempt was made to force EN, preventing potential tracheal aspiration. PN was adjusted twice daily to account for EN delivery changes. In the TICACOS trial, the infections count started 48 h after ICU admission—ie, before a nutritional intervention could have achieved an effect—whereas we considered new infections only after day 8, postulating that a minimum energy difference would be needed to achieve a clinical effect, while avoiding overfeeding.

Other infectious risk factors were strictly controlled in our study. Both ICUs apply a glycaemic control protocol, which aims to lower metabolic and infectious complications associated with PN. Additionally, both ICUs have protocols and checklists for central venous line insertion. In our trial, the catheter infection rate was low and similar in both groups. Indeed, the central catheter infection rate was lower than has been reported elsewhere. Finally, while achieving better energy provision, we simultaneously provided higher intakes of proteins, vitamins, and micronutrients, which might
also have contributed to the reduction in infection. The relation between optimum protein—energy intake and weaning time is still not well described. Compared with TICACOS, we noted a shorter mechanical ventilation time for the patients given SPN. Also noteworthy is that patients in the indirect calorimetry group in TICACOS were slightly overfed, because the investigators did not include non-nutritional energy delivery in their daily targets, resulting in a nearly systematic passing of the target (non-nutritional calories account for 100—400 kcal per day in our experience). We postulate that adequate energy and protein provision in the SPN group might have contributed to faster weaning from mechanical ventilation by decreasing nosocomial infections or decreasing skeletal muscle catabolism, particularly in the diaphragm, maintaining inspiratory muscle strength, and preventing weaning failures.

Neither overfeeding, which causes excess carbon dioxide production, nor serious adverse events attributable to hyperglycaemia, occurred in the SPN group. These results might explain why patients in the SPN group spent less time on mechanical ventilation than did those in the EN group. Indirect calorimetry optimises adequate prescription of energy, at least in the sickest patients. Phosphate deficiency has also been associated with respiratory muscle weakness and weaning failure; however, weaning failure was not an issue in our trial because phosphataemia was measured daily and treated according to the needs of individual patients.

Our results contrast with those of the Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) trial by Casaer and colleagues, which compared prolonged semistarvation to early glucose load followed by early PN; however, the studies have several differences. Our trial assessed severely critically ill patients with indications for artificial nutrition, whereas EPaNIC studied mostly patients who had had cardiac surgery, who rarely need such support, especially PN. We looked at patients staying in the ICU for at least 5 days, whereas 50% of the patients in EPaNIC stayed in the ICU for less than 3 days (only 40·5% of patients were still in the ICU by day 5, and 29·8% by day 7, compared with 90% by day 9 in our trial). Patients in the PN group of EPaNIC were given a high early glucose load from day 1, according to local practice, whereas we started the intervention on day 4 to maximise the potential for EN delivery, in keeping with European Society for Clinical Nutrition and Metabolism guidelines. Moreover, our EN group was a true control group, showing cumulative increasing energy deficit. Our population was composed exclusively of patients with a real indication for nutritional support, with a mean cumulative energy deficit of nearly −4000 kcal at day 4. These patients were generally more fragile, with a true risk of malnutrition, than were the patients assessed in EPaNIC.

In our trial, mortality at day 28 did not differ between groups, but the study was not powered to detect a mortality difference. Moreover, observed mortality was lower than expected mortality as predicted by the severity scores. Our data are in agreement with that from studies showing that optimised nutrition, whatever the route, decreases mortality in critically ill patients compared with insufficient nutrition provision.

Both participating centres included a well balanced population of medical and surgical patients, and have high standards of nutritional care, shown by low cumulative energy deficits in the EN group. Almost two-thirds of patients had indirect calorimetry at day 3 after ICU admission, allowing energy delivery as close as possible to the predefined 100% energy target, preventing overfeeding. The energy target was precisely reached in the SPN group, as shown by a neutral cumulative energy balance during the intervention period. Delivery of any energy, including non-nutritional glucose and fat, was recorded by computerised systems, reducing inaccuracies in the data.
We also showed that SPN neither compromised glycaemic control nor increased insulin needs compared with EN, thereby confirming that patients in the SPN group were not overfed. Also of note is that all results were confirmed by the per-protocol analysis.

Our trial was limited by the fact that it was not double blinded by design. However, the risk of bias was reduced because the investigators worked independently from the physicians in charge of the patients. Moreover, the difference in the energy delivery between groups was small because EN patients were not underfed intentionally (pure EN during the first week reached more than 75% of energy target by day 8). This percentage is higher than reported by others. Furthermore, stratification for body-mass index showed no significant difference between the two groups (data not shown).

Our findings could contribute to improvement of patient care by emphasising the importance of nutritional support and dedicated nutritionists. In addition to the nutritional quality improvement recorded, SPN could reduce overall health-care costs by reducing nosocomial infections, antibiotic usage, and time on mechanical ventilation, which could easily offset the costs of SPN.

Contributors

CP designed the study. CPH, MMB, SG, PD, and RT recruited patients, and CPH, MMB, and CP obtained ethical committee approval. CPH, MMB, SG, PD, RT, and CP participated in the search of the scientific literature, obtained the data, and reviewed and approved the final version of the report. WZ also helped to obtain the data. CPH, MMB, SG, WZ, RT, and CP interpreted and analysed the data, with MCC providing supervisory statistical advice. All authors helped to draft the report or critically revise the draft, and had final approval of the report.

Conflicts of interest

MMB has received research grants and consulting fees from Laboratoire Aguettant, Baxter, B Braun, Fresenius Kabi, Nestlé Medical Nutrition, and Novartis. PD was supported by an unrestricted academic research fellowship from Novo Nordisk France. RT has received consultancy fees from Baxter, B Braun, Nestlé Medical Nutrition, and Nutricia. CP has received research grants and consulting fees from Abbott, Baxter, B Braun, Cosmed, Fresenius Kabi, Nestlé Medical Nutrition, Novartis, Nutricia-Numico, Pfizer, and Solvay. CPH, SG, WZ, and MCC declare that they have no conflicts of interest.

Causal Relationship between Obesity and Vitamin D Status: Bi-Directional Mendelian Randomization Analysis of Multiple Cohorts

PLOS Med
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Background

Obesity is associated with vitamin D deficiency, and both are areas of active public health concern. We explored the causality and direction of the relationship between body mass index (BMI) and 25-hydroxyvitamin D [25(OH)D] using genetic markers as instrumental variables (IVs) in bi-directional Mendelian randomization (MR) analysis.

Methods and Findings

We used information from 21 adult cohorts (up to 42,024 participants) with 12 BMI-related SNPs (combined in an allelic score) to produce an instrument for BMI and four SNPs associated with 25(OH)D (combined in two allelic scores, separately for genes encoding its synthesis or metabolism) as an instrument for vitamin D. Regression estimates for the IVs (allele scores) were generated within-study and pooled by meta-analysis to generate summary effects.

Associations between vitamin D scores and BMI were confirmed in the Genetic Investigation of Anthropometric Traits (GIANT) consortium (n = 123,864). Each 1 kg/m^2 higher BMI was associated with 1.15% lower 25(OH)D (p = 6.52×10^{-27}). The BMI allele score was associated both with BMI (p = 6.30×10^{-62}) and 25(OH)D (−0.06% [95% CI −0.10 to −0.02], p = 0.004) in the cohorts that underwent meta-analysis. The two vitamin D allele scores were strongly associated with 25(OH)D (p≤8.07×10^{-57} for both scores) but not with BMI (synthesis score, p = 0.88; metabolism score, p = 0.08) in the meta-analysis. A 10% higher genetically instrumented BMI was associated with 4.2% lower 25(OH)D concentrations (IV ratio: −4.2 [95% CI −7.1 to −1.3], p = 0.005). No association was seen for genetically instrumented 25(OH)D with BMI, a finding that was confirmed using data from the GIANT consortium (p≥0.57 for both vitamin D scores).

Conclusions

On the basis of a bi-directional genetic approach that limits confounding, our study suggests that a higher BMI leads to lower 25(OH)D, while any effects of lower 25(OH)D increasing BMI are likely to be small. Population level interventions to reduce BMI are expected to decrease the prevalence of vitamin D deficiency.

Please see later in the article for the Editors' Summary

Editors' Summary

Background

Obesity—having an unhealthy amount of body fat—is increasing worldwide. In the US, for example, a third of the adult population is now obese. Obesity is defined as having a body mass index (BMI, an indicator of body fat calculated by dividing a person’s weight in kilograms by their height in meters squared) of more than 30.0 kg/m^2. Although there is a genetic contribution to obesity, people generally become obese by consuming...
food and drink that contains more energy than they need for their daily activities. Thus, obesity can be prevented by having a healthy diet and exercising regularly. Compared to people with a healthy weight, obese individuals have an increased risk of developing diabetes, heart disease and stroke, and tend to die younger. They also have a higher risk of vitamin D deficiency, another increasingly common public health concern. Vitamin D, which is essential for healthy bones as well as other functions, is made in the skin after exposure to sunlight but can also be obtained through the diet and through supplements.

Why Was This Study Done?

Observational studies cannot prove that obesity causes vitamin D deficiency because obese individuals may share other characteristics that reduce their circulating 25-hydroxy vitamin D [25(OH)D] levels (referred to as confounding). Moreover, observational studies cannot indicate whether the larger vitamin D storage capacity of obese individuals (vitamin D is stored in fatty tissues) lowers their 25(OH)D levels or whether 25(OH)D levels influence fat accumulation (reverse causation). If obesity causes vitamin D deficiency, monitoring and treating vitamin D deficiency might alleviate some of the adverse health effects of obesity. Conversely, if low vitamin D levels cause obesity, encouraging people to take vitamin D supplements might help to control the obesity epidemic. Here, the researchers use bi-directional “Mendelian randomization” to examine the direction and causality of the relationship between BMI and 25(OH)D. In Mendelian randomization, causality is inferred from associations between genetic variants that mimic the influence of a modifiable environmental exposure and the outcome of interest. Because gene variants do not change over time and are inherited randomly, they are not prone to confounding and are free from reverse causation. Thus, if a lower vitamin D status leads to obesity, genetic variants associated with lower 25(OH)D concentrations should be associated with higher BMI, and if obesity leads to a lower vitamin D status, then genetic variants associated with higher BMI should be associated with lower 25(OH)D concentrations.

What Did the Researchers Do and Find?

The researchers created a “BMI allele score” based on 12 BMI-related gene variants and two “25(OH)D allele scores,” which are based on gene variants that affect either 25(OH)D synthesis or breakdown. Using information on up to 42,024 participants from 21 studies, the researchers showed that the BMI allele score was associated with both BMI and with 25(OH)D levels among the study participants. Based on this information, they calculated that each 10% increase in BMI will lead to a 4.2% decrease in 25(OH)D concentrations. By contrast, although both 25(OH)D allele scores were strongly associated with 25(OH)D levels, neither score was associated with BMI. This lack of an association between 25(OH)D allele scores and obesity was confirmed using data from more than 100,000 individuals involved in 46 studies that has been collected by the GIANT (Genetic Investigation of Anthropometric Traits) consortium.

What Do These Findings Mean?

These findings suggest that a higher BMI leads to a lower vitamin D status whereas any effects of low vitamin D status on BMI are likely to be small. That is, these findings provide evidence for obesity as a causal factor in the development of vitamin D deficiency but not for vitamin D deficiency as a causal factor in the development of obesity. These findings suggest that population-level interventions to reduce obesity should
lead to a reduction in the prevalence of vitamin D deficiency and highlight the importance of monitoring and treating vitamin D deficiency as a means of alleviating the adverse influences of obesity on health.

Introduction

The prevalence of obesity has increased in the last two decades and it is presently the most common and costly nutritional problem. In the United States, one-third of the population is affected by obesity, according to the National Health and Nutrition Examination Survey. Despite a known genetic contribution, the increase in obesity prevalence has been largely attributed to lifestyle changes, which means that it is amenable to modification through public health and other interventions.

Vitamin D deficiency is another increasingly prevalent public health concern in developed countries, and there is evidence that vitamin D metabolism, storage, and action both influence and are influenced by adiposity. Observational studies have reported an increased risk of vitamin D deficiency in those who are obese; however, the underlying explanations and direction of causality are unclear. Active vitamin D (1,25-dihydroxyvitamin D) may influence the mobilisation of free fatty acids from the adipose tissue. In vitro experiments in rats have also shown that large doses of vitamin D2 lead to increases in energy expenditure due to uncoupling of oxidative phosphorylation in adipose tissues. However, randomized controlled trials (RCTs) testing the effect of vitamin D supplementation on weight loss in obese or overweight individuals have provided inconsistent findings. It has also been suggested that obesity could result from an excessive adaptive winter response, and that the decline in vitamin D skin synthesis due to reduced sunlight exposure contributes to the tendency to increase fat mass during the colder periods of the year. However, vitamin D is stored in the adipose tissue and, hence, perhaps the most likely explanation for the association is that the larger storage capacity for vitamin D in obese individuals leads to lower circulating 25-hydroxyvitamin D [25(OH)D] concentrations, a marker for nutritional status.

In the Mendelian randomization (MR) approach, causality is inferred from associations between genetic variants that mimic the influence of a modifiable environmental exposure and the outcome of interest. If lower vitamin D intake/status is causally related to obesity, a genetic variant associated with lower 25(OH)D concentrations should be associated with higher body mass index (BMI) (in proportion to the effect on 25(OH)D). Conversely, if obesity leads to lower vitamin D status, then genetic variants associated with higher BMI should be related to lower 25(OH)D concentrations. The genetic associations, unlike the directly observed associations for vitamin D intake/status, should be less prone to confounding by lifestyle and socio-economic factors and be free from reverse causation as genotypes are invariant and assigned at random before conception. The use of multiple SNPs to index the intermediate exposure of interest increases power and reduces the risk of alternative biological pathways (pleiotropy) affecting the observed associations between the genotype and the outcome.

In the present study, we investigated the relationship between BMI, a commonly used measure for monitoring the prevalence of obesity at the population level, and vitamin D status and we inferred causality by using genetic variants as instruments in bi-directional MR analyses. Meta-analysis included data from 21 studies comprising up to 42,024 individuals.

Methods
Ethics Statement

All participants provided written, informed consent, and ethical permission was granted by the local research ethics committees for all participating studies.

Participants

The collaboration investigating the association of vitamin D and the risk of cardiovascular disease and related traits (D-CarDia) consists of European ancestry cohorts from the United Kingdom (UK), United States (US), Canada, Finland, Germany, and Sweden. This study comprised a meta-analysis of directly genotyped and imputed SNPs from 21 cohorts totalling 42,024 individuals.

To replicate our findings on the association between the vitamin D-related SNPs and allele scores with BMI, we used the data from the genome-wide meta-analyses on BMI conducted as part of the Genetic Investigation of Anthropometric Traits (GIANT) consortium. The GIANT meta-analyses consisted of 46 studies with up to 123,865 adults of European ancestry, including the 1958 British Birth Cohort, Framingham Heart study, Nurses’ Health Study, Twins UK, UK Blood Services Common Control Collection, the Amish Family Osteoporosis Study, Health2000 GENMETS sub-sample, and Northern Finland Birth Cohort 1966, which were also part of the D-CarDia collaboration.

Genotyping

We selected 12 established BMI-related SNPs (fat mass and obesity-associated, \([FTO]\)-rs9939609, melanocortin 4 receptor \([MC4R]\)-rs17782313, transmembrane protein 18 \([TMEM18]\)-rs2867125, SH2B adaptor protein 1 \([SH2B1]\)-rs7498665, brain-derived neurotrophic factor \([BDNF]\)-rs4074134, potassium channel tetramerisation domain containing 15 \([KCTD15]\)-rs29941, ets variant 5 \([ETV5]\)-rs7647305, SEC16 homolog B \([SEC16B]\)-rs10913469, Fas apoptotic inhibitory molecule 2 \([FAIM2]\)-rs7138803, neuronal growth regulator 1 \([NEGR1]\)-rs3101336, mitochondrial carrier 2 \([MITC2]\)-rs10838738, and glucosamine-6-phosphate deaminase 2 \([GNPDA2]\)-rs10938397) for our analysis based on the study by Li et al. and previously published genome-wide association studies for obesity-related traits. The four vitamin D-related SNPs \([DHCR7]\)-rs12785878, \([CYP2R1]\)-rs10741657, \([GC]\)-rs2282679, and \([CYP24A1]\)-rs6013897) were chosen on the basis of the recent genome-wide association study on 25(OH)D. The studies that did not have genotyped data analysed imputed or proxy SNPs \((r^2 = 1)\) as available (with a call threshold of 0.9 for the SNPs imputed with Impute; for those imputed with MACH, a call threshold of 0.8 was used). The genetic data for most studies were obtained from genome-wide association platforms, but for some studies, variants were genotyped de novo (MRC Ely, the Canadian Multicentre Osteoporosis Study, the Hertfordshire cohort study) or obtained through metabochip custom array (MRC Ely). Five studies did not have all the BMI-related SNPs (Framingham Heart Study [one missing SNP], Hertfordshire cohort study [three missing SNPs], InCHIANTI [two missing SNPs], PIVUS [two missing SNPs], and ULSAM [three missing SNPs]) and were still included in the BMI allele score analysis.

Statistical Analysis

Analyses in each study were performed according to a standardized analysis plan. When used as outcome variables, 25(OH)D and BMI were natural log transformed to be more closely approximated by normal distributions. If multiplied by 100, coefficients from linear regression models...
with ln transformed outcomes can be interpreted as the percentage difference in the outcome. Models with BMI as an outcome were adjusted for age, sex, geographical site, and/or principal components from population stratification analysis (depending on data available); models with 25(OH)D as the outcome were additionally adjusted for month of blood sample collection (as a categorical variable) to account for seasonal variation and laboratory batch, where relevant. To assess the BMI relationship with 25(OH)D and vice versa, each study ran linear regression models adjusting for the covariates listed for each outcome, and the models were repeated stratifying by sex.

For the BMI SNPs, the effect allele was the BMI raising allele as established by Speliotes et al. We created a weighted score in each study, by multiplying each SNP (coded as 0–2) by a weight based on its effect size with BMI in the meta-analysis by Speliotes et al. The weighted BMI allele score was rescaled over the sum of weights for the available SNPs in each study to facilitate interpretation. For the vitamin D SNPs, the effect allele was the 25(OH)D lowering allele as established by the SUNLIGHT Consortium. As external weights were not available and the use of internal weights could bias the instrumental variable (IV) results, we performed an unweighted allele score analysis for the vitamin D SNPs. Vitamin D SNPs were used to form two separate allele scores: a “synthesis” allele score, created by summing the risk alleles in DHCR7 and CYP2R1, and a “metabolism” allele score, created by summing the risk alleles in GC and CYP24A1. Synthesis allele score was not created for the LURIC study (one missing SNP) and both synthesis and metabolism allele scores were not created for the MRC Ely study (two missing SNPs). The synthesis allele score included the SNPs that contribute directly to the production of 25(OH)D, and hence, for which the association with the outcome can be readily estimated based on the magnitude of the association between the score and 25(OH)D. All analyses were done separately for the “metabolism” SNPs that are involved in the clearance or transport of 25(OH)D (with possible influences on bioavailability as the quantification of the association with the outcome based on the observed SNP-25(OH)D association is more difficult. We also evaluated the joint contribution of synthesis and metabolism scores on BMI by including both vitamin D scores as separate variables in a multiple regression model.

To examine the strength of the allele scores as instruments, the F-statistic was approximated from the proportion of variation in the respective phenotype (R²) explained by the allele score, \[ F\text{-stat} = \left( \frac{R^2 \times (n-2)}{1-R^2} \right) \].

To confirm our findings on the association between the vitamin D-related SNPs and allele scores with BMI in a larger sample, we used the summary statistics for the four vitamin D-related SNPs from the GIANT consortium. These SNPs were combined into synthesis and metabolism allele scores using an approximation method as previously described. The individual SNP association with BMI is then weighted according to its predefined effect size and meta-analysed using the inverse-variance method with the other SNPs in the score. The formal MR analyses to estimate the possible causal effect of BMI on 25(OH)D (and vice versa) were done using the IV ratio method. To estimate the IV ratio for the BMI effect on 25(OH)D, the meta-analysed association of the BMI allele score with 25(OH)D was divided by the association of BMI allele score with BMI. The variance for the IV ratio was estimated using a Taylor expansion. The corresponding calculation was done to establish the 25(OH)D effect on BMI, with the IV ratio method applied separately for the two vitamin D allele scores. The joint contribution of the two vitamin D scores on BMI was assessed by multivariate meta-analysis, which incorporated the covariance matrix as estimated by study specific analyses.

In the presence of heterogeneity of association between the studies, random effects meta-analyses were run, otherwise fixed effects models were used. Univariate meta-regression models were run to assess differences in the observed associations by study level factors of sex, average BMI (BMI≥25 kg/m² versus >25 kg/m²), the average age of participants (≤40, 41–60, and ≥61 y old), continent (North America versus Europe), and vitamin D assay (radio-immunoassay, enzyme-linked radio-immunoassay, and mass spectrometry). Power calculations for IV regression were
performed by simulation on the basis of associations observed between the phenotypes and their genetic proxies. For comparability across instruments/outcomes, power was determined for 0.02 log unit increase/decrease by decile, approximately corresponding to the association observed between BMI and 25(OH)D. To evaluate the ability to detect weaker effects on BMI using the synthesis and metabolism scores, power was also calculated for a 50% weaker effect (0.01 log unit increase/decrease). All meta-analyses and power calculations were performed at the Institute of Child Health (University College London, London) using STATA version 12.

Results

Phenotypic Association between BMI and 25(OH)D Concentrations

In the meta-analyses of 21 studies, each unit (kg/m$^2$) increase in BMI was associated with 1.15% (95% CI 0.94%–1.36%, $p = 6.52 \times 10^{-27}$) lower concentrations of 25(OH)D after adjusting for age, sex, laboratory batch, month of measurement, and principal components. The inverse association between BMI and 25(OH)D was stronger among the studies from North America than those from Europe (−1.58% [−1.81% to −1.36%], $p = 1.01 \times 10^{-43}$ versus −0.91% [−1.18% to −0.64%], $p = 4.55 \times 10^{-11}$; $p_{meta-regression} = 0.004$) and for women than men (−1.43% [−1.65% to −1.22%], $p = 1.13 \times 10^{-38}$ versus −0.75% [−1.00% to −0.50%], $p = 3.89 \times 10^{-9}$; $p_{meta-regression} = 4.10 \times 10^{-4}$) while no variation was seen by average age ($p_{meta-regression} = 0.78$) or BMI ($p_{meta-regression} = 0.48$).

Evaluation of Causal Association Using MR Approach

The BMI allele score created from the 12 BMI-related SNPs showed a positive dose-response association with BMI (per unit increase 0.14% [0.12%–0.16%], $p = 6.30 \times 10^{-62}$), and both vitamin D allele scores showed the expected strong associations with 25(OH)D (per allele in synthesis score: −3.47% [−3.90% to −3.05%], $p = 8.07 \times 10^{-57}$; metabolism allele score: −5.38% [−5.84% to −4.93%], $p = 1.07 \times 10^{-118}$). The BMI allele score was also associated with 25(OH)D concentrations (per unit increase −0.06%, [−0.10% to −0.02%], $p = 0.004$), while no association with BMI was seen for either the vitamin D synthesis or metabolism allele scores (per allele in synthesis score: 0.01% [−0.17% to 0.20%], $p = 0.88$, metabolism allele score: 0.17% [−0.02% to 0.35%], $p = 0.08$). Analyses of joint effects by synthesis and metabolism scores provided no evidence for an association between 25(OH)D and BMI (per allele in synthesis score −0.03% [−0.23% to 0.16%] and metabolism score 0.17% [−0.04% to 0.37%], joint contribution $p = 0.26$).

In the analyses to establish the direction and causality of BMI–25(OH)D association by the use of the IV ratio, BMI was associated with 25(OH)D: each 10% increase in BMI lead to a 4.2% decrease in 25(OH)D concentrations (−7.1% to −1.3%; $p = 0.005$). However, the IV ratio analyses provided little evidence for a causal effect of 25(OH)D on BMI ($p ≥ 0.08$ for both).

The lack of association of the vitamin D allele scores with BMI was further confirmed using the GIANT consortium including 123,864 individuals in 46 studies: neither the synthesis nor the metabolism allele score showed any evidence for an association with BMI ($p ≥ 0.57$ for both).
Additional Analyses

Validation of the genetic instruments.

The BMI SNPs and the vitamin D SNPs were all individually associated with BMI and 25(OH)D, respectively. The exception was KCTD15 SNP, which despite previous evidence for an association, was not associated with BMI in our meta-analyses. Across the studies, the 12 BMI SNPs combined as the BMI allele score explained 0.97% of the variation in BMI (F-statistic = 316; n = 32,391). The synthesis allele score explained 0.64% (F-statistic = 230; n = 35,873) and the metabolism allele score 1.26% (F statistic = 499; n = 38,191) of the variation in 25(OH)D. There was no evidence for variation in the BMI allele score–BMI association by continent ($p_{meta-regression} = 0.15$) or BMI ($p_{meta-regression} = 0.83$). However, the BMI allele score–BMI association was slightly weaker in studies with older compared to younger participants ($-0.03\% [-0.05\% to -0.002\%]$, $p_{meta-regression} = 0.03$). The vitamin D allele score–25(OH)D association did not vary by age, BMI, continent, or assay ($p_{meta-regression} \geq 0.09$ for all comparisons).

Evaluation of the genetic outcome associations.

Of the 12 individual BMI SNPs, the SNP for FTO was the only one that showed evidence of a univariate association with 25(OH)D ($p = 0.050$). None of the four 25(OH)D SNPs were individually associated with BMI ($p \geq 0.10$). The lack of association of the four vitamin D SNPs with BMI was further confirmed using the summary data from the GIANT consortium ($p \geq 0.30$ for all the SNPs)

The association between BMI allele score and 25(OH)D did not vary by study level factors, including age ($p_{meta-regression} = 0.40$), BMI ($p_{meta-regression} = 0.18$), continent of study ($p_{meta-regression} = 0.78$), or vitamin D assay ($p_{meta-regression} = 0.23$). Similarly, there was no evidence for variation in the vitamin D allele score–BMI association by age ($p_{meta-regression} \geq 0.25$ for both scores), or continent ($p_{meta-regression} \geq 0.50$ for both scores). There was also no strong evidence for variation in the vitamin D allele score–BMI association by average BMI of the study ($\leq 25$ kg/m$^2$ versus $\geq 25$ kg/m$^2$), although for the synthesis score the meta-regression coefficient was of borderline significance ($p_{meta-regression} = 0.053$, Figure S8; $p_{meta-regression} = 0.78$ for metabolism score).

Power comparison.

In theory, we had greater power to detect an association between 25(OH)D and BMI using the metabolism score as an instrument, compared with an equal sized association between BMI and 25(OH)D using the BMI risk score. However, if the size of the association between 25(OH)D and BMI was only half that seen between BMI and 25(OH)D, our study would not have been adequately powered even with the inclusion of the GIANT results.

Discussion

Obesity, and perhaps vitamin D deficiency, are among the most important modifiable risk factors for a number of chronic diseases. Obesity and vitamin D status are known to be associated but the direction of the association and whether it is causal has been uncertain. We have presented
genetic evidence that higher BMI leads to lower vitamin D status. Conversely, our analyses provided no evidence for a causal role of vitamin D in the development of obesity, although our study was not powered to detect very small effects. These results suggest that although increases in vitamin D status are not likely to help with weight regulation, increased risk of vitamin D deficiency could contribute to the adverse health effects associated with obesity.

The association between obesity and vitamin D status was remarkably consistent across the different populations included in our meta-analyses, being apparent both in men and in women, and in the young and older cohorts alike. Interestingly, the association between obesity and 25(OH)D concentrations appeared stronger for populations in North America compared to Europe, possibly reflecting differences in the distribution of BMI across the continents. Recent intervention studies have shown that obese individuals need higher vitamin D dosages than lean individuals to achieve the same 25(OH)D concentrations. Given that North America has one of the highest rates of obesity in the world, our study highlights the importance of considering obesity as a risk factor for vitamin D deficiency with implications on the dosage requirements and possible targeting of relevant health promotion strategies.

The lack of any suggestion for an association between the vitamin D SNPs and BMI in the GIANT consortium (n = 123,864) alongside our own large meta-analyses provides a strong case against linear increases in 25(OH)D having a substantive influence on BMI. This conclusion is in accordance with a recent study on Chinese women (n = 7,000), which also failed to observe evidence for an association with BMI for genetic variants in the vitamin D pathway. Although a recent RCT (n = 77) suggested greater loss in fat mass for women receiving vitamin D, previous trials have failed to show any evidence for an effect despite larger treatment groups (n = 200–445), use of higher vitamin D dosages, and equal duration of treatment (12 mo). Dilution related to the greater volume of distribution has been recently proposed as the most likely explanation for the lower 25(OH)D concentrations in obese individuals. In that study, no evidence was found for reduced bioavailability through increased sequestration of vitamin D in the adipose tissue, which had previously been suggested to contribute to the low 25(OH)D concentrations in obesity. In contrast, intact parathyroid hormone (iPTH) levels, which stimulate the 1-α-hydroxylase (CYP27B1) enzyme that converts 25(OH)D to 1,25-dihydroxyvitamin D (the active hormonal form), have been found to be elevated in obesity, which could to some extent also contribute to the lower 25(OH)D concentrations in obese individuals. It is also possible that differences in lifestyle could contribute to lower 25(OH)D concentrations in obese compared to normal weight individuals, although the association between obesity and low 25(OH)D concentrations has been found to only modestly attenuate after adjustment for vitamin D-related lifestyle and dietary factors.

The main strengths of this study are the large sample size and the individual level population-based data from North America and Europe. We used a bi-directional MR approach to investigate the causal directions between obesity and vitamin D deficiency, observing evidence for reductions in 25(OH)D by BMI but not vice versa. However, based on the biological pathways proposed, a possible effect of 25(OH)D on BMI could be expected to be weaker than the effect of BMI on 25(OH)D. Despite including data from the large GIANT consortium to narrow the range of effects compatible with the data, we are unable to exclude very small effects. Furthermore, while the MR approach enables the approximation of life-long differences in average concentrations, with genetic markers it is not possible to examine the influences arising from the extremes of non-linear distributions. Consequently, we cannot discount a possible effect of severe vitamin D deficiency on BMI due to evidence of non-linearity seen in some studies. In contrast, associations between BMI and 25(OH)D within levels in the obesity range were consistently linear in studies.
included in our analyses (unpublished data), hence the observed association between higher BMI and lower 25(OH)D is likely to be informative in the context of obesity.

One of the methodological challenges of the MR approach relates to the large sample size requirement, arising from the availability of relatively weak instruments for most exposures. This aspect of the MR approach is also reflected in our study, notably in the relatively small amount of variation explained by all the instruments used. We used the IV ratio method on meta-analyzed coefficients since all studies were not able to share individual level participant data. This method assumes linear relationships and may have less power to detect an effect than other IV methods. However, as shown by the clear outcome of these analyses, we were able to overcome these issues by combining several cohorts with comparable information, allowing us to achieve the large numbers required (maximum \( n = 42,024 \)). To confirm the lack of association between vitamin D-related genetic variations and BMI, we were able to expand the analyses by using data from the large GIANT meta-analyses (\( n = 123,864 \)). However, this cannot be considered an independent replication, as eight of the studies that were part of the D-CarDia Collaboration were also included in GIANT. The F-statistic is used to measure the strength of an instrument, and an instrument that has a value greater than 10 is considered strong enough to use in IV analyses. In our analyses, the F-statistic was greater than 200 for all instruments used due to our large sample size.

Combining large population-based studies from North America and Europe could lead to confounding by population stratification; however, we adjusted for geographical variation/principal components in all analyses, which appeared adequate, as there was no evidence for heterogeneity by continent for the allele score meta-analyses. An important benefit of the MR approach is that it helps to overcome problems of confounding and reverse causality, which limit the ability to draw causal inferences in non-genetic observational studies. However, it could be argued that as the biological function for some of the BMI SNPs is yet to be established, there could be alternative biological pathways explaining their association with BMI. Using multiple SNPs to index BMI, we were able to minimise the risk of pleiotropic effects, as the effects of alternative pathways reflected by individual SNPs would be expected to be strongly diluted when combined in a multi marker score.

In conclusion, we demonstrated that the association between BMI and lower 25(OH)D concentrations in Caucasian populations from North America and Europe can be seen across different age groups and in both men and women. We also show that higher BMI leads to lower vitamin D status, providing evidence for the role of obesity as a causal risk factor for the development of vitamin D deficiency. Together with the suggested increases in vitamin D requirements in obese individuals, our study highlights the importance of monitoring and treating vitamin D deficiency as a means of alleviating the adverse influences of excess adiposity on health. Our findings suggest that population level interventions to reduce obesity would be expected to lead to a reduction in the prevalence of vitamin D deficiency.

**Obesity**

**Leading Avoidable Cause of Premature Deaths Worldwide: Case for Obesity**

February 2013
In the United States, 2 of 3 adults currently are overweight or obese. The prevalence of obesity has not changed in recent years, but it is still 3 times greater than in 1980. During the last several decades, there has been a systematic underestimation of the hazards of obesity. The dangers of obesity have been grossly underestimated due to several biases. The first is the failure to control for cigarette smoking. Cigarette smokers are thinner because of appetite suppression and increased metabolic rates and also die at higher rates. Thus, the failure to control for this confounder leads to the erroneous conclusion that obesity is less harmful. The second is inappropriate control for direct biologic effects of obesity such as hypertension, dyslipidemia and diabetes. Inappropriate control for direct effects of obesity, which are not confounders, leads to gross underestimates of harm. The third is failure to exclude subjects at baseline with severe weight loss due to subclinical disease. In large prospective cohort studies, lower weight at baseline due to subclinical disease leads to premature mortality, so failure to exclude such subjects underestimates the hazards of obesity.

The dangers of obesity have been grossly underestimated in clinical outcome studies because of the failure to control for cigarette smoking, inappropriate control for the biologic effects of obesity (eg, hypertension and diabetes), and failure to exclude subjects at baseline with severe weight loss due to subclinical disease. Cigarette smokers are thinner because of appetite suppression and increased metabolic rates. Failure to control for this confounder leads to the erroneous conclusion that obesity is less harmful. In addition, excessive and unjustified control for direct effects of obesity, such as hypertension and diabetes, leads to gross underestimates of harm. Finally, in large prospective cohort studies, lower weight at baseline due to subclinical disease leads to premature mortality, so failure to exclude such subjects underestimates the hazard of obesity. In the United States today, there is an approximate 10-pound weight gain per decade in middle-aged persons, so an unexplained weight loss of 10 or more pounds may be a harbinger of doom. All of these considerations are less than comforting news to a society that has been the fattest in the world and, perhaps, in the history of the world.

Body mass index (BMI), the ratio of weight in kilograms to height in meters squared, is a risk factor for many major causes of death, including coronary heart disease, stroke, and cancers of the large intestine, kidney, uterus, and breast in postmenopausal women. Even more alarming, in many populations, including developing countries throughout the world, the average BMI is increasing by several percentage points per decade.

In the Prospective Studies Collaboration, a collaborative analysis of data from 57 studies of approximately 900,000 adults, overall mortality was lowest at a BMI of 22 to 25 kg/m2 in men and women of all ages. In those with a BMI greater than 25 kg/m2, each 5 kg/m2 increase in BMI increased total mortality by 30%. These relative risks for BMI, combined with recent population BMI values, suggest that during the next decade in the United States, approximately 29% of deaths due to cardiovascular disease and 8% of deaths due to cancer will be attributable to a BMI greater than 25 kg/m2 in middle-aged people.
In adulthood, avoidance of weight gain may be easier to achieve than weight loss. In that regard, avoidance of increases in BMI from 28 to 32 kg/m² in early middle age would allow an individual to gain approximately 2 years of life expectancy. By avoiding an increase in BMI from 24 to 32 kg/m², a young adult would gain approximately 3 extra years of life. Further, for men and women, the median survival is reduced by 0 to 1 year for people aged 60 years with a BMI of 25 to 27.5 kg/m², by 1 to 2 years in those with a BMI of 27.5 to 30 kg/m², by 2 to 4 years in those with a BMI of 30 to 35 kg/m², and by 8 to 10 years for those with a BMI greater than 40 kg/m². This extreme reduction in survival with morbid obesity is as much as the 10-year reduction in survival caused by persistent cigarette smoking.

The pandemic of obesity results from genetic and environmental factors, chiefly increased caloric intake and physical inactivity beginning in childhood. More alarming, these trends also have been well documented in many developing countries. In the most populous country in the world, China, the remarkable increase in the prevalence of obesity in urban areas is already accompanied by remarkable increases in the prevalence of diabetes.

In data from a random sample of the US population aged 20 years or older, 20% have metabolic syndrome, a constellation of obesity, hypertension, dyslipidemia, and insulin resistance, a precursor of diabetes. In those aged 50 years or more, 30% have metabolic syndrome, and their 10-year risk of a first coronary event is 16% to 18%, which is approximately as high as that of a patient receiving secondary prevention. The therapeutic lifestyle changes of weight loss and increased physical activity would preclude the need for pharmacologic therapies for the majority. Unfortunately, in the United States, many prefer the prescription of pills to the proscription of harmful lifestyles. Thus, although lifestyle changes should be strongly recommended, clinicians should not let the perfect be the enemy of the possible. Evidence-based doses of statins, aspirin, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers should be prescribed as adjuncts, not alternatives, to therapeutic lifestyle changes.

At present, most of the remarkable decline in mortality from cardiovascular disease in the United States during the past several decades is due to treatment, not prevention, and the rate of decline is decreasing. As this current generation of US children and adolescents reach middle age, morbidity and mortality from cardiovascular disease will increase. It is likely that the current generation of children and adolescents in the United States will be the first since 1960 to have higher mortality rates due to cardiovascular disease, including coronary heart disease and stroke, than their parents. The alarming increases in obesity and tobacco consumption in developing countries have led to reliable estimates that cardiovascular disease has already increased from the number 5 killing disease to the leading killing disease in the world. Approximately 17.3 million people died of cardiovascular disease in 2008, a figure that will increase to approximately 23.6 million by 2030. More than 80% of premature deaths from cardiovascular disease already occur in low- and middle-income countries.

The need for primary prevention of obesity beginning in childhood is clear, but there is no consensus regarding the best approach that should include therapeutic lifestyle changes and pharmacologic therapies. Further research is certainly warranted but so are clinical and health policy measures.
Emerging Technology in Diabetes Care: The Real-Time Diabetes Monitoring System

Military Medicine
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Abstract

The majority of telemedicine interventions for diabetes have failed to show objective improvements in outcomes. We describe the Real-Time Diabetes Monitoring System (RT-DMS), which augments our successful telemedicine system for pediatric patients with type 1 diabetes by allowing automated uploads of glucometer readings. The addition of automatic transfer of glucometer readings enables RT-DMS to improve patient compliance and increases monitoring by physicians. The system is scalable for use by both children and adults with all forms of diabetes and has the potential to significantly improve clinic workflow, allowing RT-DMS to serve as a model for managing chronic disease using telemedicine.

Introduction

Caregivers for pediatric patients with type 1 diabetes must be able to communicate effectively with their physician to facilitate quality medical care. We have previously reported on the effectiveness of the Pediatric Diabetes Education Portal (PDEP) website at our institution, showing that users of the PDEP website had a significant improvement in Hemoglobin A1c when compared to nonusers. PDEP is a secure, Health Insurance Portability and Accountability Act (HIPAA) compliant, asynchronous (store-and-forward) website for pediatric diabetic patients and their families that improves communication with their physicians. PDEP allows families to log on from home using a computer or smartphone, review clinic testing results, post comments and ask questions of their diabetes care providers. Patients and families can also review educational materials on the web site.

A major limitation of PDEP, however, is that it requires patients to manually type in or upload scanned copies of their blood sugar readings for later review. Because of this, a significant amount of data captured by the patient (glucometer readings) is never transferred to the physicians for review. To address this, we have now deployed our Real-Time Diabetes Monitoring System (RT-DMS), an addition to the PDEP website that allows for automated uploading of glucometer readings to help pediatric patients with their diabetes care. Unlike previous systems described in the literature which required telephone calls, use of computer modems, potentially difficult interactions with websites, or downloading of devices that are sometimes challenging to connect to home computers, RT-DMS allows for transparent uploading of glucometer readings with minimal patient and physician effort.

Real-Time Diabetes Monitoring System
With RT-DMS, patients were given a MedApps HealthPAL device (MedApps, Scottsdale, Arizona) to connect to their glucometer as part of an institutional review board approved project at Tripler Army Medical Center (TAMC). The HealthPAL is a Food and Drug Administration approved device that plugs into a glucometer and was preconfigured for each patient's PDEP account. The device collects glucometer readings and securely transmits them via the cellular phone network to our existing PDEP website in real time. The HealthPAL uses 128-bit secure socket layer encryption and its transmissions meet all administrative requirements for full HIPAA compliance. Configuration of usernames, passwords, or other settings is unnecessary. Instead, the device is preconfigured and linked to the patient's PDEP account by the medical team. After transmission from the HealthPAL device, RT-DMS saves transmitted glucometer readings and aggregates them for posting on a weekly basis to PDEP, so there is no required time to plug in the device, emphasizing ease of use. A schematic representation of the system is shown in Figure 1.

After posting weekly glucometer readings, diabetes care providers are immediately notified by email to log on to the HIPAA compliant, secure PDEP website where they can interpret the readings and send a response to the patient. As shown in Figure 2, the parents of a 5-year-old type 1 diabetic patient plugged in the HealthPAL device to their son's glucometer at home. No other intervention was needed, and now the patient's glucometer readings are automatically ready for review by the pediatric endocrinologist and appear as a detailed table on the website in the patient's PDEP account. The endocrinologist is able to respond, and the family is automatically notified by email to log on and read the response. One week later, new readings are automatically uploaded again. The parents, who were resistant to write down glucometer readings and who had previously been nonusers of the PDEP website, now become active participants and begin to post comments (Fig. 3). The physician response can refer to educational materials posted on the website, allowing patients to continually review relevant educational material as they encounter new problems.

Discussion

Automated transfer of glucometer readings allows patients and their families to effortlessly engage their diabetes care provider with objective data for review. Although many systems have attempted to link medical devices to "health vaults" of medical information online, patient use was often limited because of difficulties sending data to the system and the lack of readily available feedback once the data was uploaded. In fact, previous studies show regular communication and feedback are linked to higher use of such systems.6 By linking seamless uploading of glucometer readings to an educational website that can provide patient-specific feedback, we hope to improve patient care beyond what we have shown previously.

Although we have not used the system long enough to formally assess the impact of such a device on changing objective outcome parameters of care (such as Hemoglobin A1c or the frequency of hypoglycemic events), we offer a description of RT-DMS to show how it can improve clinic workflow. This is because despite the extensive funding of the development of telemedicine systems over the last few years, results of many telemedicine and mHealth projects have not consistently shown definitive improvements in objective outcomes of care.7–9 Instead, it has been postulated that the greatest gains may come from simple increases in clinic efficiency and use of time.10,11 Automatic email notification of new postings and the asynchronous nature of the system allows families and providers to post messages at any time they want, with no need to interrupt other activities. For patients using RT-DMS, we no longer have to review faxed or emailed copies of glucometer readings and then call
back patients to explain recommended changes in insulin doses, saving time and effort that can now be used elsewhere. And by using billing
codes specifically designated by the Department of Defense (DoD) for telemedicine encounters, pediatric endocrinologists at TAMC are able to bill
for their time and capture workload using an integrated billing form that connects with the Armed Forces Health Longitudinal Technology
Application (AHLTA) workload module. In the case described above, we used an approved Current Procedural Terminology code for collection
and review of data electronically transmitted from the patient (Current Procedural Terminology Code 99091, bottom of Figs. 2 and 3). In this case,
we were able to bill 1.1 physician work relative value units that are paid to our military treatment facility from the DoD’s military healthcare system.
All of this done using the integrated billing module in RT-DMS that simply requires checking a box on the web page after submitting comments
back to the patient. This improves clinic workflow by decreasing time spent on telephone consults and faxes; time that is often not billed
appropriately in AHLTA.

It has been our experience that in many cases this type of data is never reviewed between appointments because patients find it too cumbersome
to use fax machines or secure email to send the relevant data. In addition, providers using AHLTA do not want to spend the time needed to enter
the appropriate codes and supporting documentation in such a cumbersome system that suffers from poor usability. It is also important to note
that providers outside of the DoD’s military healthcare system may choose to require the patient to return to clinic to review data that could
otherwise be easily transmitted electronically. This is because Medicare does not currently reimburse for this procedure code, and will again
change reimbursement codes for version 10 of the International Classification of Diseases, making it very difficult for providers to support such a
system outside of a military treatment facility.

A number of web-based and mobile applications currently exist to enhance diabetes management. The Medtronic Carelink system is one of many
programs that allows patients to upload readings from their glucometers and insulin pumps to a centralized database on the internet, where
physicians can download the results. Use of the Carelink system has been associated with improved glycemic control in children with type 1
diabetes on insulin pump therapy.12 Yet Carelink and similar systems do not automatically notify physicians that new results are available for
review. Instead, they require patients to click on a button and type in their health care provider’s email address for each report they wish to send.
In addition, they neither offer physicians the ability to send educational feedback to patients, nor do they link to a hospital billing system. These
restrictions limit their suitability for use by physicians seeking these features.

Similarly, there are now numerous mobile applications available for patients with diabetes. Analysis of these mobile applications has shown that
although clinical guidelines widely refer to the importance of personalized education, this remains an underrepresented feature in these
applications.13 This is reflected in studies that show improvements in the frequency of blood glucose monitoring in adolescents using mobile
diabetes applications,14 but studies that track objective outcomes of care (such as reduced hospitalizations and emergency department visits)
note that involvement from multiple parties is needed for successful outcomes.15 Usability issues have limited the adoption of systems designed
to integrate all aspects of diabetes care.13 Our system is designed to easily integrate all of these elements of care, with a focus on ease of use for
all parties involved.
RT-DMS is currently limited by the cost of each HealthPAL device, limiting the number of devices in use. With more devices we plan to expand RT-DMS to serve remote locations served by TAMC, such as other countries in the Pacific Rim that have access to cellular and internet technology but who, otherwise, have limited host nation resources. This will increase access to care for all of our patients. We also plan to add real-time alerts to the system for very high or low glucose readings, with an adjustable per patient threshold for when to alert physicians and family members by either phone call or text message.

We are also beginning work on phase 2 of the RT-DMS project, which was recently funded by the Army Medical Department's Advanced Medical Technology Initiative. Phase 2 will allow for a smartphone app to communicate with glucometers and insulin pumps, replacing the need for extra hardware such as the HealthPAL. We hope to deploy this smartphone app for patient use early next year.

Conclusion

By using the cellular technology embedded in the HealthPAL device, RT-DMS allows pediatric diabetic patients and their families to effortlessly transmit glucometer readings to their physicians. Pediatric endocrinologists can more effectively monitor patients and improve the quality of diabetes care with near real-time feedback when needed. We hope RT-DMS can serve as a model for managing chronic disease using telemedicine, and we are interested in joining other centers in expanding our outreach in caring for children and adults with both type 1 and type 2 diabetes.

In addition to improving the quality of medical care we can provide, it is our hope that long-term use of RT-DMS and similar systems will show significant costs/benefits related to improved clinic workflow. This will allow us to more effectively advocate for the creation of a standardized national billing model for telemedicine encounters.

Obstructive Sleep Apnea and Multimorbidity

BMC Pulmonary Medicine
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Abstract

Background: Obstructive sleep apnea (OSA) is becoming increasingly prevalent in North America and has been described in association with specific chronic diseases, particularly cardiovascular diseases. In primary care, where the prevalence of co-occurring chronic conditions is very
high, the potential association with OSA is unknown. The purpose of this study was to explore the association between OSA and 1) the presence and severity of multimorbidity (multiple co-occurring chronic conditions), and 2) subcategories of multimorbidity.

Methods: A cluster sampling technique was used to recruit 120 patients presenting with OSA of various severities from the records of a sleep laboratory in 2008. Severity of OSA was based on the results of the polysomnography. Patients invited to participate received a mail questionnaire including questions on sociodemographic characteristics and the Disease Burden Morbidity Assessment (DBMA). They also consented to give access to their medical records. The DBMA was used to provide an overall multimorbidity score and sub-score of diseases affecting various systems.

Results: Bivariate analysis did not demonstrate an association between OSA and multimorbidity ($r = 0.117; p = 0.205$). However, severe OSA was associated with multimorbidity (adjusted odds ratio = $7.33 [1.67–32.23], p = 0.05$). OSA was moderately correlated with vascular ($r = 0.26, p = 0.01$) and metabolic syndrome ($r = 0.26, p = 0.01$) multimorbidity sub-scores.

Conclusions: This study showed that severe OSA is associated with severe multimorbidity and sub-scores of multimorbidity. These results do not allow any causal inference. More research is required to confirm these associations. However, primary care providers should be aware of these potential associations and investigate OSA when deemed appropriate.

Background

Millions of North Americans are affected by the consequences of sleep disorders. Among these disorders, sleep apnea syndrome has the highest rate of mortality and morbidity. According to the Public Health Agency of Canada, 858,900 Canadians reported suffering from sleep apnea, and almost 26% of Canadians are at high risk of developing the condition. This disorder poses a major public health problem due to its prevalence, severity and socioeconomic burden. Obstructive sleep apnea (OSA) is defined as the cessation of naso-buccal air flow for more than 10 seconds, and is diagnosed based on an apnea–hypopnea index (AHI) value greater than five per hour of sleep, usually accompanied by a 4% decrease in oxygen saturation. It is estimated that 80% of obstructive sleep apnea cases remain undiagnosed, making it difficult to identify patients at risk of associated comorbidities. Reuveni et al. suggest that programs be developed to increase the level of suspicion of OSA among primary care providers.

OSA syndrome is independently associated with an increased risk of mortality. Fletcher reported that 70% to 90% of patients with OSA have hypertension. Associations between OSA and heart failure, OSA and arrhythmias, OSA and diabetes, OSA and insulin resistance and OSA and metabolic syndrome have also been reported. Successful treatment of OSA helps to better control many of the associated diseases and chronic conditions. Men, people 40 years old and over, and those with a high body mass index (BMI) or a large neck circumference are at greater risk for OSA.

Multimorbidity—the co-occurrence of two or more chronic diseases—is an emerging concept in the medical literature. One study showed that nine out of ten primary care patients had more than one chronic condition, while approximately 50% had five or more. Multimorbidity has been
associated with several adverse effects, such as a reduction in quality of life, an increase in psychological distress, medical complications and increased mortality.

Evidence of an association between OSA and multimorbidity could be an important incentive for the systematic screening for OSA in primary care settings—where the prevalence of multimorbidity is very high. The first objective of this study was to measure the association between the severity of OSA and the severity of multimorbidity, and second, to explore the association between OSA and various categories of multimorbidity.

Methods

This study used data from the sleep laboratory of the Centre de santé et de services sociaux de Chicoutimi (CSSSC), a regional health centre in the Saguenay region of Québec (Canada). As a first step in the recruitment process, a list of patients who had undergone polysomnography in 2008 was compiled. Patients were categorized according to the severity of their OSA, based on their polysomnography results (absent: AHI 0–4; mild: AHI 5–14; moderate: AHI 15–29; severe: AHI ≥ 30). We selected consecutive patients from each category to ensure a proportional representation (25% each) of the four OSA categories. French-speaking patients were selected between 30 and 75 years of age, to ensure adequate variation in degrees of multimorbidity. Each patient underwent polysomnography after January 1, 2008, either in the sleep laboratory as a full night or a split-night study: the first half of the night is used to obtain a diagnosis, the second half is used to perform continuous positive airway pressure (CPAP) titration (level I), or, at home as an outpatient (level II). Patients with a diagnosis of upper airway resistance were excluded from the study, as were people who slept less than three hours a night and those referred for a diagnosis other than apnea, such as parasomnia.

After providing informed consent, participants selected at this stage received a questionnaire covering multimorbidity and socio-demographic variables. Data related to variables of the evaluation conducted at the sleep laboratory were recorded: age, sex, polysomnography results, neck circumference, weight and height.

Several tools are available for measuring multimorbidity. The Disease Burden Morbidity Assessment (DBMA) was selected for this study as it allows to report the absence or presence of 21 predetermined chronic conditions and additional chronic conditions and to determine a functional impact score for each condition on daily life activities. The DBMA is a self-report questionnaire. For each condition present, the patient assesses a degree to which the condition limits his or her activities on a five-point descriptive scale (1: Not at all – 5: A lot). The total score is made up of the sum of all limitations. The metrological qualities and validity of this instrument have been described by Bayliss et al. and a French version was validated in a recent study: sensitivity 73.9% (62.5%-90%); specificity 92.2% (77.6%-98.6%). The questionnaire was sent by mail based on a modified Dillman method. A second questionnaire was sent to non-respondents 30 days following the first one. Estimated time to complete the questionnaire is approximately 15 minutes.

Due to the exploratory nature of the study, we based our sample size estimation on the availability of the data and feasibility. We aimed for a sample size of 120 (30 per OSA group) to ensure a good representation of each category of the independent variable. We oversampled for a potential non response of 30 to 40%. Consequently, the questionnaire was sent to a convenience sample, as recommended by Dillman, of 194
people who had undergone polysomnography at the sleep laboratory of the CSSSC for a diagnosis of sleep apnea in 2008. The study received ethics approval from the Research Ethics Board of the CSSSC.

The subject's characteristics were described using medians (in the case of asymmetric distributions), means, standard deviations (for continuous variables) and proportions (for categorical variables). A Kolmogorov-Smirnoff test was performed to test for normality of the distributions. In the absence of normality, non-parametric tests were conducted. Bivariate (Spearman rank) correlations were conducted. We dichotomized the AHI by grouping together absent and mild as well as moderate and severe to ensure sufficient size of each group. We performed logistic regression analyses to study the relationship between multimorbidity and OSA. The significance level was set at 0.05, and confidence intervals were calculated at 95%. The DBMA constituted the dependent variable and OSA classification, the independent variable. Other variables were included in the models as adjustment variables (BMI, sociodemographic variables). Neck circumference was not included, as 25% of the data was missing. We dichotomized the DBMA using the median and threshold values of 10 and 20, respectively, to explore the association with clinical variables. Cut-off points were chosen based on the definition of multimorbidity and the results of previous studies. A score of 10 means a high impact and at least two chronic conditions; a score of 20 represents a very high impact and at least four chronic conditions (considered here as severe multimorbidity). DBMA sub-groups were formed on the basis of the correlation of each disease with OSA and the conceptual association. We tested three sub-groups: vascular DBMA (hypertension, heart disease, dyslipidemia, heart failure and stroke); cardio DBMA (hypertension, heart disease, dyslipidemia, heart failure) and metabolic syndrome DBMA (hypertension, cholesterol, obesity and diabetes). Data were analyzed using the SPSS package (19.0, SPSS, Chicago. IL).

Results

Of the 194 patients solicited, seven were non-eligible: five were suffering from parasomnia, one was too old and one we were unable to reach to complete the questionnaire. In total, 187 eligible patients were invited to participate and 120 completed the questionnaire (64.2% response rate). No patients were excluded. Among these, 89.2% of participants had OSA. The average age of patients was 55.5 years, with a predominance of males (65%).

The average neck circumference (absent: 41.17 cm; mild: 40.5 cm; moderate: 42.59 cm; severe: 43.99 cm) and BMI average (absent: 32.00; mild: 30.13; moderate: 34.39; severe: 35.77) were higher in moderate and severe OSA.

The 120 respondents presented six chronic diseases in average. The average number of diseases did not increase in accordance with the severity of OSA (absent: seven diseases; mild: five diseases; moderate: eight diseases; severe: five diseases).

We were unable to demonstrate a statistically significant association between the DBMA score and dichotomized polysomnography (absent + mild vs. moderate + severe) ($r = 0.117, p = NS$) in this analysis.

Discussion
The present study revealed an association between severe OSA and severity of multimorbidity as measured by the DBMA. The relationship was still present after adjusting for several potential confounders.

These findings have implications for general practice. Many patients seen in primary care practices present with multimorbidity. In order to investigate the potential association between multimorbidity and OSA, screening could be done clinically or by using a tool such as the Epworth Instrument which is highly correlated with OSA. Patients could be referred to a sleep lab for evaluation when OSA is suspected. If OSA is confirmed, it may affect the management of the patient who could benefit from treatment that has been demonstrated to help control many associated diseases and chronic conditions.

One previous study suggests that multimorbidity exists in OSA. To our knowledge, this is the first study to report an association between severe OSA and multimorbidity. We searched for an exposure–response relationship between OSA and multimorbidity but the composition of our sample prevented us from observing such a relationship. In our sample we did not obtain the desired proportion representation (25% each) of the four severity categories of the independent variable (OSA: absent, mild, moderate and severe). We sent the DBMA questionnaire to 50 people in each OSA classification category but we had a disproportionately high response rate in the severe category (48 out of the 50 patients) compared to the others. On the other hand, we obtained a sample of relatively sicker subjects (an average DBMA of 16). Patients in this study presented more chronic conditions (six per person) than reported by Fortin (4.6 per person) or Kadam (1.3 per person) in their assessment of multimorbidity in primary care practices. We suspect that the disproportionate response rate is due to the fact that patients who were sicker were more interested in participating in this study.

Regarding other characteristics and associations, the respondents were fairly representative of the sleep apnea population, with a predominance of male subjects. Neck circumference and BMI were found to be positively associated with OSA, which was expected. We observed an association between the AHI and metabolic syndrome. This association had been previously found by other groups. Although not addressed in our study, associations were also found between OSA and each component of the metabolic syndrome. In fact, the evidence suggests that OSA is actually part of the metabolic syndrome. One study suggests that OSA symptoms (snoring, hyper somnolence) predict the development of metabolic syndrome. In addition, evaluation of OSA symptoms can help identify individuals who are at risk of developing metabolic syndrome.

Our sleep laboratory uses a definition of hypopnea which is accepted in the literature: a decrease in respiratory amplitude of 50% or more, accompanied by a desaturation of 3%. However, other laboratories require a 4% desaturation for a positive diagnosis. The method used in this study is therefore more sensitive than the diagnostic criteria used in some laboratories. This could result in higher AHI values and the number of diagnoses of patients with mild or moderate symptoms who would not have been diagnosed by other laboratories. Several epidemiological studies have established a relationship between OSA and vascular morbidity using the 4% cut-off point. This may explain why we did not observe any link between our groups of mild or moderate subjects and a measure of morbidity. It is especially important that studies showing a link between sleep apnea and morbidity examine these associations, particularly in the case of severe OSA (AHI greater than 30). Also, if OSA is an intermediate factor in the development of hypertension, diabetes, dyslipidemia or other conditions, controlling for these variables represents a case of "over adjustment," potentially affecting the association between dependent and independent variables.
For more than 20 years, cross-sectional studies, control cases and other evidence have suggested an association between OSA and heart disease, heart failure, arrhythmias and cerebrovascular diseases. A gradation of vascular risk in relation to AHI has been proposed. We observed an association between vascular DBMA and AHI when AHI was dichotomized into absent and mild versus moderate and severe. Similar results were obtained in prospective population studies, such as the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study. In the first study, Gottlieb identified an association between incident heart failure and OSA. Although there is no defined threshold value, this association is especially important in subjects with an AHI greater than 30. In the Wisconsin study, the associations were significant only in subjects with an AHI greater than 30 (odds ratios of 4.5 and 5.2, respectively, for risks of cerebral vascular disease and cardiovascular death). Furthermore, a longitudinal study showed that men are at increased risk of stroke when the AHI is greater than 19 per hour of sleep. Among women, unadjusted overall results showed an increased risk threshold at 25 AHI per hour of sleep ($p = 0.002$).

This study has limitations. With a limited response rate of 64%, we were unable to obtain a proportional representation in categories of OSA classification in our sample, and this may have confounded the relationship between the DBMA and OSA. In addition, we had to remove one variable from the analysis (neck circumference) due to a high number of missing values. Another limitation of the study is the use of the DBMA as a measure of multimorbidity. The DBMA measures self-reported disease burden that correlates well with quality of life outcomes. However, in other multimorbidity measures, disease severity is evaluated based on purely clinical criteria assessed by health professionals. The different methods of evaluating disease severity may have an impact on the association between multimorbidity and OSA.

Conclusions

In this study we found a link between severe obstructive sleep apnea and severity of multimorbidity. These results represent the first documentation of a relationship between severity of OSA and severity of multimorbidity. The study also showed an association between OSA and multimorbidity sub-scores (cardiac, vascular, metabolic syndrome). Primary care providers should be aware of these potential associations and investigate OSA when deemed appropriate. There is a need for additional research in this area, and our findings may help raise awareness among family physicians about this condition and improve access to diagnosis and treatment. Research would benefit from repeating the same study using a longitudinal study design.

**Physiological Injuries and Surgery**

**Diagnosis and Management of Prosthetic Joint Infection**

Current Opinion in Infectious Diseases
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Abstract

Purpose of review

Prosthetic joint infection remains a devastating complication of arthroplasty associated with significant patient morbidity. The demand for arthroplasty is rapidly growing with a corresponding increase in the number of infections involving the prosthesis. The diagnosis and treatment of prosthetic joint infections presents a significant challenge to orthopaedic and infectious diseases clinicians.

Recent findings

The underlying pathogenesis of prosthetic joint infections is due to the ability of the microorganisms to form a biofilm. The biofilm provides protection against host immune responses and antimicrobial therapy. In addition, it impedes standard laboratory diagnostic techniques. This review will examine new investigations to improve the diagnostic yield and rapidity of diagnosis of infections, including the use of sonication to disrupt the biofilm, new molecular tests to improve the detection of infecting microorganisms and new imaging techniques such as 18F-fluorodeoxyglucose PET.

Summary

The successful treatment of prosthetic joint infections is dependent on eliminating the biofilm dwelling microorganisms whilst maintaining patient mobility and quality of life. This review will examine current understanding of management approaches for these infections, with a particular focus on antimicrobial therapy with activity against the biofilm, such as rifampicin and fluoroquinolones.

Introduction

Prosthetic joint surgery is a common surgical procedure that has led to remarkable improvements in a patient's quality of life. With an ageing population, the demand for surgery will increase significantly over the next 20 years. Infection of the prosthesis is uncommon, occurring in 1–3% of patients; however, it is a devastating complication of this surgery. In addition, the economic burden of managing these infections is substantial.

The diagnosis and management of prosthetic joint infections (PJIs) is intimately reliant on an understanding of the underlying pathogenesis of these infections, in particular the role of biofilm formation by the infecting microorganisms. Timely diagnosis and optimal management of PJI is associated with reduced suffering for patients and improved outcomes. The aim of this review is to examine the current understanding of the pathogenesis, diagnostic and management approaches to PJI.

Pathogenesis
There are two main mechanisms of acquisition of PJI: direct inoculation at the time of surgery and haematogenous seeding of the prosthesis at a later time. When microorganisms attach to the prosthesis, they undergo a phenotypic change to become the sessile bacteria form. These sessile bacteria secrete an extracellular matrix, and these bacteria and their extracellular matrix comprise the biofilm. The presence of the biofilm impacts significantly on both the diagnostic and management approaches to PJI.

Microbiology

Staphylococci remains the most common aetiological agents in PJI with both Staphylococcus aureus and coagulase-negative staphylococci each implicated in up to a quarter of all infections. Gram-negative organisms are the next most common isolate occurring in approximately 10% of cases of PJI. Other microorganisms including enterococci, streptococci and fungal species have been reported. Of note, Propionibacterium acnes has a particular association with prosthetic shoulder joint infections, occurring in up to 40% of cases.

Clinical Classification and Presentation

There are a number of proposed classification systems for PJI. In general, PJI can be classified as early (developing in the first 3 months after surgery), delayed (occurring 3–24 months after surgery) and late (greater than 24 months). Haematogenous seeding of the prosthesis may occur at any time point following implantation but is thought to be more likely to present after 24 months of surgery.

Early PJI comprises the majority of cases encountered. Typically, patients report wound complications from close to the time of their original joint surgery. Delayed and late presentations typically are associated with history of slowly increasing pain involving the prosthetic joint. Haematogenous PJs, in contrast, typically are associated with a history of a joint that was free of any problems for several years before an acute episode of sepsis suddenly occurs.

Diagnosis

The diagnosis of PJI remains challenging. One particular issue is the lack of an internationally accepted gold standard for defining infection in a prosthetic joint. Current definitions rely on a number of parameters, including clinical, microbiological and histopathological features. The diagnosis of PJI should be considered in patients with any of the following:

Presence of periprosthetic purulence observed intraoperatively; or

Isolation of indistinguishable microorganism(s) on at least two intraoperative specimens (tissue or joint aspirate cultures); or

Presence of a sinus tract in communication with the prosthetic joint; or
Histopathological features of acute infections with at least five neutrophils per high power field (×500 magnification) in five different microscopic fields.

Figures 1 and 2 outline a diagnostic algorithm for early/haematogenous and delayed/late PJI, respectively. Of importance, to optimize microbiological diagnosis, antibiotic therapy should not be commenced until definitive surgical management and after multiple intraoperative specimens are obtained, except in the case of the septic patient. In early/haematogenous PJI, delay in time to surgical debridement is associated with treatment failure; therefore, prompt diagnosis and management is imperative. The culture of the microorganism from intraoperative sampling of the joint or from aseptically obtained joint aspirate is the most important diagnostic test allowing for confirmation of diagnosis and assessment of antimicrobial susceptibilities. Five or more periprosthetic tissue specimens should be obtained intraoperatively with each specimen placed in separate sterile containers. Infection of the prosthesis is suggested by the isolation of the same microorganism from two or more intraoperative specimens.

Techniques such as sonication may increase the diagnostic yield through disruption of the biofilm on explanted prosthetic material. In one study, the use of sonication improved the sensitivity of microbiological cultures from 60.8 to 78.5%. Sonication was particularly useful in patients who had received antibiotics in 14 days preceding surgery. Prolongation of microbiological cultures from 3 to 14 days also increases the diagnostic yield, particularly of more fastidious organisms such as P. acnes.

Other laboratory investigations increase the diagnostic yield of PJI, including biochemical tests, synovial fluid assessment, molecular methods and radiological studies. Biochemical tests, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are useful adjunctive tests for diagnosis of PJI. There are, however, limitations to the diagnostic utility of the ESR and CRP. First, these measures may have reduced clinical benefit in predicting shoulder arthroplasty infections. Second, these markers are normally elevated after uncomplicated arthroplasty; the CRP may remain elevated for 3 weeks and the ESR may remain elevated for up to a year. Other biochemical markers, including interleukin-6, have been investigated, but their clinical application has not been established.

Synovial fluid characteristics can be used to assist in diagnosis of PJIs. In patients with PJIs, the leucocyte count is higher than in patients with aseptic loosening. A synovial total white cell count of more than $1.7 \times 10^3/\mu L$ has a sensitivity of 94% and a specificity of 88% for diagnosis of PJI. In addition, a leucocyte differential of more than 65% neutrophils has a sensitivity and specificity of 97 and 98%. The biochemical properties of the synovial fluid also differ in patients with infection compared with aseptic loosening. Synovial CRP is elevated in patients with PJI; however, the sensitivity and specificity of this test is similar to serum CRP; therefore, the diagnostic utility of this test remains unclear. Likewise, simple ‘point-of-care’ tests such as leucocyte esterase have a sensitivity and specificity of 80–93.3% and 77–100% for diagnosis of PJI; however, there are issues with the reliability of this test in the presence of blood or cellular debris.

PCR is a rapid, sensitive diagnostic test in the diagnosis of PJI. A number of studies investigating the role of broad-range PCR tests such as bacterial 16S rRNA PCR have been performed. Sensitivities of this technique ranged from 63 to 100% in detecting bacteria involved in PJI.
are a number of significant limitations with broad-range PCR, including the risk of microbiological contamination of the specimen or reagents and the lack of clinical correlation in many studies. Attempts to overcome the limitations of broad-range PCR have included use of primers specific for one organism only and more recently the use of multiplex PCR.[33] Multiplex PCR uses specific primers for a number of microorganisms and allows the detection of multiple pathogens with the one assay. In one study, real-time multiplex PCR was compared with microbiological culture on sonicate fluid. The use of multiplex PCR increased the diagnostic yield from 62 to 78% and was particularly useful in patients who had received antibiotic therapy. The greatest limitation to multiplex PCR is that primers for organisms such as P. acnes are not included in commercially available kits, and therefore, these pathogens will not be detected.[34] Alteration and adaption of the kits to include the most commonly isolated pathogens of PJI will improve the utility of multiplex PCR.

Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) is a new technology that uses mass spectrometry to differentiate bacterial and fungal organisms and has the potential to improve the yield and rapidity of diagnosis. MALD-TOF has the potential ability to subtype bacterial species allowing the assessment of whether the isolates are clonally related. This is particularly useful for differentiating PJI or contamination for coagulase-negative staphylococci.

Imaging modalities have also improved the diagnostic yield for PJI. Radionuclide imaging techniques, such as triple-phase bone scintigraphy, are a sensitive test for PJI and have a high negative predictive value. However, bone scintigraphy has a low specificity and can remain positive for a year following uncomplicated arthroplasty, thereby limiting the utility. Newer modalities such as 18F-fluoro-deoxyglucose PET (FDG-PET) have improved sensitivity, specificity and rapidity for diagnosis of PJI, and hence, this may be a useful test if available. Use of computed tomography (CT) and MRI has previously been limited due to artefacts from the metal prosthesis; however, newer CT scanners can minimize this effect and may be useful in detecting abnormalities of the soft tissues in periprosthetic infections.

Treatment

The successful treatment of PJI entails the eradication of the biofilm dwelling microorganisms whilst maintaining joint function and quality of life. The strategies used to treat arthroplasty infections include one-stage or two-stage exchange procedures, removal of the prosthesis with or without arthrodesis, amputation, debridement and retention of the prosthesis (DAR), and chronic suppression. Of the above strategies, exchange procedures and DAR are the two that best meet the goals of PJI treatment. There are no randomized clinical trials comparing treatment strategies, and internationally endorsed consensus guidelines for management of PJI do not exist. In addition, management practices differ significantly between North America, Europe and Australia. Some treatment algorithms exist to guide management decisions, and these are based on factors such as duration of symptoms, the stability of implant, patient comorbidities and the type of infecting microorganism.

Exchange procedures involve removal of the infected prosthesis and all foreign material, including cement, resection of devitalized tissue and bone with reimplantation of a new prosthesis performed at the time of removal of the infected prosthesis (one-stage exchange), or delayed by a variable period of time while antibiotic therapy is administered (two-stage exchange). In two-stage exchange, a cement spacer, with or without antibiotic impregnation, is frequently used to help maintain limb length, aid with mobility and to act as a source of local antibiotic elution. Spacers
are not recommended in certain settings, including infections with 'difficult-to-treat' microorganisms such as methicillin-resistant S. aureus (MRSA), enterococci, multiresistant bacteria and fungal infections. In two-stage exchange, the duration between removal of the infected prosthesis and reimplantation is 2–4 weeks for uncomplicated infections and 8 weeks for 'difficult-to-treat' microorganisms. Previous studies had suggested that one-stage exchange was associated with a higher rate of failure than two-stage exchange; however, these studies frequently were retrospective involving small numbers of patients from single centres. The results of recent studies from larger registries and from systematic reviews have mixed results comparing the success rate of one-stage and two-stage exchange; therefore, the question of which exchange strategy is superior remains unanswered. Exchange procedures are the standard strategy for delayed and late PJI or if there is evidence of loosening of the prosthesis. Following one-stage exchange and two-stage exchange for uncomplicated infections, antibiotic therapy is continued for a total duration of 3 months. In two-stage exchange with 'difficult to treat' microorganisms, expert opinion recommends 6 weeks of antibiotic therapy and delayed reimplantation for a further 2 weeks, at which time multiple intraoperative specimens are obtained for microbiological culture. Antibiotic therapy is continued for a further 3 months if these intraoperative specimens isolate a pathogen.

DAR of the prosthesis involves open arthrotomy, removal of all infected and necrotic tissue, exchange of liners and lavage of the joint. In some centres, exchange of the mobile parts is performed. Early studies of DAR were disappointing with a high relapse rate. The outcomes from DAR have improved considerably with careful patient selection and with the specific use of antibiotics with activity against the biofilm dwelling bacteria such as rifampicin and fluoroquinolones. The duration of antibiotic therapy for DAR has not been well delineated. Expert opinion recommends duration of 3 months for hip and 6 months for knee PJI. Recent studies, however, have reported similar outcomes for patients treated with 3–6 months and more than 6 months of antibiotic therapy.

Antibiotic Treatment

From studies examining the effect of the biofilm antimicrobial activity, it was noted that the efficacy of antibiotics varied. In particular, the activity of rifampicin and fluoroquinolones was preserved in the presence of biofilm.

In staphylococcal PJI, rifampicin is the mainstay of therapy, particularly with DAR. In-vitro evidence of rifampicin efficacy has been supported by clinical studies. In a review by Senneville et al., the use of rifampicin–fluoroquinolone combination antibiotic therapy was an independent predictor of treatment success in patients with S. aureus PJI. The main limitation with the use of rifampicin is the high likelihood of generation of resistance when used on its own; therefore, rifampicin must always be administered with a second agent. In many centres, fluoroquinolone resistance in staphylococci is increasing, thus limiting the utility of rifampicin–fluoroquinolone combinations. Alternative companion drugs for rifampicin include fusidic acid, trimethoprim–sulfamethoxazole or minocycline. Newer agents such daptomycin and linezolid are under investigation; however, the results of clinical studies using these agents are mixed. Their role of these agents appears to be as companion drugs for rifampicin rather than as single agents. There are no clinical studies comparing the efficacy of different drugs used in combination with rifampicin. In addition to staphylococcal PJI, in-vitro evidence suggests that rifampicin is effective against P. acnes and Enterococcus faecalis biofilms.
For Gram-negative infections, ciprofloxacin has been shown to be effective in guinea pig tissue cage models; however, there are fewer clinical data on the management of PJI secondary to these organisms. The outcomes with Gram-negative infections vary, particularly with DAR with rates of treatment success ranging from 27 to 94%. The likelihood of success may relate to the quality of the debridement, particularly with removal of all dead and devitalized tissue and removal of all cement in the exchange procedures. A particular concern with many Gram-negative bacteria is the propensity to induce resistance to fluoroquinolones in vivo, particularly with Pseudomonas aeruginosa. In light of this, many experts recommend a 2- to 4-week course of beta-lactam antibiotics prior to commencement of ciprofloxacin to reduce the likelihood of generation of in-vivo resistance. In candidal PJI, there is emerging evidence that the activity of caspofungin is better preserved in the presence of biofilm than in fluconazole.

Conclusion

With an ageing population and the increasing popularity of arthroplasty, PJI will continue to present a diagnostic and management challenge to clinicians. The optimal treatment approach for patients with PJI is still under debate and investigation. Given the relative rarity of this clinical entity and the need for prolonged follow-up, randomized control trials investigating different treatment options are problematic. The use of large registries and the collaborative research groups are the key to furthering our understanding of PJI. This understanding is of paramount importance to improve patient outcomes.

**Transforaminal Lumbar Interbody Fusion: Prognostic Factors Related to Retention in an Active Duty Military Population**

Military Medicine
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Abstract

Little information is available regarding patient-based factors that may influence results following transforaminal lumbar interbody fusion (TLIF) in younger, high-demand individuals. A query of all TLIF procedures performed on active duty military personnel at our institution was conducted for the time period 2005 to 2008. Data was abstracted, including age, gender, military rank, preoperative diagnosis, complications, and ability to remain in the military. Favorable outcome was defined as the ability of the patient receiving TLIF to remain on active duty, without medical separation (Medical Evaluation Board [MEB]), at a minimum of 1 year postsurgery. Univariate analysis was conducted to identify potential risk factors for MEB. Factors with a univariate p value <0.2 were included in multivariate analysis and sensitivity testing to identify independent
predictors of outcome. The cohort included 143 patients with an average age of 36.3 years and mean follow-up of 34.9 months. Younger age (odds ratio 0.93 per year increase in age; 95% confidence interval 0.87, 0.98) and Junior Enlisted rank (odds ratio 6.42; 95% confidence interval 2.20, 18.74) were found to increase the risk of MEB, and these relationships were maintained in the sensitivity analyses. These findings highlight the potential role of activity level and sociodemographic status in outcomes after TLIF in a military population.

Introduction

Since its introduction by Harms and Rolinger in 1982, transforaminal lumbar interbody fusion (TLIF) has gained wide popularity as a surgical intervention capable of providing 360° arthrodesis from a posterior approach. Purported advantages of the TLIF procedure include interbody graft placement through a unilateral approach that preserves the posterior tension band and limits manipulation of the neural structures. The placement of an interbody structural graft also increases arthrodesis rates, off-loads posterior segmental instrumentation, and restores disc space height as well as lumbar lordosis. TLIF has been advocated as an intervention suitable for spondylolisthesis, degenerative scoliosis, adjacent segment degeneration, pseudarthrosis, and degenerative disc disease.

Within the last decade, numerous studies have been published regarding the efficacy of TLIF and its safety, relative to other techniques of interbody arthrodesis. Several investigations have documented satisfactory results, albeit with mostly short-term follow-up, for open, and minimally invasive TLIF. In spite of this, various aspects regarding the efficacy of TLIF remain incompletely explored. Most research that has been conducted to date involve cohorts of fewer than 100 patients, mostly middle-aged with varying activity levels, and relatively short-term follow-up.

Moreover, there is scant research addressing patient-based factors that may influence clinical outcomes following TLIF. For example, in a study of 100 patients who underwent TLIF, Potter et al reported that 24% of all individuals were found to have poor outcomes despite a successful arthrodesis rate exceeding 90%. Despite repetitive documentation of such realities, however, no predictive models with respect to the impact of patient-based factors on outcomes following TLIF have been developed.

The current investigation sought to establish factors capable of predicting outcome among a large, consecutive, series of patients undergoing TLIF at a single center. As the study was limited to individuals who were active duty service members, this research was also intended to characterize results for TLIF within a population of younger age patients with higher activity levels than in previously published works. Furthermore, to the best of our knowledge, this study involves one of the largest series of consecutive patients receiving TLIF to be presented in the literature.

Materials and Methods

This investigation received institutional Investigational Review Board approval before its commencement. Using our institution's surgical database, a query of all TLIF procedures performed on active duty military personnel within the Department of Orthopaedic Surgery was conducted for the time period January 1, 2005 to December 31, 2008. The Department of Defense electronic health care record system (AHLTA) was subsequently reviewed for each individual identified as receiving a TLIF in the preliminary search. Patient documentation contained within the Department of
Orthopaedic Surgery was also abstracted. Data obtained for each service member receiving TLIF included age, gender, military rank, branch of service, smoking status, preoperative diagnosis, number of levels arthrodesed, postoperative complications, whether the patient subsequently required revision surgery, status of the arthrodesis at the time of final evaluation, and ability to remain in the military. A patient's capacity to continue on active duty was assessed by determining whether the patient received a medical separation from a Medical Evaluation Board (MEB) following their TLIF. If the patient was receiving medical separation for different reasons, a determination was made based on documentation in the patient record whether the spinal condition for which the TLIF was performed met military retention standards. If the service member's spinal condition failed to meet retention standards, they were also considered medically separated/retired for this issue.

For the purposes of this investigation, outcome was defined as the ability of the service member receiving TLIF to remain on active duty at a minimum of 1 year following surgery. Therefore, all individuals who did not have documented follow-up at time points equal to or exceeding 1-year were excluded from this analysis, unless documentation was present indicating they had received an MEB within the first year of surgery. All individuals undergoing MEB, regardless of the postoperative time point at which MEB was initiated, were included in the study.

Patient-based factors potentially influencing outcome included age, gender, smoking status, preoperative diagnosis, number of levels arthrodesed, presence of postoperative complications, need for revision surgery, presence of pseudarthrosis, activity level, and socioeconomic status. Smoking status was graded according to whether the patient was a current smoker at the time of surgery. Preoperative diagnosis was binned as degenerative disc disease or other (spondylolisthesis, spinal stenosis, other). Number of levels arthrodesed was categorized as 1-level (i.e., L4-5) or multilevel (2-, or 3-level TLIF). Military rank was classified as Junior Enlisted (enlisted service members excluding noncommissioned officers), Senior Enlisted (noncommissioned officers), and Officers. Because of the limited number of non-Army service members in the cohort, branch of service was categorized as Army, or other branch (Navy, Air Force, or Marine Corps).

In this analysis, military rank was used as a proxy for activity level, with Junior Enlisted personnel felt to have higher physical activity levels than either Senior Enlisted or Officers. Military rank was also used as a surrogate marker for socioeconomic status, with Junior Enlisted individuals felt to represent a lower stratum relative to Senior Enlisted and Officers. Numerous studies have substantiated this fact, identifying Junior Enlisted personnel as deriving from lower socioeconomic classes and at similar risk for medical conditions and events that are prevalent among counterparts of similar background who are not serving in the military. Moreover, several previous investigations have endorsed the use of military rank and branch of service as proxies for activity level and socioeconomic status, respectively, in epidemiological research.

Statistical Analysis
For the purposes of statistical evaluation, a patient receiving medical separation/MEB for the spinal condition treated by TLIF was considered the dependent variable. Age, gender, military rank, branch of service, smoking status, preoperative diagnosis, number of levels arthrodesed in the index procedure, postoperative complications, necessity for revision surgery, and presence of pseudarthrosis at the time of final evaluation were considered the independent variables. Initially, univariate logistic analysis was conducted, using the χ2 statistic for both continuous and categorical variables, to identify the risk factors potentially influencing medical separation following TLIF. All factors found to be statistically significant (p value < 0.05) in univariate analysis, as well as those with a p value <0.2, were subsequently included in multivariate logistic analysis. Multivariate logistic
regression analysis was then utilized to determine risk factors independently influencing medical separation after TLIF, while controlling for other factors present in the model.

Because there was concern that a small cohort of patients (n = 8) who had not achieved 2-year follow-up, and also did not receive an MEB, might skew the results of the study because of the relatively short length of follow-up, two sensitivity analyses were conducted and compared to the multivariate findings. One sensitivity analysis consisted of a worst-case scenario, where those patients who had failed to achieve 2-year follow-up were all considered as having undergone medical separation/MEB. The second sensitivity analysis simply excluded the eight patients from the study. True independent risk factors, influencing the potential for medical separation after TLIF, were maintained to be those that demonstrated statistical significance in the original multivariate analysis as well as both sensitivity analyses.

Results

Demographic Characteristics
In the time period under investigation, 155 active duty service members underwent TLIF in the Department of Orthopaedic Surgery at our institution. Twelve patients did not meet the minimum 1-year follow-up criteria, had no evidence of undergoing an MEB, and were excluded from further consideration. Ultimately, 143 patients were included in the analysis, 135 of whom achieved 2-year follow-up and/or underwent MEB.

The average age of the cohort was 36.3 years (SD 8.07; range 20–59). Eighty-seven percent of the patients were male and 95% were members of the Army (Table I). Seventy percent of the cohort was classified as Senior Enlisted, whereas 21% were Junior Enlisted and 9% were Officers. Degenerative disc disease was the most common preoperative diagnosis encountered in 83% of those undergoing TLIF.

Operative Characteristics
Fifty-three percent of patients underwent a one-level TLIF, whereas 43% received TLIF at two levels. Six service members (4%) had TLIF performed at three or more levels. Seven individuals (5%) were found to have sustained a complication following surgery. Complications included postoperative infection (n = 3, 2%), seroma (n = 3, 2%), and L5 radiculitis (n = 1, 0.7%). All individuals who were not medically separated from the military received minimum 1-year follow-up, with all but eight patients exceeding 2-year follow-up. The average follow-up for the entire cohort was 34.9 months (range 3–66 months). Mean follow-up for those who were not medically separated was 42.5 months (range 14–66 months).

At the time of final follow-up, 6 patients (4%) were definitively found to have a pseudarthrosis, whereas arthrodesis was considered incomplete in 12% (n = 17), and fusion could not reliably be assessed in 54 individuals. Seven service members (5%) required revision surgery. Ultimately, 50 patients (35%) underwent an MEB for medical separation after their TLIF surgery. Two of the seven individuals requiring revision procedures were medically separated, as were two of the patients who had postoperative complications. Sixty-five percent of those receiving TLIF were able to remain on active duty at the time of final evaluation.

Statistical Analysis
In light of the number of patients with an indeterminate fusion status, categories of fusion were considered as pseudarthrosis, incomplete arthrodesis, solid arthrodesis, and unknown in the statistical evaluation. Additionally, the small number of individuals undergoing revision procedures (n = 7) prevented the evaluation of the effect of revision on outcome.

Univariate analysis identified younger age (p < 0.001) and Junior Enlisted rank (p < 0.001) as significant risk factors for medical separation after TLIF. Gender (p = 0.09) and fusion status (p = 0.14) also met the criteria for inclusion in multivariate testing (Table II).

Multivariate logistic regression analysis, controlling for other factors in the model, maintained statistically significant associations between age (p = 0.01) and military rank (p < 0.001) and the risk of medical separation (Table III). Once again, younger individuals were found to be at an increased risk of separation after TLIF (odds ratio [OR] 0.93 per each year increase in age; 95% confidence interval [CI] 0.87, 0.98). Likewise, Junior Enlisted personnel were found to be at an increased risk of medical separation when compared to Senior Enlisted and Officers (OR 6.42; 95% CI 2.20, 18.74). Both sensitivity analyses maintained the associations between age, rank, and the risk of medical separation. (Table III).

Discussion

Over the last 10 to 15 years, TLIF has become a popular treatment for a number of spinal conditions, including degenerative disc disease, spondylolisthesis, adjacent segment degeneration, and failed lumbar spine surgery.1–8,13 Although the relative safety and short-term efficacy of the procedure has been expounded in a number of publications, much remains to be discerned regarding this arthrodesis technique, including long-term results and factors that may be predictive of outcome after surgery. Furthermore, with respect to the comparatively young, and high-demand, military population, it is unclear whether findings documented among older and more sedentary individuals are necessarily translatable.9

This investigation sought to determine predictive factors for outcome among a large, consecutive, series of military personnel receiving TLIF for spinal disorders. Results presented here documented a 65% retention rate for service members receiving TLIF at an average of close to 3 years following surgery. Age and military rank were found to be statistically significant predictors of outcome in multivariate analysis, with more advanced age, and Senior Enlisted or Officer rank, protective against medical separation/MEB. These associations were maintained in the sensitivity analyses.

In terms of age and length of follow-up, the cohort under study here was younger and followed for periods longer than individuals presented elsewhere in the literature. Previous studies documenting outcomes in TLIF among civilian patients report mean ages ranging from 43 to 57. Lowe et al reported an average follow-up of 36 months (range 31–42 months) in their series of 40 patients, whereas Villavicencio et al assessed outcomes at an average of only 21 months (range 14–28 months). Among studies with more than 50 patients, only Hackenberg et al documented average follow-up periods exceeding 4 years in duration.

Similarly, when considered alongside other investigations regarding lumbar fusion conducted in the military, the cohort under study compares favorably. (Table IV) McGuire and Amundson presented results in 28 service members with an average age of 35, whereas Molinari et al
examin ed outcomes in two series where the average age was reported to be 36. In both of Molinari’s studies, however, outcomes were determined at an average of only 14 months following surgery. Although the work of Potter et al was not exclusive to active duty military, a large component of their cohort consisted of uniformed service members. In this series with an average age of 38, mean follow-up was found to be 34 months. Additionally, the complication profile and revision rates in the present series do not appear markedly different when compared to previous works regarding TLIF.

Only three prior works have assessed retention rates in the military following lumbar surgery and these have been conducted in small populations ranging from 15 to 30 individuals. McGuire and Amundson published a retention rate of 63% after minimum 2-year follow-up for instrumented and uninstrumented posterolateral lumbar fusion. The studies of Molinari et al, investigating posterior lumbar interbody fusion, reported retention rates of 90% and 100%. However, these results should be appreciated in light of their small population size and mean follow-up that only slightly exceeded 1 year. We maintain that, based on the size of our cohort, as well as substantially longer follow-up, the present estimation of 65% retention following TLIF is likely a more realistic measure of the capacity for fusion techniques to maintain personnel on active duty status.

When considering these findings as a whole, it appears that the population in this work is sufficiently similar to prior efforts such that the validity of our prognostic model can be maintained. Age and military rank were the two factors primarily impacting retention after TLIF, and both maintained statistical significance following multivariate and sensitivity testing. The influence of military rank on outcome in this analysis is likely multifactorial but may represent the impact of activity level as well as socioeconomic factors on surgical results. Junior Enlisted personnel were at a significantly increased risk of medical separation in this study. Such individuals are also engaged in more rigorous physical activities relative to Senior Enlisted and Officers. Mroz et al previously identified patients with heavy-labor occupations as being at risk of inferior outcomes following fusion for chronic low back pain. It is possible that even following successful arthrodesis and symptomatic reduction, the rigorous physical demands placed on Junior Enlisted cannot be met after TLIF, and medical separation still occurs.

Similar postulations could be made with regard to the effect of age on outcome in this study. Younger patients, by definition, often occupy the more junior positions in the chain of command and these individuals maintain higher activity levels than more senior personnel while deployed and in garrison. Additionally, younger individuals will have less time in the military before surgery and may, consequently, be less inclined to avoid medical separation. More senior personnel, with more time invested in a military career, might attempt to stave off medical separation to reach the 20-year retirement time point. Furthermore, higher ranking individuals may hold more, sedentary, leadership positions that can facilitate retention.

Relatively little research has been conducted regarding the role of socioeconomic factors on outcomes following spine surgery in general, and fusion in particular. A recent systematic review regarding sociodemographic factors and spine surgery only highlighted that litigation patients, those with high-demand occupations, and patients on sick leave were at risk for inferior outcomes following treatment for low back pain. The authors of that study concluded that more work was necessary to determine the role that sociodemographic factors play in outcomes after treatment for spinal conditions. Findings related to the Junior Enlisted group could be viewed as a herald of the effect of socioeconomic status on the results of TLIF. It may be that social support networks among patients of lower economic means are not well developed or that cultural attitudes toward the health care system, as well as illness, lead to adverse effects on outcome. Conversely, the military itself may be more
invested in retaining senior personnel, in light of their experience, position within the rank structure, and resources invested in training and development. Although other research on spine surgical results among socioeconomic and ethnic minorities has pointed to inadequate access to care and health care disparities as the cause of inferior outcomes, such an etiology is less likely in the military, which operates under a universal health care system.

No prior investigation has discussed the effect of socioeconomic status on outcomes related to TLIF. Several works have highlighted arthrodesis status, and the presence of pseudarthrosis, as a poor prognostic indicator of outcome. Unfortunately, because of the design of this study and its reliance on electronic medical records and a surgical database, we were unable to assess the success of arthrodesis in a scientifically rigorous fashion for a plurality of cases. Although some investigations have shown success rates to be high among individuals with solid arthrodeses, 25% to 35% clinical failure rates have been reported even in the face of successful fusion procedures. As a result, the 65% retention rate among patients receiving TLIF in this work cannot necessarily be viewed as a measure of the status of arthrodesis. We recognize this fact as one of the limitations of this study. Another limitation includes the fact that outcomes in this work were not assessed using accepted metrics such as the Oswestry Disability Index or SF-36. Lastly, although retention status is an acceptable outcome measure for members of the military, its use as a proxy for surgical efficacy potentially limits translation to a civilian population.

Although we acknowledge the limitations outlined above, it should be recognized that this study still demonstrates the efficacy of TLIF as a treatment option for a variety of spinal conditions, with a low complication profile, and acceptable retention rate for uniformed service members in the medium term. In addition, the prognostic model in this analysis identified risk factors for failure after TLIF, including activity level, socioeconomic status, and age that warrant attention in future studies. When one considers the large number of consecutive patients and duration of follow-up in this work, the findings presented here may be considered reasonable evidence regarding the impact of TLIF on military retention. When reflecting on this last contention, we seek to emphasize that although military cohorts have been utilized in the past as corollaries to young, high-demand, civilian populations, evidence-based research is also necessary for the uniformed service member to inform presurgical counseling, frame postoperative expectations, and develop long-term prognostications regarding outcome.

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**Comparative Effectiveness Research on Robotic Surgery**

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20 February 2013

During the last 10 years, the use of robotic-assisted surgery has substantially increased, beginning with urologic procedures and expanding to include gynecologic procedures and many others. Robotic-assisted surgery is a type of minimally invasive procedure that in fact facilitates laparoscopic surgery. Both approaches provide benefits compared with open surgery, including smaller incisions, shorter hospital stays, less
postoperative pain, and possibly quicker return to function. As of 2009, more than 200,000 robotically assisted operations had been performed worldwide. The reason for its rapid dissemination in the United States may be linked to a number of converging factors, including better ergonomics for the surgeon, marketing campaigns, and the national fascination with technology and innovation. Under other circumstances, this might be an unparalleled success story of US medical ingenuity. However, critics of robotic surgery claim that it is more expensive without providing a concomitant benefit.

In this issue of JAMA, Wright et al compared the use of robotically assisted hysterectomy for benign gynecologic disease with other approaches. Whereas past research relied on smaller samples in single institutions with limited generalizability, this study used a large national database involving 264,758 women who underwent hysterectomy at 441 hospitals and included detailed clinical variables, comorbidities, and outcomes of perioperative mortality and morbidity. The findings were stark. From 2007 to 2010, overall use of robotically assisted hysterectomy increased from 0.5% to 9.5%, and at hospitals that performed robotic procedures, robotically assisted hysterectomy accounted for 22.4% of all hysterectomies within 3 years. In addition, compared with laparoscopic surgery, robotic surgery was much more expensive—$2000 more per case or nearly a third higher than the median total cost for laparoscopic hysterectomy—without a significant advantage in clinical outcomes.

The study by Wright et al leaves some important unanswered questions. Robotic surgery may have a shorter learning curve than laparoscopic surgery, making it an enabling technology that allows surgeons otherwise unable to perform minimally invasive surgery to offer this benefit to their patients. Because either approach tends to have better outcomes than open laparotomy, in a cost-blind world there may be benefit from the rapid dissemination of a technique that enables access to a minimally invasive procedure for more patients. However, this presumes that laparoscopic surgery is unavailable in areas that offer robotic surgery. The study by Wright et al tracked the apparent replacement of laparoscopic surgery by robotic surgery in hospitals that have machines but did not indicate whether and how often minimally invasive alternatives were available. In addition, training surgeons is expensive. Would it be a better use of resources to train more surgeons in laparoscopic techniques than to spend the money on more robot machines?

A second issue is whether robotic surgery could be valuable for subgroups of patients with select comorbidities or anatomy. It may be necessary to continue to collect detailed registry data to understand if this is the case. Similarly, the results of this study should not be generalized to other clinical conditions for which benefits may accrue from the use of robotic surgery. As always is the case with observational studies, possible selection bias can affect results, although the authors were careful in their analyses by using propensity score methods.

A third issue involves the commercialization of this technology, which has raised eyebrows in the media and elsewhere. Considerable debate surrounded the emergence of direct-to-consumer advertising of prescription drugs in the 1990s. Robotic surgery takes this marketing to a higher level with advanced campaigns not only by industry, but also by surgeons and the hospitals that own the machines. Such consumer-directed advertising is not without merit if it uses consumer awareness to advance underused medical discoveries that benefit the population. However, when the innovation being advertised is of questionable advantage, direct-to-consumer promotion may only fuel unnecessary utilization. Consumer advertising of expensive devices should be subjected to the same scrutiny as that of new and expensive medications.
In the absence of additional research or decreases in price, the path taken by the medical and payer community should be one of caution. At a minimum, manufacturers might begin by voluntarily restricting their promotional activities. Public health entities could consider exercising greater oversight over claims that appear on websites. Meanwhile, physicians and hospitals have a duty to inform their patients of the benefits, risks, and costs of the options. There may also be a role for medical societies, which could join other specialties in the Choosing Wisely initiative of the American Board of Internal Medicine, aimed at identifying services whose “use should be reevaluated by patients and clinicians.”

As reimbursement policies stand today, payments for laparoscopic surgery are the same whether or not the procedures are robotically assisted. Therefore, neither patients, physicians, nor hospitals have the motivation to pursue the less expensive option. The results of this study could inform the development of medical payment policy, that is, the set of decisions made by public and private payers about whether to cover a procedure or service or, if covered, how to manage its utilization. The application of research findings to payment policy can be thought of as a matrix of scenarios depicting value to the health system, with comparative effectiveness (better, equal, worse) on one axis and comparative cost (higher, equal, lower) on the other. Different scenarios suggest different opportunities. For example, in the current US political environment, restricting coverage is difficult when a new technology is more effective, even if it is much more expensive than the technology currently available. Decisions should be more straightforward, however, when a new technology is equally or less effective and more expensive than a current technology. Robotic surgery for conditions such as benign gynecologic disease would seem to fall into the latter category.

Several potential strategies exist. If patient preferences drive the increase in use, it may be appropriate to institute higher copayments or even a reference payment whereby the insurer only covers the cost of the less expensive but equally effective technology. If physicians and hospitals are driving the increase in utilization, they could be asked to justify using the more expensive technology for certain cases. Alternatively, episode-based payments and global contracts promoted under the Affordable Care Act seek to change the payment system so that the incentive to provide high-value care rests with health care organizations, thereby avoiding intrusion by payers into medical decision making. For example, if accountable care organizations or other risk-bearing entities consider robotic surgery a low-value option, they may discourage their surgical groups from making the capital purchase or limit the number of purchases. What is not available cannot be overused.

Inefficiency in health care delivery can trace some of its roots to the use of new and expensive interventions for conditions where other effective treatment options already exist. Evidence-based medicine and comparative effectiveness research (CER) can help ensure the optimal treatment for a given class of patients by reducing the influence of nonclinical factors. By generating evidence comparing the benefits and harms of 2 or more medical interventions, CER can lead to improved patient outcomes, lower cost, or both.

The nation's pursuit of CER will be worthwhile only if the results are used to inform treatment decisions by payers, physicians, hospitals, and patients. The United States is embarking on an unprecedented era in support of evidence-based medicine. The Patient-Centered Outcomes Research Institute was created under health care reform to move the field forward and will have significant resources. The hope is that better and more widely available research will reduce the uncertainty around choosing the optimal intervention, thereby reducing the effect of nonmedical factors such as clinician bias for newer technologies or the profit potential of manufacturers. The medical and surgical community can move more quickly to improved patient outcomes and higher value by not spending scarce resources on less-effective options.
Vascularized Plantar Myocutaneous Free Flap Transfer for Amputee Stump Preparation: A Proof of Concept Cadaver Study

Military Medicine
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ABSTRACT

Lower extremity amputee stump ulceration, irritation, and pain have been a deterrent to consistent long-term or continuous use of lower extremity prosthetics. This study is the first in a series that hypothesizes that these complications can be minimized through the insetting of a vascularized plantar free flap (VPFF) on the amputee stump. Using three hip disarticulated cadaver specimens, a VPFF was designed, dissected, and implanted on one transfemoral and two transtibial stumps. Using accepted vascular anastomosis techniques, the posterior tibial artery was anastomosed to the distal femoral or popliteal artery with corresponding anastomoses for venous drainage. In addition, the possibility of a limited to partial sensate flap may be created with a neurorrhaphy of the associated nerves. This potentially sensate area would provide plantar skin that aids the existing local sensate flap used to close the defect. It is hypothesized that this procedure offers significant rehabilitative and long-term benefits to battlefield or other acute causes for lower extremity amputation. The procedure can be accomplished in battlefield surgical setting as an immediate or delayed inset for some but not all traumatic amputations. Salvaging a partial or complete VPFF from a traumatized foot will obviously be predicated on the degree of trauma to the donor tissue.

INTRODUCTION

One of the most difficult problems that a lower extremity amputee faces today is being able to transition to the use of the new prosthetic quickly. In some cases, patients may take years to fully adapt to the prosthesis. This delay in the use of the prosthesis is attributable to the physiologic changes that occur in the extremity during healing and afterward during normal daily activities. This transition to use is further complicated by the skin of the stump and the boney prominences of the stump preventing comfortable and consistent use of the prosthesis because the skin covering the amputation is not physiologically or anatomically suited for the pressures involved in walking. Various authors have reported that upward of 25% of patients experience ulcerations and delayed wound healing from this physiological mechanical skin mismatch on the amputee stump. Use of the prosthetic is further limited by pain (phantom or real) and discomfort in the stump with its use. On average, amputees receive a new prosthetic every 2 years for reasons that range from replacement of a worn out or broken prosthetic to need for a better fitting socket to prevent pain and ulcerations. For these reasons, it seems evident that attempts to reconstruct or transplant the evolutionary adapted weight-bearing and friction-tolerating glabrous skin of the foot to the amputee stump would help mitigate some of these complications.
The successful use of vascularized plantar glabrous skin free flaps in reconstruction of like-skinned areas has been documented, including its use on transtibial amputations. These successes have been achieved because the vascular anatomy of the foot and its plantar surface has been reported from over a century ago in “Gray's Anatomy” to today using modern dissection and angiographic studies. These studies have demonstrated that the glabrous skin and deep muscles of the plantar surface of the foot receive their blood supply from the posterior tibial artery (PTA) and its distal divisions—the medial and lateral plantar arteries, plantar arch, and metatarsal branches. It is not the intent of this study to demonstrate this vascular anatomy of the foot but instead to demonstrate a feasible myocutaneous flap that can be developed using the knowledge of this anatomy.

MATERIALS AND METHODS

Materials

The cadaver dissections were preformed in the Psychomotor and Surgical Skills Lab at the University of Florida, Department of Orthopaedics, Orthopaedic and Rehabilitation Institute in Gainesville, Florida. Three cadaver lower extremities were used in the proof of concept dissections. One complete hip disarticulated extremity and two below-the-knee disarticulated extremities were used to develop the three flaps. These same specimens were used to create two transtibial and one transfemoral amputation that the plantar flaps were inset on. Standard surgical instruments, sutures, and techniques were used to design, dissect, and remove the plantar flaps. Faux vascular and neurorrhaphy procedures were performed as these techniques have been well documented.

Methods

Partial lower extremity cadaver legs were used for development of vascularized plantar free flap (VPFF) and creation of below-the-knee (BKA) or above-the-knee (AKA) amputations. Dissection of the VPFF was then undertaken on three separate lower extremities as outlined below.

- First, the VPFF area to be harvested was outlined with this area including all the skin of the plantar surface of the foot. The line of dissection was the junction of the glabrous and nonglabrous skin as the guide for the skin incision on the foot. A cuff of normal skin was included in an attempt to avoid the development of hypertrophic scarring around the VPFF.

- The line of dissection was then carried posterior just inferior to the medial and lateral malleolus of the ankle and joined posterior at the Achilles tendon above its calcaneus insertion and just inferior to the medial and lateral malleolus.

- The approach to the PTA was outlined to demonstrate the medial line of the anterior surface of the tibia.

Two routes of dissection for exposure of the PTA were planned.
— The first involved exposure of the PTA by incising the skin just medial to the medial edge of the tibia and identifying the greater saphenous vein, which was preserved and harvested for use if needed as a vascular conduit when attaching the flap to the vascular supply or drainage. This also provides access to the vein for drainage of the VPFF if needed.

— The plane between the flexor digitorum longus inferior and the soleus superior was then identified, and using this fascial plane, the posterior neurovascular compartment is easily entered, exposing the PTA, veins, and nerve.

— The PTA and posterior tibial nerve were then used as the plan of dissection carrying the dissection distally behind the medial malleolus of the ankle. The PTA, posterior tibial nerve, and the venae comitantes were reflected posterior with the developing flap.

— The entire plantar surface of the foot was then dissected free by incising through the skin into and below the periosteum of the medial and lateral metatarsals, incising the superficial and deep plantar flexors (flexor digitorum longus and brevis, lumbricals, and flexor hallucis longus and brevis) into the periosteum. The dissection was then carried along the periosteum and the plane of dissection transitioned into the deep plantar space. This space creates a natural plan of dissection from which to harvest the fully vascularized plantar myocutaneous free flap. The dorsal perforating artery is ligated proximal to the greater metatarsal–phalangeal joint as it penetrates dorsally. The flap is developed proximal toward the calcaneus. The short flexors are carried with the flap taking the quadratus plantae with the flap but leaving the lumbricals, interosseous, abductors muscles, and the long plantar ligament in place. The PTA is superficial to this plane of dissection and its passage between the quadratus and the flexor digitorum brevis. The goal of the deep dissection is to preserve the medial and lateral plantar arteries and nerves superficial to the plane of dissection. Also, the deep dissection provides a more durable flap. By harvesting the thicker flap, it is then possible to remove the flexor hallucis brevis, flexor digitorum brevis, and flexor digiti minimi if so desired. A thicker flap would provide a better weight-bearing surface and protection of the weight-bearing implant but could compromise viability because of the vascular demands.

— Using the deep plantar compartment, the dissection is carried to and below the periosteum of the calcaneus, using this plane to free the flap from the calcaneus. The periosteum serves as a durable payer and includes the possibility of calcification.

— The skin is incised over the Achilles tendon and the tendon bisected. The dissection is then carried deep medial and lateral down to and including the ankle's ligamentous capsule. This keeps the vascular pedicle safely reflected away from the plane of dissection. All flexor tendons are cut as they rotate behind the ankle into the plantar surface of the foot, protecting the neurovascular pedicle during these divisions.

— The dissection is then carried over to and below the periosteum of the calcaneus where the insertion of the Achilles tendon is then freed and the flap is left tethered to the neurovascular pedicle.

— The posterior peroneal artery is not dissected although identified laterally ligated at its termination of the external calcanean, which communicates with the internal calcanean of the PTA.
Two free microvascular plantar tissue grafts were dissected free with this technique with little risk to the vascular pedicle as it is deep to all planes of dissection. The pedicle is at some risk when freeing the neurovascular pedicle as it passes posterior and deep to the medial malleolus. This flap can be debulked, if desired, of flexor tendons and excess muscle if done carefully without injuring the vascular pedicle distribution. The one flap not dissected with this method was a subcutaneous supramuscular plantar dissection that lacked significant bulk and fibrous tissue such as calcaneus periosteum and flexor tendons and muscles.

Two standard surgical proximal and distal transtibial amputations were created on two separate cadaver legs. The proximal PTA and anterior tibial artery were identified for possible anastomotic vessels along with the proximal tibial nerve. A VPFF was placed over the exposed surface of the transtibial stumps with the neurovascular pedicle matched to its corresponding proximal counterpart with a simulated microvascular anastomosis and neurorrhaphy completed. The neurovascular pedicle is positioned to prevent pressure that could compromise blood flow during healing. The flaps were then sutured into position by placing the heel anterior and distal plantar skin posterior.

DISCUSSION

The partial loss of a lower extremity has been part of humankind's existence on earth since our first days here. With the advent of warfare, the manner in which amputations of all types occur has changed with the advancement of the weapons of war. On today's battlefields, explosive injuries account for the majority of lost appendages. For civilians, in one study, the major traumatic reasons for lower extremity amputations involved blunt or penetrating trauma with motor vehicle accidents and gunshot wounds the two most common causes, respectively. However, according to the National Limb Loss Information Center, vascular disease is the leading cause of lower extremity amputation in the United States with trauma the second.

As of 2005, approximately 1.6 million people lived with the loss of an appendage and this number is expected to double by 2050. Statistically, the majority of these amputations will be the result of diabetes and peripheral vascular disease but 8 to 10% will be trauma related. As the mid-eastern conflicts continue, military trauma will continue to represent a statically meaningful number of these traumatic amputations. It has been reported that 20% or higher of transfemoral and transtibial amputees are unable to wear their prosthesis and a larger percentage is unable to wear it consistently. Even among traumatic amputees over time, upward of 30% have increasing difficulty using their prosthetics successfully, further limiting their activities and opportunities. Given these numbers, it seems reasonable to explore new techniques of amputation flap reconstruction that focus on increasing utilization of the prosthetic, improved mobility for the amputee, and fewer complications associated with the use of their prosthesis. It is with this in mind that this study was designed and has demonstrated a technically feasible technique of using a VPFF to close an amputee's wound. By transferring the evolutionary designed hairless glabrous skin of the foot to the future weight-bearing area of the new amputation, it is believed that patients will rehabilitate quicker with fewer long-term complications of ulcers and wounds on the stump. With increased mobility, the amputee will be more independent and be able to work toward economic independence.

From a military perspective, there will probably be few situations were any salvageable plantar tissue is available. This would be particularly true for land mine injuries and near proximity blast with shrapnel injuries that mangle the distal extremity. However, when possible, every effort should be made to bring the amputated extremity remnants in with the evacuated soldier or civilian. Given the different vascularized flaps that can be
made from the plantar surface, consideration for salvaging any vascularized area of the glabrous surface and insetting it into the remaining lower extremity for later use should be considered. In time, a grading scale of plantar injury and salvage of glabrous skin will need to be created. One patient population that may benefit would be those patients who fail limb salvage surgery with a partial or complete plantar surface. This flap if still would be worth consideration for vascular transfer. Overall, this method lends itself to situations where the patient's foot is intact or with mangled limbs that include limited vascular injuries to the foot: specifically, those patients with unreconstructable intercalary segments, failed limb salvage patients, oncology patients, and select military and civilian traumatic amputations. For some vascular patients, angiography may demonstrate that their proximal and distal circulation is adequate for VPFF use. The VPFF can be used as the primary closure of the amputation defect or as a myocutaneous graft over a de-epithelized standard amputee closure. Including periosteum in the dissection may introduce sites for bone formation or calcification that are not secured to the underlying tibia or femur. This may not be advantageous but does provide a durable tissue foundation. From a general vascular supply point of view, the smallest most efficient flap is the most likely to survive but the thicker more durable flap should provide a stronger more durable surface. In addition, the reinnervated flap offers the prospect for sensory recovery with the need for sensory re-education but the issue of phantom limb sensation will still be a ubiquitous problem. Clinical trials will ultimately determine the optimal flap design.

If the estimate of 3 million plus amputees by 2050 is correct, then it is important for medicine and society to provide them with their best opportunity to be productive and active members of our society. For those young men and women who have lost or will loss an extremity in service to this country, in Iraq, Afghanistan, or any other future conflict, providing them with proven state-of-the-art reconstructive and rehabilitative techniques is critical. This study has demonstrated through cadaver dissection one possible reconstructive surgical improvement to the now 500-year-old Ambroise Pare technique of amputation. If this technique reduces complications associated with long-term use of prosthetics and helps integrate the amputee back into society, then it will be of immense long-term economic value to the country. A happy, fully engaged, and working individual will provide better for his family and society in general.

**High-performance neuroprosthetic control by an individual with tetraplegia**

The Lancet
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Summary

Background
Paralysis or amputation of an arm results in the loss of the ability to orient the hand and grasp, manipulate, and carry objects, functions that are essential for activities of daily living. Brain—machine interfaces could provide a solution to restoring many of these lost functions. We therefore tested whether an individual with tetraplegia could rapidly achieve neurological control of a high-performance prosthetic limb using this type of an interface.

Methods

We implanted two 96-channel intracortical microelectrodes in the motor cortex of a 52-year-old individual with tetraplegia. Brain—machine-interface training was done for 13 weeks with the goal of controlling an anthropomorphic prosthetic limb with seven degrees of freedom (three-dimensional translation, three-dimensional orientation, one-dimensional grasping). The participant's ability to control the prosthetic limb was assessed with clinical measures of upper limb function.

Findings

The participant was able to move the prosthetic limb freely in the three-dimensional workspace on the second day of training. After 13 weeks, robust seven-dimensional movements were performed routinely. Mean success rate on target-based reaching tasks was 91·6% (SD 4·4) versus median chance level 6·2% (95% CI 2·0—15·3). Improvements were seen in completion time (decreased from a mean of 148 s [SD 60] to 112 s [6]) and path efficiency (increased from 0·30 [0·04] to 0·38 [0·02]). The participant was also able to use the prosthetic limb to do skilful and coordinated reach and grasp movements that resulted in clinically significant gains in tests of upper limb function. No adverse events were reported.

Interpretation

With continued development of neuroprosthetic limbs, individuals with long-term paralysis could recover the natural and intuitive command signals for hand placement, orientation, and reaching, allowing them to perform activities of daily living.

Funding

Defense Advanced Research Projects Agency, National Institutes of Health, Department of Veterans Affairs, and UPMC Rehabilitation Institute.

Introduction

Brain—machine interfaces transform neural activity into control signals for an external device. Functional electrical stimulators, exoskeletons, and sophisticated prosthetic limbs are being developed with the goal of restoring natural function. For many activities of daily living, an individual needs to be able to position the hand in space, orient the palm, and grasp an object. These hand movements are normally smoothly coordinated and
follow the general principles of natural movement. Ideally a brain—machine interface will translate neural activity into control of an external device with the capability of producing natural movements in accordance with the general principles.

The natural features of movement have been captured in recordings of motor cortical neural activity using intracortical microelectrodes in a study in non-human primates. In other animal studies, a robot arm was controlled in four dimensions for self-feeding tasks and in seven dimensions for orientation and grasping. Motor cortical activity has also been used to electrically activate paralysed muscles of the upper limb. Results of studies in people have shown three-dimensional translational control, and control over a single grasping dimension. We therefore tested whether an individual with tetraplegia could rapidly achieve control of a state-of-the-art anthropomorphic prosthetic limb (modular prosthetic limb [MPL], Johns Hopkins University, Applied Physics Laboratory, Baltimore, MD, USA).

Methods

Participant

The participant was a 52-year-old woman who was diagnosed with spinocerebellar degeneration 13 years before she took part in this study. Thorough chart review and discussions with her neurologist showed no indication of cerebellar involvement. The participant's injury was motor complete with manual muscle test scores 0 of 5 for the upper limb. Physical examination showed that she had generally intact sensation with some hypersensitivity.

This study was approved by the institutional review boards at the University of Pittsburgh (Pittsburgh, PA, USA) and the Space and Naval Warfare Systems Center Pacific (San Diego, CA, USA). We obtained verbal informed consent from the woman before her participation in the study; consent was signed by her legal representative.

Array implantation

We implanted two intracortical microelectrode arrays (4 mm × 4 mm, Blackrock Microsystems, Salt Lake City, UT, USA), about 14 mm apart, each with 96-electrode shanks (length 1·5 mm) in the participant's left motor cortex on Feb 10, 2012, using stereotactic image guidance (Brainlab, Westchester, IL, USA) with structural (MRI) and functional imaging (fMRI) to guide placement. The prosthetic arm was mounted on a stand next to the participant. Two cables ran from connectors on the participant's head to the recording apparatus and another cable ran from the computer to the prosthetic arm.

Array location and setup of experiment

(A) Preoperative functional MRI activation maps of a participant-specific brain model during video-guided attempted movement. The colours in the activation maps represent blood-oxygenation-dependent activities during video-guided attempted movements—yellow is sequential finger flexion, red hand grasping, blue shoulder shrug, and green lip pursing. Approximate array locations are shown as black squares on the inset figure. (B)
MPL and seven-dimensional sequence task setup. The participant was not presented with physical targets, instead light-emitting diodes (indicated by the arrow) were used to instruct the participant to hit the near (0.35 m from the shoulder) or far (0.52 m from the shoulder) translation target corresponding to one of the white circles on the board in front of the MPL. Orientation and grasp targets were presented by a computer-generated verbal command. (C) Diagram of the MPL and translation targets (red and blue spheres) for the seven-dimensional sequence task. The red sphere illustrates the single target of an example trial. The MPL coordinate system (red, green, and blue arrows labelled x, y, and z, respectively) is shown centred at the shoulder. Translation targets had an 8 cm radius and the MPL endpoint (centre of the palm) had to be within this region for a successful trial. The MPL endpoint also had to be within the translation target success region to successfully achieve the orientation (±15°) and grasp the targets that were given as audio cues. The timeout was set to 10 s. CS=central sulcus. MPL=modular prosthetic limb.

Neural recording

Generally, we recorded neural signals three times per week for 13 weeks; each session was about 4 h. The signals were recorded with the NeuroPort data acquisition system (Blackrock Microsystems). Single-unit and multi-unit events were classified with manually set thresholds and time-amplitude windows. Daily setup time, including unit sorting, took about 30 min. The neural activity was converted to a firing rate in 30 ms bins and low pass-filtered using an exponential smoothing function with a 450 ms window.

Observation-based calibration and neural decoding

Brain—machine-interface training progressed from three-dimensional endpoint translation control (weeks 2 and 3 after implantation), to four-dimensional control of translation and grasp (week 4), to seven-dimensional control of translation, orientation, and grasp (weeks 5—14). Joint angles of the fingers and thumb of the MPL were combined into a single dimension. The neural decoder, based on a model that linearly related neural firing rate to movement velocity (equation 1), was calibrated daily with a two-phase calibration similar to the methods used in studies of non-human primates.

During the observation phase, the MPL moved automatically, driven by a proportional controller, to targets that spanned the reachable workspace of the arm as part of a seven-dimensional sequence task. In this task, a target was indicated by a light-emitting diode on a board in the frontal plane (80 cm × 80 cm), 70 cm in front of the MPL shoulder. Once the MPL was moved to the correct three-dimensional position, computer-generated verbal prompts described an orientation to be performed by rotating the palm in one of six directions or a grasp target (open or closed hand). Possible orientations included pronation—supination (±45°), ulnar—radial deviation (±20°), and flexion—extension (±45°) of the wrist. The participant was instructed to carefully watch the limb as it moved automatically to the targets. Neural data and information about the MPL state—endpoint position, joint angles, and joint torque—were recorded at a rate of 33 Hz. We gathered data from 80 trials (6 min) of the seven-dimensional sequence task to train the initial observation-based seven-dimensional neural decoder. Equation 1 was used to relate the activity of each unit to MPL movement velocity, where \( f \) is the firing rate of a unit during movement described by the seven-dimensional velocity vector \( V (v_x, v_y, v_z, v_{\theta_x}, v_{\theta_y}, v_{\theta_z}, \text{and } v_g) \), and the coefficients for each unit are \( b_0, b_x, b_y, b_z, b_{\theta_x}, b_{\theta_y}, b_{\theta_z}, \text{and } b_g \). \( V \) consists of the coordinates for the
three-dimensional endpoint translation (x, y, and z), three-dimensional orientation (θx, θy, and θz), and one-dimensional grasp (g) velocities. Units that did not fit the model ($R^2 \leq 0.1$) were excluded. Indirect optimal linear estimation with ridge regression was used for the coefficient matrix B.

During a second phase of calibration, the participant controlled the MPL using the observation-based neural decoder while orthoimpedance was applied to the command signal. In this phase, orthoimpedance attenuated the brain-command component perpendicular to the ideal seven-dimensional trajectory by 100%, restricting movements to directions directly toward or away from the target. Data from 80 trials of the seven-dimensional sequence task gathered during the second phase of calibration were used to build the final decoder with optimal linear estimation as described above. This second round of calibration allowed the participant to actively engage in the task, while minimising errors and corrective movements. Calibration was done daily and took about 15 min. Early in the experiment (weeks 2—4), similar calibration procedures were used to generate lower-dimensional neural decoders. Although this report is a communication of the seven-degrees-of-freedom study, it should be noted that the participant was able to move the MPL in the three-translational dimensions of the workspace, without computer assistance, on the second day of the recording experiments (week 2 after the implant).

Target-based brain-control task

After completing the calibration, we used the seven-dimensional sequence task for brain—machine-interface testing. The computer randomly selected targets from a possible combination of ten translation, seven orientation, and two grasp targets. Endpoint velocities derived from the recorded neural firing rates were sent from the computer to the MPL controller, which converted them to joint motor commands every 20 ms. As with calibration, a translation target was specified by a light-emitting diode and then an orientation or grasp target was announced by a computer-generated voice. The participant had control of all seven dimensions (translation, orientation, and grasp) throughout the task.

Orthoimpedance was adjusted throughout the initial learning phase of the task (up to day 66). In this phase, computer-assisted stabilisation was also used. Stabilising control blended an ideal endpoint velocity control signal determined by the proportional MPL controller with the control signal derived from the participant's brain activity. The contributions of each signal were specified by the experimenter. Stabilising control was only applied to domains that were not being actively controlled—ie, the position was stabilised at a specified percentage (10—100%) during the orientation phase or orientation and grasp posture were stabilised during translation. Similarly, the experimenter could also specify the percentage of orthoimpedance. The experimenter adjusted both forms of computer assistance subjectively to keep the participant engaged and motivated with the aim of maintaining a 60—80% success rate. Importantly, after week 10 (day 66), the participant did all tasks without computer assistance. A maximum movement time of 10 s was enforced for each trial phase (translation, orientation, or grasp).

Performance metrics (success rate, completion time, and path efficiency) were calculated during the test sessions. Success was determined by MPL kinematics recorded in real time. All seven dimensions were controlled continually and had to be correct during all three phases of movement for a trial to be judged a success. The experimenter could also manually mark a trial as being successful (or unsuccessful) if the participant rotated too far in the specified direction or if mechanical limitations of the MPL prevented movement along one dimension. The probability of completing the task by chance was ascertained with random-walk signals as input to the assist parameters (if any) and target sizes used during the experiment. 200 simulations were run per trial and the median daily chance levels from these simulations are reported. For each trial, path
efficiency was computed for each control domain with equation 2, where LOT is the length of the optimal trajectory from the starting position to the end target location and LBCT is the length of the brain-controlled trajectory for a particular trial; each was calculated in three domains—translation (m), orientation (rad), and grasping (arbitrary units). LBCT was calculated by numerical integration of the magnitude of the velocity vector V for the duration of one trial.

Functional brain-control tasks

The participant used the MPL under full brain control to do nine tasks (selected from 19 possible tasks) on the action research arm test (ARAT), which is an assessment of the unilateral upper limb function used commonly in patients who have had a stroke. ARAT is psychometrically sound and tracks the ability of an individual to undertake activities of daily living. The selected tests include all six items from the grasp subscale and three of four items from the grip subscale. Standard administration procedures were followed with a few modifications. One of the items was a ball, which was positioned inside a loose coil of wire to keep it from rolling off the table, although it was still possible for the participant to bump the ball hard enough to roll outside the wire coil. The MPL hand started about 12 cm from the table surface, with the palm facing towards the left instead of on the table. Each test item was timed and scored as 0 (no movement possible), 1 (task partly done), 2 (task done, but not correctly), or 3 (task done correctly). Movements that required more than 5 s to complete were scored as 2. The participant attempted each assessment three times and was instructed that only the best score counted. This method was designed to keep her motivated and open to trying new strategies.

The participant also did a cone-stacking task—moving three plastic cones (height 30 cm, diameter 4.1—6.4 cm) from a base and stacking them sequentially on a second base located at a distance of 30 cm. The time to complete the task and the number of drops were recorded for each attempt. This test was a measure of the participant's ability to grasp, transport, and position objects with precision.

Role of the funding source

The sponsors of this study had no role in study design, data gathering, analysis, and interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

The arrays were implanted on Feb 10, 2012, and the first day of testing was on Feb 20, 2012. The last day of testing was May 18, 2012. The range of recorded single-unit and multi-unit neural activity was from 209 units per day to 271 units per day. There seemed to be an initial settling period during which the number of units started off high until day 21 after the implant and then fell in week 4 (day 24). Starting at day 24, the neural activity began to increase linearly at a rate of 0.368 units per day or 2.58 units per week (y = 0.368x + 210.0, where x is the number of days after implant, $R^2 = 0.356, p < 0.0001$). The neural activity tuned to movement velocity with an $R^2 > 0.1$ (equation 1) increased linearly with time for the duration of the recording at a rate of 0.388 units per day or 2.72 units per week (y = 0.388x + 24.3, $R^2 = 0.155, p = 0.0097$).
The blue dots represent the number of neural units recorded during brain—machine-interface sessions done 10—98 days after the implant. The red squares represent the neural units tuned to movement velocity with $R^2 > 0.1$ (equation 1). For reference, four-dimensional training began on day 24 and seven-dimensional training on day 32.

The participant's success rate in both computer-assisted and full-brain control trials during all 24 sessions of testing of the seven-dimensional sequence task, and the chance level for each day. Orthoimpedance and stabilising computer assistance were only used until week 10 (day 66). After day 66 following the implant, all performance data (seven dimensional) were gathered with full brain control without computer assistance. We did not do any MPL testing on days 52—58. The participant's performance improved during the 34 sessions over 13 weeks of training. During the last 2 weeks of training, without computer assistance, the participant achieved a mean success rate of 91·6% (SD 4·4) and a median chance level of 6·2% (95% CI 2·0—15·3) calculated by use of simulations with random-walk data as an input signal. The mean success rate at the beginning of the trial was 76·0% (SD 14·9) with a median chance level of 36·7% (95% CI 12·9—72·8).

Summary of seven-dimensional brain-control performance

(A) Participant's success rate on the seven-dimensional sequence task for each block of 20 trials of brain-control training. The red dots with error bars represent the median chance and 95% CI, respectively, calculated from 200 simulations per trial. (B) Normalised performance index for each day of the seven-dimensional brain control. For each block of 20 trials, the success rate was normalised to the median chance level. (C) Block completion time, excluding the presentation phase time. (D) Mean seven-dimensional path efficiency of the MPL under brain control. (E) Path efficiency for three-dimensional translation during the seven-dimensional sequence task. Only successful trials were included in the calculation of path efficiency. For parts C—E, each dot represents the mean block time or path efficiency for one block of 20 trials of the seven-dimensional sequence task completed by the participant. Linear fits to the participant's data are shown as a red line. The mean block time or path efficiency of the MPL under autocontrol is shown as a solid horizontal black line. MPL=modular prosthetic limb.

The participant's performance increased exponentially with time even as the difficulty of the task increased ($y = 1.812x^{0.04}(x — 32)$, $R^2=0.114$, $p = 0.001$).

The participant also showed improved MPL control—reduced block completion time and increased path efficiency. Block completion time decreased linearly from a mean of 148 s (SD 60) to 112 s (6) during the seven-dimensional training and became less variable ($y = -0.632x + 171.4$, $R^2 = 0.142$, $p < 0.0001$). Mean path efficiency increased linearly from 0·30 (0·04) to 0·38 (0·02) as the participant moved along a straighter, more coordinated path ($y = 0.001x + 0.228$, $R^2 = 0.160$, $p < 0.0001$). Mechanical constraints sometimes forced the MPL to deviate from an ideal linear trajectory, causing the maximum achievable efficiency under autocontrol to be less than 1. The greatest improvement in control seemed to be in the translation domain, which increased linearly with time ($y = 0.003x + 0.317$, $R^2 = 0.165$, $p < 0.0001$).

The participant was able to rapidly reach the target position in the specified control domain (translation, orientation, or grasp) while maintaining her position in the other two domains.

Translation (A), orientation (B), and grasp aperture (C) of the MPL during four seven-dimensional sequence task trials under full brain control
The black horizontal bars denote whether a translation, orientation, or grasp target was being attempted in (A), (B), and (C), respectively, although the participant had control of all seven dimensions at all times. The beginning of each new translation target indicates the start of a new trial. MPL kinematics, controlled by the participant, are shown as solid lines (with each colour representing movement in a different direction of the coordinate system). The target for each dimension is shown as a dotted line. Grey regions indicate presentation phases in which the MPL was paused and the participant was listening to a computer-generated verbal command. A grasp aperture of 1 indicates that the hand was fully closed. The participant was successful in maintaining the position of the prosthetic limb in one control domain while changing position in another, as instructed. Video 1 shows the participant’s performance of these four trials with the MPL. MPL=modular prosthetic limb.

Neural changes were also noted during the seven-dimensional brain control testing. The percentage of units tuned to seven-dimensional MPL velocity (equation 1) showed a linear increase. The percentage of units with $R^2 > 0.1$ increased during the late training phase (weeks 11—14) compared with the early phase (weeks 5—8). Early values of $R^2$ had a median of 0.038 (IQR 0.019—0.077) and the late values had a median of 0.041 (0.019—0.093); the late values were significantly larger (Wilcoxon rank-sum test, $p < 0.0001$). The increase in the number of units with $R^2$ in the range 0.15—0.30 suggests that the participant was learning to modulate her brain activity to better fit the neural encoding model to improve performance.

(A) Percentage of neural units for which firing rate predicted seven-dimensional MPL endpoint velocity (equation 1) with an $R^2 > 0.1$ on each day of seven-dimensional brain-control training. Each dot represents data from a single decoder. The red line is the regression to the data ($y=0.002x+0.100$, $R=0.119$, $p=0.066$). On a single day, decoders were trained with observation data and brain-control data with orthoimpedance. (B) Percentage of units tuned to MPL kinematics with given $R$ values for early training (weeks 5—8) of seven-dimensional brain—machine-interface training compared with late training (weeks 11—14). Each bar is centred between the upper and lower bound of $R^2$ values for a particular bin. All $R^2 > 0.5$ were combined into a single bin. With time, the percentage of units with an $R^2 < 0.1$ decreased and the percentage of units tuned to kinematics with $0.1 \leq R^2 \leq 0.5$ increased. MPL=modular prosthetic limb.

Table 1 shows the completion time and total score, for each test item on the days that ARAT was completed. If no time is listed, the score for that item was 1 because the task was partly completed. For items with completion times listed, the score was 2 because it took longer than 5 s (roughly equivalent to the time taken by an adult without any impairment to complete the task). The participant’s performance was consistent as indicated by her total score of 15—17 on the 7 days of testing. She was unable to move her own upper limbs volitionally and therefore scored 0 without the use of the brain—machine interface or other assistive technology. Video 2 shows her ARAT performance on day 87. The movements were generally smooth, direct, and fast. The participant reported that she was thinking about the goal of the action, such as “grab the block,” rather than issuing specific kinematic commands to the MPL, suggesting that the control was intuitive.

Dropped cones were repositioned by the experimenter. The participant achieved her fastest performance on the last day of testing (day 95), although she dropped the cones more often than on day 87. The participant knocked the first cone off the base six times before quickly moving all three cones, with only one additional dropped cone. She completed this task consistently on all 4 days of testing.

Discussion
In this study, an individual with tetraplegia rapidly learned to routinely reach and grasp using coordinated and robust seven-dimensional control (three-dimensional translation, three-dimensional orientation, one-dimensional grasping) of a high-performance anthropomorphic prosthetic limb. The participant did the manoeuvres with coordination, skill, and speed almost similar to that of an able-bodied person. Performance on reaching and grasping tasks consistently improved during the 34 training sessions in 13 weeks. The improvement was steady and robust, and the participant was consistently learning. In this context, learning is defined as the modification of the correspondence between neural activity and action. Although the mechanism of this modification is not known, clear and consistent change in neural tuning is a feature of the brain—machine-interface model and our results show that the population of neurons became more tuned to MPL movement velocity with time. The use of neural extraction algorithms derived from natural movement with an anthropomorphic effector is likely to have increased the acquisition of the skill necessary to achieve the MPL performance. This type of brain—machine-interface control is model based, by contrast with classifiers that operate on predefined libraries of discrete input—output categories. With our approach, continuous three-dimensional translation of the hand was achieved with a few hours of training, and seven-dimensional control was done routinely in less than 4 months. The movements were smooth, coordinated, and skillful. The participant had the flexibility to explore a range of arm or hand configurations to complete tasks with different strategies.

The use of observation-based calibration, computer-assist methods, and extraction algorithms used in our study was established in studies of non-human primates. The findings of previous human studies have shown that intracortical electrodes could be used to provide rudimentary control of computer cursors and robotic manipulators. Our study builds on this work by adding degrees of freedom that allow for more natural and coordinated movements, a broader workspace, and the ability to interact with various objects in different orientations. During several days of testing, the participant was able to improve her ARAT score from 0 to 15—17 of 27. This range is much greater than the threshold of 5·7 points for a clinically significant improvement in function, showing that use of a neuroprosthetic device has the potential to provide clinically significant functional benefit. As shown in video 2, movements were smooth and coordinated, with speeds nearly similar to those of able-bodied adults. Because we used a velocity-based decoding model, the MPL speed was controlled directly by the participant. The level of control achieved by the participant allowed for subtle corrective movements and object manipulation. ARAT testing began once the participant had achieved consistent seven-dimensional control on the target-based task and her performance in terms of clinical measures was consistent during the last 3 weeks of testing.

Panel

Research in context

Systematic review

We did a literature review in PubMed without date or language restriction using the search terms “neuroprosthetics”, “brain-machine interface”, or “brain-computer interface”. Because our goal was to restore upper limb function, we restricted our survey to studies in which robotic technology or functional electrical stimulation was used to achieve the same goal as ours. Additionally, we drew from our own substantive reference libraries. Two published reports of robotic arm and hand control in individuals with motor impairments were identified. The four-dimensional control of a robotic arm in a self-feeding task was investigated in one study of non-human primates, and in studies of functional electrical stimulation of the
upper limb. For some individuals with amputation or residual muscle activity, other prosthetic control techniques, including non-invasive approaches, targeted reinnervation, or direct peripheral neural control, might be appropriate.

Interpretation

The results of previous work have shown that neural activity can be recorded from the motor cortex and translated to movement of an external device or the individual's own muscles. However, until now, the results of human studies have not shown whether the natural and complex movements can be done consistently for different tasks. Here, we have shown that a person with chronic tetraplegia can do complex and coordinated movements freely in seven-dimensional space consistently over several weeks of testing. This study is different from previous studies in which investigators had little control in translation dimensions, used staged control schemes, or had insufficient workspace to complete very structured tasks. Increasing dimensional control allows our participant to fully explore the workspace by placing the hand in the desired three-dimensional location and orienting the palm in three dimensions. This study is the first time that performance has been quantified with functional clinical assessments. Although in most human studies only a few days of performance data were reported, we have shown that the participant learned to improve her performance consistently over many days using different metrics. By using training methods and algorithms validated in non-human primate work, individuals with long-term paralysis can recover the natural and intuitive command signals for hand placement, orientation, and reaching to move freely in space and interact with the environment.

We expect further developments in brain—machine-interface technology in the near future. A wider range of tasks will become possible by adding hand shape to the repertoire of volitional control. Tactile feedback will be transduced by fingertip sensors and transmitted to the sensory cortex. Telemetry will remove the need for transcutaneous leads and connectors. Paralysed arms will be reanimated by activation of the individual's own muscles, which we know is one of the priorities for people with tetraplegia. Our results and the very rapid developments in this specialty show the potential to restore much of the function lost in individuals with tetraplegia or upper limb amputation, allowing them to regain natural behaviours to interact with the world around them. With further development of neuroprosthetic technology and use of validated training methods and algorithms, these individuals could more fully recover their innate and intuitive command signals for routine arm and hand manoeuvres.

PTSD

Stellate Ganglion Block Improves Refractory Post-Traumatic Stress Disorder and Associated Memory Dysfunction: A Case Report and Systematic Literature Review

Military Medicine
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Abstract

The prevalence of post-traumatic stress disorder (PTSD) has reached epidemic proportions among U.S. veterans, many of whom also have concurrent alcohol use disorder. This case report describes improvements in PTSD symptom severity and memory dysfunction in a combat-exposed veteran with persistent PTSD and alcohol use disorder following two treatments of stellate ganglion block (SGB). PTSD severity was measured using the PTSD Checklist, Military Version. Memory function was evaluated using the Rey Auditory Verbal Learning Test. One month after the first SGB, a 43.6% reduction in PTSD severity was observed along with increases in immediate memory (50%), recent memory (28%), and recognition memory (25%). Following a second SGB, PTSD severity decreased by 57.7% and memory function substantially improved, with pronounced changes in immediate memory (50%), recent memory (58%), and recognition memory (36%). One year after SGB treatments, the patient has stopped drinking alcohol, continues to have sustained relief from PTSD, has improved memory function, and has become gainfully employed. Future studies that employ robust epidemiologic methodologies are needed to generate confirmatory evidence that would substantiate SGB’s clinical utility as an adjunctive treatment option for PTSD.

Introduction

The prevalence of post-traumatic stress disorder (PTSD), the complex pathological anxiety condition that substantially impairs mental and physical function, has reached epidemic proportions among the nearly 23 million U.S. veterans. Another concerning trend is that 40% to 84% of veterans with PTSD also have concurrent alcohol or substance use disorders depending on the cohort and severity of combat exposure. There are numerous adverse consequences of comorbid PTSD and alcohol use disorder, the most alarming of which is that mortality is more than twice as high among patients with PTSD and comorbid alcohol dependence as compared to patients with PTSD alone. One of the more limiting comorbidities that substantially reduces the patient’s quality of life when PTSD and alcohol use disorder are jointly present is impairment of memory function. A plethora of studies have shown that as many as 80% of military veterans undergoing PTSD treatment with comorbid alcohol use disorder report difficulties with memory and concentration.

Self-medication as a coping mechanism is often used to explain the strong association between PTSD and alcohol and substance use disorders. In essence, alcohol is used to reduce the distress and heightened anxiety that accompany PTSD. Although current gold standard treatments for PTSD utilized by the Military Health System and Veterans Administration (VA) are pharmacotherapy (e.g., selective serotonin reuptake inhibitors), psychotherapies (e.g., cognitive and exposure modalities), or both, these therapeutic modalities have demonstrated little success in patients with chronic or refractory PTSD and comorbid alcohol use disorder. The reasons for this lack of treatment success are multifactorial.

Interventions targeting patients with PTSD and co-occurring alcohol use disorder typically experience early and high attrition rates in excess of 50%, primarily because of the time demands of extended therapy. In addition, insufficient patient motivation and other characteristics (e.g., male gender) that lead to differential access to care and nonadherence have been reported as influencers of treatment success among veterans with...
PTSD and comorbid alcohol use disorder. Multiple studies have found that while more than 50% of those with PTSD access mental health services, fewer than 20% of those with comorbid PTSD and problem drinking do so. Furthermore, there is no consensus on the most appropriate means of treating PTSD and comorbid alcohol or substance use disorders with pharmacotherapies given their reduced efficacy in these patients. With a few exceptions, most large-scale trials of exposure treatment modalities have excluded participants with comorbid alcohol and substance use disorders, leading to a significant gap in our knowledge base.

In light of the dilemmas clinicians face in treating refractory PTSD and co-occurring alcohol use, some have employed a novel therapeutic approach. Since 2008, the application of a commonly used pain management procedure for the face and upper extremities known as a stellate ganglion block (SGB) has been published in a series of case reports across multiple health care settings as a promising adjunctive treatment option for PTSD. These studies have mostly focused on active duty military service members or veterans suffering from persistent PTSD. Collectively, the results from these preliminary reports provide evidence suggesting that SGB has the potential to significantly and rapidly improve PTSD symptoms.

The purpose of our case report is to add to the growing body of literature on the potential benefits of SGB in reducing PTSD symptom severity. To the best of our knowledge, our case report is the first to provide evidence of improvements in memory dysfunction as a secondary outcome following SGB treatment for refractory PTSD in a combat-exposed veteran with comorbid alcohol use disorder.

Methods

SGB Treatment Procedure

Once informed consent was obtained from the patient, an intravenous line was started with a 22G IV in the left hand. The patient was positioned supine on a fluoroscopy table, placed into cervical extension with a shoulder roll, and hemodynamically monitored (e.g., pulse oximetry and electrocardiogram). After radiographic confirmation of the right-sided C6 vertebral body, the skin was anesthetized with 2 cc of 1% lidocaine. Using an anterior paratracheal approach, a 22-gauge Quincke needle was passed under fluoroscopic guidance until contact with the anterolateral vertebral body of the C6 was made, at which time the needle was pulled back 1 mm. Appropriate needle position was then confirmed by the injection of 2 cc of iohexol (180 mg/mL) radio-opaque dye to monitor spread. After negative aspiration, a 0.5 cc test dose of 0.5% bupivacaine was injected. No side effects were noted after the test dose, thus sympathetic blockade was achieved by the slow injection of 6.5cc of 0.5% bupivacaine. The patient was observed for facial anhidrosis and Horner’s signs (i.e., enophthalmos, ptosis, miosis, and anhidrosis) to confirm successful blockade of the cervical sympathetic ganglia. In addition, the patient’s right hand temperature was monitored for 15 minutes following the anesthetic administration as evidenced by an increase of at least 1.5°C for further confirmation of sympathetic blockade.

Clinical Measurements and Analysis
Data were extracted retrospectively from the patient's medical records. PTSD symptom severity was measured using the PTSD Checklist, Military Version (PCL-M), a validated instrument composed of 17 items with Likert-type response scales (ranging from 1 = not at all to 5 = extremely) that capture anxiety symptom clusters related to re-experiencing, avoidance, and hyperarousal. Auditory learning and episodic declarative memory were measured by the Rey Auditory Verbal Learning Test (RAVLT), a standardized instrument that consists of five presentations of a 15-item word list (list A) with recall, one presentation of a 15-item Interference List (list B) with recall, and a Short Delay Free Recall of list A (Trial VI). The RAVLT provides scores based on the total number of words remembered correctly for each trial to assess immediate memory, new verbal learning, susceptibility to interference (proactive and retroactive), retention of information after a period of time, and memory recognition.

Case Report

A 41-year-old Naval chief who had experienced multiple combat-related traumatic events while deployed in Afghanistan and Iraq presented with symptoms associated with persistent PTSD including nightmares, night sweats and shaking, daytime flashbacks, heart palpitations, apathy, self-isolation, avoiding situations that reminded him of his trauma, shortness of breath, feeling constantly guarded and easily startled, severe mood swings, irritability, and anger outbursts. The patient reported persistence of these symptoms for multiple years.

Additionally, the patient reported problems with insomnia spanning 5 to 8 years. At presentation, he stated he was sleeping between 4 to 6 hours nightly only after lying in bed for 3 to 4 hours before he could fall asleep with 4 to 5 nightly arousal episodes. The patient also reported having poor memory function. No formal records of baseline memory function were available but the patient reported no difficulties with memory during schooling or Naval training. He had no history of traumatic brain injury, a condition that is known to adversely affect sleep patterns and memory function.26

The patient had a history of heavy alcohol use which included drinking 10 to 12 or more beers daily, a habit that had been sustained for multiple years but which had been reduced to three to four daily alcohol drinks after rehabilitation. He was considered medically disabled by his VA physicians. Moreover, the patient believed himself to be “unemployable” because of his persistent PTSD and memory dysfunction. His treatment history included group and individual psychotherapy spanning several years and citalopram at a daily dose of 20 mg.

The patient underwent neuropsychologic testing (NPT) 2 weeks following his initial clinic visit for the purposes of obtaining baseline measures of PTSD symptom severity and memory function (Table I). Thereafter, the patient underwent his first SGB treatment. Approximately 30 minutes after completion of SGB injection, his skin temperature had risen 2°C indicating an appropriate sympathetic block with Horner’s signs noted. At follow-up, 43 days after the initial SGB treatment, the patient reported marked improvements in PTSD symptoms as evidenced by a 43.6% reduction in his PCL-M score. He also reported an improvement in memory function, which was confirmed by repeated NPT that showed increases in immediate memory (50%), recent memory (28%), and recognition memory (25%). Furthermore, the patient reported total cessation of alcohol use.

Eighty-six days after his first SGB treatment, the patient spontaneously reported a partial relapse of his PTSD symptoms and requested a second SGB which was performed 90 days after the first SGB. The patient returned for a follow-up NPT visit 2 days later. He reported an improvement in
PTSD symptoms as well as memory function. The patient stated he perceived the improvements as more pronounced following the second SGB as compared to the first SGB. Relative to his baseline and first SGB outcomes assessments, following the second SGB treatment, the patient's PCL-M score had decreased 57.7% and 25%, respectively. Compared to his baseline NPT evaluation, the patient's memory function had substantially improved after his second SGB treatment, with the most pronounced improvements observed in immediate memory (50%), recent memory (58%), and recognition memory (36%). Of interest, changes in immediate memory were sustained but not improved with repeated SGB treatments. However, a 41.6% increase in recent memory was evident between the first and second SGB procedures.

At the time of this report, 1 year after the patient's first SGB treatment, he has stopped drinking alcohol except on social occasions stating “I just don't want it anymore.” Moreover, he has sustained relief from PTSD symptoms and improved memory function. Pursuant to these positive outcomes, the patient was able to secure and consistently maintain employment in the construction industry.

Discussion

We observed simultaneous improvements in PTSD symptoms, alcohol use, and cognitive function in a veteran with persistent PTSD after SGB treatment. Although past studies have reported improvements in PTSD symptoms following treatment with SGB, to the best of our knowledge, our case report is the first in which the triad of alcohol use, cognitive impairment, and PTSD has been documented to improve after SGB. This empirical observation is important because of the high comorbidity of PTSD and alcohol use disorder coupled with the fact that individuals with both conditions often do not seek out or do not adequately respond to existing evidence-based treatment modalities. It may also offer insight into the ways PTSD and alcohol use disorder combine to lead to impairments in cognitive function, and how SGB might help to reverse these deficits.

Intrusive memories and deficits in declarative memory function are hallmarks of PTSD. Memory dysfunction is also commonly present in individuals with alcohol use disorder. For patients with both PTSD and alcohol use disorder, memory dysfunction and limited concentration are almost always present.

Three brain areas share an association with memory function and the stress response: the hippocampus, amygdala, and prefrontal cortex (PFC). The hippocampus mediates factual (declarative) memory, whereas the amygdala primarily controls emotional (nondeclarative) memory. Comparatively, the PFC is responsible for modulating input from the amygdala and the emotional valence assigned to specific memories.

In PTSD, the inter-relation between various brain structures, neurochemistry, and memory functionality have been studied at length. Hippocampal tissue (gray and white) volume, parahippocampal cortical volume, and total cerebral volume have all been shown to be smaller in PTSD positive patients as compared to PTSD negative patients. Moreover, research has shown that heightened amygdala responsivity is positively associated with PTSD symptom severity. In contrast, studies have found that the PFC is volumetrically smaller with hyporesponsivity during symptomatic states and the performance of emotional cognitive tasks in PTSD. Thus, it appears that PFC responsivity is inversely associated with PTSD symptom severity.
When alcohol use disorder is present, the accumulated evidence has shown the presence of brain abnormalities via electrophysiological, morphological, and functional metabolism, and a wide range of neuropsychological deficits. Taken together, these studies have shown that chronic alcohol use causes changes in brain morphology including enlargement of the ventricular system, in particular of the third ventricle, with cerebellar atrophy evident in earlier stages, whereas in later stages, a shrinkage of the PFC occurs leading to neuropsychological deficits. Inhibition, flexibility, categorization, deduction of rules, organization, and planning have mostly been found to be impaired in patients with alcohol use disorder. Moreover, attention, working memory, speed of processing, visuospatial abilities, executive functions, learning, memory, and verbal fluency have all been shown to be impaired in alcoholism. In the most severe and chronic cases, alcoholics may develop Korsakoff’s syndrome, Wernicke’s encephalopathy, or alcohol-related dementia, which are characterized by cognitive decline, mental confusion, confabulation, and profound memory impairment involving both retrograde and anterograde amnesia.

In aggregate, the adverse consequences of PTSD and alcohol use disorder on various dimensions of memory function are clear. However, reports on cognitive recovery in alcoholism are diverse and conflicting, ranging from rapid, full, or partial recovery within several weeks, months, or years to studies that yield residual deficits or no cognitive improvement after 1 year or more of abstention from alcohol. Although relief of PTSD symptom severity has most often been the primary outcome of focus for clinicians and researchers, measuring change in memory functionality as a secondary outcome in relation to treatment modalities warrants greater attention in future research.

The interrelatedness of symptoms related to sleep disturbances and memory deficits is not well understood. Research implicates sleep to have a direct effect on central nervous system restoration, memory consolidation, and affect regulation. In PTSD, researchers have shown that the disorder is associated with increased awakenings and decreased plasma levels of growth hormone, which is related to sleep fragmentation and sleep-dependent memory consolidation. However, research on the effects of sleep on patients with chronic PTSD are somewhat contradictory, with some studies suggesting that sleep deprivation may actually provide prophylactic benefits resulting in reduced PTSD severity because sleep enhances emotional memories and preserves emotional reactivity.

Whether SGB can be added to the existing portfolio of treatment options for PTSD, alcohol use disorder, and/or memory impairment cannot be inferred from a single case report. However, presuming that SGB can improve these three conditions simultaneously has interesting implications about how the conditions may be interrelated, and what the mechanism of action for SGB might be. It is possible that SGB results in some form of primary improvement, such as in pain, PTSD, substance craving, sleep, or cognitive function. Subsequently, this primary improvement may lead to wider gains such as were observed in our case report. Conversely, it is possible that a single neurobiological action of SGB influences multiple domains. Further research is needed to provide confirmatory evidence specific to both the clinical utility of SGB and its mechanism of action.

Our findings must be viewed in light of certain limitations. First, given our lack of sufficient knowledge about the temporal effects of reduced alcohol consumption on memory function, we do not know to what degree improvements in memory function can be directly attributable to SGB. Second, because of the usual limitations of retrospective chart review, there was insufficient information available specific to changes in sleep patterns in our case report following the SGB treatments. However, data captured by repeated PCL-M assessments suggest that sleep is associated with concentration ability, although which dimensions of sleep (e.g., quality or duration) are the most affected cannot be inferred. Third,
since our case report is the first to discuss memory function secondary to SGB treatment, we do not have a comparator against which to gauge our results for interpretive accuracy. Of particular interest would be assessing the presence of a placebo effect which has been documented in interventions involving injections. Future comparative studies that examine SGB treatment relative to sham placebo are needed to address this knowledge gap.

Despite its limitations, our case report supports the growing body of preliminary evidence that suggests SGB treatment results in favorable health outcomes and improved quality of life among patients with persistent PTSD. Future studies that employ more robust epidemiologic methodologies (e.g., placebo-controlled randomized clinical trials) with sufficiently powered samples of relatively complex patients, such as those with PTSD and comorbid alcohol use disorder, are needed to substantiate the true added value of SGB as an adjunctive therapeutic modality for PTSD.

Stellate Ganglion Block for the Treatment of Posttraumatic Stress Disorder

Psychiatric Annals
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The following article by Capt. Anita H. Hickey, MD, and colleagues on stellate ganglion block is an excellent addition to the literature on innovative therapies for posttraumatic stress disorder (PTSD).

It could be argued that this technique does not fall under the rubric of complementary and alternative medicine, which traditionally focuses on herbal medicine and acupuncture. That is somewhat true. It is a standard invasive procedure commonly performed in ambulatory facilities, outpatient surgical centers, procedure suites in physicians’ offices, as well as in hospitals. However, it is a new, promising, and as yet unproved technique for the treatment of PTSD.

It is clear that new methods of treatment for PTSD are desperately needed. Although psychotherapy and pharmacotherapy are effective for many who are willing to go through the treatment regimen, they are not effective for all. Perhaps more importantly, many service members will not go to the current treatment regimens or stick to it for the 20 sessions often required for prolonged exposure therapy or the weeks or months for pharmacotherapy. The time required is too much for most service members, who usually have a very full schedule of deployments or trainings in the field.

I am not at all dismissing the benefits of psychotherapy or pharmacotherapy. They are evidence-based treatments. However, I do suggest this exciting new technique is a modality that should be further studied. Other modalities in the treatment of PTSD will be explored in Psychiatric Annals, including virtual reality, acupuncture, and animal-assisted therapy, throughout 2013.
Editor’s note: Elspeth Cameron Ritchie, MD, MPH (Col. US Army, retired) is the guest editor for Psychiatric Annals’ ongoing series in 2013 on complementary and alternative treatments for posttraumatic stress disorder.

Introduction

Posttraumatic stress disorder is growing as one of the most intractable psychiatric conditions faced by clinicians and patients. Recent research into influencing the peripheral sympathetic nervous system indicates that there might be applications in psychiatric conditions, particularly in refractory cases of posttraumatic stress disorder.

Nerve blocks have long been used to treat both acute and chronic pain. When performing regional anesthesia procedures, clinicians realized that pain relief could be achieved not only by blocking the afferent somatic nerves but also by anesthetizing the efferent nerves of the sympathetic nervous system at sites containing regional collections of autonomic ganglia.

The sympathetic nervous system (SNS) is a key mediator of the “fight or flight” response. During periods of stress, pre-ganglionic, cholinergic nerves in the spinal cord fire, releasing the neurotransmitter acetylcholine. Some of these pre-ganglionic neurons transmit directly to the adrenal medulla, causing bulk release of adrenalin and other stress-hormones. However, most pre-ganglionic SNS neurons synapse with peripheral neurons and release noradrenalin at nerve terminals, which induce stress-appropriate responses specific to the tissue involved. Masses of postganglionic, adrenergic neurons can be found in a chain of ganglia that lay along the spinal cord.

The stellate ganglion (SG) is the result of the fusion of the inferior cervical ganglion (C7) and the first thoracic ganglion into a single, star-shaped mass measuring about 1.5 cm³. It is normally situated lateral and posterior to the lateral edge of the longus colli muscle anterior to the first rib and posterior to the subclavian artery. About 80% of individuals will have fused anatomy, with the remaining 20% having unfused ganglia that lay in a similar area anterior to the transverse process of the C7 vertebra. All pre-ganglionic sympathetic nerves innervating the head and neck, as well as many to the upper extremity, either synapse here or pass through to more distal sites. The anatomically distinct nature of each ganglion and their position outside the spinal cord make them appropriate targets for regional anesthetic blocks, one of the most common being SGB.

**SGB Technique**

Several techniques and sites have been reported and commonly utilized by anesthesiologists and interventional pain management physicians to perform SGB. The authors do not recommend a nonguided technique, given the increased risk for injury. A more acceptable technique is performing SGB at the level of the C6 or C7 vertebra utilizing either fluoroscopy or ultrasound guidance. SGB at the level of the C6 vertebra is preferred due to a more successful sympathetic blockade to the head and neck when compared with injection at the C7 vertebra, which has been shown to be associated with a greater risk for injury to the vertebral artery because it has no anterior tubercle and lies posterior to the vertebral artery at this level. The risk for pneumothorax is also increased with injection at the C7 level due to the proximity of the C7 vertebra to the pleura.

There is no standardized technique used by physician specialists to perform a SGB. However, the approach described herein is common practice and one that has been adopted by the primary author. Following peripheral intravenous access, the patient is positioned supine on a fluoroscopy...
table, placed into cervical extension with a shoulder roll and hemodynamically monitored (eg, pulse oximetry, electrocardiogram). Sedation may be used or the procedure may be performed under local anesthesia. Fluoroscopy is utilized to verify that the anesthetic is safely injected and to prevent intravascular injection. The right C6 vertebral body is identified and a local anesthetic (ie, lidocaine 1%) skin wheal is made at the needle entry site. A 22-gauge needle is directed percutaneously to the anterolateral C6 vertebral body at its junction with the right C6 tubercle. A right-sided SGB is necessary because right-sided blocks affect right hemisphere structures that are pertinent to PTSD since the right hemisphere is responsible for producing autonomic responses to emotional stimuli and the right amygdala is critically linked to unconscious emotional memories.

Following confirmation of proper location by fluoroscopy, and negative aspiration for blood and cerebrospinal fluid, approximately 2 mL of non-ionic contrast media is injected through the needle. The dye is visualized to spread over the pre-vertebral plane. This step is followed by digital subtraction angiography to further confirm lack of vascular uptake. A 1 mL test dose of a local anesthetic is administered. If no signs of vascular uptake are observed, 7 cm³ of 0.5% ropivicaine or bupivacaine is injected incrementally. The needle is then removed and the procedure is considered complete. Evidence of a temporary Horner’s syndrome (ie, myosis, ptosis, and enalpathalmos) and associated conjunctival injection, nasal congestion and facial anhidrosis following the SGB injection are signs of a successful sympathetic block.

Potential Complications of SGB

Mortality and morbidity related to SGB are rare, thus the procedure is considered to be very safe. The complication rate associated with SGB is extremely low at 1.7 per 1,000 procedures. SGB is sometimes used as a one-time treatment, but also commonly repeated when symptoms return within days to weeks of the initial procedure. The direct effects of the anesthetics on neurons last only a few hours, so it is unclear why the benefits are often of longer duration.

When explaining the potential risks of SGB to patients, physicians generally divide complications into three categories: technical, infectious, and pharmacological. Technical complications can include injury to the nerves and nearby viscera during insertion of the needle. This includes damage to the brachial plexus, trauma to the trachea and esophagus, injury to the pleura and lung (pneumothorax or hemothorax), bleeding at injection site and local hematoma. Airway compression and vasovagal attacks can also occur. Infectious complications can result if there is a breach in the aseptic barrier. These can include local abscess, cellulitis, and osteitis of the vertebral body and transverse process.

Pharmacological complications are related to the dose, volume, type of local anesthetic and site of deposition of the solution. This includes hoarseness of voice due to paralysis of the recurrent laryngeal nerve. Additionally, phrenic nerve paralysis may lead to respiratory distress, especially if there is contralateral dysfunction of the phrenic nerve. Other adverse events may include seizures, loss of consciousness, profound hypotension due to a high spinal anesthetic blockade, air embolism, and loss of cardioaccelerator activity that may lead to various bradyarrhythmias and hypotension.

Therapeutic Utility of SGB

Nonpsychiatric Conditions
SGB has been shown to have utility for diagnostic, therapeutic, and prognostic purposes for a variety of conditions, including: chronic regional pain syndrome types I and II to the upper extremities (CRPS I and II); chronic and acute vascular insufficiency/occlusive vascular disorders of the upper extremities, such as Raynaud’s disease, intra-arterial embolization and vasospasm. SGB has also been found an effective treatment for poor lymphatic drainage and local edema of the upper extremity following breast surgery; postherpetic neuralgia; and phantom limb pain or amputation stump pain. Patients with quinine poisoning; sudden hearing loss and tinnitus; hyperhidrosis of the upper extremity; cardiac arrhythmias and ischemic cardiac pain; Bell’s palsy and a variety of orofacial pain syndromes, including neuropathic orofacial pain and trigeminal neuralgia; vascular headache such as cluster and migraine headaches; and neuropathic pain syndromes among cancer patients are all also candidates for SGB.

SGB has also been recommended for improving blood flow to the cranium for angiography and following stroke/cerebrovascular accident and hyperhidrosis to the upper extremities. Additionally, SGB’s use has been reported in the treatment of Ménière’s syndrome and hot flashes.

Psychiatric Conditions

It might seem counterintuitive that treating the peripheral nervous system could affect psychiatric conditions presumably mediated in the brain. Most psychiatrists, however, are probably familiar with the observation that vagal nerve stimulation improves depression. As early as 1947, reported cases of improvements in depression subsequent to SGB treatment began emerging in the literature. More recently, unexpected benefits of SGB have been reported for hallucinations in schizophrenia, and in “climacteric psychosis” (a term for mental illness associated with menopause).

Although not specifically SGB, similar techniques of lesioning the sympathetic chain has been reported widely as a potential treatment for social phobia.

In the case of social phobia, the mechanism is presumably because the techniques prevent blushing. For patients with both blushing and social phobia, sympathectomy proved as good as or better than sertraline in improving anxiety. Taken together, the evidence suggests that techniques that influence the peripheral sympathetic nervous system could potentially be used to treat psychiatric conditions.

Application of SGB to PTSD

The earliest published report of SGB’s use in a patient with PTSD was in 1990 in an adolescent with co-occurring reflex sympathetic dystrophy (RSD). In that case report, the authors concluded that SGB was primarily treating the patient’s chronic pain as an associated symptom of RSD, not PTSD.

In subsequent years, multiple case reports of patients with PTSD who experienced marked improvements in symptom severity after one or more SGB treatments began emerging in the literature. These studies were implemented across diverse health care settings and were in both civilian and military populations (ie, US veterans and active duty service members). In all of these reports, patients had refractory PTSD (eg, persistent symptoms for at least 1 year despite standard treatment).
Cumulatively, the growing body of preliminary evidence about the potential therapeutic benefits of SGB for PTSD is compelling. Starting in 2008, a series of case reports were published in which SGB relieved symptoms of PTSD, even when co-occurring pain was not present among patients in a private clinic practice. The effect was usually immediate and often dramatic. SGB appeared to produce some form of a “calming effect” that primarily impacted symptoms associated with avoidance and hyperarousal. However, to experience sustained symptom relief, patients often required at least two SGB injections over a short follow-up period (< 30 days). In some cases, radiofrequency ablation of the SG was needed to prolong the duration of benefit.

Similar clinical observation of improved PTSD symptoms after SGB was reported by other researchers in cases of combat-related PTSD at Walter Reed Army Medical Center. Early or sub-threshold PTSD often spontaneously resolves, thus a placebo effect may be suspected. However, investigators at Naval Medical Center San Diego (NMCSD) observed comparable improvements in a case series of active duty service members for whom the diagnosis of PTSD was confirmed by structured interviews. All of those patients had chronic PTSD subsequent to failed responses to evidence-based treatments. The improvements reported in the case series at NMCSD were not universal, and PTSD symptoms often resurfaced within 1 month of SGB treatment. This finding was inconsistent with earlier reports in which PTSD symptom improvements lasted at least many months and resulted in full remission.

The body of research specific to the utility of SGB as a potential treatment for PTSD continues to grow as evidenced by a new case report in which SGB proved to be a successful therapeutic option for a more complex patient with comorbid PTSD and alcohol use disorder.

**Possible Mechanisms of Action**

The specific mechanisms responsible for the actions of local anesthetics on the SG have yet to be fully elucidated. Regarding its effect on PTSD, SGB might best be considered within the broader framework of the neural network connecting several cortical regions that regulate the formation of memory, cognition, and behaviors. This complex interaction involves numerous neurochemicals, including corticotropin-releasing hormone, cortisol, the locus coeruleus-norepinephrine system, neuropeptide Y, galanin, dopamine, serotonin, testosterone, estrogen, and dehydroepiandrosterone (DHEA).

An extensive network of noradrenergic terminals project from the locus coeruleus and cell groups in the medulla and pons to innervate the entire neuraxis from the olfactory bulb to spinal cord, visceral organs, and integument. This widespread organization allows the noradrenergic system, by means of both central connections and peripheral sympathetic nervous system to influence the entire nervous system under conditions of elevated levels of norepinephrine (NE).

Some investigators have proposed that SGB may influence PTSD via connections that exist between the SG and insular cortex and other intracerebral structures. Yet other researchers have focused on the extensive transneuronal labeling in sympathetic related regions of the cerebral cortex with viral tracing methods after injecting the adrenal gland, SG, and celiac ganglion. The cortical areas labeled included the extended amygdaloid complex, lateral septum, insular and ventromedial temporal cortical regions, and deep temporal lobe structures. Alternative theorized explanations suggest that the overall mechanism of SGB involves changes in melatonin rhythm and sleep.
An overall decrease in sympathetic tone also might be involved in improving PTSD symptoms. SGB is known to result in decreased levels of circulating noradrenalin, and although this neurotransmitter does not freely cross the blood-brain barrier, it is postulated that decreased peripheral nonadrenaline represents reduction of central non-adrenaline levels due to a shared nucleus controlling both systems.

SGB can also reduce the expression of peptides, such as nerve growth factor (NGF), that play a role in maintaining the perpetual hyperarousal state. NGF encourages sprouting of sympathetic neurons in the brain, and is able to cross the blood-brain barrier where it has a number of complex interactions with the brain-body communications in stress regulation.

The reduction of NGF by SGB removes the necessary peptide for maintenance of PTSD, reverting intracerebral sympathetic nerves to a pretrauma state. Similar, downstream mechanisms might explain why the apparent benefit of SGB lasts long beyond the direct period when the anesthetic is slowing nerve conduction.

Conclusions

SGB is dramatically different from all current, evidence-based treatments for PTSD. The typical course for current therapeutic options for PTSD with either psychotherapy or psychopharmacology takes weeks to months to be effective and is often plagued by high attrition. By contrast, SGB is a minimally invasive procedure that shows promise to have an almost immediate effect. Although getting an injection in the neck to treat PTSD might seem off-putting to some, SGB has been used for many decades as a successful pain management technique, where it has proven to be popular, tolerable, and safe. An additional benefit of SGB is that it offers a biologic approach to treating PTSD; the medical nature of such an intervention might lower the stigma of seeking mental health-based treatment for PTSD.

Current published evidence for the use of SGB in PTSD and other psychiatric conditions is based entirely on case reports. Randomized controlled trials are clearly needed to establish if SGB is an effective therapeutic option for PTSD. Furthermore, although in some of the case reports, long term, full remission of PTSD have been documented, such results are not universal. Thus, additional research is needed to discover what factors impact the sustained effects of SGB in resolving PTSD symptoms, the frequency by which the SGB procedure may need to be repeated for preservation of effect, and how SGB might be combined optimally with other evidence-based treatment modalities.

Lastly, it will be important to further investigate the potential mechanism of action for SGB in the treatment of PTSD to discover if a new pathway may be at play specific to the pathology of the disorder, or if SGB could be a viable treatment option for other psychiatric conditions.

BACK TO TOP
Sleep and Resilience: A Longitudinal 37-Year Follow-up Study of Vietnam Repatriated Prisoners of War

Military Medicine
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Abstract
This study examined sleep histories associated with resilience after trauma defined as a continuous lack of psychiatric illness across 37 years. Data were drawn from a 37-year follow-up examination of the effects of the Vietnam prisoner of war (POW) experience. The Robert E. Mitchell Center for POW Studies is a unique institution holding the only longitudinal study of the effects of the American POW experience in existence. The study used a sample of 440 Vietnam repatriated prisoners of war (RPWs). Psychiatric disorders were assessed at repatriation (1973) and were continued annually by a psychiatrist or clinical psychologist. Sleep issues before, during, and after captivity were assessed during medical examinations. Odds ratios examining presence of sleep symptoms show resilient RPWs reporting fewer symptoms compared to nonresilient RPWS before, during, and after captivity. Logistic regression comparing before, during, and after indicates fewer reported sleep disturbance symptoms after captivity was the strongest predictor of resilience (b = −0.82, Wald $\chi^2$ (1) = 16.70, $p < 0.000$). Reporting fewer sleep complaints, but not necessarily an absence of them before, during, and after the trauma predicts resilience across time.

Introduction
As the United States remains in prolonged military conflicts, reports of soldiers coming back from combat with psychiatric illness has been of growing concern. Efforts to understand the factors contributing to certain illnesses such as post-traumatic stress disorder (PTSD) have spurred considerable interest in identifying the factors involved in trauma exposure which put individuals at risk for psychiatric illness. One such factor is the relationship between sleep disturbance and psychiatric and physical disorders. Sleep problems are common in patients with anxiety, depression, bipolar depression, attention-deficit hyperactivity disorder, and PTSD. Sleep difficulties before and after trauma predict psychiatric disorders. Studies find sleep disturbance in the period immediately before a traumatic event predicts development of subsequent psychiatric disorders. In a sample of traumatically injured patients, participants who displayed sleep disturbance before the injury were more likely to develop a psychiatric disorder 3 months later. Similarly, sleep disturbance after a traumatic event predicts future psychiatric and physical symptoms.

The efforts to understand sleep's relationship to psychiatric illness have been guided by a disease model, the reigning paradigm in the study of most illnesses, in which the focus is on the elimination of the disease/ disorder. In relation to sleep and psychiatric disorders, this paradigm has focused primarily on those who develop sleep problems after exposure to a stressor. The issue with focusing solely on illness, however, is that not all individuals exposed to trauma develop symptoms and/or illness after their traumatic experience(s). This is especially true when dealing with psychiatric illness. In this study, we use a positive health paradigm to examine the psychologically healthy.
Looking closely, at the rate of military personnel who develop PTSD indicates a large percentage of individuals do not develop it. The National Vietnam Veterans Readjustment Study, for example, indicated 31% of male and 27% of female Vietnam veterans suffered from lifetime PTSD. Rates of PTSD stemming from the Gulf War range from 9% to 18%. And, although the full impact of the conflicts in Iraq and Afghanistan are still underway, preliminarily studies indicate lower incidents of PTSD (i.e., 18% and 11%).

The positive health model encompasses a large array of different terms for describing the maintenance of health. Resilience, exhibiting intact psychological functioning despite exposure to trauma, has drawn a lot of attention. In fact, the emphasis paid to positive health within the past couple of decades contributed to the growing research on resilience. But what resilience is and how to operationalize it is not clearly delineated. The literature indicates two conceptualizations: as process and as outcome. Reivich and Shatte define resilience as a set of abilities (i.e., emotion regulation, empathy, causal analysis). Others define resilience as an outcome conceptualizing it as an individual's ability to maintain stable psychological and physical functioning when exposed to an isolated traumatic event such as a life-threatening situation. Currently, there is no agreed upon conceptual framework or definition of resilience. Whether defined as process or outcome, researchers in neither field have incorporated sleep's pivotal role. Given the importance of sleep to psychological functioning, it is puzzling why there are few if any studies examining the relationship between sleep and resilience.

We conceptualized resilience as an outcome because we were interested in identifying whether sleep quality before, during, and after trauma exposure predicts resilient functioning later in life. To do this, we examined a military population exposed to extreme trauma. The Vietnam prisoner of war (POW) repatriate was exposed to prolonged captivity, malnourishment, and physical and psychological torture. This population could help us further understand the relationship of sleep to maintenance of psychological functioning. These findings may provide valuable information for other personnel at risk of exposure to similar trauma (i.e., military on the front lines of combat, police, firefighter personnel) and may assist in determining whether sleep plays a role in effectively completing their missions and returning to baseline functioning without developing a psychiatric illness.

Method

Participants
The Robert E. Mitchell Center for Prisoner of War Studies is a unique institution, which holds the only longitudinal study of the long-term effects of the POW experience currently in existence. Repatriates from all services and recent U.S. conflicts (Vietnam, Gulf War, Somalia, Bosnia, and Iraq) are in this program. Participants travel from all over the United States and different parts of the world to receive annual evaluations at the Robert E. Mitchell Center for Prisoner of War Studies. The Department of Defense provides all repatriated prisoners of war (RPWs) full funding to cover trip expenses. To ensure uniformity in measurement technique, war-specific stressors, and to avoid uneven sample sizes, only data from the Vietnam-era participants, the largest, longest held group, were included in this retrospective study.
Six hundred and sixty-two military service personnel survived captivity in Vietnam and were repatriated. Of these, 568 men were repatriated in the spring of 1973, as part of Operation Homecoming, and 94 were repatriated early (1962–1972) after escaping or accepting early release; 88% of these repatriates were officers. Since 1973, these repatriates have been eligible for annual voluntary medical and psychological follow-up within programs provided by the Department of Defense and most have participated. As of July 2011, there have been 121 deaths (101 within the Operation Homecoming cohort). Therefore, recent medical/psychiatric outcome data are available on 440 of the living repatriates. Of these participants, we had 224 with complete sleep data available collected back then (1973) with outcome measures determined now (2010). Chi-square analysis indicated no statistically significant differences in their demographics between the RPWs with complete and the ones with incomplete data with the exception of service branch (Air Force personnel totaled 61% of this sample) and officer/enlisted status (officers totaled 91% of this sample). This is virtually identical to the overall Vietnam RPW group, which totaled 88% officers.

This research was reviewed by an institutional review board and all participants included in this report consented to be included in the study.

Procedure
When Vietnam-era repatriates were returned (1973), they were examined using the Initial Medical Evaluation Form (IMEF), a 29-section-477-page document. The IMEF included instructions for conducting a number of medical and psychological examinations and method of documentation. These examinations and debriefings were conducted over several weeks by a team of physicians and mental health specialists. Most of the repatriates have voluntarily been routinely medically and psychiatrically evaluated since 1973 to date. The latter evaluations have been conducted by a psychiatrist or clinical psychologist using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criterion available for diagnosis at time of evaluation (i.e., DSM-II, DSM-III, DSM-IV).

Measures
Demographic Variables (Obtained in 1973)
Captivity duration was measured in number of months and was obtained in 1973. Solitary confinement was defined as a prisoner alone in a cell with minimal environmental stimulation and no meaningful social interaction. It was measured in weeks: short (M = 2 weeks, range 0–5), medium (M = 13 weeks, range 6–25), or long (M = 81 weeks, 26–390).

The torture variable was determined using a 25-item scale assessing exposure to incidents including withholding food and water, sleep deprivation, and specific physical mistreatments (e.g., punishment with torture devices). It also consisted of such items such as attempts to provoke guilt concerning military activities, threats of harm to fellow prisoners, and threats of nonrepatriation. Response options were 0 = “never” to 3 = “very often.” An average item score was used for analyses (Cronbach's α 0.91).

Other demographic variables included education measured in number of years and age at time of capture.

Outcome Measure: Resilience (Obtained in 2010)
We categorize resilient Vietnam RPWs using a definition of resilience which entailed the traumatic event an individual was exposed to must entail a sufficient risk to which an individual shows resilience and must be demonstrated across a broad spectrum of outcomes and long time span.15 Vietnam RPW's experiences of prolonged captivity, physical and psychological torture, and malnourishment go beyond sufficient risk. To be defined as resilient, RPWs must have never received any psychiatric diagnosis over a 37-year follow-up period.

Using this resilience criterion, 131 of the 224 RPWs were categorized as resilient by this definition, and 93 RPWs were nonresilient because they had received a psychiatric diagnoses at some point during the 37 years since repatriation. No diagnosis of PTSD was made before 1980, the year the DSM III was published.

Sleep Difficulties: Predictor Measures (Obtained in 1973)
All sleep difficulties were assessed during the IMEF assessment. For the “period before captivity,” RPWs were asked “Did you ever have a sleep problem before captivity?” to which they were given a “Yes” or “No” response option. If “Yes” RPWs were asked to indicate how much of a problem any of the following were by checking off the appropriate answer to indicate how often they had the problem: “Trouble falling asleep,” “Trouble staying asleep,” “Wake up early in the morning and can't get back to sleep,” “Bad dreams or nightmares.” Response options were “Never or almost never,” “Sometimes,” and “Always or almost always.” For the “period during captivity,” RPWs were asked “Did you ever have a sleep problem during captivity?” to which they were given identical response options as listed above.

For the “period after captivity” (1973), RPWS were asked to report about “Sleep and Dreams: (Check all applicable).” Response categories were as follows, “Difficulty falling asleep,” “Early morning awakening,” “Fragmented sleep,” and “Nightmares.”

For analyses, two variables were generated. Presence or absence of sleep disturbance (0 or 1) regardless of number of symptoms reported and a score for total number of symptoms representing severity of symptoms.

Analyses
First, descriptive statistics were computed for all variables. Next, t-test analyses were used to conduct a covariate analysis examining whether there were any significant differences between resilient and nonresilient RPWs on captivity duration, solitary duration, torture, age at time of capture, and education. Only age at time of capture was a significant covariate. Two groups (younger and older RPWs), based on a median split, were created and an odds ratio analysis for each group examined, first, percent of resilient and nonresilient RPWs reporting presence of sleep disturbances before captivity, during captivity, and after repatriation and, second, subsequent odds of resilience. Because of negligible differences between the younger and older RPW group, the groups were merged and timing of sleep disturbance was further examined. Specifically, a regression analysis was conducted to determine whether severity of sleep disturbance symptoms across time epochs (i.e., before, during, or after) determined odds of resilience. Finally, because of the relative rarity of sleep disturbances reported before captivity, an odds ratio analysis was conducted examining only reports of sleep disturbance during and after captivity, allowing for an analysis of change in severity of symptoms across time epochs.
Results

Descriptive Statistics
Table I provides descriptive information for captivity duration, solitary confinement duration, torture, age at time of capture, and education. A covariate analysis indicated no significant differences between resilient and nonresilience RPWs with the exception of age; older RPWs (M = 30.45, SD = 5.48) were more likely to be resilient then their younger (M = 27.86, SD = 5.46) counterparts (t (419) = −4.78, p < 0.000).

Presence of Symptoms: Resilient vs. Nonresilient RPWs

Resilient RPWs are less likely to report presence of sleep disturbance at each stage (before, during, and after captivity) compared to nonresilient RPWs regardless of age (Tables II and III). Odds ratio analyses demonstrated the presence of sleep disturbances with the nonresilient RPWs indicating significant prevalence at each stage regardless of age. When examining the younger group (Table II), RPWs reporting presence of sleep disturbances before captivity were 2.40 times (95% confidence interval [CI] 0.68–8.52) less likely to be resilient. Similarly, RPWs reporting presence of sleep disturbances during captivity were 1.21 times (95% CI 0.65–2.25) less likely to be resilient. And lastly, RPWs reporting presence of sleep disturbances after repatriation were 2.36 times (95% CI 1.13–4.94) less likely to be resilient. A similar trend emerged when examining the older cohort: RPWs reporting presence of sleep disturbances before captivity were 13.13 times (95% CI 1.51–111.82) less likely to be resilient. RPWs reporting presence of sleep disturbances during captivity were 2.01 times (95% CI 1.04–3.87) less likely to be resilient. And lastly, RPWs reporting sleep disturbances after repatriation were 4.43 times (95% CI 2.2–8.91) less likely to be resilient.

Although results suggested sleep was a variable with slightly more predictive validity for the older age cohort (Tables II and III), effect size analysis indicated the following: younger group (Cohen's d = 0.47, 95% CI 0.18–0.76) and older group (Cohen's d = 0.82, 95% CI 0.49–1.15). The overlapping of CIs suggests the difference in odd ratios is not statistically significant. This confirms the general finding, at each stage (i.e., before, during, after), regardless of age, odds ratios performed between the two groups demonstrates the nonresilient RPWs were the most vulnerable to sleep difficulties particularly if reporting them after repatriation.

Severity of Symptoms: Resilient vs. Nonresilient RPWs

Despite odds ratio analysis, it remained unclear whether the timing of the sleep disturbance (before, during, or after captivity) determined its importance as a predictor of resilience. A logistic regression was conducted to predict resilience using total number of sleep disturbance symptoms reported before, during, and after captivity as predictors. A test of the full model against a constant-only model was statistically significant, indicating the predictors, as a set, reliably distinguished between resilient and nonresilient RPWs, χ² (3 df) = 36.51, p < 0.000. The results of the Hosmer and Lemeshow goodness-of-fit test demonstrated the observed data were reasonably approximated by the model, χ² (4 df) = 2.172, p = 0.704. The variance in resilience accounted for by the model was moderate with Nagelkerke's R² of 0.14. Prediction success overall was 66% (29.1 for nonresilient and 90.5 for resilient). The Wald criterion demonstrated fewer reported sleep disturbance symptoms after captivity was the strongest predictor of resilience, followed by sleep disturbance during, with reports of sleep disturbance before the trauma indicating
marginal significance. Regardless of time epoch, RPWs become less resilient as sleep disturbance increases. EXP (B) values indicate the following: sleep difficulties before captivity (b = −0.329, Wald χ² (1) = 2.977, p < 0.08), during captivity (b = −0.177, Wald χ² (1) = 5.660, p < 0.02), and after captivity predict lack of resilience (b = −0.82, Wald χ² (1) = 16.69, p < 0.000). As RPWs report greater number of sleep disturbances, the odds of not being resilient compared to being resilient are 0.72 (before), 0.84 (during), and 0.44 (after).

Change in Symptoms Across Time Epochs: Resilient vs. Nonresilient RPWs

Because of the relative rarity of sleep disturbances reported before captivity (Tables II and III), an analysis was conducted examining only reports of sleep disturbance during and after captivity (Table IV). It indicated RPWs fell into four general sleep category groups: those who reported no sleep difficulties during and after captivity (N/N), those who reported sleep difficulties during but not after captivity (Y/N), those who did not report sleep difficulties before but did after captivity (N/Y), and those who reported sleep difficulties both during and after captivity (Y/Y). In looking at Table IV, odds ratio analyses indicate that the least resilient group was those who experienced sleep disturbances both during and after repatriation (Y/Y). The greatest resilience was for those who never experienced any sleep disturbance during or after captivity (N/N). In comparison of these two groups (i.e., A vs. D; Table IV), these RPWS (N/N) were 4.28 (95% CI 2.08–8.68) times more likely to be resilient than those reporting sleep disturbance during and after captivity (Y/Y). The next group most likely to be resilient was those that bounced back from sleep difficulties reporting them during captivity but not after repatriation (Y/N). In comparison of these two groups (i.e., B vs. D; Table II) these RPWs (Y/N) were 2.46 (95% CI 1.15–5.26) times more likely to be resilient than the group that reported sleep difficulties during and after captivity (Y/Y). All other odds ratio analyses were not significant (i.e., C vs. D; Table II).

Discussion

The disease model paradigm literature suggests the following: for the average person, trauma leads to sleep problems and sleep problems in turn lead to psychiatric illness. The resilience literature, however, indicates different people react differently to the same event with a number of individuals maintaining intact psychological functioning. In this study, we provide a more detailed review of the sleep quality and psychiatric illness relationship providing a review of the sleep profiles of people who have suffered trauma and remained resilient. We learn their sleep is also affected. And we can provide support for the assumption the opposite is also true: better sleep quality is proportional to maintenance of positive health. None of these questions could be answered using solely the disease model paradigm.

This study helps provide a more complete picture of sleep and maintenance of health. Prior studies have indicated poor sleep can be used as a proxy for current bad health, or soon to be bad health, but whether the opposite was also true was not well understood. Neither was it understood if and to what degree the general trend of sleep and health remained consistent even in the most extreme of traumatic circumstances. This study provides insight into this line of inquiry. People who maintain positive health after a traumatic event are also the same individuals who are better sleepers before, during, and after a traumatic event relative to their nonresilient counterparts. During times of extreme stress, they exhibit similar although fewer sleep disturbances than their less healthy counterparts, and after the trauma, they are less likely to report them.
Timing: Before, During, and After the Trauma
Understandably, during the trauma RPWs reported the most sleep difficulties and were at their highest for both resilient and nonresilient RPWs. The findings suggest resilient individuals do succumb to the stressor of the trauma, and their sleep reactions to abnormal circumstances indicate similar, albeit less-exacerbated patterns than their nonresilient counterparts. This study additionally indicates succumbing to these stressors during the trauma does not necessarily rule out an individual's ability to maintain positive health after trauma. Rather, reports of sleep disturbance during the trauma do not decrease individuals' chances of resilience as much as do reports of sleep disturbance after the trauma. In fact, statistically, the best predictors of resilience are fewer reported sleep disturbances before and after the traumatic event. As such, the study expands upon current literature by confirming the links between reports of sleep disturbance pre- and post-trauma, and expanding upon it in its demonstration that reports of sleep disturbance during the trauma are not as significantly related to psychiatric illness as is the post-trauma time epoch. It suggests if pressed for focus on a specific time epoch focus on reports of sleep issues during the trauma can tell us the least.

Additionally, the results are intriguing in terms of what they tell us about returning to base level sleep quality, that is, a number of individuals reporting sleep issues during the trauma did not report them after the trauma. In fact, RPWs who reported sleep problems during captivity and later no sleep problems were 2.5 times more likely to remain psychologically resilient 37 years later. This finding indicates awareness of when the sleep disturbance occurs in relation to the trauma is a variable of critical importance in provider care.

The findings on the “during” time epoch suggest an apparent importance to improving quality of sleep during prolonged stressors. Research indicates if someone is reporting sleep disturbances this might indicate current stress isolated from psychiatric illness; however, if the reports occur after the traumatic event(s), sleep disturbance(s) might be an indicator of possible psychiatric illness. Either way, although the science is not completely clear, further studies would need to examine what some already suggest: successful early psychological and/or pharmacological intervention may ward off the development of certain psychiatric illness after the trauma. These studies indicate during times of stress if an individual's environment cannot be changed (i.e., the stressor cannot be removed as is the case for U.S. service members deployed to war zones), coping styles can be corrected or enhanced to ensure an individual is able to maintain positive health.

Limitations
Assessing the reliability of self reports particularly underreporting among participants indicating complete absence of sleep complaints during captivity is difficult. Recent studies comparing subjective to objective measures of sleep disturbance have addressed related issues. Studies with individuals afflicted with psychiatric illness associated with sleep disturbance (i.e., PTSD) have failed to find a significant relationship between objective measures of sleep disturbance (i.e., ambulatory monitoring, polysomnographic studies) and subjective measures. The failure to find such corroborations between subjective and objective measures has led some researchers to suggest it is the perception of sleep issues rather than actual sleep disturbance, which may be key to psychiatric issues. Our study suggests the perception of sleep disturbance not only predicts resilience but also does so across time. Additionally, the mere presence or absence of a psychiatric diagnosis to define resilience is in itself an insufficient measure for capturing the multitude of responses to trauma. The study's definition of resilience as lack of psychiatric diagnosis can potentially ignore a whole subset of individuals that is emotionally affected but does not meet the diagnostic criteria for a diagnosis. It also ignores people that get a psychiatric diagnosis but recover; many of whom go on to live happy, functional lives. Other studies particularly ones that
examine different reactions to trauma such as post-traumatic growth can address these issues. In fact some would argue that the falling apart and positively growing after a trauma, the trademark feathers of post-traumatic growth, make these individuals more resilient than those who do not experience psychological distress.

Implications for Screening People for Sleep Difficulties
The importance of sleep quality is beginning to gain salience in military settings as researchers find significant associations between sleep symptoms and mental health issues. A recent study, for instance, found 41% of U.S. service members recently deployed to Iraq and Afghanistan reported sleep problems at initial screening and those who had reported sleep issues, specifically insomnia, also reported significantly higher scores of PTSD severity at follow-up than did service members without sleep issues. Such studies in addition to this current one may aid in assisting the military to design more effective pre- and postdeployment screening tools. It has been reported upon return from deployment, soldiers may not want to report their psychiatric problems because of shame, embarrassment, or fear it will have a negative impact on their career. Sleep issues, however, are symptoms which may not be as stigmatizing and soldiers may be more likely to report. Research with military service members supports this. Service members appear to be better willing to report physical symptoms than mental health ones. Mental health practitioners can better assist military service members by forming collaborations with primary health care physicians and vice versa.

More recently, the U.S. Army has started focusing on positive health, centering their training programs on maintaining health rather than focusing solely on assisting those who are physically or mentally ill. To date, however, none of the Army's resilience programs have fully integrated improving sleep quality. This suggests sleep quality is an overlooked variable amenable to manipulation, which has not been given full attention.

Conclusions
Using a resilience framework, we are able to show self-reported sleep quality as a particularly promising area of study for identifying the sleep histories best associated with maintaining health despite trauma. From a prevention perspective, knowing ahead of time whether an individual has sleep problems may help clinicians and leaders identify those at risk for developing psychiatric issues, and from a post-trauma perspective, knowing the importance of sleep's relationship with psychiatric illness is also promising for there are many psychological and pharmacological treatments for alleviating sleep difficulties.
Describe the prevalence of sleep disorders in military personnel referred for polysomnography and identify relationships between demographic characteristics, comorbid diagnoses, and specific sleep disorders.

Design:
Retrospective cross-sectional study.

Setting:
Military medical treatment facility.

Participants:
Active duty military personnel with diagnostic polysomnogram in 2010.

Measurements:
Primary sleep disorder rendered by review of polysomnogram and medical record by a board certified sleep medicine physician. Demographic characteristics and conditions of posttraumatic stress disorder (PTSD), mild traumatic brain injury (mTBI), anxiety, depression, and pain syndromes determined by medical record review.

Results:
Primary sleep diagnoses (n = 725) included: mild obstructive sleep apnea (OSA), 207 (27.2%); insomnia, 188 (24.7%); moderate-to-severe OSA, 183 (24.0 %); and paradoxical insomnia, 39 (5.1%); behaviorally induced insufficient sleep syndrome, 68 (8.9%) and snoring, 40 (5.3%) comprised our control group. Short sleep duration (< 5 h) was reported by 41.8%. Overall 85.2% had deployed, with 58.1% having one or more comorbid diagnoses. Characteristics associated with moderate-to-severe OSA were age (adjusted odds ratio [OR], 1.03 [95% confidence interval {CI}, 1.0–1.05], sex (male) (adjusted OR, 19.97 [95% CI, 2.66–150.05], anxiety (adjusted OR, 0.58 [95% CI, 0.34–0.99]), and body mass index, BMI (adjusted OR 1.19 [95% CI, 1.13–1.25]; for insomnia, characteristics included PTSD (adjusted OR, 2.12 [95% CI, 1.31–3.44]), pain syndromes (adjusted OR, 1.48 [95% CI, 1.01–2.12]), sex (female) (adjusted OR, 0.22 [95% CI, 0.12–0.41]) and lower BMI (adjusted OR, 0.91 [95% CI, 0.87, 0.95]).

Conclusions:
Service-related illnesses are prevalent in military personnel who undergo polysomnography with significant associations between PTSD, pain syndromes, and insomnia. Despite having sleep disorders, almost half reported short sleep duration. Multidisciplinary assessment and treatment of military personnel with sleep disorders and service-related illnesses are required.

Substance Abuse

Pharmaceutical Overdose Deaths, United States, 2010

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METHODS

Data are from the National Vital Statistics System multiple cause-of-death file, which is based on death certificates submitted by medical examiners or coroners. Drug overdose deaths were those assigned an underlying cause of death using the International Classification of Diseases, Tenth Revision (ICD-10) codes X40-X44 (unintentional), X60-X64 (suicide), X85 (homicide), and Y10-Y14 (undetermined intent). Pharmaceutical-related overdose deaths were those assigned specific ICD-10 codes T36-T39, T40.2-T40.4, T41-T43.5, and T43.8-T50.8; psychotherapeutic and central nervous system pharmaceuticals were defined as T40.2-T40.4, T42, T43.0-T43.5, T43.8, T43.9; and opioid analgesics were those assigned codes T40.2-T40.4. Pharmaceutical deaths by this definition are predominately due to prescription drugs; a small minority involve over-the-counter or illicit drugs combined with prescription drugs in the same ICD-10 T codes. Institutional review board approval was waived because no personal identifiers were involved.

RESULTS

In 2010, there were 38,329 drug overdose deaths in the United States; most (22,134; 57.7%) involved pharmaceuticals; 9,429 (24.6%) involved only unspecified drugs. Of the pharmaceutical-related overdose deaths, 16,451 (74.3%) were unintentional, 3,780 (17.1%) were suicides, and 1,868 (8.4%) were of undetermined intent. Opioids (16,651; 75.2%), benzodiazepines (6,497; 29.4%), antidepressants (3,889; 17.6%), and antiepileptic and antiparkinsonism drugs (1,717; 7.8%) were the pharmaceuticals (alone or in combination with other drugs) most commonly involved in pharmaceutical overdose deaths. Among overdose deaths involving opioid analgesics, the pharmaceuticals most often also involved in these deaths were benzodiazepines (5,017; 30.1%), antidepressants (2,239; 13.4%), antiepileptic and antiparkinsonism drugs (1,125; 6.8%), and antipsychotics and neuroleptics (783; 4.7%).
Opioids were frequently implicated in overdose deaths involving other pharmaceuticals. They were involved in the majority of deaths involving benzodiazepines (77.2%), antiepileptic and antiparkinsonism drugs (65.5%), antipsychotic and neuroleptic drugs (58.0%), antidepressants (57.6%), other analgesics, antipyretics, and antirheumatics (56.5%), and other psychotropic drugs (54.2%). Among overdose deaths due to psychotherapeutic and central nervous system pharmaceuticals, the proportion involving only a single class of such drugs was highest for opioids (4903/16 651; 29.4%) and lowest for benzodiazepines (239/6497; 3.7%).

COMMENT

Death certificate data have limitations, but they are the sole source for detailed death information at the national level. This analysis is limited by the 25% of death certificates in which the type of drugs involved was not specified, an omission due to lack of toxicological testing or failure to record the results of such tests on the death certificate. Therefore, the numbers reported in this analysis are undercounts. Additionally, the degree to which drugs are specified on death certificates might vary across the United States and therefore differentially undercount types of drugs more common in areas in which death certificates are less complete.

This analysis confirms the predominant role opioid analgesics play in pharmaceutical overdose deaths, either alone or in combination with other drugs. It also, however, highlights the frequent involvement of drugs typically prescribed for mental health conditions such as benzodiazepines, antidepressants, and antipsychotics in overdose deaths. People with mental health disorders are at increased risk for heavy therapeutic use, nonmedical use, and overdose of opioids. Screening, identification, and appropriate management of such disorders is an important part of both behavioral health and chronic pain management. Tools such as prescription drug monitoring programs and electronic health records can help clinicians to identify risky medication use and inform treatment decisions, especially for opioids and benzodiazepines.

Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries

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Summary
The 2011 UN high-level meeting on non-communicable diseases (NCDs) called for multisectoral action including with the private sector and industry. However, through the sale and promotion of tobacco, alcohol, and ultra-processed food and drink (unhealthy commodities), transnational corporations are major drivers of global epidemics of NCDs. What role then should these industries have in NCD prevention and control? We emphasise the rise in sales of these unhealthy commodities in low-income and middle-income countries, and consider the common strategies that the transnational corporations use to undermine NCD prevention and control. We assess the effectiveness of self-regulation, public—private partnerships, and public regulation models of interaction with these industries and conclude that unhealthy commodity industries should have no role in the formation of national or international NCD policy. Despite the common reliance on industry self-regulation and public—private partnerships, there is no evidence of their effectiveness or safety. Public regulation and market intervention are the only evidence-based mechanisms to prevent harm caused by the unhealthy commodity industries.

Introduction

At the 2011 UN high-level meeting on non-communicable diseases (NCDs), the political declaration presented the case for prevention of NCDs in low-income and middle-income countries. Participants agreed that no one factor could fully address the burden of NCDs and called for collaboration with “non-health actors and key stakeholders, where appropriate, including the private sector and civil society, in collaborative partnerships to promote health and to reduce non-communicable disease risk factors”. To achieve the agreed goal to reduce premature mortality due to NCDs of 25% by 2025 will need a massive scale-up of concerted action to reduce consumption of unhealthy commodities—mainly tobacco, alcohol, and ultra-processed food and drink products (panel 1). National governments, non-governmental organisations, academics, and civil society need to consider what the appropriate role of the private sector will be in NCD prevention and control. The debate is most contentious about the unhealthy commodities industries, which are major drivers of NCD epidemics worldwide. What role should these industries have in NCD prevention and control? What type of interaction—defined here as a reciprocal action or influence—with these industries promotes health and protects the public from conflicts of interest? The global health community has different views about how to proceed, which range from collaborative partnerships to outright criticism.

Panel 1
Ultra-processed products

Ultra-processed products are made from processed substances extracted or refined from whole foods—eg, oils, hydrogenated oils and fats, flours and starches, variants of sugar, and cheap parts or remnants of animal foods—with little or no whole foods. Products include burgers, frozen pizza and pasta dishes, nuggets and sticks, crisps, biscuits, confectionery, cereal bars, carbonated and other sugared drinks, and various snack products.

Most are made, advertised, and sold by large or transnational corporations and are very durable, palatable, and ready to consume, which is an enormous commercial advantage over fresh and perishable whole or minimally processed foods. Consequently, their production and consumption is rising quickly worldwide. In the global north—it, North America and Europe—ultra-processed products have largely replaced food systems and...
dietary patterns based on fresh and minimally processed food and culinary ingredients that have less fat, sugar, and salt. In the global south—ie, Asia, Africa, and Latin America—ultra-processed products are displacing established dietary patterns, which are more suitable socially and environmentally.

Ultra-processed products are typically energy dense; have a high glycaemic load; are low in dietary fibre, micronutrients, and phytochemicals; and are high in unhealthy types of dietary fat, free sugars, and sodium. When consumed in small amounts and with other healthy sources of calories, ultra-processed products are harmless; however, intense palatability (achieved by high content fat, sugar, salt, and cosmetic and other additives), omnipresence, and sophisticated and aggressive marketing strategies (such as reduced price for super-size servings), all make modest consumption of ultra-processed products unlikely and displacement of fresh or minimally processed foods very likely. These factors also make ultra-processed products liable to harm endogenous satiety mechanisms and so promote energy overconsumption and thus obesity.

Although there is now consensus that the tobacco industry’s conflict of interest with public health is irreconcilable, whether the competing interests of the alcohol, food, and drink industries are similarly irreconcilable is debated. This lack of clarity stems partly from the absence of a coherent and agreed upon framework for interaction; the normalisation of unhealthy commodities in many countries; the financial and institutional relations many public health researchers, non-governmental organisations, and national and international health agencies have with these companies; and little appreciation that the purpose of corporations is to maximise profits. These conflicts are largely unstudied in public health. The science of the effect of corporate behaviour on health is an emerging area of public health that needs to be developed substantially; it studies the health risks of transnational corporations and the distribution of the unhealthy commodities that they make and market. The term industrial epidemic, has been used to describe health harms associated with various goods including tobacco, alcohol, vinyl chloride, asbestos, cars, and the food and drink industries. In industrial epidemics, the vectors of spread are not biological agents, but transnational corporations. Unlike infectious disease epidemics, however, these corporate disease vectors implement sophisticated campaigns to undermine public health interventions. To minimise the harmful effects of unhealthy commodity industries on NCD prevention, we call for a substantially scaled up response from governments, public health organisations, and civil society to regulate the harmful activities of these industries.

Key messages
Transnational corporations are major drivers of non-communicable disease epidemics and profit from increased consumption of tobacco, alcohol, and ultra-processed food and drink (so-called unhealthy commodities)

Alcohol and ultra-processed food and drink industries use similar strategies to the tobacco industry to undermine effective public health policies and programmes

Unhealthy commodity industries should have no role in the formation of national or international policy for non-communicable disease policy
Despite the common reliance on industry self-regulation and public—private partnerships to improve public health, there is no evidence to support their effectiveness or safety
In view of the present and predicted scale of non-communicable disease epidemics, the only evidence-based mechanisms that can prevent harm caused by unhealthy commodity industries are public regulation and market intervention.

Unhealthy commodities in low-income and middle-income countries

In 2010, tobacco was estimated to have been responsible for 6·3 million deaths and alcohol accounted for 4·9 million deaths. Together tobacco and alcohol—the second and third leading risk factors for the global disease burden, respectively—cause nearly 12% of global disability-adjusted life-years. The consumption of energy-dense ultra-processed foods, unlike low-energy foods such as fruits and vegetables, promotes obesity. Similarly, consumption of sugar-sweetened beverages is associated with increased rates of obesity and diabetes, childhood obesity, long-term weight gain, and cardiovascular disease. In addition to the deaths caused by tobacco and alcohol, more than 18 million deaths every year are caused by high blood pressure (9·4 million), high body-mass index (3·4 million), high fasting blood glucose (3·4 million), and high total cholesterol (2·0 million), much of which could be attributed to the consumption of ultra-processed foods and drinks (panel 1). Almost all growth in the foreseeable future in profits from the sale of these unhealthy commodities will be in low-income and middle-income countries.

Saturation of markets in high-income countries and the high global average of income that people spend on food (20%) has caused the alcohol and ultra-processed food and drink industries to rapidly penetrate emerging global markets, as the tobacco industry has done. Transnational corporations are major drivers of the acceleration of the nutrition transition—ie, from traditional diets of whole or minimally processed foods to highly processed foods and drinks. The substantial growth of ultra-processed products, has paralleled and contributed to the increase in obesity, diabetes, and other diet-related chronic diseases, especially in low-income and middle-income countries. To assess existing and future trends in unhealthy commodities, activities of the major corporations need to be monitored. For low-income and middle-income countries, we used official market sales data because survey data for the consumption of unhealthy commodities, measurable across countries and over time, are scarce. Additionally, market data are not subject to recall biases, which complicate the recording of individuals’ consumption of unhealthy commodities. We used market data for commodity sales from the EuroMonitor Passport Global Market Information database 2011 edition, covering up to 80 countries between 1997 and 2010 (panel 2).

Panel 2
EuroMonitor Passport Global Market Information Database

Data include per-person volumes for packaged foods—including snacks, snack bars, ice cream, oils and fats, chilled processed food, dried processed food, canned food, soft drinks, hot drinks, and ready-to-eat meals—which are all ultra-processed products, except for oils and fats, which are culinary ingredients. Industry data for retail sales of tobacco were also obtained from EuroMonitor. These official market data, as reported by governments, have similar limitations to other frequently used macroeconomic data such as gross domestic product and trade statistics. Additionally, these data capture only sales volumes, which are imperfect measures of consumption because they do not include food and drink products produced at home or that are wasted, or smuggled alcohol and tobacco.
Tobacco, alcohol, and several categories of packaged food—a good proxy for ultra-processed food and drink products—are rising most rapidly in low-income and middle-income countries (table 1). Little, if any, growth is expected in high-income countries in the next 5 years because of the economic recession (figure 1), strict tobacco-control policies, and saturation of established markets with ultra-processed food and drink products. The frequently used term competitive market suggests a wide variety of traders; however, the most powerful corporate sectors of the world’s food system are increasingly concentrated to the point of oligopoly. For example, in the USA, the ten largest food companies control more than half of all food sales. Worldwide, this proportion is about 15% and is rising rapidly. More than half of global soft drinks are produced by large transnational companies, mainly Coca-Cola and PepsiCo. 75% of world food sales are of processed foods, whose largest manufacturers control more than a third of the global market. The industry body International Center for Alcohol Policies (ICAP) states that the branded alcohol market accounted for 38% of global alcohol consumption in 2005, and the top ten producers accounted for 66% of the global market share for beer, 59% for spirits, and 16% for wine. Leading alcohol transnationals, Diageo, Pernod Ricard, and SAB Miller, all claim growth in sales in low-income and middle-income countries in recent annual reports. For example, SAB Miller reported earnings growth in 2011 of 33% for Asia, 20% for Africa, and 11% for Latin America compared with 4% for Europe. The aim of their African division is for a two-times increase in the opaque (millet) beer market and a six-times increase in the affordable beer market.

Table 2 lists the top five companies responsible for sales of packaged foods in Brazil, China, India, Mexico, South Africa, Russia, and the USA. With the exception of China, there is a high degree of transnational penetration into the food systems of low-income and middle-income countries already similar to that in the USA. For example, Kraft Foods, the main seller of packaged food in the USA, is responsible for about 6-8% of all sales in the USA, and Nestlé already has 8-4% of all packaged food sales in Brazil. An even higher degree of concentration is evident for sales of specific categories of ultra-processed products.

To understand the causes of illness in populations, we need to assess both individual-level and population-level factors. Both supply and demand factors contribute to the rising population consumption of unhealthy commodities. On the demand side, as economies grow and purchasing power of people strengthens, unhealthy commodities become more affordable; as people have less time, convenience of these products becomes important, which enhances consumption. Economic growth seems to be strongly correlated with rising consumption of unhealthy commodities, but only when markets are highly integrated, and therefore enable the large-scale entry of transnational corporations into low-income and middle-income countries. Additionally, the systematic and aggressive mass-marketing campaigns of alcohol, ultra-processed foods and drink, and tobacco contribute to demand. A contributory factor to supply is economic policy and trade agreements that open markets to foreign investment, and provide entry for tobacco, alcohol, and ultra-processed food and drink corporations through takeovers of domestic companies. For example, free-trade agreements with the USA are associated with high consumption of fizzy drinks in several countries. Deregulation also contributes to market spread of unhealthy commodities because it constrains the ability of governments to introduce fiscal policies to limit their consumption. These supply and demand drivers are similar in the tobacco, alcohol, and ultra-processed food and beverage industries and it is therefore not surprising that these unhealthy commodities stimulate complementary epidemics. Nationally, there is a strong correlation between tobacco, alcohol, and processed food and drink product sales (figure 2). Where tobacco markets are the greatest, so too are markets for alcohol and for processed food products. The relation between tobacco, alcohol, and ultra-processed food and beverage corporations show the failure of public
health policy makers and professionals to respond to the effect of unhealthy commodities on global health, and shows how these industries undermine public health.

Strategies by industry to undermine effective public health policies and programmes

Industry documents released because of tobacco and asbestos litigation show how these industries affect public health legislation and avoid regulation with both hard power (ie, building financial and institutional relations) and soft power (ie, influence of culture, ideas, and cognitions of people, advocates, and scientists). There is now evidence to show that the food, drink, and alcohol industries use similar tactics and strategies to the tobacco companies to undermine public health interventions. We outline the common strategies that these industries use, as reported in the disclosure of industry documents relating to alcohol marketing, and in reviews of the similarities between tobacco and food and the similarities between alcohol and tobacco.

The first strategy is to bias research findings. For example, Philip Morris International implemented the Whitecoat project to hire doctors to publish ghost-written confounder studies purporting to negate links between environmental tobacco smoke and harm. The tobacco companies created quasi-independent organisations to publish biased and partial scientific reports, deny harm, and suppress health information. Similarly, funding from transnational food and beverage corporations biases research. A meta-analysis of research publications showed systematic bias from industry funding, with articles sponsored exclusively by food and drinks companies four-times to eight-times more likely to have conclusions favourable to the financial interests of the sponsoring company than those that were not sponsored by food or drinks companies. The International Center for Alcohol Policies, an organisation established and funded by large global alcohol producers, commissioned reports from scientists that resemble WHO documents. These reports were “incomplete, not subject to traditional peer review, and either supportive of industry positions or emphasizing high levels of disagreement among scientists”.

The second stratgey is to co-opt policy makers and health professionals. To undermine tobacco control research, the US Tobacco Institute promoted partnerships with scientists. They hired researchers and disseminated health promotion strategies to mislead the public about the harmful effects of smoking. Like the tobacco industry, the food and drink industry develops customers as young as possible, using tactics such as early-childhood health promotion schemes. SAB Miller and the International Center for Alcohol Policies have assisted the Lesotho, Malawi, Uganda, and Bostwana Governments to write their national alcohol control policies. The four draft National Alcohol Policy documents were “almost identical in wording and structure and that they are likely to originate from the same source”, and were designed to “serve the industry's interests at the expense of public health by attempting to enshrine ‘active participation of all levels of the beverage alcohol industry as a key partner in the policy formulation and implementation process’”.

The third strategy is to lobby politicians and public officials to oppose public regulation. Tobacco transnationals lobby policymakers and fund campaigns of politicians who support tobacco use. The lobbying power of alcohol and ultra-processed food and drink corporations is also substantial. According to US Senate records, the largest alcohol companies spent US$150 million lobbying compared with $40 million for tobacco between 1999 and 2011. US Senate Office of Public Records shows that PepsiCo alone reported spending more than $9 million in 2009 to lobby
On the basis of filings with the Federal Elections Commission, in the 2008 election cycle, the company's Political Action Committee so-called Concerned Citizen Fund alone contributed $547,700 to candidates for federal office. Its policy emphasises contributions to candidates who are “pro-business”, and who have a “commitment to improving the business climate” pending the “candidate's position on key committees where legislation of importance to PepsiCo is considered”. In another example, the Sugar Association threatened WHO that it would lobby the US Government to withdraw its funding because WHO strategy on diet, physical activity, and health highlighted a strong link between sugar and NCD risk. Several people from these industries were billed in the official agenda of the September, 2011 UN high-level meeting on NCDs as the lead representatives of civil society, and gave keynote statements designed to guide policies. One was a former US Ambassador who is now Vice President, Global Public Policy and Government Affairs, at PepsiCo. The high-level meeting civil society list also included representatives from alcohol transnationals such as Diageo, SAB Miller, and Molson Coors Brewing.

The fourth strategy is to encourage voters to oppose public health regulation. For example, the tobacco industry has, and continues to campaign for, a restricted role of government, and against taxation and regulation. Their campaigns emphasise that tobacco use is an individual responsibility and raise arguments against so-called nanny state governments. Contrastingly, public health highlights the importance of social, economic, and political factors, and ethical considerations. The differences between high-risk individual and population approaches underline the gap between public health and industry perspectives. Similarly, blame-the-victim campaigns by transnational food corporations reduce public support for government interventions. As an alternative to regulatory measures, alcohol and food industries promote ineffective individually-targeted information and educational approaches, and sometimes employ counter-productive covert marketing. Their social-marketing campaigns place responsibility for the purchasing decision on the individual, and in doing so, separate these choices from the circumstances in which they are made. The media regularly emphasise personal choice and responsibility and convey government intervention as coercive and oppressive. Despite the industries' professed faith in these information-based approaches, they avoid disclosure of relevant health information to consumers.

From the denial of tobacco addiction as late as 1994 to the obstruction of traffic-light labelling of unhealthy food and the recent detraction of alcoholic drinks from EU labelling legislation, the tobacco, alcohol, and food industries have all tried to block access to objective health information and to manipulate channels of communication.

To deflect criticism, corporations promote actions outside their areas of expertise. For example, tobacco corporations promote the prevention of violence against women and ultra-processed food and drink corporations emphasise physical inactivity. Tobacco and alcohol producers also highlight illegal distribution and smuggling to deter policy makers from introducing regulation that will curtail their own activity. The similarities between strategies used by the tobacco, alcohol, and food and drink corporations are unsurprising in view of the flow of people, funds, and activities across these industries, which also have histories of joint ownership—eg, Philip Morris owned both Kraft and Miller Brewing; Altria is a lead shareholder in tobacco and food companies that have shared directorships; SAB Miller Board includes at least five past or present tobacco company executives and board members; and the Diageo Executive Director, responsible for public affairs, spent 17 years in a similar role at Philip Morris. Additionally, tobacco and food and drink corporations use the same public relations firms to lobby worldwide and to design stakeholder marketing campaigns such as Pernod Ricard's drink Responsib'All Day. The alcohol and food and drink industries are united in intense opposition to the development of an equivalent to the WHO Framework Convention on Tobacco Control. Article 5-3 of this convention outlines the protection of public health policies for tobacco control from commercial and other vested interests of the tobacco industry and is
relevant to the alcohol and ultra-processed food and drink industries. The actions of transnational corporations have generated such major concerns in the public health community, that there is now an emerging willingness to address these issues with scientific methods and systematic analysis.

Public health responses to unhealthy commodity industries

What is the most effective way to address the disease burden caused by unhealthy commodities: voluntary self-regulation, public—private partnerships, or regulation and market intervention?

Industry-operated, voluntary self-regulation is the default approach of many governments and the UN, and the preferred approach of industry. It is argued that market forces, driven by informed individual choice, correct for negative results caused by high consumption of unhealthy commodities. For example, the UK Government based much of its initial public health strategy on nudge theory and voluntary action of the food and alcohol industries with the Public Health Commission, and the Responsibility Deals. The UK’s obesity control policy has been criticised heavily by British public health experts as a smokescreen for publicly endorsed marketing. A new alcohol strategy for England released in March, 2012 is more evidence-based than the obesity control policy and, as in Scotland, sets a minimum price per unit of alcohol.

The second model of interaction is public—private partnership, which is based on the belief that association with industry leads to greater success than does acting independently of them. Although the argument against this approach is clear for tobacco and alcohol, the situation for the food and drink industries is more complex. Supporters of this view claim that people need to eat and drink, that not all processed foods are unhealthy, and that partnership with industry might lead to reformulation of some products to less unhealthy compositions. It is argued that the world's population will consume more ultra-processed foods and drinks over the coming decades than ever before; therefore, a compromise that minimised their harm might have substantial public health benefit. Many public—private partnerships exist—eg, the recently announced 3 year partnership between the International Diabetes Federation and Nestlé, which was announced in April, 2012. However, there is little objective evidence that public—private partnerships deliver health benefits, and many in the public health field argue that they are just a delaying tactic of the unhealthy commodity industries. Brownell believes that “when the history of the world’s attempt to address obesity is written, the greatest failure may be collaboration with, and appeasement of, the food industry”. Potential benefits are less apparent and the risks are greater in low-income countries than in high-income countries (panel 3). The UN and many national governments presently favour such partnerships, but definitive outcomes of existing partnerships need to be independently and objectively monitored to establish whether they are effective. Another public—private partnership model is conditional engagement, which supports so-called round-the-table interaction with industry to promote evidence-based policy, the critical appraisal of industry-based approaches, and the establishment and independent observation of objectives and outcomes. A concern is that public—private partnerships are simply a means for industry to co-opt public health.

Panel 3
Product reformulation
A reason frequently given for public—private partnerships with food and drink corporations—whose profits largely depend on ultra-processed products—is the encouragement of product reformulation, so that at least some of the products will contain less trans-fats or less salt. The case for reformulation is most apparent in high-income countries where markets might be saturated with ultra-processed products—ie, more than 60% of total energy intake. If the market is saturated, consumers might prefer the new product without consuming more ultra-processed products—eg, in the USA, sales of sugared soft drinks are unchanged, and alternatives such as designer water have increased. Nonetheless, in such countries, the main emphasis on and support of national governments and the public health community should be promotion of healthy meals, dishes, and foods.

Discussions about product reformulation, with or without public—private partnerships, have focused on risks and benefits in high-income countries. However, in low-income countries, benefits are less obvious, and the dangers are very apparent. In such countries, consumption of ultra-processed products is low. These countries are therefore the prime targets of transnational corporations. If they reformulate, advertise, and promote some of their less unhealthy products as healthy—eg, sodium-reduced (but still high energy-dense) packaged snacks or artificially sweetened (but still nutrient-devoid) soft drinks—the overall consumption of ultra-processed products is likely to increase, which would undermine long-established dietary patterns based on fresh or minimally processed foods. In low-income countries, the reformulation of ultra-processed food and drink products is similar to the tactics of the tobacco industry in introduction of filtered cigarettes and low-tar cigarettes.

The reformulation approach is a damage-limitation exercise, to avoid evidence-based approaches such as the restriction of availability and of advertising, and pricing policies designed to promote healthy food, such as now being undertaken by order of the Mayor and municipal authorities of New York City.

The third model of interaction is public regulation, which specifically recognises the conflicts of interest between promotion and protection of public health and the corporations that profit from unhealthy commodities. Because growth in sales, turnover, and profit are the main goals of transnational corporations, supporters of public regulation believe that self-regulation and working from within are ineffective and counterproductive. Most advocate statutory regulations, analogous to those used to control firearms, road traffic, drugs and tobacco, and to protect parks, forests, and open spaces. Public regulation is a model of very active critical analysis that can be achieved in three ways. First, by galvanisation of an evidence-based constituency that implements effective and low-cost policies by making apparent the need for regulation and market intervention. Second, directly pressuring industry to change by making harmful practices obvious. Third, by raising of public awareness of the negative actions of these industries—an approach that is effective in changing the behaviour of the tobacco industry. To make the regulation of tobacco, alcohol, salt, sugar, and trans-fats politically feasible in most countries, constant active public pressure is needed.

The case for public regulation

On the basis of evidence and experience so far, the tobacco industry is ruled out of any interaction with public health policy makers, researchers, and practitioners, other than what is consistent with the Framework Convention on Tobacco Control. Guidelines for implementation of article 5·3 of the Convention state that the "parties should interact with the tobacco industry only when and to the extent strictly necessary to enable them to
effectively regulate the tobacco industry and tobacco products”. No plausible rationale exists for action by public health interests with alcohol and ultra-processed food and drink industries, except when action is driven by the threat of government regulation, such as the UK partnership on salt reduction. However, a similar partnership in Australia has not yet resulted in reduced salt consumption because the companies implicated do not profit from the process, and there is no threat of regulation or sanctions. Engagement with industry needs to generate profit, but legitimate mechanisms through which public health institutions and professionals could contribute to increasing industry profits are hard to identify. To promote health, the food and drink industries need to move consumption patterns away from ultra-processed food and drink products; however, these products are more profitable than less-energy-dense, nutrient-rich foods. In the alcohol industry, sales and profits are dependent on many consumers drinking at risky quantities. As Coca-Cola states, “increasing public concern about these issues; possible new taxes and governmental regulations concerning the marketing, labelling or availability of our beverages; and negative publicity resulting from actual or threatened legal actions against us or other companies in our industry relating to the marketing, labelling, or sale of sugar-sweetened beverages may reduce demand for our beverages, which could affect our profitability”. Thus, industry maintains profit only if it undermines attempts to tax and regulate, or if people who consume more healthy commodities continue to consume profitable, but unhealthy commodities; neither is desirable from a health perspective.

The precautionary principle argues against public—private partnership because there is no evidence that the partnership of alcohol and ultra-processed food and drink industries is safe or effective, unless driven by the threat of government regulation. Similarly, there is little evidence that self-regulatory approaches are effective. For example, the so-called voluntary decision by Kraft to ban trans-fats was a result of threatened litigation. Furthermore, legislation for clean air, asbestos, road trauma, and tobacco was introduced only after the repeated failures of the industries responsible for solving these problems through self-regulation. The argument against self-regulation is that even if some progressive food and alcohol companies use healthier approaches, the gap in the market would be filled by others. Another counter argument is that ill-conceived partnerships with industry can lead to procrastination and delay—a standard industry tactic to avoid regulation.

We believe that civil society should be aligned with government, which has the responsibility and power to protect public health, although compromised by transnational corporations. To fulfil this aim, governments need information and support from civil society and from public health interests. Regulation, or the threat of government regulation, is the only way to change transnational corporations; therefore, the audience for public health is government and not industry. Discussions with unhealthy commodity industries will be helpful only if they are with government and if the goal is for government to use evidence-based approaches. To respond to the scale and urgency of the global NCD epidemics, the industrial drivers that underpin them, and the tactics used by the unhealthy commodity industries so far, we have ten recommendations for action (panel 4).

Panel 4
Recommendations of action for non-communicable diseases

For public health policy making, research, and programmes

Unhealthy commodity industries should have no role in the formation of national or international policy for non-communicable diseases
Interactions with the tobacco industry should be restricted and made consistent with recommendations of the Framework Convention on Tobacco Control.

Discussions with unhealthy commodity industries should be with government only and have a clear goal of the use of evidence-based approaches by government.

In the absence of robust evidence for the effectiveness of self-regulation or private—public partnership in alcohol, food, and drink industry, rigorous, timely, and independent assessment is needed to show that they can improve health and profit.

For public health professionals, institutions, and civil society:

Highly engaged, critical action is needed to galvanise an evidence-based constituency for change to implement effective and low-cost policies, to place direct pressure on industry to change, and to raise public awareness of the unhealthy effects of these industries.

Funding and other support for research, education, and programmes should not be accepted from the tobacco, alcohol, and ultra-processed food and drinks industries or their affiliates and associates.

For governments and international intergovernmental agencies:

Evidence-based approaches such as legislation, regulation, taxation, pricing, ban, and restriction of advertising and sponsorship should be introduced to reduce death and disability from non-communicable diseases.

For governments, foundations, and other funding agencies:

All approaches in the prevention and control of non-communicable diseases—i.e., self-regulation, public—private partnerships, legislation, pricing, and other regulatory measures—should be independently and objectively monitored.

Funding of policy development research into modes of regulation and market interventions should be accelerated and prioritised.

A new scientific discipline that investigates industrial diseases and the transnational corporations that drive them, should be developed.

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ABSTRACT

Objectives: This study identifies predictors of prescription drug misuse among U.S. active duty service members (ADSM). The 2008 Department of Defense Survey of Health-Related Behaviors (HRB) Among Active Duty Military Personnel indicated that ADSM misuse pain relievers, tranquilizers, sedatives, and stimulants at levels ranging from 2% to 17%. Methods: Secondary, multivariate analyses of HRB survey data examined predictors of self-reported prescription drug misuse for 4 distinct drug categories. Results: Receipt of a pain reliever prescription in the past month, year, or previous year were strong predictors (adjusted odds ratio above 2.0) of misuse for all drug categories; receipt of a prescription for anxiety or depression medication in the past year was the strongest predictor of sedative misuse (adjusted odds ratio = 4.46, 95% confidence intervals 3.18–6.24). Absence of a drug testing program was significantly related to the likelihood of drug misuse for all drug categories. Conclusions: ADSM with a history of treatment for pain and mood disorders, and who self-report headaches, sleep disorders, and fatigue are at higher risk for misusing prescription drugs, perhaps in an effort to self-manage symptoms. The results should be interpreted as a starting place for future exploration, not as the sole basis for policy or program development.

INTRODUCTION

Misuse of psychoactive (mood altering) prescription medications by U.S. active duty service members (ADSM) has implications for military readiness and the health care systems that deliver military health care. Military Service programs aim to prevent drug abuse by focusing on education and awareness, deterrence through surveillance (e.g., random drug screening), and discipline. Despite these programs, the nonmedical use of prescription drugs among enlisted service members appears to have increased in the past decade. The 2005 and 2008 Department of Defense (DoD) surveys of Health Related Behaviors (HRB) Among Active Duty Military Personnel indicate that self-reported illicit drug use and prescription drug misuse increased from 5% in 2005 to 12% in 2008, most of the increase being attributable to prescription drugs. National surveys find between 2.1% and 6.3% of adults over age 18 use psychotherapeutic drugs for nonmedical purposes. Among civilian adults age 18 to 34, the age of most military personnel, the rate of pain reliever misuse increased from about 2% to greater than 13% from 1998 to 2008, consistent with the HRB survey findings.

In the civilian population, predictors of prescription drug misuse include physical health status, younger age, female gender, and non-White race/ethnicity. Among individuals with mental and physical health symptoms, misuse appears to be associated with self-regulation of symptoms that have been inadequately treated or not treated at all. Individuals exhibiting mental health symptoms are more likely to be prescribed...
medication that contributes to drug use disorders. Further, individuals who have history of prescription drug misuse have an increased likelihood of continued use and/or initial use of other illicit substances.

Information about prescription drug misuse in military-related populations chiefly derives from research conducted at veterans' medical centers. For example, in one study of veterans treated in a primary care clinic for pain disorders, 78% reported misusing prescription drugs at least once in the previous year; the strongest predictor of misuse was history of substance abuse. Other studies of veteran populations treated in veterans' medical centers suggest that strong predictors of prescription drug abuse are chronic pain, symptoms of depression, illicit drug use, and seeking symptom relief.

Recently, prescription drug misuse among military personnel gained the attention of the U.S. Congress, senior military leaders, and the media. In response, a secondary data analysis was conducted using HRB survey data to elucidate factors associated with misuse of prescribed medications including pain relievers, sedatives, tranquilizers, and stimulants within ADSM. Notably, the use of secondary data did not permit the addition of survey questions that may have provided insight into other predictors of prescription drug misuse. Consistent with other research, this study defines prescription drug misuse as the use of prescribed medications not prescribed to oneself, or the misuse of one's own prescription.

METHODS

Data Source and Sample

The 2008 HRB survey is the tenth in a series of Department of Defense (DoD) surveys among ADSM conducted since 1980. The eligible survey population consisted of all ADSM except recruits, Service academy students, personnel absent without official leave, and personnel who had a permanent change of station at the time of data collection. Participants represent men and women in all pay grades of the active force throughout the world.

The HRB survey is self-administered and anonymous; thus, individual responses cannot be linked to personnel or medical records. Where possible, group session data collection was used at military installations, including aboard ships. A total of 70 installations were sampled with at least 2 installations per major command included. The second stage of sampling was then done based on gender and pay grade with women and officers being oversampled. Sampling with replacement was done if during data collection it was determined that a service member had undergone a permanent change of station, were away on temporary duty or official leave, were separated from the service, hospitalized/ill, inaccessible/at sea/deployed, incarcerated, absent without official leave, deceased, or unknown at the installation. Replacement lists were created during the original sampling process with replacement based on pay grade and gender.

Of the 45,800 individuals eligible for participation, 5,200 were classified as remote or overseas and were mailed surveys. The overall response rate was 70.6%; of these, 28,546 surveys were usable for further analysis. The HRB survey data were weighted to represent the population of all eligible active duty personnel. The final survey weights, as applied within this study, included adjustments to correct for potential nonresponse bias.
The study was reviewed by the TRICARE Management Activities Human Research Protection Program Oversight Office and determined to be exempt from full review by the DoD Institutional Review Board.

Measures

Survey instructions, questions, and response categories related to prescription drug misuse were borrowed heavily from the National Survey on Drug Use and Health administered by the Substance Abuse and Mental Health Services Administration to civilian populations, and the Monitoring the Future Study administered by the National Institute on Drug Abuse. No pilot survey with a military population was conducted to test these prescription drug-related questions newly added to the 2008 HRB survey.

The dependent variables in this study are independent misuse of 4 distinct categories of prescription drugs. Survey respondents were instructed that nonmedical use of prescription drugs meant: any use of prescription drugs without a doctor’s prescription, in greater amounts or more often than the drug was prescribed, or for reasons such as to get “high,” or for “thrills” or “kicks.” Examples of drug categories provided in the survey instrument included sedatives or barbiturates, pain relievers, stimulants other than methamphetamine, and tranquilizers or muscle relaxers. The survey also listed commercial drug names to help respondents understand the drug-related questions. Analysis focused on self-reported use of sedatives, pain relievers, stimulants other than methamphetamine, and tranquilizers.

We identified respondents who indicated at least 1 day of prescription drug misuse in the past 12 months. Differentiating between frequent and occasional users was not done because of the low numbers of self-reported misuse in the 2008 HRB survey data; doing so would have resulted in an inadequate sample size to perform logistic regression.

In total, we tested 27 independent variables, 6 of which were summed composite measures or continuous variables. Since this study is a secondary data analysis of anonymous survey data, variables were chosen to approximate intention of misuse and source of prescription (self vs. undetermined other) based on mental and/or physical condition; history of drug, alcohol and smoking use; and spiritual beliefs. Demographic variables and deployment-related variables were also used in the analysis. Although anonymous, this survey asks potentially incriminating questions; nonresponse to these questions cannot be interpreted. In some cases we kept “unknown” as a response because of a large proportion of unanswered questions.

Continuous or summed variables included age, stress, receipt of counseling or therapy, alcohol consumption, illicit drug use, and experience of injury during deployment. Stress was measured from a series of questions asking “During the past 12 months, how much stress did you experience from the following?” Twenty-two different scenarios were examined for inclusion. If an individual reported experiencing stress “a little,” “some,” or “a lot,” the response was counted as positive for stress. A composite measure was created as the sum of each individual’s positive responses to each of the 22 scenarios, with higher numbers indicating more experiences of stress. For receipt of counseling or therapy for mental health or substance abuse, respondents were asked where they sought treatment; each source of therapy counted as a positive for counseling and values were summed. Alcohol and illicit drug use were measured using summed composite measures for number of types and how often used. The alcohol composite was based on the answers to 4 different questions regarding beer, liquor, wine, or other alcoholic drink consumption.
Illicit drug use was based on the series of questions asking about use of marijuana, cocaine, LSD, PCP, MDMA (Ecstasy), other hallucinogens, methamphetamine, heroin, GHB/GBL, and inhalants. Experience of injury during deployment was also asked of respondents via multiple scenarios. Each experience of a scenario counted as a positive and values were summed.

Categorical variables included race/ethnicity, marital status, education, feeling nervous, on edge, or anxious; getting tired easily; having trouble falling or staying asleep; trouble concentrating, suicidal ideation, perceived difficulty meeting service requirements for weight, whether spiritual beliefs affected how personal decisions were made, smoking, self-reported prescription history (not actual receipt or pharmacy dispensing of the medication), ability to predict drug testing, the likelihood of using drugs if the military stopped random testing, deployment since September 11, 2001, range of months deployed, traumatic experiences during deployment, and the effects of deployment on headaches.

Statistical Analysis

The HRB survey is a multistage questionnaire requiring complex statistical procedures to account for survey-specific characteristics and design features. Population weighting adjustments were used to account for specific characteristics of survey design, including oversampling of proportionately smaller subpopulations (e.g., women, officers). All data editing, cleaning, and recoding were performed using SAS 9.2 (Cary, North Carolina). Statistical testing and analysis was performed using SUDAAN (Research Triangle Park, North Carolina) to properly account for HRB survey design characteristics with respect to variance and significance level estimation.

Demographic distributions were assessed for all HRB survey respondents and for each prescription drug category (sedatives, pain relievers, tranquilizers, or stimulants). Bivariate analyses were conducted for all explanatory variables of interest in conjunction with the prescription drug outcome variables. Collinearity between variables was assessed using chi-squares, correlations, and factor analyses.

Multivariate logistic regression was performed independently for each prescription drug category outcome with the assumption that there are different effects and motivation associated with each drug type. Modeling assessed the probability of a positive response to drug misuse while adjusting for predictors. Backward stepwise elimination was used to assess confounding factors and to help assess variable contribution to the overall model. The \( -2 \log\)-likelihood test assessed the magnitude of contribution of each variable to the model, based on a \( \chi^2 \) distribution.

RESULTS

Among the 2008 HRB survey population, 3,060 survey respondents indicated at least 1 day of prescription drug misuse in the past 12 months.

Rao-Scott \( \chi^2 \) analysis found all independent variables were statistically significant against dependent variables (\( p \leq 0.05 \)). This analysis also showed that between 60% and 71% of survey respondents for all 4 drug categories had a prescription for a pain reliever in the past year. Fewer survey respondents who indicated misuse of a pain reliever or tranquilizer had a prescription for anxiety/depression medication, 13% and 25%, respectively, compared to those who indicated misuse of a sedative or stimulant, 42% and 31%, respectively.
The strongest predictors of reported pain reliever misuse were having received a pain reliever prescription previously. Survey respondents who reported having been prescribed a pain reliever within the last month had twice the odds of pain reliever drug misuse (AOR = 2.56, 95% CI 2.23–2.94), as did those having been prescribed a pain reliever during the past year (AOR = 2.51, 95% CI 2.25–2.81). Moderate predictors, defined here as AOR between 1.35 and 1.99, included Black/African American race (AOR = 1.78, 95% CI 1.47–2.16), reporting that drug use would be somewhat or very likely if there were no random drug tests (AOR = 1.54, 95% CI 1.31–1.81), race classified as non-White, non-African American (AOR = 1.49, 95% CI 1.20–1.84), and Hispanic race (AOR = 1.35, 95% CI 1.12–1.64) and having received a prescription for anxiety/depression in past year (AOR = 1.41, 95% CI 1.04–1.91).

Weak predictors, defined here as an AOR between 1.0 and 1.35, of pain reliever misuse were reporting headaches since deployment, lower education, getting tired easily in the past month, ineligible to answer headache question because never deployed, agreeing that spiritual beliefs influence decision making, having received a prescribed pain reliever more than a year ago, perceiving that was somewhat easy to very easy to predict the last drug test, trouble staying or falling asleep in past month, illicit drug use, injury during deployment, and alcohol consumption. When compared to the referent Service level of Army, branch of Service weakly predicted less misuse of prescription pain relievers: Navy (AOR = 0.73, 95% CI 0.62–0.86), Air Force (AOR = 0.76, 95% CI 0.66–0.89), Coast Guard (AOR = 0.78, 95% CI 0.65–0.93), and Marine Corps (AOR = 0.80, 95% CI 0.64–0.99). Although statistically significant, the interaction term retained in the model (former smoking × alcohol consumption) contributed negligibly to the regression model.

The odds of prescription tranquilizer misuse increased more than 3-fold with the receipt of a pain reliever prescription in the past 30 days (AOR = 3.89, 95% CI 2.93–5.16) and the receipt of a pain reliever prescription in the past year (AOR = 3.34, 95% CI 2.43–4.60). The odds of misuse doubled for those reporting that they would be somewhat likely or very likely to use drugs if there were no random drug tests (AOR = 2.05, 95% CI 1.63–2.58). Moderate predictors included having received a prescription for anxiety/depression in the past year (AOR = 1.90, 95% CI 1.35–2.68), having received a prescription for anxiety/depression more than a year ago (AOR = 1.58, 95% CI 1.24–2.00), reporting that headaches began or got worse since deployment (AOR = 1.53, 95% CI 1.24–1.88), Hispanic ethnicity (AOR = 1.46, 95% CI 1.11–1.92), ineligible to answer question about postdeployment headaches because of no deployment history (AOR = 1.46, 95% CI 1.19–1.78), and trouble staying or falling asleep in past month (AOR = 1.43, 95% CI 1.19–1.72). Illicit drug use, injury during deployment, and age were weak predictors. The odds of tranquilizer misuse for Navy and Air Force members were lower, an AOR less than 1, compared to Army service members.

Among respondents who reported prescription sedative misuse, the odds of misuse increased more than 4 times if the respondent reported having received a prescription for anxiety/depression in past year (AOR = 4.46, 95% CI 3.18–6.24). The odds increased more than 3-fold if a prescription for anxiety/depression had been received in past 30 days (AOR = 3.55, 95% CI 2.31–5.46), and the odds more than doubled if a prescription for anxiety/depression was received more than a year ago (AOR = 2.60, 95% CI 1.93–3.50). Further, having received a pain reliever prescription in the past month (AOR = 2.04, 95% CI 1.30–3.19) and reporting that drug use would be somewhat likely or very likely if there were no random drug tests (AOR = 2.14, 95% CI 1.50–3.07) independently doubled the odds of prescription sedative misuse. Moderate predictors of reporting sedative misuse were trouble staying or falling asleep in past month (AOR = 1.85, 95% CI 1.28–2.66), having received a pain reliever prescription in the past year (AOR = 1.78, 95% CI 1.23–2.59), ineligible to answer question about postdeployment headaches because never deployed (AOR = 1.54, 95% CI 1.09–2.17) and not married (AOR = 1.35, 95% CI 1.01–1.82). Unknown marital status (AOR = 0.16, 95% CI 0.05–0.48) and never having
received a drug test (AOR = 0.42, 95% CI 0.20–0.86) decreased the likelihood of misuse, although the small numbers in each group suggests spurious findings. Compared to the Army, the odds of members of the Coast Guard, Navy, and Marines to report misuse of prescription sedatives were lower, an AOR less than 1.

Individuals who reported they would be somewhat likely or very likely to use drugs in the absence of drug testing had twice the odds of reporting prescription stimulant misuse (AOR = 2.45, 95% CI 1.63–3.67). Having received a pain reliever prescription in the past year (AOR = 2.44, 95% CI 1.37–4.35) or having received a pain reliever prescription in the past month (AOR = 2.36, 95% CI 1.38–4.05) likewise doubled the odds of stimulant misuse. Moderate predictors of stimulant misuse were ineligibility to answer the headache question because the respondent was never deployed (AOR = 1.91, 95% CI 1.32–2.77); reporting that headaches began or got worse since deployment (AOR = 1.89, 95% CI 1.32–2.72); other, non-Hispanic race (AOR = 1.80, 95% CI 1.18–2.73); Black/African American race (AOR = 1.66, 95% CI 1.00–2.75); trouble concentrating in the past month (AOR = 1.57, 95% CI 1.12–2.20); agreeing that spiritual beliefs influence decision making (AOR = 1.56, 95% CI 1.05–2.31); and not married (AOR 1.51, 95% CI 1.15–1.98). Unknown marital status was a strong predictor of less stimulant misuse (AOR = 0.15, 95% CI 0.05–0.46), most likely a statistical artifact owing to the few respondents in this group. Reporting illicit drug use and alcohol consumption in the past month were weak predictors of stimulant misuse. Variables related to gender, stress, difficulty meeting Service weight, length of deployment, and trauma during deployment were not statistically significant in regression models for all 4 drug categories.

DISCUSSION

Across all groups of drugs, prescription misuse was strongly associated with having received a prescription in the past month, year, or previous year, particularly the receipt of a pain reliever prescription. For sedatives, the prescription of medications for mood disorders was highly predictive of reported misuse. As expected, previous exposure to these drugs increases the risk of misuse, findings that are highly consistent with the results of national studies. Results of this analysis also indicated that having received a prescription for a mood disorder in the past year increased the risk of misuse of prescribed pain relievers and tranquilizers. This finding mirrors the results of a recent study that found an association between earlier use of benzodiazepines. The results also show an association between intention to misuse prescription drugs and the presence of a drug deterrence program, which may be an indicative of the effectiveness of the current military policies and practices regarding drug misuse. Random drug testing of service members began in 1975 with the focus of screening for illegal substances; in 2005, testing was expanded to include controlled substances.

For any one regression model, the moderate and weak predictors are not particularly useful; examining the models together, a different picture emerges. Across all 4 drug categories, drug misuse was consistently related to symptoms typically associated with stress including headaches, trouble concentrating, trouble staying or falling asleep, and getting tired easily. Although the survey did not inquire about motivation for prescription drug misuse, these findings strongly suggest that ADSM may be self-medicating to control physical and mental health symptoms, and to improve their military readiness. These results coincide with findings from studies of military veterans who have a high risk for prescription drug misuse or abuse in the presence of pain conditions. In these other studies, higher risks for misusing or sharing prescriptions were also attenuated by substance abuse disorders, similar to our findings that showed illicit drug use and alcohol consumption increase the chances of prescription drug misuse. Race, defined as Black, Hispanic or “other,” also appears to increase the chances for prescription drug misuse. Previous studies with
adolescent populations indicate that misuse of prescription drugs and type of misused drug varies by cultural and racial/ethnic affiliation; one study found higher misuse among whites. Another finding is that membership in Services other than the Army moderately decreases the chances of misuse. We speculate that this latter finding may be related to deployment experiences, e.g., less availability of prescribed medications while in the field, high rates of musculoskeletal injuries not classified as war wounds, and differences in the way units are organized.

There are several limitations to this study. First, the HRB survey was not designed to examine predictors of prescription drug misuse; the survey contains no direct questions about motivation for use, the source of the prescription medications, details on past or current health, the nature and quality of reported pain, nor the impact of misuse on military readiness. Additionally, since the survey is anonymous and self-reported, respondents cannot be linked to their medical records to verify responses. Hence, for those respondents who self-reported receipt of prescription(s), we have no medical or pharmacy data to verify the circumstances by which individuals were prescribed pain relievers, anxiolytics, antidepressants, or stimulants, no information on the length of time these medications were prescribed, and no information on whether the medications were self-administered as prescribed.

Although the questions about prescription drug use are consistent with theoretical definitions found in the research literature, they may be inadequate to understand prescription drug misuse among ADSM. The survey questions about drug use or misuse were developed for a civilian population and were not cognitively tested nor validated in a military population. We have no information on how the survey respondents interpreted the questions as positive answers to the prescription drug misuse questions may reflect a range of behaviors extending from 1 extra dose to alleviate pain to persistent misuse for recreational purposes. Also, some of the survey questions included in our analysis may not adequately measure the underlying constructs, such as alcohol abuse, stress, and pain. Questions about alcohol abuse, stress, and pain were limited in the survey, and we acknowledge that they do not fully measure these experiences among military survey respondents. The sample inclusion criteria for survey participation excluded those who were hospitalized or experienced deployment-related trauma or injury; thus, deployment-related variables, and perhaps stress, were likely to have weak associations in the regression models.

As with all surveys, there are inherent biases. Although the HRB survey specifically outlines a timeframe to be considered for individual questions, recall and generalization about numeric episodes of a particular behavior is necessary. Furthermore, the military population has rigorous standards regarding health maintenance and substance abuse, and responses may not reflect true prescription drug misuse because of concerns about confidentiality.

Other limitations are of a statistical nature. Several variables, such as war-related trauma, deployment status, mental health status, and pain status, were assumed to be strongly correlated with prescription drug misuse. However, we only adjusted for these variables, rather than stratify the models. Even with statistical adjustment, the large sample size contributed to the statistical significance of most variables entered into the regression models. Thus, moderate and weak predictors should be interpreted cautiously. Lastly, the manner in which we created a summed composite for 6 independent variables (stress, receipt of counseling or therapy, alcohol consumption, illicit drug use, and experience of injury during deployment) and the approximations used to assess prescription drug misuse are likely to lead to overestimates of the strength between these variables as opposed to examining each variable separately.
CONCLUSION

The findings of this study offer a first look at predictors of prescription drug misuse among all 3 Service branches of the active duty military population. Despite methodological limitations of this secondary analysis, these findings provide important data informing treatment practices of ADSM. Results from logistic regression and post hoc analysis suggest that this overwhelmingly young, male population are likely suffering mild to moderate pain and stress, and are likely misusing their own prescriptions to self-manage symptoms and reduce distress instead of being encouraged to access nonpharmacological approaches (e.g., psychological counseling, relaxation techniques, acupuncture, and spirituality). Prescription drug misuse may be an indication of unsuccessful treatment, undocumented medical problems that need to be addressed, or risk-taking behavior that negatively affects a service member's ability to perform duties. Thus, we recommend that patient outcomes be systematically measured to evaluate treatment effectiveness and that individuals with unsuccessful treatment be managed closely. Staff training on the warning signs of misuse, electronic medical records, pharmacy claims, and the results of drug screening surveillance can be used in concert to help identify and track aberrant patterns of prescription use and to evaluate the need for alternate treatment. This study, although insufficient to direct changes in military clinical practice or policy, suggests that further research is needed to examine how prescription drug misuse by ADSM impacts their physical and mental health, operational readiness, force retention, family relationships, and overall quality of life. Future research is needed to inform health care providers and health policy makers about preventive strategies to minimize the misuse of prescription drugs, such as providing alternative approaches to symptom control. Lastly, intervention research is needed to identify programs that successfully educate ADSM about risks associated with the misuse of prescribed medications and nonpharmacologic self-management strategies to control physical and mental health symptoms.

Suicide

Perspectives on Suicide in the Army National Guard

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Abstract

Suicides in the US military were observed rising in 2004, most notably in the Army and Marine Corps, and particularly, in the Army National Guard (ARNG). Alarmed, Army leaders and researchers have offered various explanations and prescriptions, often lacking any evidence. In the present study, three data sets were used to examine evidence for various perspectives on suicide—dispositional risk, social cognitive, stressor-strain, and
social cultural/institutional, each having different emphases on relevant explanatory variables and underlying mechanisms of suicide. Primary risk factors associated with having committed suicide among the 2007–2010 ARNG suicide cases were age (young), gender (male), and race (white), supporting the dispositional risk perspective on suicide. Some evidence supported the stressor-strain perspective in that postdeployment loss of a significant other and a major life change showed statistically significant, yet weaker associations with increased suicide intentions. Implications of results are discussed for future research and preventive strategies.

Since 2004, suicides in the US Army have risen, particularly in the Army National Guard (ARNG). Suicide rates for the Army climbed from about 13.7 per 100,000 in 2005 to 20.2 in 2008—higher than the most recently available suicide rate for the matched age civilian population, which was 19.2 per 100,000. Suicide rates for the ARNG increased starting in 2006 and, in 2010, exceeded that of the active component Army (31 per 100,000 vs. 25 per 100,000) and the Army Reserve (24 per 100,000) as well as the most recently available civilian age-adjusted rate of 20.3 per 100,000. These increases are especially disconcerting when considering that suicide rates for the military, historically, have been well below those of age adjusted civilian rates and that suicide rates have been lowest during wars. Army leaders and researchers have sought to understand this increase and reverse the apparent trend. The literature on suicide contains several perspectives on suicide, each with somewhat different emphases on relevant explanatory variables for the underlying mechanisms of suicide, and which therefore offer potentially multiple explanations for this recent increase in the ARNG. The present study uses available data to test the evidence for each perspective, and thus has implications for the treatment and prevention of suicide. The four perspectives are dispositional risk, stressor-strain, social cognitive, and social cultural/institutional. Each perspective is treated in more detail below.

Dispositional Risk Perspective

Individual background or demographic characteristics are often gathered in suicide research. The extent to which these characteristics describe those who commit suicide when compared with those who do not shows those who have greater risk and raises possible underlying mechanisms for suicide, for example, antecedent conditions and pathways leading to suicidal behaviors. Individual characteristics commonly focused on include regional domicile, gender, race, and age. Civilian suicide research literature has consistently shown age (young adults and seniors), gender (male), and race (white) to be associated with suicide. Indeed, the primary factors associated with suicide risk in both the active component US Army and ARNG have been shown to be age (under thirty years), gender (male), and race (white). Similar suicide factors such as age (young adults and seniors), gender (male), and race (non-Hispanic white) are found to be significant in the civilian population. This perspective is called dispositional risk, which identifies individual-level or demographic risk factors for the disease examined and targeted. The perspective implies narrowing the group who might be suicidal by focusing on the demographics of previous suicide cases and using those patterns for screening those at greatest risk and in need of possible preventive treatment. Identifying which individuals are at risk, targeting populations for preventive medicine, and examining possible underlying processes of risk factors for suicide constitute the methodology of this approach. Preventive strategies are aimed at screening individuals for risk factors and providing appropriate protective measures based on the particular intersection of demographic characteristics.

Stressor-Strain Perspective
Negative health outcomes have been explained by life circumstances experienced by the individual, such as excessive or lack of work, work–family imbalance or conflict, and interpersonal problems. These circumstances then lead to strain on individual physical and emotional health, and over time, result in exhaustion and depletion and often lead to negative outcomes, including depression and suicide.

In a similar vein, it was thought initially that military personnel who had experienced combat or had deployed multiple times experienced high levels of strain and distress. Indeed, research had shown deployment experiences, such as the number and length of deployments, as well as engagement in combat, were associated with increased posttraumatic stress disorder (PTSD) and related symptoms.

The services that endured much of the ground combat operations in Iraq and in Afghanistan (the Army and Marine Corps) were in fact first to show possibly linked rises in suicide rates. Rates for the Marine Corps and the Army first showed increases starting in 2001. Suicide rates for the Army climbed from about 13 per 100,000 in 2005 to about 20 in 2008—higher than the age-matched civilian population rate of about 19 per 100,000. Such linkages between stressful or traumatic events and dysfunctional outcomes lead to the perspective being labeled “stressor-strain.” The perspective implies examining the personal history surrounding suicide; in particular, events preceding the suicide likely to cause distress and necessitate individual coping and adjustments, such as having been deployed, number and length of deployments, and combat exposure, with possible loss of significant relationship and financial difficulties as associated or independent events.

Observed relationships between these experiences and suicide would imply mitigation strategies that would lessen stressful conditions (e.g., frequency and intensity), in addition to augmenting individual resources that would facilitate adopting more adaptive coping alternatives.

Social Cognitive Perspective

A third perspective emphasizes the importance of the individual’s appraisal of social relationships, which ideally can provide the individual with a sense of belonging, meaning and purpose, and sense of self. Perceiving a lack of these connections, the individual can experience estrangement and become socially marginalized, often increasing the risk for suicide. Given the emphasis on individual perceptions in relation to social groups, this perspective is labeled “social cognitive.” Joiner’s interpersonal theory of suicide exemplifies this perspective. Suicide is explained by psychological conditions, largely related to social context. Two conditions, “thwarted belongingness” and “perceived burdensomeness” to others, frame the potential desire for suicide. Thwarted belongingness occurs when individuals feel disconnected from others and perceive that nobody truly cares about them or can understand their individual situations. Perceived burdensomeness describes when individuals no longer feel as if they are making worthwhile contributions to others and, in particular, to groups with which they had previously identified. Rather, individuals believe they have become a liability to others. A third condition is “acquired capability,” where through painful events (e.g., repeated attempt or witnessing pain, violence, and suffering) the individual has overcome the fear of death and become accustomed to the eventual physical pain of suicide. The relationships of these conditions to suicidal behaviors have been supported by several recent studies. This perspective understands suicide in terms of the individual’s appraisal of his or her role in social groups and its importance to self-identity (reference groups).
The assessment of such perceptions can identify who is at risk for suicide, and the individual can subsequently be targeted for cognitive behavioral therapy which would aim to alter these negative perceptions of the self in relation to reference groups. In the Army, such reference groups would include the soldier’s squad or team, as well as the soldier’s family. Family and chaplain support would obviously be critical with regard to possibly helping or improving perceptions regarding the latter. Military team-training would be expected to promote positive interpersonal relations within such small groups, leading to the individual’s sense of contribution and worth to the larger group.

Social–Cultural/Institutional Perspective

Durkheim’s historical analysis of suicide cases, written in late nineteenth-century France, described broad social influences related to this behavior in Europe. Noting differences in suicide rates between Protestants and Catholics, Durkheim proposed two forces connecting the individual and social group—regulation and integration. Norms and customs that prescribed acceptable behaviors, in particular with others, described regulation. Internalization of group practices determined the extent to which the individual became attached and committed to the group and described integration. Extremes of the two influences yielded suicides having different motivations—low levels of regulation and integration resulted in “egoistic” (marginalized from group) and “anomic” (devoid of meaningfulness) suicides, while high levels of each produced “altruistic” (sacrifice for the group) and “fatalistic” (hopelessness) suicides.

In Durkheim’s typology, the military, much like the strong, community-based religious institution, theoretically provides some degree of social–cultural protection from egoism and anomic-generated suicide. At the same time, the risk of altruistic suicide is potentially higher, although the US military arguably lacks the kind of extreme normative forces that would legitimate such behavior (cf. kamikaze pilots and suicide terrorist bombers). Regarding a reserve military force such as the ARNG, given the less life-encompassing nature of its service members’ commitment, one would expect a relatively less prophylactic effect against egoistic and anomic suicide compared with full-time active duty service members.

Some studies of suicide have made associations between broad societal shifts and changes in suicide rates. Stockard and O’Brien and O’Brien and Stockard examined the distribution of suicide rates by age groups for birth cohorts 1930, 1965, and 2000. Over time, they observed that the age distributions of the suicide rates shifted such that in 2000 there were relatively more suicides committed by younger age groups (late teens to mid-twenties) than in 1930 or 1965. They speculated that decreased social integration and regulation among more recent cohorts as a result of increased cohort size and proportionally more disrupted families were associated with these shifts in suicides and homicides. Most recently, Mastroianni and Scott described the importance of broader social factors in understanding suicides in the military. These factors include differences between those who now primarily serve in the all-volunteer force and American society as a whole; tenuous legitimization of the current wars by policy makers and the media; and society’s collective understanding or lack thereof regarding the US’s involvement in Iraq and Afghanistan. They argued that these factors heavily influence whether soldiers interpret their military service and, in particular, combat tours, as worthwhile and meaningful, and how readily soldiers can assimilate and integrate their military experiences.

Social–cultural influences on individual and group behavior can also be found within the organization of the military itself. Indeed, a hallmark of military life is its institutional character, which heavily influences individual and group values, norms, and behaviors. Life in the military occurs
almost entirely in one setting under supervisory authority. Daily activities occur in the presence of others who are treated alike and required to do specific activities, defined and imposed by established procedures and authority to achieve the goals of the large institution. In such settings, it would be expected that the institutional character reflected in norms, values, and expected behaviors would greatly influence individual behavior. Again, such military life among reserve forces like the ARNG is somewhat less circumscribed and certainly more erratic than among the regular active duty force, and thus less “total” in its institutional character.

This perspective, then, focuses on broad social and institutional characteristics impacting relationships the individual has with primary groups, organizations, and society, and implies that changes in social-cultural and institutional practices, norms, and values can influence processes associated with lower suicide risk. Preventive strategies recognize and minimize, to the extent possible, the negative effects of social-cultural and institutional changes associated with suicide risk. Such strategies are necessarily ambitious due to the broad and political level of their application.

Study Purpose and Analytic Approach

The purpose of the present study was to examine evidence for each perspective in explaining suicides in the ARNG using available archival data.

Description of Suicide Cases

The US Army began collating and publishing data on suicide cases at the beginning of 2007. The focus of the present study is the ARNG, which also began data collection at this time. Thus, analyses were limited to ARNG suicide cases that occurred during calendar years 2007, 2008, 2009, and 2010. Most of the ARNG suicide cases (2007 through 2010, N = 294) occurred among soldiers who serve part-time as opposed to full-time (86.4 percent of the total 2007 through 2010 suicides). This comes as no surprise, as ARNG soldiers predominately serve part-time except when activated for deployment missions. Additionally, most of the suicides occurred outside the military context—not during weekend drill, not during annual training, and not while performing other active duty military service, but rather in civilian status (90.5 percent). The most frequent methods for suicide were gunshot (65.3 percent) and hanging (16.3 percent). Table 1 displays the percentages of suicide cases (2007 through 2010) falling within various demographic groups. Suicides were predominately male (94.6 percent) and white (89.8 percent). Over one-half were single (56.5 percent), non-prior service (59.9 percent), young in age (42.5 percent seventeen to twenty-four years old and 20.1 percent twenty-five to twenty-nine years old), and never had been deployed (56.5 percent). (Also shown are percentages of soldiers in each demographic group for the 2007–2010 ARNG population.)

These statistics, while informative, do not consider all of those “eligible” who had committed suicide. For this, prevalence rates for groups are reported (see last column of Table 1). The overall ARNG suicide rate across 2007–2010 was 20.5 per 100,000 and was slightly larger than the best available civilian age-adjusted rate (about 19 per 100,000 in 2009). Soldiers having a higher rate than the ARNG overall rate were younger, white, male, single, lower enlisted ranks; having alternative high school degrees; and living in western states.

Data Sources for Perspectives on Suicide
Three existing data sets were used to examine support for the various perspectives on suicide. Each had strengths as well as limitations largely due to having been collected before the plan of the present study. The first data set (CY2007 through CY2010) was derived from the ARNG’s personnel data system (ALURRT). This data set was primarily used to examine support for the dispositional risk perspective.

This personnel system offered data on both suicides and non-suicides and was suited for use in logistic regression analyses to examine the relative predictive power of specified variables. Data on having been deployed and combat-related military occupation a specialty also allowed examining evidence for the stressor-strain perspective. The major limitation of the data involves few variables which could be used in analyses, largely due to data reliability issues.

Downloaded from afs.sagepub.com by guest on February 25, 2013 primarily used to examine support for the stressor-strain perspective. Soldiers responded to standardized questionnaires (called the Unit Risk Inventory-Reintegration or URI-R) about their deployment and postdeployment experiences, including questions about suicide intentions.

Note: Alternative high school educations are those soldiers having nontraditional high school credential, including high school degree in 365 days, home study diploma, high school certificate of attendance, test-based equivalency diploma, overseas graduate equivalency degree, occupational program certificate, and correspondence school diploma.

Less than average aptitude are those soldiers having an Armed Forces Qualification Test (AFQT) score less than 50 and are below the 50th percentile. Non-prior service soldiers are those having no previous military service prior to joining the ARNG. Part-time military service are those soldiers who are “mobilization” (M-day) or part-time soldiers who drill one weekend a month and complete fifteen days annual training (vs. serving full-time).

Combat military specialty are those soldiers having occupations directly related to combat, for example, infantry, armor, artillery, and so on. Combat military occupational specialties (MOS) for males included the series 11, 13, 19, 21, 25, 31, 68, 79, 88, 89, and 91; and for females included the series 15, 21, 25, 31, 68, and 92.

Never deployed are soldiers who have never been mobilized and served full-time deployment tour. Not in training are soldiers not currently waiting for training or not enrolled in training, such as officer basic course, individual active duty training status, awaiting or in basic officer leader course, and in split-phase training.

Western states are those soldiers serving in units in states west of the Mississippi River. Strengths of the data were that soldiers responded to questions both during deployment and after deployment. The data set was very large, containing survey data from nearly 5,000 soldiers in fifty units. Due to the intended anonymity of the survey, little soldier background information was available, resulting in several limitations, such as inability to match results to personnel and other data, to include soldiers’ age, gender, and race.
The third data set was obtained from tabulations of Army reserve component soldiers’ responses to the 2009 Status of Forces questionnaires. These data were primarily used to examine support for the social–cultural/institutional perspective.

Responses of junior-ranking enlisted soldiers from the ARNG were compared to those from the US Army Reserve (USAR). The USAR has had consistently lower suicide rates than the ARNG. Thus, the analytic question was whether soldiers perceived reserve military service in the ARNG more negatively than soldiers in the USAR and, in particular, regarding experiences representing broad-based social–cultural and institutional characteristics, such as leadership and cohesion. A sample of junior-ranking enlisted was chosen for comparison, since the majority of suicides occur among young, non-prior service soldiers. Data for this group were reported in publicly available tabulation volumes. There were limited data available to directly assess evidence for the social–cognitive perspective on suicide.

Dispositional Risk Perspective

Prevalence rates show the risk related to demographic variables for suicide. Lacking, however, is the risk of one demographic relative to others.

To address this shortcoming, logistic regression analysis was conducted. Logistic regression analysis is best suited for multivariate analyses when the outcome or criterion variable is dichotomous, such as having committed suicide or not. Output of logistic regression in the current analysis showed the likelihood of a soldier with specified demographics to commit suicide relative to other demographic groups (odds ratio). Regression coefficients showed the direction and magnitude of the variable’s relationship with having committed suicide or not. Soldier demographic background and military-related experiences variables were used to predict having committed suicide or not. All ARNG suicide cases from calendar years 2007 through 2010 were included in the analysis along with a corresponding random sample of 1,000 living soldiers drawn from each year’s ARNG population (total N = 4,293). Variables included age, gender, race, level and type of high school graduation, mental category (based on the Armed Forces Qualification Test), marital status, rank, prior service, military status (M-day or part-time vs. full-time military service), military occupational specialty (coded into combat arms vs. others), in-training, and ever deployed. Hierarchical entry was used to examine the contribution of each variable set to explained variance. (Only the last column in the table is affected by the order of variable set entry and not the regression coefficient, standard error, or likelihood ratio.)

The order of entry was based on the temporal occurrence of variables, that is, basic demographics (e.g., age, gender, and race) were entered first followed by variable values of successively later temporal occurrence. Suicide cases and the random samples of non-suicide cases across the calendar years were considered together in one equation to achieve more power in analyses. Year was entered as the final predictor variable (with 2010 as the reference category) in order to detect any year effects by having combined suicide cases across the four years of data. Due to the inter-relatedness of variables contributing to multicollinearity, not all available variables were entered as predictor variables. Table 2 displays results of the logistic regression analysis.
The overall equation was statistically significant, Wald $w^2(14) = 82.17$, $p < .001$. Variables associated with having committed suicide included the following: younger ages of seventeen to twenty-four years (1.74 times more likely than the over twenty-nine years age group), younger ages of twenty-five to twenty-nine years (1.43 times more likely than the over twenty-nine years age group), being male (3.05 times more likely than females), and being white (1.85 times more likely than other race groups). A strong year effect was evident for odd ratios associated with the year of the data collection. The likelihoods (odds ratio) of soldiers committing suicide in 2007, 2008, and 2009 were each about 0.50 less than that in 2010 (the reference category). Of particular note is that the demographic variables—age, male, white, and single—accounted for over half (59.1 percent) of the explained variance (see Table 2, far right-hand column). The explained variance for year, or cases in 2010 compared to the cases in the other years, was 24.5 percent. Military-related variables (prior service, M-day, in-training, combat military occupational specialty, and having been deployed) added 14.3 percent to the explained variance.

This evidence strongly supported the dispositional risk perspective compared to the stressor-strain and other perspectives. Those who committed suicide were largely part-time reservists while in civilian status. Soldier demographic characteristics most associated with having committed suicide were being male, white, and aged seventeen to twenty-four years. Military-related variables, including having been deployed and having a combat military occupational specialty, did not show significant independent association with having committed suicide.

**Stressor-Strain Perspective**

Responses of returning ARNG soldiers to the URI-R survey were used to examine the stressor-strain perspective. The inventory consisted of about ninety survey items, and its primary purpose was to screen for high-risk behaviors and dysfunctional attitudes of soldiers, which may have occurred during deployment or postdeployment.

As a part of reintegration activities, soldiers were asked to complete the URI-R at any time from sixty to ninety days after returning from deployment. Survey data were available from those soldiers who had returned from deployments in calendar year 2010, numbering fifty company-sized units, with 4,642 responding soldiers.

The survey data provided reasonably good estimates from the surveyed units, as most of the unit members had taken the survey. The mean response rate of units was 90.2 percent, with a range of 55 percent–100 percent. Most of the soldiers had returned from Operation Iraqi Freedom (OIF; 84.2 percent) and some (15.8 percent) from Operation Enduring Freedom (OEF). Additionally, the type of units comprising the sample (i.e., combat arms, combat support, and combat service support) was proportional to the unit types actually deployed.

Note: The sample used in this analysis was the combined cases of 2007–2010 suicide cases (N = 294) plus random samples of 1,000 soldiers each calendar year for comparison (see Note 32 for explanation). Listwise deletion N = 4,288.

Variable values were “dummy coded,” where “1” is condition present and “0” as condition absent. To avoid multicollinearity problems, not all variables were entered in the regression analysis due to being correlated with predictor variables. Omitted variables were AFQT and rank.
Odds ratio is the likelihood that soldiers having the variable value (e.g., male) is more likely to commit suicide than the reference group (e.g., female), that is, males are 3.05 times more likely than females to commit suicide, and so on. Eighty-eight percent of the soldiers reported having returned from deployment within three to six months, equally divided between having returned after one to three and four to six months. Two-thirds (64.9 percent) of the soldiers had no previous deployments, only the current. About one-third (34 percent) of the soldiers in the sample reported having been previously deployed, two or more times. ARNG units are predominately combat arms and combat support, which was reflected in the percentages of soldiers in these units, respectively 38 percent and 29 percent.

The URI-R data provided suicide intentions during and after deployment. Suicide intentions were assessed by asking soldiers questions typically used to assess suicide ideations and tendencies, such as questions about having thoughts of suicide, having made a plan, and having attempted suicide. Soldiers were asked to respond to the items twice—one set applied to when deployed and another set applied to after having returned—or in other words, deployment suicide intentions and postdeployment suicide intentions. See the top portion of Table 3. Soldiers who reported suicide intentions during deployment generally reported the same intentions after deployment, and the association of combat experiences with suicide symptoms was negligible (bottom portion of Table 3).

Of the soldiers, 2.8 percent had reported suicide intentions both during Table 3. Percentage of 2010 Deployed ARNG Soldiers Who Reported Suicide Intentions during Deployment and after Deployment and By Combat Exposure (from URI-R Survey Data)

A small percentage of soldiers reported suicide intentions only after deployment (1.4 percent) and likewise during deployment but not after deployment (1.7 percent). Combat experiences showed very weak associations with suicide intentions. Net change in intentions was examined during deployment and postdeployment among those who experienced combat versus those who did not. The vast majority of soldiers reported no suicide intentions during deployment as well as afterward, that is, 95.3 percent of those having no combat experiences and 93.3 percent of those having combat experiences. Combat experiences were associated with a 0.6 percent increase for those who had no suicide intentions during deployment but had intentions after deployment ($z = 1.74$, $p < .10$), and with a 1.3 percent increase for those who reported intentions both during deployment and after, which was statistically significant ($z = 2.77$, $p < .01$).

The URI-R data allowed further examination of evidence for the stressor-strain perspective on suicide. Stressors, such as war exposure and postdeployment challenges or adjustments, were used to predict postdeployment suicide intentions.

Combat experiences were assessed by asking soldiers about having witnessed a trauma, having been engaged in combat, seeing another individual wounded or killed, having lost a friend in combat, and having killed anyone. These items, though abbreviated, are very similar in content to those in recently developed combat experience scales. Postdeployment negative events were assessed by soldier responses to having experienced end of a significant personal relationship, having financial difficulties, and having experienced significant life change after having returned from deployment (Table 4). Deployment suicide intentions were entered first in the multiple regressions, thereby yielding a change score as the criterion variable. Predictor variable sets—war exposure and postdeployment stressors—were then entered hierarchically based on their temporal occurrence.
The overall equation was statistically significant, $F(11, 4040) = 258.17, p < .001$, explaining 41.1 percent of the variance in postdeployment suicide intentions. The total variance explained was largely accounted for by suicide intentions during deployment (39.6 percent). Suicide intention during deployment was also the strongest predictor of the set of predictors (standardized regression coefficient $= .60$). Both war experiences and postdeployment stressors accounted for little of the explained variance. Considering the individual predictor variables, having had a significant life change and having lost a significant personal relationship after returning from deployment were both significantly associated with changed suicide intentions from deployment to postdeployment. Standardized regression coefficients were .07 and .08, $p < .001$, respectively. War experiences showed little association with suicide intentions.

Evidence generally did not support the stressor-strain perspective on suicide. Few soldiers expressed suicide intentions either during deployment (4.5 percent) or after deployment (4.2 percent). Few soldiers changed intentions toward suicide from deployment to postdeployment (1.4 percent) and more soldiers showed persistent suicide intentions (2.8 percent). Having experienced direct combat showed low associations with changed suicide intentions. Evidence for the stressor-strain perspective applied mainly to postdeployment stressors rather than combat exposure. Having experienced combat and number of deployments showed marginal associations with changed suicide intentions. By comparison, postdeployment stressors of a loss of significant relationship and a major life change showed statistically reliable associations with changed suicide intentions. Also of note is the strong association of suicide intentions during deployment with those after deployment—evidence that suicide intention show consistency among individuals over time. Suicide included soldiers who had committed suicide, coded as 1s, and those who had not and were part of the living, non-suicide sample, coded as 0s. Griffith and Vaitkus’ intentions are not the same as completed suicide, that is, the latter includes the additional dynamic of action, despite its correlation with intention.

Social Cultural/Institutional Perspective

The ARNG has had consistently higher suicide prevalence rates than the USAR, and thus, a lingering question was—Were soldiers in the ARNG experiencing military service more adversely than USAR soldiers? To respond to the question and to initially test the broader perspective of a social cultural/institutional cause for suicide, comparisons were made between responses of ARNG and USAR soldiers to the 2009 Status of Forces Survey. The Status of Forces Survey is a web-based questionnaire, which asked reserve military members about their attitudes and opinions on a wide range of personnel issues. Response percentages of junior-ranking soldiers to questions were calculated for items that tapped different aspects of organizational climate and likely are indicative of social cultural/institutional milieu, including leadership, cohesion, readiness, job satisfaction, and retention intentions. Junior-ranking enlisted responses were chosen because this is the group that has had the highest prevalence of suicide. Table 5 displays responses of ARNG and USAR soldiers. Soldiers responded similarly, and in some cases, ARNG soldiers gave more positive responses concerning their unit and service.

Given these results, the difference in USAR and ARNG suicides is likely explained by proportionally more soldiers who are at risk in the ARNG than in the USAR (young, male) due to the force structure differences. That is, the ARNG has more combat arms and less combat support units than the USAR, with the former units staffed by young men. As shown in Table 6, the ARNG has proportionally more soldiers having dispositional
at-risk factors than does the USAR, that is, younger in age (eighteen to twenty-four years old), more males, and more junior ranking enlisted. In addition, the ARNG, compared to the USAR, has more junior ranking enlisted who have less military experience and are yet to be integrated into military service, that is, fewer prior service and more awaiting training.

In summary, ARNG and USAR soldiers did not differ in their experiences of leadership, cohesion, readiness, job satisfaction, and retention. Insofar as these content areas reflect broad social–cultural and institutional aspects of integration, ARNG and USAR soldiers did not report differences.

Discussion

In the present study, three data sets were used to examine evidence for various perspectives on suicide, each having different emphases on relevant explanatory variables and underlying mechanisms of suicide. Notwithstanding the limited scope and detail of the data available, several summary statements are possible.

Evidence supported the dispositional risk perspective of suicide. Primary risk factors for having committed suicide were age (younger than twenty-five years), gender (male), and race (white). Military-related variables, including having been deployed and combat exposure, showed little relationship to suicide. These findings are consistent with analyses of the active component Army suicides. US Army Public Health Command has consistently reported suicide cases as occurring disproportionately among males, Caucasians, younger in age (eighteen to twenty-four years), and often having an untreated behavioral condition and/or substance abuse. Initial findings of the Army’s comprehensive study of suicide, STARRS: Assess Risk and Resilience in Servicemembers,” also showed the highest suicide risk profile to include: gender (male), age (young), and race (white). Suicide rates increased over time for soldiers in all settings (i.e., those never deployed, currently deployed and previously deployed).

Similar suicide risk factors such as age (young adults), gender (male), and race (non-Hispanic white) have been identified in the civilian population. There was some evidence that postdeployment stressors were associated with suicide intentions, namely, a loss of significant other and a major life change. This finding is consistent with US Army Public Health Command research studies which described relationship problems as an additional risk factor for active component Army suicides. Other research studies have also shown the negative effects of postdeployment events on mental well-being (e.g., PTSD and substance abuse). In the present study, a loss of significant other was related to increased suicide intentions after deployment. The connection between such a loss and Joiner’s interpersonal theory of suicide is clear, in particular among men who rely on relatively less social support. Thus, with a loss of a significant other, the soldier could feel a lack of belonging and more like a burden to others, and over time through habituating to pain, more likely to commit suicide. In regard to broader contextual experiences and suicide, there were few differences in the way ARNG soldiers experienced reserve military service when compared to USAR soldiers. Suicide rates have been consistently higher among ARNG soldiers than USAR soldiers, but findings here suggest no organizational differences associated with suicide in this case.

How then can the three consistent factors associated with suicide be reconciled within an interpretative framework? Griffith has offered a tentative interpretation, though speculative, that ties together these three primary factors in relation to stress adaptation. Demographic risk factors likely

Perspective Supporting evidence Findings Future research questions Dispositional risk

Strong evidence Factors most associated with suicide are age (17–24 years), gender (male), and race (white). Concurrent Army research also adds past or current behavioral health condition, largely untreated, and substance abuse. What are mechanisms associated with suicide that underlie these basic demographic characteristics? Are behavioral health conditions the consequences, antecedents, and/or co-occurring conditions of suicide?

Stressor-strain Limited evidence Having been deployed and various combat exposure events showed little relationship to suicide. Few changes in suicide intentions from deployment to postdeployment. Postdeployment stressors, such as a loss of significant other, are associated with suicide. Do stressors interact with dispositional risk factors (the above as well as negative affectivity, childhood trauma) leading to greater personal distress? Social cognitive Not examined due to lack of data

Growing evidence in the suicide literature Do social cognitive factors play a larger role among dispositional risk groups when under stressful conditions?

Some evidence of more recent generational cohorts at greater risk for suicide due to broad societal changes What are social changes in generations associated with cohort prevalence rates of suicide? To what extent are these changes associated with suicides in the military? Why does the Army not appear to offer the same socially integrative protection against suicide as it once did?

Race and gender define the context of coping. Race can determine the nature and amount of informal support available to the individual. Gender is associated with differences in the benefit of support, in addition to being variably socialized to be competitive and aggressive, and having familiarity and comfort with weapons of violence. Age-specific tasks are further elaborated below, in particular, in the context of gender and race.

Suicides in the Army occur largely from seventeen years of age through the midtwenties. This age span prescribes specific tasks for the individual, which define who individuals are and how their identities relate to others. For individuals at this age, major tasks in their psychosocial development are (1) developing a coherent, positive identity as opposed to being confused about self-identity; and (2) having intimate relationships as opposed to being isolated. Major suicide theorists Joiner, Van Orden, Witte, and Rudd and Durkheim have included in their theories of suicide the lack of self-identity in the context of others. Self-identity provides the individual with a sense of worth and meaning, characteristics often absent in suicide cases.
Race is likely associated with the nature and amount of informal support available to the individual, especially during stressful circumstances, to help augment the individual's coping. Documented in the general literature is the extended support network experienced by African Americans.

Thus, under stressful circumstances, whites would be expected to have more negative consequences than African Americans, due to the buffering effects of indigenous social supports. Some have also described African Americans' higher level of participation in religion, compared to whites' generally lower level, as an additional inhibition against self-harm. Others have also described the greater resiliency among African Americans in adapting to adverse life circumstances, to include discrimination, unemployment, poverty, and urban challenges.

Maris, Berman, and Silverman offered several reasons for the gender association with suicide, including that males are more likely to engage in suicide-risk behaviors, such as alcohol abuse and accessing firearms, along with deeper shame from failure. Males are also less likely to engage in protective behaviors, such as seeking help for problems, being aware of signs of personal distress, having flexible coping skills, and having developed social supports. Many of these associations are a result of different socialization patterns between males and females, in particular, regarding interpersonal behaviors. Males' aggressiveness and competitiveness, along with greater exposure, familiarity, and comfort with weapons often lead to their greater availability and less inhibition to use them for self-harm. There is also evidence that women benefit more than men from social integration, and with its absence men are more vulnerable to the negative effects of stressful circumstances.

Directions for Future Research

The primary risk factors, being basic demographic characteristics, suggest strong underlying socialization and/or physiological bases for suicide risk. These processes remain to be examined in future research studies. Future research studies need to elaborate on the underlying mechanisms of the primary risk factors for suicide—namely, young age, male, and white. Given the three primary factors, it might be that certain soldiers experience postdeployment stressors more adversely than others. Recent research on suicide has shown the greater vulnerability of males to loss of social support than females.

Other studies have shown childhood experience and negative affectivity worsen the negative effects of trauma, and childhood trauma appears to more adversely affect men than women in these relationships. Lacking basic soldier demographic information in the survey data examined here (due to anonymity requirements), the combination of the primary risk factors and postdeployment stressors could not be examined. This, then, remains an area for future research, especially in view of these findings concerning important personal dispositional factors. Examining these relationships is likely important in understanding processes that underlie the primary risk factors identified in this study. Related questions are: To what extent are reported behavioral health problems of suicidal soldiers, such as substance abuse and depression, the consequences, antecedents, and/or co-occurring conditions of suicide intention? Do social cognitive factors play a larger role among dispositional risk groups when under stressful conditions? Regardless of dispositional risk factors, how do we explain the increases in suicide rates over time, given the presumed social integrative advantage previously displayed by the Army? Has the dynamic of suicide intention versus completion in the Army changed and, if so, why?
Directions for Preventive Policy

Findings here and elsewhere imply that there is a personal, though not fully understood, disposition to being at risk for suicide. What this means is that not everyone is at the same degree of risk. Having been deployed and combat exposure can be traumatic for some soldiers, often leading to behavioral health conditions, such as PTSD and depression. Yet, most soldiers will be exposed to such events without negative behavioral health consequences, in particular, suicide intentions—as results here have shown. Soldier demographic attributes were associated most highly with suicide risk and may be associated with dispositional risk to suicide, along with childhood trauma and negative affectivity. These findings may explain why suicide intentions in the present study showed consistency during and after deployment.

Erbes et al. also reported regularity in personal difficulties and distress among National Guard soldiers before, during, and after deployment. Findings then imply only some soldiers having some underlying disposition to suicide will likely be suicidal.

Preventive strategies might include systematic screening for suicide intentions and a standard set of questions, for example, recent thoughts of killing oneself, plans made, and attempts, given as a part of records review and the annual periodic health examination. Screening might also include the experiences of interpersonal difficulties and loss, and substance abuse, as these have been found to be co-occurring conditions of suicide. Some military researchers have even proposed questions about early childhood, for example, “By today’s standards, do you think the punishment you received from your parents would be considered abusive?”). After identifying those at risk, soldiers need to be managed and provided appropriate support and care.

Analyses of active component Army suicides have shown that the majority of suicide cases had behavioral health problems, which were largely untreated or underwent occasional treatment. Similar analyses cannot be done for reservists due to the lack of medical data. Medical care delivery data outside of military service are not maintained on reservists. Reservists not in full-time military status have to rely on private health care, which is often lacking among junior-ranking soldiers. Thus, there are fewer options available for treatment. This is an area needing further attention by policy makers.

TBI

Self-Reported Mild TBI and Postconcussive Symptoms in a Peacetime Active Duty Military Population: Effect of Multiple TBI History Versus Single Mild TBI

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Abstract

Objective

To investigate the potential cumulative impact of mild traumatic brain injury (MTBI) on postconcussive symptoms.

Participants

A total of 224 active duty soldiers reporting MTBI within 1 year of testing. For 101, this MTBI was their only reported traumatic brain injury (TBI); 123 had sustained at least 1 additional MTBI during their lifetime. A No TBI control group (n = 224) was included for comparison.

Main Measure

Self-report symptoms data via questionnaire. Within time since injury subgroups (≤3 months; Post–3 months), symptom endorsement (no symptoms, 1 or 2 symptoms, 3+ symptoms) among soldiers with 1 MTBI was compared with that of soldiers with 2 or more MTBIs. Injured soldiers’ symptom endorsement was compared with that of soldiers who had not sustained a TBI.

Results

Among the recently injured (≤3 months), those with 2 or more MTBIs endorsed significantly more symptoms than those with 1 MTBI: 67% of soldiers with 2 or more MTBIs reported 3+ symptoms, versus 29% of One MTBI soldiers. Among Post–3 month soldiers, there were no significant differences between MTBI groups. Overall, soldiers with MTBI endorsed significantly more symptoms than those without TBI.

Conclusion

Past experience of MTBI may be a risk factor for increased symptom difficulty for several months postinjury. Clinicians should ascertain lifetime history of brain injury when evaluating patients for MTBI.

Introduction

THE well-being of US Armed Forces’ members is of critical importance, with ramifications for military readiness as well as overall public health. Among the risks faced by military personnel, during peacetime as well as wartime, is traumatic brain injury (TBI). An investigation of soldiers recently returned from combat in Iraq by Terrio et al found that 22.8% had sustained a TBI, and that most of these were mild. An investigation by Hoge et al found that nearly 15% of returned combat soldiers had sustained a mild TBI (MTBI), similar to the 12% rate of MTBI among Iraq and
Afghanistan combat veterans found by Schneiderman et al. Mild TBI can be followed by physical, cognitive, and behavioral symptoms in the weeks immediately after the injury. Most patients recover completely from postconcussive symptom complaints within 3 months of MTBI. However, there is evidence suggesting that, in a minority of individuals, symptoms may persist for 6 months or even longer. No one is certain why symptoms persist after MTBI in some individuals, or to what degree the postinjury symptoms may be attributable to the MTBI as opposed to other medical conditions or problems (eg, migraines, psychiatric disorders, posttraumatic stress disorder [PTSD]) that may result in similar complaints. A possible factor that has not been extensively explored is the potential cumulative effect of multiple MTBIs. Much of the research on the effects of repetitive TBI comes from sports medicine literature. Findings among these investigations have varied. A prospective study found that among college football players who sustained 2 MTBIs within the same season, symptom endorsement after the second injury did not differ significantly from symptom endorsement after the first injury. Along similar lines, a 6-year prospective examination of football players found that those with multiple MTBIs during the study period did not endorse significantly more symptoms than players with 1 MTBI. A study by Wall et al also found that there was no significant difference in the number of postconcussive symptoms endorsed by jockeys with multiple concussions, and jockeys with a single concussion. Iverson et al also found no evidence of cumulative effect of a history of concussion; there were no symptom differences detected among athletes reporting no concussions, athletes reporting a single concussion, and those reporting multiple concussions. Other sports studies have found evidence of increased symptom complaints among athletes with multiple MTBIs. A study of college football players by Collins et al found that players who sustained multiple concussions during the playing season reported more symptoms than those who had a single concussion during the same time period. Another NCAA football study found that longer symptom duration was associated with multiple concussions, as did an investigation of collegiate athletes. There may be unique features of sports-related injuries including specific mechanisms of injury, as well as the overall capacity of athlete populations to recover from injury, that limit the extent to which findings from sports studies can be applied to mild TBI generally. Although sports concussion and MTBI are often defined similarly, a consensus panel on sport concussion stated that the terms sports concussion and mild TBI “refer to different injury constructs and should not be used interchangeably.” It was also acknowledged by the panel that that the majority of sports concussions (80%-90%) resolve within 7 to 10 days, and are characterized by absence of abnormalities on standard structural neuroimaging studies. The potential cumulative effect of MTBI has not been examined in soldiers, a group for whom both the short- and long-term impact of MTBI has become a particular concern. The purpose of this article was to explore the effect of multiple MTBI on subjective symptom complaints in a peacetime sample of active duty US Army soldiers. On the basis of prior investigations that have implicated multiple concussions in the persistence of symptom complaints, we hypothesized that soldiers who sustained an MTBI within a year of testing and who had a prior lifetime history of MTBI would have greater endorsement of postconcussive symptoms than those soldiers with only 1 MTBI sustained within 1 year of testing. These soldiers with MTBI were also compared with a matched group of soldiers who reported no TBI, who provided a “background level” of symptom experience among soldiers without brain injury.

Methods and Materials

A computerized self-report questionnaire was administered to a convenience sample of 2337 active-duty US Army soldiers at Fort Bragg, North Carolina, who were surveyed between December 1999 and December 2000 (prior to the beginning of US combat operations in Afghanistan and Iraq) as part of a larger institutional review board–approved study examining the consequences of brain injury among paratroopers. Soldiers were recruited for testing through their respective units, and participants provided written consent. The questionnaire asked the soldiers to report...
whether they had ever experienced a head injury; the number of injuries they experienced; and to provide details on up to 6 separate previous head injury occurrences including the month and year of each injury, severity, and whether they were hospitalized. The soldiers were instructed to include injuries that were not medically attended and those that were. These injuries could include, but were not limited to, those that resulted in loss of consciousness (LOC). For injuries that did not result in LOC, the soldiers were asked to report whether they experienced any alteration of consciousness (AOC), such as being dazed or confused, at the time of injury. Traumatic brain injury was defined as a head injury for which any LOC or any alteration of mental state without LOC was reported. MTBI was defined as a head injury accompanied by any LOC of 20 minutes or less or any AOC. These characteristics are largely consistent with the criteria for MTBI established by the Centers for Disease Control and Prevention (CDC) and the American Congress of Rehabilitation Medicine, except that the CDC and American Congress of Rehabilitation Medicine criteria specify 30 or fewer minutes of LOC, and also include memory dysfunction or posttraumatic amnesia criteria. Posttraumatic amnesia was ultimately not used as criteria for MTBI in this investigation; however, because of the fact that posttraumatic amnesia was difficult to establish with self-report instruments. Thus, reports of AOC and LOC were used to establish the presence of MTBI. Soldiers completed the Post MTBI Symptom checklist, developed by Cicerone and Kalmar, in which they were asked to rate their experience with each of 22 symptoms within the 2-week period before testing on a 5-point scale. From the 22 symptoms on the inventory, we selected for examination in this study the following core set of symptoms, which have been used in other studies of post-TBI symptoms: headache; dizziness; fatigue/loss of energy; irritability; sleep difficulty; poor concentration/attention problems/distractions; decision making difficulty; slowed thinking/difficulty with organization or finishing tasks; forgetfulness; and poor frustration tolerance/easily overwhelmed. This list is also similar to the symptoms used in the International Classification of Diseases, Tenth Revision, criteria for postconcussive syndrome. Soldiers were asked to classify each symptom according to its impact in the 2 weeks before testing on a 5-point severity scale, with the following categories: none, mild, moderate, severe, and very severe (see Table, Supplemental Digital Content 1, Postconcussive symptoms and rating scale, available at http://links.lww.com/JHTR/A63). The threshold for “symptomatic” in this investigation was an endorsement of at least moderate for a particular symptom, as it represented the point at which the symptom caused a disruption of normal daily activities. A threshold was established because we were interested in ascertaining the degree to which symptoms represented a significant problem in the soldiers’ daily lives, and because it is not uncommon for symptoms to be endorsed to some degree by healthy people and individuals without TBI. We examined 3 categories of symptom endorsement in our analyses: (1) no symptoms, (2) 1 or 2 symptoms, and (3) 3 or more symptoms. These 3 categories were not inherent in the format of the questionnaire, but we established them as variables of interest because we deemed that they represented practical distinctions in terms of the impact on the soldiers. There were few soldiers who endorsed more than 3 symptoms in this small sample, and thus it seemed reasonable to combine into 1 group those who endorsed 3 or more. Numbers of soldiers who endorsed 1 and 2 symptoms were small, and we deemed that combining them into a single category was warranted because of the relative similarity in the difficulty their symptom(s) were likely to pose for them.

Data Analysis

Data were analyzed using IBM SPSS Statistics 19.0.0 for Windows. Statistical analyses consisted of χ2 tests, with a significance level at P ≤ .05, to determine independent/dependent relationships between variables of interest.

Study participants
The total number of soldiers who underwent testing as part of the Fort Bragg study was 2337. The overall lifetime rate of TBI (any severity) among these soldiers was 40.6% (n = 948). It is notable, however, that paratroopers had significantly higher prevalence of any TBI (43.3%) than nonparatrooper soldiers (28.6%; P = .000; χ² = 31.79; df = 1). A study by Ivins et al found that parachute-related TBI accounted for this difference. All of soldiers in this study were paratroopers, by selection criteria. In order for soldiers reporting TBI to be selected for participation in this study, their TBI(s) could not have exceeded mild severity, and the most recent injury must have occurred within 12 months of testing. Additional selection criteria included age of 35 years or less, enlisted military rank (E1-E9), and paratrooper status (see Table, Supplemental Digital Content 2, Selection of study participants, available at http://links.lww.com/JHTR/A63). There were 101 selected soldiers who reported only 1 MTBI; this group was defined as “One MTBI” for the purposes of this study. The One MTBI group was compared with soldiers who reported sustaining 1 or more additional MTBI during their lifetimes (n = 123), defined as the “Two+ MTBI” group. One MTBI and Two+ MTBI groups were also compared with a matched control group of “No TBI” soldiers. A random sample of 224 soldiers without TBI was selected from the 1002 who met the matching criteria of age, grade/rank, and paratrooper status. Like soldiers with MTBI, soldiers in the No MTBI group were considered to be symptomatic if they endorsed any of the 10 criteria symptoms at a moderate or higher level. One MTBI and Two+ MTBI groups were divided into subgroups according to time since injury for the purpose of symptom analysis. This was done to enable examination of soldiers in 2 distinct intervals of postinjury recovery: within 3 months since injury, the interval during which recovery from MTBI is typically expected, and the postinjury period of 3 months. In this investigation, we defined the “Recent” subgroup to include soldiers who sustained their sole, or most recent MTBI up to and including 3 months before testing, and “Post–3 month” subgroup to include soldiers who sustained their sole, or most recent MTBI more than 3 months to 12 months before testing. Among soldiers in the Recent group, the mean time since injury was an average of 1.6 months. For the Post–3 month group, the mean time since injury was 6.6 months. One MTBI, Two+ MTBI, and No TBI groups were generally similar with respect to demographic and injury-related characteristics (Table 1). The only statistically significant difference found was in the percentage nonwhite between the Post–3 month, Two+ MTBI group (27.4%), and the No TBI group (40.6%; P = .03; χ² = 4.59; df = 1). There were no significant differences in demographic characteristics between One MTBI and Two+ MTBI groups, in either time since injury group. Most of the injuries in this study were jump-related (74% overall; 74.3% for One MTBI and 73.2% for Two+ MTBI). This factor differentiates the soldiers in this study from other military populations. Specific mechanism of injury data for non–jump-related injuries (motor vehicle accidents, falls, etc) were not collected.

No data were collected on whether soldiers had combat exposure, for example, deployment in the Persian Gulf War (August 1990 to February 1991). However, most soldiers in this study (80%) were 25 years old or younger at the time of testing in 1999 and 2000, and thus were too young to have served in the Army during the Gulf War. The oldest of the sampled soldiers were 35 years old, ruling out combat in earlier military conflicts. Although it is possible that a small number of the soldiers in this study may have been deployed in the Gulf War, combat exposure is not believed to have been a significant factor in the symptom reporting in this sample. Many of the participants had occupations in combat-related career fields, which included infantry, combat engineer, field artillery, and air defense artillery. Combat-related occupations typically carry a higher exposure to injury agents, but it should be noted that a “career field related to combat” does not indicate that soldiers had combat exposure or combat-related injury. Soldiers were asked to report up to 6 lifetime injuries; the range of number of injuries reported in this MTBI study group was 1 to 5. In the Recent group, 53.6% had 1 MTBI only, whereas 40% of the Post–3 month soldiers had sustained 1 MTBI only. Table 2 shows the distribution of
number of MTBIs among soldiers with 2 or more MTBIs, which were similar for both time since injury groups. For both the Recent and Post–3 month groups, the majority reported 2 only (71.8% and 70.2%, respectively).

Because soldiers were asked to report on injuries that occurred over their lifetimes, there was a wide range of intervals between injuries among those who reported 2 or more MTBIs. For these soldiers, the interval between the injury that occurred within 1 year of testing and the next most recent injury ranged from as short as 1 month, to as long as 25.8 years. Table 2 shows the distribution of intervals between injuries. As with the number of lifetime MTBIs, there were no significant differences in interval distributions between Recent and Post–3 month soldiers.

Results

Table 3 shows symptom endorsement comparisons of Recent and Post–3 month soldiers in both time since injury groups, and No TBI soldiers.

In the Recent group, there was a significant difference in symptom endorsement between soldiers with 1 MTBI and those with 2 or more MTBIs. Individuals with 1 MTBI predominantly reported either no symptoms, or 1 or 2 symptoms. In the Two+ MTBI group, however, most (66.7%) reported 3 or more symptoms, compared with 28.9% in the Recent One MTBI group and 19.6% in the No TBI group reporting 3 or more symptoms. In total, 79.5% of the Two+ MTBI group reported at least 1 symptom, compared with 57.8% in the One MTBI group and 42.4% in the No TBI group. The median number of symptoms in the Two+ MTBI group was 4, whereas the median for the One MTBI group was 1. In the Post–3 month group, no significant differences in symptom prevalence were observed between MTBI subgroups. One MTBI and Two+ MTBI groups endorsed a median of 1 and 2 symptoms, respectively. There were significant symptom endorsement differences between the No TBI controls and 3 of the 4 MTBI subgroups: Recent Two+ MTBI, Post–3 month One MTBI, and Post–3 month Two+ MTBI. Only the No TBI versus Recent One MTBI comparison fell short of statistical significance (P = .156; χ² = 3.71; df = 2). We explored possible confounders that might have affected these findings, including the influence of MTBI severity, and, for those with 2 or more MTBIs, the number of previous MTBIs as well as the length of time between the 2 most recent MTBIs. Significant differences were not found in regard to injury severity (LOC versus altered consciousness; see Table, Supplemental Digital Content 3, Exploratory analysis of injury severity, available at http://links.lww.com/JHTR/A63), 2 versus 3 or more MTBIs, or interval between TBIs (see Table, Supplemental Digital Content 4, Exploratory analysis of number of, and interval between MTBIs, available at http://links.lww.com/JHTR/A63). Low cell counts may have limited the power to detect significant differences. To further explore potential confounding factors, we repeated symptom analyses excluding those soldiers whose short interval between injuries, or higher number of injuries, might have disproportionately affected the outcome. In the Recent group, we selected those who had more than 1 year separating their 2 most recent MTBIs (n = 29) and compared them to the 45 soldiers in the One MTBI group. The difference in symptom endorsement remained (69% Two+ MTBIs versus 28.9% One MTBIs with 3 or more symptoms; P = .002; χ² = 12.20; df = 2). Similarly, we compared symptom endorsement among soldiers with only 2 injuries (n = 28) with that of the One MTBI group, and found that the significant difference in proportions endorsing 3 or more symptoms also remained (64.3% of the Two MTBI group, versus 28.9% of the One MTBI group; P = .01; χ² = 9.13; df = 2). This suggests that the finding of more symptoms with the Recent Two+ MTBI group was not likely to have been disproportionately influenced by soldiers with a high number of injuries, or a shorter interval between injuries.
Discussion

The findings of this study indicate that having at least 1 previous mild TBI may make a difference in the likelihood of postconcussive symptoms in the early months following a subsequent mild injury. This is not a longitudinal study, but the similarity in symptom endorsement among soldiers 3 months postinjury suggests that initially increased difficulties experienced as a result of multiple MTBI may diminish as time since injury increases, to a level comparable with that experienced by individuals with 1 MTBI. In this investigation, the proportion of symptomatic soldiers without TBI was significantly lower overall than that of the MTBI groups. Nonetheless, 42.4% of the soldiers without TBI reported having at least 1 symptom, and 19.6% reported 3 or more. Postconcussive symptoms include problems such as headache, fatigue, and irritability, which are not peculiar to TBI and may be endorsed by individuals without brain injury for a variety of reasons. Studies of persons without TBI have found high rates of postconcussive-type symptoms, including 63% to 82% of a college student sample reporting difficulty with concentration, tiredness, and impatience, and 59% reporting poor concentration and forgetfulness in a general population. The lower symptom rate in the current study may be explained by the higher symptomatic threshold used in this investigation, in which problems had to have caused a moderate or higher level of disruption to their normal daily activities to be counted. Existing literature on multiple MTBI and symptoms is scant. Some sports-related concussion studies found no differences in reported symptoms between athletes with single and multiple MTBI, whereas this investigation found symptom differences between MTBI groups for recently injured soldiers. One possible explanation may be differences between the groups in willingness to report symptoms. There is a characteristic reluctance on the part of athletes to report symptoms,28 because of not recognizing the potential seriousness of the injury, or out of concern that they may be removed from play. However, it is unknown whether soldiers are more likely than athletes to report lingering symptoms. Another explanation may be differences in injury severity. The mild TBIs sustained by the participants in this study, which were accompanied by LOC for 36%, may have been more severe overall than those typically sustained on the playing field. There is some agreement among researchers of sports-related MTBI that sports injuries are predominantly minor and usually without accompanying LOC, and that postinjury problems tend to resolve within 7 to 10 days in 80% to 90% of cases. However, we are unable to determine if there were actual severity differences between the participants in the current study and those in sports-related concussion studies. In this study, soldiers with MTBI reported difficulty with at least 1 symptom at rates ranging between 58% and 80%, which are higher than those reported in other studies of MTBI (32%-44%). This is despite the fact that factors such as female sex, older age, lower education, and comorbidity, which have been found to be associated with postconcussive symptoms, are notably underrepresented in our population, with its preponderance of males (97%) who are young (maximum age = 35 years; 91% aged 30 years or less), educated at a high school level or higher (95%), and in generally good physical health. Nonetheless, as mentioned earlier, this population of soldiers may have had injuries that were more serious, within the mild spectrum, than those sustained by other individuals. Preexisting emotional problems and expectation of symptom difficulty following brain injury are additional factors that have been linked to postconcussive symptoms; the extent to which these factors may be present in our population of soldiers is unknown. Symptoms that can follow TBI are associated with other problems relevant to soldiers, notably PTSD and depression. In this investigation, the potential interaction of PCS and PTSD is mitigated by the fact that this is a study of a peacetime military population, tested in 1999 and 2000. As such, this study provides a profile of symptom experienced during peacetime, both for soldiers with and without TBI, which may be useful for symptom comparison with soldiers deployed in combat theaters, who would be influenced by factors such as PTSD, depression, and pain. A recent study by Lew et al of veterans returning from combat in Iraq and Afghanistan found that persistent postconcussive symptoms, PTSD, and chronic pain occurred most often in combination with one another, with 42.1% diagnosed with all 3 conditions simultaneously.
Postconcussive symptoms was defined as 3 or more symptoms lasting longer than 3 months, and was present in 66.8% of veterans. This proportion is substantially higher than the 41.5% endorsing 3 or more symptoms in this study (One and Two+ MTBI groups combined), indicating either some important difference in the MTBIs sustained by the combat soldiers as compared with their noncombatant counterparts, and/or a comorbidity effect involving other factors, such as PTSD and chronic pain. Because this is a study of self-reported symptoms, malingering is a possible explanation for high rates of symptom reporting. However, there are several reasons why soldiers may have been unlikely to have exaggerated their reporting of symptoms. Soldiers cannot hold the government liable for their injuries; therefore, motivation for compensation was unlikely to be a factor. Additionally, this was a noncombatant group of soldiers, sampled and tested prior to September 11, 2001, and thus would not have had been motivated to exaggerate claims to avoid war duty. Finally, concerns about potential career ramifications of seeking treatment among this population of largely elite, highly motivated paratroopers might have resulted in a tendency to underreport rather than over report symptoms. This study is strengthened by the presence of a noninjured control group, which is often lacking in analysis of postconcussive symptoms. However, there are several limitations to note in this study, including its use of self-reported injury data. Although self-report of TBI history is useful in studies of mild TBI, because many individuals who sustain an MTBI do not seek medical treatment, the fact that injuries were not clinically verified increases the likelihood of injury misclassification. The predominance of paratroopers in this study limits the extent to which findings can be generalized to other military and civilian populations. Low numbers within the time since injury subgroups limit the power of some analyses to detect differences between groups. As a cross-sectional study and not a longitudinal one, caution should be exercised in drawing any conclusions about the course of symptom experience over time. Given the suggestive nature of the findings of this study, it would be helpful to investigate whether the finding of increased symptom reporting in the first few months after injury for those with 2 or more MTBIs would be replicated in other studies. Specifically, this investigation characterizes MTBI and postconcussive symptoms in a peacetime military population. With findings from this study as a noncombatant comparison, it would be beneficial to investigate symptoms of multiple MTBI in other samples of soldiers who have experienced combat-related TBI, to delineate differences in symptom experience that may be associated with combat injuries and comorbidities. Further research aimed at more sensitively ascertaining the relationship between subsequent injury and increased short-term symptoms would also be useful. Ideally, a prospective study design could enable comparison of the symptom experience between initial and subsequent injury. This would mitigate limitations such as retrospective recall and reporting of MTBI, as well as the wide range of intervals between injuries that were seen in this study. Our findings indicate that past experience of MTBI may be a risk factor for increased symptom difficulties for several months after injury. When evaluating patients for mild TBI, clinicians should ascertain a patient's TBI history and be aware that even a mild TBI in the past may impact a patient's likelihood of experiencing postconcussive symptoms in the period of up to several months following the injury. This study adds to existing literature on mild TBI by characterizing postconcussive symptom problems both within and after the acute postinjury period of up to 3 months. Unlike some sports studies that detected no difference in the acute period between those with single mild TBIs and those with additional MTBIs, we found that postconcussive symptoms were significantly more prevalent in the acute period among soldiers with 2 or more lifetime MTBIs than in soldiers who had reported 1 injury only. This study provides further support that the sequelae of mild TBI can present significant problems for some patients, and suggests that additional TBI may explain why some individuals have longer periods of symptoms in the acute period.
PET Scanning of Brain Tau in Retired National Football League Players: Preliminary Findings

The American Journal of Geriatric Psychiatry
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Objective
Mild traumatic brain injury due to contact sports may cause chronic behavioral, mood, and cognitive disturbances associated with pathological deposition of tau protein found at brain autopsy. To explore whether brain tau deposits can be detected in living retired players, we used positron emission tomography (PET) scans after intravenous injections of 2-(1-{6-[2-[F-18]fluoroethyl}(methyl)amino)-2-naphthyl)ethylidene)malononitrile (FDDNP).

Methods
Five retired National Football League players (age range: 45 to 73 years) with histories of mood and cognitive symptoms received neuropsychiatric evaluations and FDDNP-PET. PET signals in subcortical (caudate, putamen, thalamus, subthalamus, midbrain, cerebellar white matter) and cortical (amygdala, frontal, parietal, posterior cingulate, medial and lateral temporal) regions were compared with those of five male controls of comparable age, education, and body mass index.

Results
FDDNP signals were higher in players compared with controls in all subcortical regions and the amygdala, areas that produce tau deposits following trauma.

Conclusions
The small sample size and lack of autopsy confirmation warrant larger, more definitive studies, but if future research confirms these initial findings, FDDNP-PET may offer a means for premorbid identification of neurodegeneration in contact-sports athletes.

For the first time, researchers have been able to see the brain damage caused by repetitive head injury in living athletes, a finding that may help facilitate early identification and intervention in those suffering from trauma-related neurodegeneration.

Using PET imaging with FDDNP, a novel chemical tracer that binds to tau and amyloid in the brain, investigators at the University of California, Los Angeles, found that compared with control individuals, tau protein deposits were higher in all subcortical regions and in the amygdala in a group of 5 retired National Football League (NFL) players.
Tau proteins have previously been linked to chronic traumatic encephalopathy (CTE) as well as Alzheimer's disease (AD). A degenerative condition caused by the accumulation of tau in the brain, CTE has been associated with memory loss, confusion, progressive dementia, depression, suicidal behavior, personality changes, abnormal gait, and tremors.

However, until now, researchers were only able to confirm the presence of these proteins on autopsy.

"Early detection of tau proteins may help us to understand what is happening sooner in the brains of these injured athletes. Our findings may also guide us in developing strategies and interventions to protect those with early symptoms, rather than try to repair damage once it becomes extensive," principal investigator Gary Small, MD, said in a statement.

The study was published online January 22 in the American Journal of Geriatric Psychiatry.

Common Occurrence

With an estimated incidence of 1.6 to 3.8 million, sports-related repetitive mild traumatic brain injury due to contact sports are common.

According to the authors, research has shown that retired contact-sport athletes such as NFL players show higher rates of personality, behavioral, and mood disturbances, mild cognitive impairment, and dementia compared with control individuals.

In addition, there appears to be a dose-dependent effect. The investigators note that research in NFL players has shown that those with 3 or more reported concussions during their career were 3 times more likely to be diagnosed with depression and 5 times more likely to be diagnosed with mild cognitive impairment (MCI).

To determine whether brain tau deposits can be detected in living athletes using FDDNP-PET, potentially paving the way for early detection and intervention, the investigators conducted a study in 5 former NFL players who ranged in age from 45 to 73 years and who had a history of 1 or more concussions and cognitive or mood symptoms.

The players represented a range of positions, including linebacker, quarterback, guard, center, and defensive lineman.

Study participants underwent neuropsychiatric evaluations with the Hamilton Rating Scale for Depression and the Mini–Mental State Examination (MMSE) and underwent FDDNP-PET. PET signals in subcortical and cortical regions of the brain were then compared with those of 5 matched control participants.

Critical First Step

Results showed that the players had more depressive symptoms than the control participants and generally had lower MMSE scores, suggesting evidence of cognitive decline.
Three players had MCI, 1 had dementia, and 1 was cognitively normal.

The investigators found that FDDNP signals were higher in players compared with control participants in all subcortical regions and the amygdala areas that produce tau deposits following trauma. They also found that players who had experienced a greater number of concussions had higher FDDNP levels.

"The FDDNP binding patterns in the players’ scans were consistent with the tau deposit patterns that have been observed at autopsy in CTE cases," study author Jorge R. Barrio, PhD, said in a release.

The investigators note that although FDDNP also binds to beta amyloid, a hallmark of AD, previous research has shown that amyloid plaques are found in less than one third of CTE cases, suggesting that the FDDNP signal in the NFL players mainly represents tau deposits.

"Providing a noninvasive method for early detection is a critical first step in developing interventions to prevent symptom onset and progression in CTE," said Dr. Small. He added that FDDNP is the "only imaging marker currently available that can provide a measure of tau in living humans."

The researchers added that in 2000, direct and indirect costs of traumatic brain injury was approximately $77 billion in the United States alone.

"Given the large number of people at risk — not just athletes but military personnel, auto accident victims, and others — the potential public health impact is considerable."

Dr. Small and Dr. Barrio report that they are among the inventors of FDDNP-PET, that they have received royalties, and that they may receive royalties on future sales. Dr. Small reports having served as a consultant and/or having received lecture fees from Janssen, Lilly, Novartis, and Pfizer. Dr. Barrio reports having served as a consultant and having received lecture fees from Nihon Medi-Physics Co, Bristol-Meyer Squibb, PETNET Pharmaceuticals, and Siemens. The other study authors have disclosed no relevant financial relationships.

The Relation Between Posttraumatic Stress Disorder and Mild Traumatic Brain Injury Acquired During Operations Enduring Freedom and Iraqi Freedom

The Journal of Head Trauma Rehabilitation
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Objective: To understand the relations of mild traumatic brain injury (TBI), blast exposure, and brain white matter structure to severity of posttraumatic stress disorder (PTSD).
Design: Nested cohort study using multivariate analyses.

Participants: Fifty-two OEF/OIF veterans who served in combat areas between 2001 and 2008 were studied approximately 4 years after the last tour of duty.

Main Measures: PTSD Checklist-Military; Combat Experiences Survey, interview questions concerning blast exposure and TBI symptoms; anatomical magnetic resonance imaging (MRI), and diffusion tensor imaging (DTI) scanning of the brain.

Results: PTSD severity was associated with higher 1st percentile values of mean diffusivity on DTI (regression coefficient \( r = 4.2, P = .039 \)), abnormal MRI \( (r = 13.3, P = .046) \), and the severity of exposure to combat events \( (r = 5.4, P = .007) \). Mild TBI was not significantly associated with PTSD severity. Blast exposure was associated with lower 1st percentile values of fractional anisotropy on DTI (odds ratio \( [OR] = 0.38 \) per SD; 95% confidence interval \( [CI] \), 0.15–0.92), normal MRI \( (OR = 0.00, 95\% \text{ likelihood ratio test CI, 0.00–0.09}) \), and the severity of exposure to traumatic events \( (OR = 3.64 \text{ per SD; 95\% CI, 1.40–9.43}) \).

Conclusions: PTSD severity is related to both the severity of combat stress and underlying structural brain changes on MRI and DTI but not to a clinical diagnosis of mild TBI. The observed relation between blast exposure and abnormal DTI suggests that subclinical TBI may play a role in the genesis of PTSD in a combat environment.

POSTTRAUMATIC STRESS DISORDER (PTSD) is a debilitating psychiatric illness characterized by the reexperiencing of a traumatic event through nightmares and flashbacks, avoidance of stimuli related to the event, and hyperarousal (difficulty concentrating and sleeping). The pathogenesis is thought to involve increased activation of the amygdala and reduced inhibitory control by the ventromedial prefrontal cortex and the hippocampus. Direct, personal exposure to traumatic events, such as those experienced in combat, is necessary for the development of PTSD.

The prevalence of PTSD among Operation Enduring Freedom/Operation Iraqi (OEF/OIF) veterans ranges from 13% to 17% compared with 4% of the US adult population. The diagnosis of PTSD is based on symptoms alone. There are no objective diagnostic aids. These symptoms overlap considerably with those related to mild traumatic brain injury (mild TBI), which also commonly affects military personnel in Iraq and Afghanistan. Mild TBI is characterized by a brief loss or alteration of consciousness and a period of amnesia or change in mental state at the time of the injury. A RAND study estimated that 320 000 OEF/OIF service members had suffered a mild TBI as of January 2008, often as a result of exposure to blast. As with PTSD, the diagnosis of mild TBI is made clinically because there are no accepted diagnostic adjuncts.

Rates of PTSD seem to be higher among those exposed to mild TBI. A 2009 Institute of Medicine report concluded that there was evidence of an association between TBI and PTSD, based on observational studies conducted in military personnel who served in Iraq and Afghanistan. For example, one study reported the prevalence of PTSD to be more than 3 times higher after mild TBI, supporting the notion of an interaction between the them. The reason for this interaction between mild TBI and PTSD is not clear and is the focus of the current report.
Understanding the nature of this interaction may provide direction for future efforts to prevent and treat PTSD, especially when it co-occurs with mild TBI. However, it is also important for clinicians currently providing postdeployment medical care to veterans. Symptom overlap and lack of diagnostic aids makes it difficult to separate the effects of TBI from those of PTSD in clinical care of individual soldiers. This has given rise to controversy regarding the nature of the interaction between these 2 entities. Some maintain that postdeployment symptoms are due to both mild TBI and combat stress/PTSD. Others hold that combat stress is responsible for most postdeployment symptoms. Hoge et al found that PTSD and depression—but not mild TBI—were associated with poor neurobehavioral outcomes among 2525 army infantry soldiers following their return from Iraq. Two additional studies found similar associations. In all 3 studies, mild TBI was diagnosed by symptom self-report. However, even in controlled medical environments, a clinical diagnosis of mild TBI can be difficult to ascertain accurately, especially when a description of the event and associated symptoms are elicited months after the event. Mild TBI ascertainment in a combat environment is especially problematic because symptoms of loss of consciousness or altered mental state can also occur as a result of dissociation in the face of emotional trauma. Finally, exposure to blast, a frequent occurrence in the current conflicts, can cause subtle brain injury without frank loss of consciousness or amnesia.

At the heart of this controversy, thus, is an incomplete understanding of the relations among blast, mild TBI, combat stress, and PTSD. The use of a symptom-based mild TBI diagnosis, without an objective measure of brain injury, may be obscuring the contribution of traumatically induced brain injury to the development of PTSD. When objective diagnostic measures of brain injury are used, TBI seems to play a more prominent role in the genesis of PTSD. Animal studies using histopathologic techniques to determine brain injury suggest that TBI—or even just exposure to blast—increases the vulnerability to PTSD. Until recently, the lack of an objective in vivo measure of brain injury has prevented studying the mild TBI-PTSD relation in humans.

Diffusion tensor imaging (DTI) has now matured to the point where it can potentially fill the role of an objective diagnostic adjunct to the detection of brain injury. This form of magnetic resonance imaging (MRI) has detected subtle changes in the white matter (WM) associated with civilian mild TBI and with mild TBI experienced by military personnel involved in OEF/OIF. However, DTI has not yet been used to study the TBI-PTSD relation, despite a 2009 recommendation from a working group of US government and civilian physicians and scientists published as the St. Louis Workshop Report.

In the current study, we sought to understand the relations of mild TBI and blast exposure to brain WM structure on DTI and how these may interact to affect the development of PTSD.

METHODS

We performed a nested cohort study of 52 OEF/OIF veterans who served in combat areas between 2001 and 2008. The parent cohort consisted of 500 OEF/OIF veterans from Veterans Integrated Service Network (VISN) 2 recruited between August 2008 and January 2010 as part of a study of cognitive, affective, and behavioral correlates of veterans with and without TBI funded by VA Health Services Research and Development. These subjects were enrolled through several VA medical centers in Upstate New York. A special modification to the original grant (Cognitive Assessment of Veterans After TBI: DTI Substudy) permitted DTI scanning of a subset of these individuals.
The subjects in this subset were chosen for their willingness to travel to the DTI site, to undergo DTI scanning, and for lack of contraindications to scanning (retained metallic foreign bodies and claustrophobia). At the time of study, DTI was not available at any VISN 2 VA facilities.

DTI image data were correlated with information already gathered during the parent study, including mild TBI diagnostic data, blast exposure, severity of PTSD, and severity of combat experiences. These variables were defined in the following way:

**PTSD severity** was taken from the PTSD Checklist-Military. The PTSD Checklist-Military is a very widely used 17-item checklist developed at the National Center for PTSD that follows *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnostic criteria. Subject rate the extent to which they have been bothered over the last month by each of the 17 listed problems on a 5-point Likert scale ranging from 1 (“not at all”) to 5 (“extremely”). Thus, total scores can range from 17 to 85. The internal consistency coefficient (Cronbach α) for the total scale is 0.939. With a cutoff score of more than 44 used to define PTSD, overall diagnostic efficiency has been reported at 0.90, with a sensitivity of 0.94 and a specificity of =0.86, although a cutoff of 50 or more is also commonly used. As part of the parent study protocol, subjects underwent several assessments of PTSD severity at varying time points after return home. We analyzed the assessment that was administered nearest to the time of the DTI scan.

*Mild TBI diagnosis* was determined by in-person interview using a 22-item questionnaire developed to establish the nature, probability, and severity of deployment-related TBI among OEF/OIF veterans. The interview followed previously published TBI diagnostic criteria, which include confirmation of a possible TBI event, confirmation of alteration of consciousness, and confirmation of postconcussion symptoms. On the basis of the standardized clinical interview, interviewers rated the likelihood of mild TBI according to a 6-point scale: “not at all likely,” “very unlikely,” “somewhat unlikely,” “somewhat likely,” “very likely,” and “almost certainly.” These likelihood categories were used in all analyses. However, for descriptive purposes, subjects were defined as having mild TBI if interviewers rated them “very likely” or “almost certainly.”

*Severity of exposure to traumatic events* was taken from the Walter Reed Army Institute of Research Combat Experiences Survey. The Combat Experiences Survey is a 36-item scale that measures combat intensity based on frequency and type of combat experiences. The first 33 items are various deployment-related experiences that range from combat-related questions (“being attacked or ambushed”) to deployment duties (“handling or uncovering remains”) to possible deployment or combat-related events (“knowing someone seriously injured or killed,” “had a close call, dud landed near you,” and “provided aid to the wounded”). Item responses are on a 5-point scale related to how often the event was experienced, ranging from 0 (“never”) to 5 (“10 or more times”). The last 3 items of the scale are each scored differently than the first 33 items and pertain to how often a service member was in serious danger of being injured or killed, how many times one engaged in an enemy firefight, and whether 1 or more nights were spent in the hospital. These 3 items were excluded from the current study because of the differences in meaning and scaling. Total scores thus range from 0 to 165. Although formal psychometric data are not available for this instrument, an exploratory factor analysis conducted at the University of Buffalo suggested that 3 factors represented the scale well: exposure to combat environment, physical engagement, and proximity to serious injury and death. These 3 factors showed high internal consistency, with Cronbach α scores of 0.94, 0.81, and 0.82, respectively. Evidence for construct validity was shown by estimates convergent and discriminant validity of the factors with demographic data, other war experience scales, and cognitive, affective, and behavioral measures. (K. Donnelly, PhD, 2012, written communication)
Exposure to blasts

Blast exposure was determined by responses to interviews conducted during the parent study. The interviewers used a semistructured questionnaire to ask for a description of events in which they were exposed to any of the following: blast, improvised explosive device, bullet above the shoulder, rocket-propelled grenade, mortar, landmine, grenade, blow to the head, vehicular accident, fall, or assault. Among these, only events specifying exposure to a blast (blast, improvised explosive device, rocket-propelled grenade, mortar, landmine, and grenade) were considered. Events causing injury (ie, fall, assault, vehicular accident, or blow to head) that may have contributed to head injury—but did not involve exposure to a blast—were not considered blast-exposed. Responses were reviewed by the interviewing clinician for detail and clarity (ie, how occurred, the sequence of events, and the specifics of the blast exposure). Blast exposure was summarized as “yes” if an individual had 1 or more blast exposures. The number of events reported ranged from 0 to 3.

DTI data acquisition

Images were acquired on a Siemens 3T Trio MRI scanner (Siemens Medical, Erlangen, Germany) equipped with a 32-channel head coil. In addition to scout images for subject localizations, the following scans were acquired: (a) 3-dimensional structural T1-weighted images are collected using a magnetization prepared rapid gradient echo sequence with parameters such as time-of-repeat (TR) = 2350 ms, time-of-echo (TE) = 3.4 ms, 256 × 256 matrix, field-of-view (FOV) = 25.6 cm, 1-mm slice thickness; (b) 2-dimensional axial fast gradient-recalled echo (GRE) dual-echo sequence, with slice thick = 2 mm with no gap, FOV = 256 × 256 mm², matrix = 128 × 128, echo times = 6.2/8.66 ms; (c) 2-dimensional axial DTI using a single-shot pulsed-gradient dual-echo spin-echo echo planar imaging sequence with TR/TE = 8900/81 ms, slice thick = 2 mm with no gap, matrix = 128 × 128, FOV = 256 × 256 mm², integrated parallel acquisition techniques with generalized autocalibrating partially parallel acquisitions acceleration factor = 2, diffusion weighting direction = 60 with $b = 700$ s/mm² and 1 average, and $b = 0$ images with 10 averages. For the whole-brain coverage of about 70 slices, total scan time for DTI was about 11 minutes. Standard T1/T2-weighted MRI images were acquired during the same session. GRE mages were reviewed for hemosiderin and fluid-attenuated inversion recovery (FLAIR) images for WM abnormalities. A FLAIR image is a T2-weighted image in which the fluid signal has been suppressed. Typically, fluid is bright white on a T2-weighted image, but in the FLAIR images, this signal is suppressed to further enhance the sensitivity. White matter signal abnormalities detected using FLAIR are considered relatively nonspecific and more common with advanced age. They may reflect gliosis resulting from small-vessel ischemia or demyelination such as that seen in multiple sclerosis. Other etiologies include hypertension and migraine.

DTI postprocessing

A custom software tool based on Matlab (The Mathworks, Natick, Massachusetts), C++, and various functions in the FSL package (FMRIB Analysis Group, Oxford University, Oxford, England,) was used for image processing and statistical analysis. To ensure an accurate representation of data, the following processing steps were performed: (a) Motion and eddy current artifacts were simultaneously removed using the Eddy_Correct Tool of the FSL package. This step allows better alignment of images among the DTI data volumes scanned with different diffusion gradient directions. An additional step using the field map from dual-echo GRE images and the algorithm (FUGUE Toolbox from FSL package) removed the susceptibility artifacts from the original DTI data. (b) Diffusion tensor as well as 2 tensor-derived parametric maps, fractional
anisotropy (FA) and mean diffusivity (MD), were estimated for individual subjects using the DTIFIT tool in FSL. (c) Using the 12-\textit{df} affine registration with the FLIRT toolbox in FSL, nondiffusion-weighted images (\(b = 0\)) in each individual DTI data set were registered with the 3-dimensional T1-weighted image obtained by the magnetization prepared rapid gradient echo sequence, which has high image contrast between WM/gray matter (GM)/cerebrospinal fluid (CSF) and high image resolution.

Whole-brain WM analysis of FA and MD values

The segmentation of WM/GM/CSF based on the 3-dimensional T1-weighted image was performed for each individual using the FAST toolbox in FSL. The resultant high-resolution WM mask was then inversely projected into each individual's DTI space, using the inverse transformation matrix obtained in step \(c\) to generate the region of interest (ROI) mask for statistical analysis of FA and MD within the whole WM.

Automated ROI segmentation

The John Hopkins White Matter Parcellation Atlas Type II (JHU WMPM) was used to segment the whole brain into 56 WM regions, 22 deep GM regions, and 52 cortical GM regions. A 2-step image-processing approach was used to transform the JHU WMPM Atlas into individual subject's native space based on DTIStudio software package (cmrm.med.jhmi.edu, H. Jiang and S. Mori, Kennedy Krieger Institute, Johns Hopkins University, Baltimore, Maryland). In the first step, a 12-\textit{df} affine linear registration was performed between each individual's FA map and the John Hopkins FA Atlas to achieve global adjustment of the size and orientation of the brain. In the second step, a nonlinear registration using Large Deformation Diffeomorphic Metrix algorithm was used to achieve more accurate transformation of the atlas into individual's native space. To further improve the transformation, the dual-contrast Large Deformation Diffeomorphic Metrix Mapping algorithm was adapted in which both FA image and the nondiffusion-weighted image (\(b = 0\)) were used for the nonlinear registration simultaneously. In the end, the JHU WMPM Atlas was transformed to each individual's native space and the binary masks for 130 ROIs were then automatically generated for ROI-based analysis.

The efficiency of the automated ROIs segmentation is illustrated in Figure 1, where the ROIs from transformed JHU WMPM Atlas are superimposed on the FA map from 4 study subjects. For each ROI, the mean value of FA/MD over all pixels within the ROI was calculated for statistical analysis. Each cortical GM region defined by the JHU WMPM Atlas is actually a mixture of cortical GM and a layer of “superficial” WM close to it. Unlike the deep WM structures inside which WM tracts are well organized, these superficial WM layers are the regions where WM fibers become smaller and branch into the GM. Therefore, fiber crossing and the partial volume effect make FA measurement in these WM layers less robust. Because of these concerns, the 52 GM cortical regions were not included, leaving 78 ROIs for analysis. The left (L) and right (R) hemispheric components of each structure were combined, yielding a total of 39 ROIs in the final analysis.

Analysis

Multiple linear regression models were used to model PTSD severity as a function of mild TBI likelihood and whole-brain DTI indices, with control for blast exposure, severity of exposure to traumatic events, prior head injury, time since last tour of duty, age, and gender. All subsets and stepwise selection methods were used to refine and stabilize the models by removing candidate predictors that were not statistically significant at the 2-sided nominal 0.05 level. The effect of each predictor was summarized by its regression coefficient, standard error (SE), 95% confidence
interval (CI), and 2-sided $P$ value. Swapping the roles of PTSD severity and mild TBI likelihood, similar linear models were used to model the latter with the same set of variables.

Multiple binary logistic regression models were used to model the odds of exposure to at least 1 blast as a function of DTI indices, adjusted for PTSD severity, mild TBI likelihood, severity of exposure to traumatic events, time since last tour of duty, prior head injury, age, and gender. Stepwise selection was used to refine and stabilize the models by removing candidate predictors that were not statistically significant at the 2-sided nominal .05 level. The effect of each predictor was summarized by its odds ratio (OR), along with its associated 95% Wald CI, and likelihood ratio test $P$ value. Profile likelihood CI values were used in place of Wald CI when parameter estimates were on the boundary (OR = 0). Nonparametric kernel density estimates, using the Silverman normal-based rule-of-thumb bandwidth selector, were used to graphically depict the distributions of DTI indices, stratified by blast exposure.

FA and MD values of the whole-brain WM were summarized with a quantile approach that uses FA and MD values from each WM voxel in a native, nonnormalized space. The adult human brain has approximately 30,000 WM voxels 2 mm$^3$ in size. Each subject's WM FA and MD values were summarized by 3 preselected percentiles (1st, 50th, and 99th percentiles), covering both extremes as well as the center (median) of the distribution. Thus, each subject's WM voxels were represented by 6 DTI values. A seventh indicator was added by considering the findings of abnormal T1/T2-weighted MRI found in the process of DTI data. The rationale behind using relatively extreme percentiles (1st and 99th) as summary statistics is that we expect a head injury to affect only a relatively small proportion (1%-10%, for example) of the subject's brain, and the location could be different from subject to subject. Thus, when analyzing the whole brain, we would not necessarily expect the median to be strongly affected—unless most of the brain was injured. In a prior publication, we found the 1st percentile MD to be significantly decreased among civilian mild TBI subjects.

In the ROI analysis, PTSD severity, mild TBI likelihood, and blast exposure were modeled similarly as in the whole-brain WM analyses, but each of the 234 ROI-DTI outcome-specific models contained only a single DTI measure: either mean FA or mean MD for 1 of the 39 WM and deep GM regions identified by the JHU WMPM Atlas. Furthermore, model selection was not performed separately for each model but rather each model was adjusted for those covariates significant in the whole-brain WM analyses. Since about 12 values of $P < .05$ would be expected by chance under the null hypothesis when performing 234 tests, ROI-based $P$ values were adjusted for multiple comparisons using the Benjamini-Hochberg method to control the false discovery rate (FDR), assuming nonnegative dependence.

RESULTS

Thirty subjects experienced at least 1 mild TBI, defined as a clinical interview rating of “almost certainly” or “very likely,” and 7 subjects had more than 1 mild TBI. Two subjects sustained mild TBI while on active duty but before being deployed; one of these subsequently suffered another mild TBI while deployed. Thirty-one subjects (60%) were exposed to 1 or more blasts. Fifteen participants met the diagnostic criteria of PTSD with a score of 50 or more.
Predictors of PTSD severity

PTSD severity was associated with severity of exposure to combat events, age, time since last tour, abnormal T1/T2-weighted MRI, and 1st percentile of MD on DTI. PTSD severity increased with increasing whole-brain 1st percentile MD values. After adjustment for covariates, PTSD severity was an average of 13.3 points (SE = 6.5) higher in the 5 subjects with abnormal T1/T2-weighted MRI than the 46 subjects with normal scans ($P = .046$, with 1 subject omitted because of missing traumatic events exposure information). These clinical and DTI variables accounted for 33.4% of the variation in PTSD severity among the subjects, whereas the clinical variables alone explained only 20.6% of the variance. There was insufficient evidence that either mild TBI likelihood or self-report of exposure to blasts was related to PTSD severity.

Predictors of exposure to blast and of mild TBI likelihood

Blast exposure was associated with 1st percentile of FA on DTI (OR = 0.38 per SD; 95% CI, 0.15–0.92), abnormal T1/T2-weighted MRI (OR = 0.00; 95% likelihood ratio test CI, 0.00–0.09), and the severity of exposure to traumatic events (OR = 3.64 per SD; 95% CI, 1.40–9.43). Compared with unexposed subjects, those exposed to blast were more likely to have reduced 1st percentile FA values. The odds of being exposed to at least 1 blast increased with severity of exposure to traumatic events and decreased with abnormal T1/T2-weighted MRI. None of the 5 subjects with abnormal T1/T2-weighted MRI was exposed to blast compared with 66% of subjects with normal T1/T2-weighted MRI. Removing these individuals from the logistic regression model did not substantially alter the OR for the 1st percentile of FA or the severity of exposure to traumatic events.

Modeling mild TBI likelihood as the outcome, those with a prior head injury had a mean mild TBI likelihood of 1.09 (SE = 0.48) points lower than those with none ($P = .027$) whereas subjects exposed to at least 1 blast had a mean TBI likelihood of 0.95 (SE = 0.44) points higher than those unexposed ($P = .035$). Since these effects cancel one another (and there is insufficient evidence of interaction, $P = .25$), the mild TBI likelihood for the 8 subjects with both a prior head injury and exposure to at least 1 blast (mean ± SD = 3.88 ± 1.89) was almost identical to that for the 14 subjects with neither (mean ± SD = 3.86 ± 1.88).

Specific brain regions differentially affected by PTSD and mild TBI

Of the 39 WM and deep GM regions analyzed, 10 seemed to be associated with PTSD, TBI, or blast after adjustment for covariates but before control for multiple comparisons. DTI changes in the caudate nucleus and the inferior cerebellar peduncle were associated with both PTSD and TBI. After application of the Benjamini-Hochberg FDR procedure to adjust for multiple comparisons, none of these regions were significantly associated with PTSD, TBI, or blast exposure (FDR and Bonferroni/Holm-corrected $P$ values >0.7).

DISCUSSION

In the current study, we examined the relations among combat-acquired PTSD, mild TBI, and several clinical and neuroimaging variables. As expected, PTSD severity was most strongly associated with the severity of exposure to traumatic combat events. However, PTSD severity was also associated with high 1st percentile of MD on DTI and WM lesions on MRI. Although the association of PTSD with combat intensity has been reported by prior investigators, we are the first to find an association between DTI abnormalities and PTSD acquired in a combat setting. Several
authors have examined DTI images in veterans but either did not include PTSD measures or did not find a statistical relation to PTSD. Levin et al analyzed DTI scans in 37 OEF/OIF veterans with blast-related mild-moderate TBI, using fiber tracking and found an association between low FA in the corpus callosum and higher PTSD severity, but the results were not statistically significant ($r = 0.30$, $P = .07$). Similarly, Davenport et al did not find a relation between PTSD symptoms and DTI indices among 58 blast-exposed OEF/OIF veterans. MacDonald et al performed DTI scans on 63 OEF/OIF veterans with blast-related mild TBI but did not examine the effect of PTSD.

There are several potential explanations for our observed associations between PTSD and abnormal DTI. The first is that combat stress produces changes on DTI that are unrelated to the physical forces to which the brain may be exposed. There is limited evidence to support this notion. Chronic stress in rodent models has been shown to induce the retraction and debranching of neuronal dendritic spines in medial prefrontal cortex, possibly via prolonged supranormal glucocorticoid levels. Reduced dendritic spine density could theoretically increase interaxonal water diffusion and lead to the increased MD observed in our subjects. Three authors reported changes in FA—but not MD—in adult human subjects who acquired PTSD in noncombat environments. In all 3 studies, these FA abnormalities were confined to the cingulum. In the current study, we did not find DTI abnormalities in the cingulum but we did observe a trend toward DTI abnormalities being associated with PTSD in other brain regions, several of which were also associated with a clinical diagnosis of mild TBI. These areas included the caudate nucleus and the inferior cerebellar peduncle. Thus, while chronic stress alone may be capable of inducing DTI changes, our results suggest that DTI changes associated with combat stress may be different from those associated with noncombat situations and possibly related to TBI.

An alternative explanation is that physical forces to the brain encountered during the course of combat operations—such as blast exposure or frank mild TBI—lead to brain injury that increases the vulnerability to PTSD. Prior evidence exists to support this notion as well. Several investigators have demonstrated that the brains of rodents exposed to sublethal blast display axonal swelling, disrupted axonal transport, glial reaction, and demyelination. This neuronal injury may provide the substrate for the development of prolonged periods of anxiety after exposure to stress. Kwon et al demonstrated that rats exposed to chronic stress and a single blast had a significantly longer period of anxiety and memory impairment than rats exposed to chronic stress alone. The blast plus stress–exposed rats showed evidence of neuronal and glial cell loss, whereas the stress-only rats did not. Our observation of a significant association between exposure to blast and DTI abnormalities suggests that increased PTSD vulnerability may be due in part to exposure to blast.

A final explanation involves the makeup of our subjects. Our subset is a slightly biased subset of the parent cohort compared with our subset that had similar mean PTSD scores but a higher proportion of subjects with mild TBI. Among our mild TBI subjects, the mean PTSD score was significantly lower than that of mild TBI subjects in the parent cohort (43.6 ± 15.4 vs 53.7 ± 16.3, $P = .002$). These differences may have obscured an association between mild TBI and PTSD, permitting DTI abnormalities to become relatively more significant in our sample. However, the mean PTSD score of 43.6 among our mild TBI subjects is similar to that in the study of Hoge et al (mean of 39 in those without loss of consciousness and 46 in those with loss of consciousness), showing a strong relation between PTSD and TBI.

Why PTSD would be associated with WM lesions on MRI is less clear, although we are not the first to report this. Five of 52 subjects in our cohort had lesions in periventricular and/or subcortical WM regions, and these individuals had significantly higher PTSD scores. Prior reports examining the relation between MRI and PTSD have found significant reductions in the volume of the hippocampus and, to a lesser extent, the amygdala.
However, only one study reported an association with WM abnormalities. Canive et al identified WM lesions on MRI scans among 8 of 42 veterans with combat-related PTSD. These lesions were located in periventricular areas and at the WM/GM cortical junction. Similar to our findings, these lesions were identified only on the FLAIR images. The etiology of these WM lesions is uncertain. The GRE images failed to reveal hemosiderin deposits in these regions of FLAIR signal abnormalities, significantly reducing the likelihood that these WM lesions were due to trauma. In fact, in our multivariate analysis, neither mild TBI nor blast exposure was related to subjects with these lesions. White matter lesions in young adults can be associated with migraines, hypertension, and cocaine or opiate dependence. Lack of detailed information on medical history prevented us from adjusting our analyses for these conditions. Among older adults, WM lesions on MRI are often associated with demyelinating and cerebrovascular diseases. Although neither disease has not been shown to be linked to the development of PTSD, cerebrovascular disease has been associated with the reemergence of PTSD symptoms after initial resolution. Finally, WM lesions such as the ones we observed have also been found among 8% to 18% of asymptomatic, healthy adults. Regardless of etiology, these lesions may be useful in identifying those at increased risk of PTSD. However, the low proportion of subjects with abnormal MRI (9.6% in our cohort) may limit the practical application of MRI as a risk stratifier.

Mild TBI likelihood (linear, dichotomized ≥5, or otherwise) was not associated with PTSD severity. Objective evidence of brain injury on DTI, however, was associated with PTSD severity. Taken together, these findings suggest that self-report of mild TBI is either inaccurate or correlates poorly with cellular evidence of injury on DTI. Inaccurate self-report of mild TBI in the current study could certainly be possible, given the prolonged period of time (4 years on average) between the last tour of duty and recollection of mild TBI symptoms. Underreporting of mild TBI symptoms is also possible and has been reported by other researchers studying military cohorts.

Even if self-report were accurate, however, a clinical diagnosis of mild TBI may not correlate well with underlying brain injury. Some mild TBI patients have no postconcussive symptoms, no demonstrable cognitive deficits, and normal neuroimaging, suggesting the absence of brain injury. On the contrary, some patients who suffer a blow to the head but do not meet the clinical definition of mild TBI do have objective evidence of brain injury. This poor correlation to brain injury likely confounds attempts to understand the relation between mild TBI and PTSD and underscores the urgent need to develop objective aids to the diagnosis through the use of biomarkers such as neuroimaging, electroencephalography, and serum protein tests.

Another important finding in the current study is the strong association between lower values of 1st percentile FA on DTI and blast exposure. Although others have found low FA among veterans with blast induced-mild TBI, we are the first to demonstrate disruption of WM integrity independent of a clinical diagnosis of mild TBI. Warden et al found reduced FA in the cerebellum of a single blast-injured soldier, whereas MacDonald et al found reduced FA in several ROIs among 63 OIF/OEF veterans with blast-related mild TBI. Davenport et al reported reduced whole-brain FA among 25 OIF/OEF service members with blast-related mild TBI (and, just as in our study, FA reduction was located primarily in the 1st percentile region). In all 3 studies, FA changes were found among those with a clinical diagnosis of mild TBI; the independent effect of blast exposure was not explored.

The observed association of blast exposure with abnormal DTI, independent of mild TBI, suggests that blast induces subclinical brain injury. Two recent civilian studies support this idea. In the first, significant WM damage on DTI was found after a sports season among 6 high school football and hockey players who did not report concussion In the second, regional cortical activation on functional MRI was significantly altered in 4 of 8
high school football players who did not report concussion after a season of play. In both studies, the extent of brain injury on neuroimaging correlated with the number of subconcussive head blows. While these studies do not involve blast as the mechanism of injury, they both support the emerging concept that brain injury can occur in the absence of symptoms typically used to define mild TBI such as loss of consciousness, amnesia, or a brief period of confusion.

It is unclear why normal MRI was associated with blast exposure in our analysis. Of the 5 subjects with WM abnormalities, none were exposed to blast. It is very likely that these WM lesions predated exposure to blast and are not related to trauma.

In summary, PTSD severity seems to be related not only to the severity of combat stress but also to underlying structural brain changes on MRI and DTI. These brain changes may be due to neurochemical alterations induced by chronic stress or, more likely, by subclinical brain injury from blast exposure. A clinical diagnosis of mild TBI does not seem to play a role, either because it is inaccurately reported or because it correlates poorly with underlying brain injury. Our findings suggest that physical forces such as blast may play a role in the genesis of PTSD in a combat environment. Both MRI and DTI may be uniquely suited for the detection of these structural brain changes and the identification of veterans at risk for PTSD. While screening thousands of service members with MRI or DTI may not be feasible, our results highlight the pressing need to develop practical mild TBI biomarkers (blood, electroencephalogram, etc) that correlate with underlying brain injury.

**LIMITATIONS**

Our results should be interpreted in light of several limitations. First, the relatively small number of analyzed subjects may have reduced our ability to detect small but significant relations among DTI changes in individual brain ROIs and PTSD, blast exposure, and mild TBI. Rigorous control for multiple comparisons resulted in nominally significant covariate-adjusted ORs of several regions, including the cerebellum and corpus callosum, to rise above the $P$ value threshold of .05. Interestingly, others have found DTI abnormalities in the cerebellum associated with blast exposure and in the corpus callosum among those with mild TBI. These regions might serve as the focus of future studies.

There is no validated method for determining cumulative blast exposure from self-report. The physical forces experienced by the brain after an explosion depend on the strength of the blast and its proximity to the subject. The method of determining blast exposure in the current study captured neither of these variables. An objective measure of blast exposure would greatly facilitate our understanding of the relation between multiple blast exposures and PTSD. Although several blast pressure sensors are currently under development, multiple technical hurdles remain.

Finally, while we found 1st percentile FA in WM to be significantly associated with blast, FA values in this region have potential to be contaminated by GM and WM fiber crossings. Low FA values are typically found at the boundaries between WM and GM, and the segmentation algorithm performs poorly in these regions. However, to mitigate against this, we used empirical threshold values of FA less than 0.2 and MD more than $1.2 \times 10^{-3}$ mm$^2$/s during the creation of the whole-brain WM mask to remove voxels potentially contaminated by CSF and/or GM. Unlike FA, the 1st percentile of MD is relatively safe since the difference of MD values between GM and WM is very small. The values of FA may also be decreased by WM lesions, such as the ones seen in 5 subjects. However, when these 5 subjects were excluded from the logistic regression model, we found no statistically significant change in the OR for prediction of blast exposure.
CONCLUSION

PTSD severity was associated with high 1st percentile of MD on DTI, WM lesions on MRI, and the severity of exposure to combat events, in addition to age and time since last tour of duty. Self-report of mild TBI was not significantly associated with PTSD severity. We speculate that brain changes detected on MRI and DTI may be due to neurochemical alterations induced by chronic stress or by subclinical brain injury from blast exposure. Our observation that blast exposure was associated with low 1st percentile of FA on DTI supports the latter. While MRI and DTI may be uniquely suited for identifying veterans at risk for PTSD, their high cost and limited availability may limit their use as screening tools. Nevertheless, accurate and object measures of brain injury, practical or otherwise, are clearly needed to better understand the complex relations among blast exposure, combat stress, and PTSD.

PET Imaging Reveals Damage From Head Injury in Living Athletes

Medscape
Caroline Cassels
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For the first time, researchers have been able to see the brain damage caused by repetitive head injury in living athletes, a finding that may help facilitate early identification and intervention in those suffering from trauma-related neurodegeneration.

Using PET imaging with FDDNP, a novel chemical tracer that binds to tau and amyloid in the brain, investigators at the University of California, Los Angeles, found that compared with control individuals, tau protein deposits were higher in all subcortical regions and in the amygdala in a group of 5 retired National Football League (NFL) players.

Tau proteins have previously been linked to chronic traumatic encephalopathy (CTE) as well as Alzheimer's disease (AD). A degenerative condition caused by the accumulation of tau in the brain, CTE has been associated with memory loss, confusion, progressive dementia, depression, suicidal behavior, personality changes, abnormal gait, and tremors.

However, until now, researchers were only able to confirm the presence of these proteins on autopsy.

"Early detection of tau proteins may help us to understand what is happening sooner in the brains of these injured athletes. Our findings may also guide us in developing strategies and interventions to protect those with early symptoms, rather than try to repair damage once it becomes extensive," principal investigator Gary Small, MD, said in a statement.
The study was published online January 22 in the American Journal of Geriatric Psychiatry.

Common Occurrence

With an estimated incidence of 1.6 to 3.8 million, sports-related repetitive mild traumatic brain injury due to contact sports are common.

According to the authors, research has shown that retired contact-sport athletes such as NFL players show higher rates of personality, behavioral, and mood disturbances, mild cognitive impairment, and dementia compared with control individuals.

In addition, there appears to be a dose-dependent effect. The investigators note that research in NFL players has shown that those with 3 or more reported concussions during their career were 3 times more likely to be diagnosed with depression and 5 times more likely to be diagnosed with mild cognitive impairment (MCI).

To determine whether brain tau deposits can be detected in living athletes using FDDNP-PET, potentially paving the way for early detection and intervention, the investigators conducted a study in 5 former NFL players who ranged in age from 45 to 73 years and who had a history of 1 or more concussions and cognitive or mood symptoms.

The players represented a range of positions, including linebacker, quarterback, guard, center, and defensive lineman.

Study participants underwent neuropsychiatric evaluations with the Hamilton Rating Scale for Depression and the Mini–Mental State Examination (MMSE) and underwent FDDNP-PET. PET signals in subcortical and cortical regions of the brain were then compared with those of 5 matched control participants.

Critical First Step

Results showed that the players had more depressive symptoms than the control participants and generally had lower MMSE scores, suggesting evidence of cognitive decline.

Three players had MCI, 1 had dementia, and 1 was cognitively normal.

The investigators found that FDDNP signals were higher in players compared with control participants in all subcortical regions and the amygdala areas that produce tau deposits following trauma. They also found that players who had experienced a greater number of concussions had higher FDDNP levels.
"The FDDNP binding patterns in the players' scans were consistent with the tau deposit patterns that have been observed at autopsy in CTE cases," study author Jorge R. Barrio, PhD, said in a release.

The investigators note that although FDDNP also binds to beta amyloid, a hallmark of AD, previous research has shown that amyloid plaques are found in less than one third of CTE cases, suggesting that the FDDNP signal in the NFL players mainly represents tau deposits.

"Providing a noninvasive method for early detection is a critical first step in developing interventions to prevent symptom onset and progression in CTE," said Dr. Small. He added that FDDNP is the "only imaging marker currently available that can provide a measure of tau in living humans."

The researchers added that in 2000, direct and indirect costs of traumatic brain injury was approximately $77 billion in the United States alone.

"Given the large number of people at risk — not just athletes but military personnel, auto accident victims, and others — the potential public health impact is considerable."

Hemodynamic Complications Common in Traumatic Brain Injury

Medscape
Pauline Anderson
7 Feb 2013

A new study shows that cerebral arterial vasospasm (VSP) and intracranial hypertension are common outcomes of combat-related traumatic brain injury (TBI), so much so that its authors are recommending daily transcranial Doppler (TCD) monitoring to better recognize and manage these complications.

TCD ultrasound technology is portable and cost-effective, although dedicated and knowledgeable personnel are needed to properly administer the tests, according to the study's lead author, Alexander Razumovsky, PhD, director, Sentient NeuroCare Services, Hunt Valley, Maryland.

The research was presented here on February 6 at the International Stroke Conference (ISC) 2013.

Retrospective Evaluation

The study included 122 consecutive patients with TBI admitted to Walter Reed National Military Medical Center from October 1, 2008, to November 30, 2012, and identified through a computerized registry. Of these, 88 had sustained a penetrating injury and 34, a closed-head injury. The mean age of the cohort was 26.1 years, and the mean time from injury to hospital admission was 6.7 days.
Researchers retrospectively evaluated the patients for TCD-determined incidence of posttraumatic cerebral vasospasm and intracranial hypertension. TCD recordings included pulsatility indices of the anterior and posterior circulation vessels and mean cerebral blood flow velocities (CBFV, in cm/s).

Mild, moderate, and severe vasospasm was considered present if mean CBFV was 100 to 139 cm/s, 140 to 199 cm/s, and greater than 200 cm/s, respectively.

The study found that mild, moderate, and severe VSP involving anterior circulation vessels was present in 71%, 42%, and 16% of patients, respectively. Mild, moderate, and severe VSP involving posterior circulation vessels was found in 57%, 32%, and 14% of patients, respectively.

Intracranial hypertension was recorded in 43% of the patient sample.

Eight patients (7%) underwent transluminal angioplasty for posttraumatic symptomatic vasospasm treatment.

According to Dr. Razumovsky, the study results suggest that TCD may help detect early signs of cerebral vasospasm and facilitate better management strategies, for example, determining urgent aggressive treatment and continuous invasive monitoring, where appropriate.

Surrogate Test

According to another study author, Rocco Armonda, MD, Colonel, Medical Corp, U.S. Army; director, cerebrovascular surgery and interventional neuroradiology, Walter Reed National Military Medical Center, a neurological examination "trumps all other means of monitoring." However, he said the Doppler test serves as a "surrogate" in cases where a good neurologic examination is not possible, including emergency situations.

"We're talking about the most severe brain injuries," with patients coming in comatose and with multiple traumas that could include orthopedic injuries and chest injuries and often heavily sedated, said Dr. Armonda.

He stressed that information from Doppler imaging "has to be used in context" and along with other appropriate measures and bedside tools. "The idea here is that it's not the tool that makes the difference; it's the therapy that the tool then helps define."

A limitation of the study was that it included only younger patients and that there are no established criteria for vasospasm in young people, said Dr. Razumovsky.

Very Select Group

Approached to comment, David T. Lackland, PhD, professor of epidemiology and neurosciences, Medical University of South Carolina, Charleston, said this was a "nice preliminary study" but because it was carried out on a "very, very select group of individuals," additional work needs to be done in other populations.
Larry B. Goldstein, MD, professor of neurology at Duke University Medical Center, Durham, North Carolina, had a few issues with the study. For one thing, the patient population was "difficult" because it was a mix of patients with closed-head and penetrating head injuries, he told Medscape Medical News. "Complications of those 2 can overlap but there are certainly differences."

As well, said Dr. Goldstein, it wasn't clear whether the patients in the study also had traumatic subarachnoid hemorrhage. "We know from other studies that traumatic subarachnoid hemorrhage carries a risk of vasospasm not too different from non-traumatic subarachnoid hemorrhage."

Dr. Razumovsky is a full-time employee of the private practice (Sentient NeuroCare Services) that currently is under contract with the Army Medical Department. Dr. Lackland and Dr. Goldstein have disclosed no relevant financial relationships.

Other

Restoring the Blood-Brain Barrier

Journal of the American Medical Association
Tracy Hampton, PhD
6 February 2013

Mice lacking an anti-inflammatory protein called annexin A1 (ANXA1) exhibit significant decreases in the integrity of the blood-brain barrier, reports a team led by researchers at the Queen Mary, University of London, in England (Cristante E et al. Proc Natl Acad Sci U S A. doi:10.1073/pnas.1209362110 [published online December 31, 2012]).

The investigators also found a significant reduction in circulating ANXA1 in the plasma of patients with multiple sclerosis and a loss of the protein in the cerebral microvasculature of patients who died with the disease. Exposing in vitro cerebrovascular endothelial cells to recombinant ANXA1 restored cellular features (such as cytoskeleton integrity) needed to reinstate the integrity of the blood-brain barrier. Also, giving ANXA1 to mice that lacked the protein decreased leakage through the blood-brain barrier.

The findings suggest that administration of ANXA1 might have the potential to help in the treatment of various degenerative neurological diseases such as multiple sclerosis, Alzheimer disease, and Parkinson disease—all conditions that compromise the blood-brain barrier.
The death of Claire Squires, a 30-year-old hairdresser who died one mile from the finish line of the 2012 London Marathon, was likely caused by consuming Jack3d (USPlabs), a performance-enhancing supplement that contained the amphetaminelike stimulant 1,3-dimethylamylamine (DMAA).

Jack3d was banned by the Medicines and Healthcare Products Regulatory Agency (MHRA) four months after Squires's death. DMAA has been linked to psychiatric disorders, MI, and stroke and is banned by the World Anti-Doping Agency (WADA), as well as banned in Australia, Canada, and the US. In 2012, two US soldiers taking the supplement died of cardiac arrest while performing military exercises. Despite these bans, it is still widely available online.

According to a report in the Guardian, Squires purchased Jack3d online. Her boyfriend, Simon Van Herreweg, told the newspaper that Squires took the supplement "a couple of times" before the marathon but "didn't really get on with it." She was hoping to break her previous marathon best of four hours and planned to take one scoop of the mixture in a drink to see if it could push her through to the end of the marathon.

Complicating the picture slightly is that Squires also had an irregular heartbeat, which might have made her particularly vulnerable to the supplement. However, the coroner does not believe that the arrhythmia played a role in her death. Dr Jon van der Walt, the physician who conducted the postmortem, said the "balance of probability" suggested that the cause of death is cardiac failure caused by extreme physical exertion complicated by DMAA. Squires, according to van der Walt, had been active for many years, something he regarded as a stress test. "She had been able to do all this before; therefore, it is unlikely that she had fatal arrhythmia."

Speaking with heartwire, Dr Aaron Baggish (Massachusetts General Hospital, Boston) said the situation is somewhat tricky because the presence of DMAA in Squires's system doesn't establish that this was the cause of her death but added that the product can fairly be described as a health risk. He said that DMAA is also banned by the US Anti-Doping Agency and the International Olympic Committee (IOC) because it is considered performance enhancing. Taken during intense exercise, DMAA not only would increase heart rate but also contractility, which has the overall effect of increasing the heart's workload.

"If somebody was teetering on the edge of having a rhythm problem, and I know there was some concern about the young lady having an irregular heartbeat, for what that's worth, this could be the final straw," said Baggish.
As the cardiologist for the Boston Athletic Association, the organizers of the prestigious Boston Marathon, Baggish said the medical directors are preparing to send out a mass email to registered runners training for the April race encouraging them to become aware of these banned substances and to avoid any stimulants, such as DMAA. "Without any clear evidence that this is what killed this woman, it still makes sense for people to stay away from it and other similar products."

**Socioeconomic Inequalities in Lung Cancer Treatment: Systematic Review and Meta-Analysis**

PLOS Medicine
Lynne F. Forrest, Jean Adams, Helen Wareham, Greg Rubin, Martin White
5 February 2013

Abstract

**Background**

Intervention-generated inequalities are unintended variations in outcome that result from the organisation and delivery of health interventions. Socioeconomic inequalities in treatment may occur for some common cancers. Although the incidence and outcome of lung cancer varies with socioeconomic position (SEP), it is not known whether socioeconomic inequalities in treatment occur and how these might affect mortality. We conducted a systematic review and meta-analysis of existing research on socioeconomic inequalities in receipt of treatment for lung cancer.

**Methods and Findings**

MEDLINE, EMBASE, and Scopus were searched up to September 2012 for cohort studies of participants with a primary diagnosis of lung cancer (ICD10 C33 or C34), where the outcome was receipt of treatment (rates or odds of receiving treatment) and where the outcome was reported by a measure of SEP. Forty-six papers met the inclusion criteria, and 23 of these papers were included in meta-analysis. Socioeconomic inequalities in receipt of lung cancer treatment were observed. Lower SEP was associated with a reduced likelihood of receiving any treatment (odds ratio [OR] = 0.79 [95% CI 0.73 to 0.86], p<0.001), surgery (OR = 0.68 [CI 0.63 to 0.75], p<0.001) and chemotherapy (OR = 0.82 [95% CI 0.72 to 0.93], p = 0.003), but not radiotherapy (OR = 0.99 [95% CI 0.86 to 1.14], p = 0.89), for lung cancer. The association remained when stage was taken into account for receipt of surgery, and was found in both universal and non-universal health care systems.

**Conclusions**
Patients with lung cancer living in more socioeconomically deprived circumstances are less likely to receive any type of treatment, surgery, and chemotherapy. These inequalities cannot be accounted for by socioeconomic differences in stage at presentation or by differences in health care system. Further investigation is required to determine the patient, tumour, clinician, and system factors that may contribute to socioeconomic inequalities in receipt of lung cancer treatment.

Please see later in the article for the Editors' Summary

Editors' Summary

Background

Lung cancer is the most commonly occurring cancer worldwide and the commonest cause of cancer-related death. Like all cancers, lung cancer occurs when cells begin to grow uncontrollably because of changes in their genes. The most common trigger for these changes in lung cancer is exposure to cigarette smoke. Most cases of lung cancer are non-small cell lung cancer, the treatment for which depends on the “stage” of the disease when it is detected. Stage I tumors, which are confined to the lung, can be removed surgically. Stage II tumors, which have spread to nearby lymph nodes, are usually treated with surgery plus chemotherapy or radiotherapy. For more advanced tumors, which have spread throughout the chest (stage III) or throughout the body (stage IV), surgery generally does not help to slow tumor growth and the cancer is treated with chemotherapy and radiotherapy. Small cell lung cancer, the other main type of lung cancer, is nearly always treated with chemotherapy and radiotherapy but sometimes with surgery as well. Overall, because most lung cancers are not detected until they are quite advanced, less than 10% of people diagnosed with lung cancer survive for 5 years.

Why Was This Study Done?

As with many other cancers, socioeconomic inequalities have been reported for both the incidence of and the survival from lung cancer in several countries. It is thought that the incidence of lung cancer is higher among people of lower socioeconomic position than among wealthier people, in part because smoking rates are higher in poorer populations. Similarly, it has been suggested that survival is worse among poorer people because they tend to present with more advanced disease, which has a worse prognosis (predicted outcome) than early disease. But do socioeconomic inequalities in treatment exist for lung cancer and, if they do, could these inequalities contribute to the poor survival rates among populations of lower socioeconomic position? In this systematic review and meta-analysis, the researchers investigate the first of these questions. A systematic review uses predefined criteria to identify all the research on a given topic; a meta-analysis is a statistical approach that combines the results of several studies.

What Did the Researchers Do and Find?
The researchers identified 46 published papers that studied people with lung cancer in whom receipt of treatment was reported in terms of an indicator of socioeconomic position, such as a measure of income or deprivation. Twenty-three of these papers were suitable for inclusion in a meta-analysis. Lower socioeconomic position was associated with a reduced likelihood of receiving any treatment. Specifically, the odds ratio (chance) of people in the lowest socioeconomic group receiving any treatment was 0.79 compared to people in the highest socioeconomic group. Lower socioeconomic position was also associated with a reduced chance of receiving surgery (OR = 0.68) and chemotherapy (OR = 0.82), but not radiotherapy. The association between socioeconomic position and surgery remained after taking cancer stage into account. That is, when receipt of surgery was examined in early-stage patients only, low socioeconomic position remained associated with reduced likelihood of surgery. Notably, the association between socioeconomic position and receipt of treatment was similar in studies undertaken in countries where health care is free at the point of service for everyone (for example, the UK) and in countries with primarily private insurance health care systems (for example, the US).

What Do These Findings Mean?

These findings suggest that patients in more socioeconomically deprived circumstances are less likely to receive any type of treatment, surgery, and chemotherapy (but not radiotherapy) for lung cancer than people who are less socioeconomically deprived. Importantly, these inequalities cannot be explained by socioeconomic differences in stage at presentation or by differences in health care system. The accuracy of these findings may be affected by several factors. For example, it is possible that only studies that found an association between socioeconomic position and receipt of treatment have been published (publication bias). Moreover, the studies identified did not include information regarding patient preferences, which could help explain at least some of the differences. Nevertheless, these results do suggest that socioeconomic inequalities in receipt of treatment may exacerbate socioeconomic inequalities in the incidence of lung cancer and may contribute to the observed poorer outcomes in lower socioeconomic position groups. Further research is needed to determine the system and patient factors that contribute to socioeconomic inequalities in lung cancer treatment before clear recommendations for changes to policy and practice can be made.
Objectives: To examine health indicators of same-sex partnered veterans as compared with their opposite-sex partnered veteran and nonveteran peers. Methods: Same-sex partner status was derived by self-reported same-sex partnerships in data from the 2004 Behavioral Risk Factor Surveillance System. Outcome variables included health risk disparities associated with sexual minority status (e.g., frequent mental distress) and veteran status (e.g., firearm ownership). Stratified multiple logistic regression models were used to examine the association of same-sex partnered veteran status with health indicators. Results: Same-sex partnered veterans had higher odds of being overweight and keeping firearms in the house compared with same-sex partnered nonveterans. Same-sex partnered veterans were less likely than opposite-sex partnered veterans to be overweight, and they were more than twice as likely to be current smokers when compared with opposite-sex partnered nonveterans. Conclusions: Findings suggest both that some health disparities patterns identified by same-sex partnership status among the general population also exist among veteran populations, and that some unique distinctions may exist, particularly related to BMI and firearm ownership. Collection of information about sexual minority status within Department of Veterans Affairs data sources is needed to more accurately assess the health of this minority population.

Introduction

The universe of approximately 22 million U.S. veterans of military service is not a homogenous population, and disparities exist among different subpopulations of veterans. For instance, American Indian/Alaska Native veterans have higher odds of being uninsured than their White veteran counterparts, and McGinnis et al found that Black and Hispanic veterans diagnosed with HIV had higher rates of mortality than their HIV-positive White peers. In addition to racial/ethnic differences, disparities among veterans may also exist by sexual orientation. Numerous health disparities identified among general samples of lesbian, gay, and bisexual (i.e., sexual minority) populations—such as smoking, poor mental health, and health care coverage—may exist among sexual minority veterans. To date, there are little to no published reports about the health and risk behaviors of the nearly 1 million sexual minority persons estimated to be among the U.S. veteran population.

Studies using general samples of sexual minority individuals document several differences in health and risk behaviors, such as significantly higher rates of smoking, alcohol use, and overweight/obesity (particularly among lesbians compared with heterosexual women). There are also significantly greater rates of poor mental health (e.g., depression, distress) and suicidal ideation and suicide attempt among sexual minority populations, as well as victimization, particularly adverse childhood experiences. The literature is less clear about access and health insurance coverage. Some studies report significantly lower access and coverage among sexual minority persons compared with their heterosexual peers, whereas others report no differences, depending on gender and method of identifying sexual minority status.

Given the mounting evidence of health inequities identified among sexual minority populations, sexual minority veterans may be a group within the general veteran population that is likely to experience several health disparities, and recent preliminary evidence seems to support this. For instance, Blosnich et al reported that sexual minority veterans had higher prevalence of suicidal ideation than their heterosexual veteran peers. In a large sample of women veterans, Booth et al found that women who reported same-sex sexual partners had higher prevalence of lifetime substance use disorders and sexual assault. Even after adjusting for demographic characteristics and sexual assault, women veterans who had same-sex sexual partners were over three times more likely to report a lifetime substance use disorder.
In addition to empirical evidence, there is also theoretical underpinning for disparities among sexual minority veterans. Generally, the minority stress framework has been used to explain elevated negative health outcomes among sexual minority persons. Minority stress maintains that members of a devalued minority status experience unique, elevated, and persistent stress derived from social persecution and bias. Building from this framework, sexual minority veterans may have experienced particularly pronounced stress, stigma, and harassment since they were part of an institution (i.e., the military) that overtly discriminated against lesbian, gay, and bisexual people under the policy that was commonly referred to as “Don’t Ask, Don’t Tell” (DADT).

Although this information sheds some light on the sexual minority veteran population, basic demographic and health and risk behaviors of sexual minority veterans are not well documented in population-based data. Using a national probability-based sample of U.S. adults, the present analyses aimed to examine demographic characteristics (e.g., income, education), health and risk indicators (e.g., frequent mental distress, current smoking), and health care utilization among veterans with same-sex partners and compare them with their same-sex partnered nonveteran, opposite-sex partnered veteran, and opposite-sex partnered nonveteran peers.

Methods

The data for this project are from the 2004 National Behavioral Risk Factor Surveillance System (BRFSS) dataset, which is deidentified and publically available from the CDC web site. The BRFSS is currently the world’s largest telephone-based national survey, which is conducted in all 50 U.S. states, the District of Columbia, and U.S. territories (i.e., surveying entities). Respondents are drawn using probability-based methods for each surveying entity’s sampling frame of noninstitutionalized adults aged 18 years or older. Each year the CDC compiles a required core questionnaire that must be asked by all surveying entities and reported back to the CDC. The 2004 BRFSS had a median response rate of 52.7%. Further information about the BRFSS methodology is available from the CDC web site.

In 2004, the CDC added a Family Planning module to the core questionnaire, which asked respondents about behaviors related to birth control and having children. The module was asked to all male respondents ages 18 to 60 and to all female respondents ages 18 to 44 who never had a hysterectomy and who currently were not pregnant (n = 146,690). The first question of the Family Planning module asked, “Are you or your [partner] doing anything now to keep from getting pregnant?” Response options included “Yes; No; No partner/not sexually active; Same sex partner; Do not know/not sure; Refuse to answer.” For the present analysis, same-sex partnered persons were defined as those who indicated having a same-sex partner (n = 1,077). Persons who indicated yes or no to using birth control methods were defined as the opposite-sex partnered reference group (n = 119,610). Because the same-sex partnered sample was comprised of only those persons in same-sex couples (i.e., people who were partnered), we excluded from the analytic sample anyone who responded “no partner/not sexually active” (n = 22,572), those who indicated “don’t know/not sure” (n = 333), and refusals (n = 3,098), creating a sample of 120,687 partnered persons.

All persons who indicated that they had a history of active duty military service were asked “Which of the following best describes your service in the United States military?” Response options included (1) currently on active duty, (2) currently in a National Guard or Reserve unit, (3) retired...
from military service, (4) medically discharged from military service, and (5) discharged from military service. Respondents indicating current active duty (n = 1,934) were excluded from analysis, creating a final analytic sample of 118,753 respondents. Other demographic variables included education (college degree vs. less than a college degree), sex, and a continuous measure of age that was derived from a variable supplied by the CDC, in which mean imputation was used for respondents who did not report their ages. Approximately 0.7% of the sample had imputed ages. Income was recoded to those who earned less than $25,000/year vs. those who earned $25,000/year or more. Because of the small sample size of same-sex partnered veterans, race was recoded to non-Hispanic White vs. a combined group of non-White and Hispanic persons.

Health care utilization was operationalized by three different questions. Veterans were asked if they had received any care from a Veterans Health Administration (VHA) facility in the last 12 months (yes/no). Having health care coverage plan (yes/no) was gathered from the question, “Do you have any kind of health care coverage, including health insurance, prepaid plans such as HMOs, or government plans such as Medicare?” Not seeking care because of medical cost (yes/no) was defined from responses to “Was there a time in the past 12 months when you needed to see a doctor but could not because of cost?”

Risk behaviors included current smoking (i.e., smoking >100 cigarettes within one’s lifetime and currently smoking on some days or every day), being overweight (BMI ≥ 25 but <30) or obese (BMI ≥ 30), and risk for binge drinking (any adult having ≥5 alcoholic drinks in one sitting in the past 30 days). Of note, in 2004, the CDC did not use sex-specific definitions of binge drinking. Also, because sexual minority persons have high rates of suicidal behavior, and ownership of firearms has been associated with increased risk for suicide both in the general population and specifically among veterans, we also examined whether respondents indicated having a firearm in their homes (yes/no). Health indicators included frequent mental distress, defined as reporting ≥6 days of poor mental health in the last 30 days, self-rated fair/poor general health status, and experiencing any limitation in activities as a result of physical, mental, or emotional problems.

Prevalence estimates, stratified by both same-sex partnership status and veteran status, were compared through χ2 tests of independence (except age, which was analyzed with independent samples t-tests). We employed a Holm’s sequential Bonferroni adjustment when examining the bivariate differences in order to prevent type I error. However, given that Bonferroni adjustments inflate type II error, we elected to report all crude p-values to demonstrate where significant findings would have occurred without an adjusted significance level (i.e., if the typical significance level of p < 0.05 had been used). However, only p-values less than or equal to the Bonferroni-adjusted significance level are indicated as statistically significant. Odds of health indicators among same-sex partnered veterans, adjusted for demographic characteristics, were tested with three different sets of multiple logistic regression models comparing same-sex partnered veterans with (1) same-sex partnered non-veterans, (2) opposite-sex partnered veterans, and (3) opposite-sex partnered nonveterans. Adjusted odds ratios are reported with 95% confidence intervals. Both because the analytic sample was a subset of the national BRFSS dataset and because the sample size of same-sex partnered veterans was small, estimates are unweighted. All analyses were conducted using Stata/SE ver. 12. This study was approved by the Institutional Review Board at the Syracuse Veterans Affairs Medical Center.

Results
Overall, both same-sex partnered veterans and opposite-sex partnered veterans were significantly older than their nonveteran counterparts, and same-sex partnered veterans were significantly younger than opposite-sex partnered veterans (Table I). A substantially greater proportion of same-sex partnered women reported veteran status than opposite-sex partnered women. Similar proportions of same-sex partnered veterans and opposite-sex partnered veterans used VHA services and had any health care coverage. However, significantly more same-sex partnered veterans than opposite-sex partnered veterans reported not seeking medical care because of cost (p = 0.01); although after adjustment for multiple testing, this was not statistically significant.

In multivariate models adjusted for demographic confounding variables, different constellations of higher/lower odds of outcomes surfaced in health risk behaviors among same-sex partnered veterans. When compared with their opposite-sex partnered veteran counterparts, same-sex partnered veterans had lower odds of obesity and lower odds of keeping firearms in the home (Table II). Same-sex partnered veterans had elevated, but not significantly higher, estimates of binge drinking and smoking compared with their opposite-sex partnered veteran peers. The lack of statistical significance could be as a result of lower power because of small sample size as the lower bounds of both confidence intervals for these two outcomes were 0.93 and 0.92, respectively.

Several differences were also found in comparisons between same-sex partnered nonveterans and same-sex partnered veterans. First, among same-sex partnered respondents, veterans more than twice as likely to keep firearms in their homes, and veterans were 61% more likely to be classified as overweight than their nonveteran counterparts. When same-sex partnered veterans were compared with opposite-sex partnered nonveterans, same-sex partnered veterans were less likely to have firearms in their home and were more than twice as likely to be current smokers. Some health indicators were also elevated, but not significant, in comparisons between same-sex partnered veterans and opposite-sex partnered nonveterans, particularly fair/poor health status and experiencing activity limitations. Again, with lower confidence interval bounds relatively close to 1.00, the inability to detect significance may have been as a result of small sample size.

Discussion

To our knowledge, this article uses data from the first year in which the BRFSS collected a measure of sexual minority status (i.e., same-sex partnership) in the core questionnaire, and it is the first report about demographic and health information about same-sex partnered veterans from a national probability-based sample. Some health-related differences surfaced that corroborate previous findings among general samples of sexual minority persons, namely higher prevalence of smoking and lower prevalence of obesity (at least among men). This alignment with general population trends in differences noted by sexual orientation suggests that similar patterns of disparities may exist among the general veteran population. However, findings suggest that same-sex partnered veterans have some unique distinctions that may be related to having a history of military service.

First, when compared with their same-sex partnered nonveterans peers, a higher proportion of same-sex partnered veterans were overweight. Since physical exercise and fitness are components of military training, this finding seems contradictory in that one may hypothesize that veterans would be in better shape given both the military requirement of physical fitness and the initial health screening to get into the military. One
explanation may be BMI misclassifying physically fit persons—particularly muscular persons—as overweight. This bias stems from the inability of BMI as a height–weight calculation to account for muscle mass. Thus, if same-sex partnered veterans tend to exercise more or be more physically fit than their same-sex partnered nonveteran peers, excess muscularity may be misclassified in BMI as being overweight. However, given documented weight-related disparities among sexual minority and heterosexual populations, future research is needed to further explore veteran status as a potential modifier of weight status among sexual minority persons.

Second, same-sex partnered veterans had twice the odds of their same-sex partnered nonveteran counterparts of keeping firearms in the home. Again, history of military service likely explains this difference since part of military instruction includes familiarity with firearms through weapons training. The elevated likelihood of keeping firearms in the home may be of particular concern for sexual minority veterans for three key reasons.

First, sexual minority populations in general may have higher prevalence of suicidal ideation, suicide attempt, and poor mental health associated with suicide risk. Second, veterans in general have higher rates of firearm-related suicide. Third, having firearms in the home is an independent risk factor for gun-related suicide. At the intersection of these three factors are sexual minority veterans, but data are unavailable to examine if they have higher risk for suicide. Future studies are needed to explore, for example, if among a high-risk group (i.e., sexual minority persons), a subpopulation that has greater access to firearms (i.e., sexual minority veterans) may have greater risk of suicide. Unfortunately, there are currently no data to facilitate such analyses, but inclusion of sexual minority measures on large national surveillance projects would help in addressing this paucity of data.

In terms of health care coverage, same-sex partnered persons were no different than opposite-sex partnered persons, which aligns with some findings from other studies that show no difference in health insurance coverage, but contrasts with other research that suggests inequity in health care access. For example, Conron et al did not find a difference in health care coverage among persons who self-identified as sexual minority persons, nor did Cochran et al who measured sexual minority status using self-report sexual behavior. Conversely, Heck et al and Buchmueller and Carpenter both identified health insurance disparities among sexual minorities defined by being in a same-sex couple.

The present findings seem to stand somewhere in between these studies in that these results used a measure of same-sex couples, but had findings more similar to studies that used self-reported and behavioral measures of sexual minority status. The discordant findings among these studies and the present results may result from differences in operationalization of sexual minority status. Further research is needed to clarify these findings.

There was no difference detected in VHA utilization among same-sex partnered veterans and opposite-sex partnered veterans. These results suggest that, despite the potential impacts of “Don't Ask, Don't Tell” or the potential harassment experienced during military service, same-sex partnered veterans may utilize VHA services at the same prevalence as their opposite-sex partnered veteran peers. Assuring competent and sensitive health care for sexual minority patients is a developing area in health services, and numerous studies have documented bias, discrimination, and lack of knowledge about health issues unique to sexual minority populations within clinical systems. Furthermore, The Joint Commission has recently issued a field guide explaining accreditation standards that have been amended to gauge sexual minority issues in
health care facilities. Given both the clear presence of same-sex partnered veteran patients in the VHA and changing accreditation standards, the VHA may benefit from several activities, such as self-assessment of health professionals’ needs and experiences with providing care for sexual minority veterans and amending data collection systems to enable examination of outcomes and unique needs of sexual minority patients.

The use of same-sex partnership status as a measure of sexual minority status presents potential issues of misclassification since both bisexual persons and unpartnered gay or lesbian person may not be identified through such a measure. Additionally, some of the risk measures examined may be modified by having a partner. For example, smoking behaviors have been shown to be modified by being in an intimate partnered relationship. Future research is needed to examine whether significant differences arise in health indicators using different definitions of sexual minority status (e.g., self-identity vs. same-sex partnership) among veteran populations.

Several other limitations must be noted. First, as cross-sectional data, no causal statements are possible between the outcomes and explanatory variables. Second, generalizability of results are limited by several factors, including the response rate to the 2004 BRFSS, the analytic sample being a subset of only partnered adults, and the survey question having specific exclusion criteria. Additionally, given both the limits of the sample and the small numbers of same-sex partnered minority veterans, the estimates are unweighted, thus not accounting for complex survey design or nonresponse coverage. Lastly, the measure of veteran status did not permit ascertainment of either objectively confirming actual military service or gathering information pertinent to veteran health, such as tour of duty, number of deployments, and combat exposure.

Conclusions

With the recent repeal of DADT, military servicepersons can now serve openly, but clearly sexual minorities have served well before—and during—the era of DADT. Thus, there is a need to monitor and address health issues of sexual minority veterans. Our results indicate that, among this sample, similar percentages of sexual minority and heterosexual veterans received care through the VHA in the previous year, yet nothing is known about whether the potential disparities that affect sexual minority populations—such as HIV, asthma, different forms of cancer, and suicidal behavior—also occur in VHA veterans or among veterans in general. Unfortunately, these issues will remain invisibly embedded amidst the population until data sources include measures of sexual minority status.