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March 2013
Executive Summary

March 2013 – Journal coverage for March mirrored coverage from February with behavioral health, medical protocol and training, and TBI comprising a significant amount of journal articles, while research of note focused on family presence during CPR and its effect on anxiety from the *New England Journal of Medicine*, and information on a new assessment tool for TBI from *Military Medicine*.

*The Lancet* focused on the Iraq War’s impact on the behavioral health of the military population and non-behavioral health effects on civilian and military populations. Regarding medical protocol and training, *Military Medicine* primarily discussed information related to alternative opportunities and/or best practices: the mixture of various methods for aeromedical evacuations, the safe and effective transport of gauze, the use of ultrasound for diagnosis, and the relationship of anxiety on the individual when present during CPR.

With recent media coverage questioning TBI measuring tools, *Military Medicine* released research on the Assessment of Military Multitasking Performance, a new tool to measure and classify forms of mTBI to more effectively provide treatment options.

Contrary to previous reporting periods, nutrition and obesity were absent from peer-reviewed journals during March.

Medical Journal Coverage

Behavioral Health

The Lancet: When the violence of war comes home

While a significant amount of research has focused on the psychopathological results of deployment-related trauma, few studies have sought to determine the resulting risk of violence arising from deployments. This article summarizes the findings of the first study to assess a potential link between violent offenses and UK military personnel deployed to Iraq and Afghanistan. The article focuses on the severity of interpersonal violence in comparison to those who suffer non-personal trauma, and it notes the impact of moral injury on Soldiers’ mental health and underscores the importance of better understanding the potential interactions between risk factors and violence.
Legislators have expressed concern over the number of ex-military personnel who are in the criminal justice system for violent offenses, and no studies have examined the link between deployment and arrests for violence. Results of this groundbreaking study indicate that violent offenders are the most prevalent offender types, violent offenses are most common in men aged 30 years or older, and deployments are not independently associated with increased risk of violent offending. Markers that increased risk of violent offending included combat exposure, increased exposure to traumatic events, alcohol misuse, and PTSD.

A series of 46 interviews of deployed male Soldiers comprises research in an effort to analyze driving-related stressors and their effect on Soldiers’ anxiety. Results indicate a significant percentage, 96 percent, of these Soldiers had experienced a violent act while driving, and they also reported driving differently following exposure to combat. Research on post-combat driving anxieties and situations that may trigger aggressive responses allows Army Medicine to better understand potential PTSD triggers.

For Soldiers who received enlistment waivers for medical concerns, researchers sought to determine the relationship between those waivers and potential negative behavioral health concerns. The study features 8,943 Soldiers with enlistments ranging from 2003 to 2008. These Soldiers were more likely to test positive for illegal drug use or exhibit misconduct. Information related to the origins of Soldier misconduct allows Army Medicine to message on possible non-combat causes of these behaviors.

The presence of visceral leishmaniasis (VL) on a US contractor recently deployed to Iraq and Afghanistan spurred researchers to review and determine the rates of VL among Soldiers in the Middle East. The study determined that cases of VL acquired in the Middle East show signs of
fever, abdominal pain, and hepatosplenomegaly though there were rare cases of diffuse lymphadenopathy. Research such as this underscores Army medical research’s benefit to international civilian medicine.

**Military Medicine: Tuberculosis Among Nonimmigrant Visitors to U.S. Military Installations**

The lack of a requirement to evaluate nonimmigrant visitors for tuberculosis (TB) presents a challenge for managing the disease in an at-risk military population. In studying six unique case studies, researchers emphasize the need for TB screening in visitors from high-risk countries as well as diagnosis and treatment for visitors with TB.

**Military Medicine: Building Military Influenza Surveillance Capacity in West Africa**

Detailing the military responsibility to account for containing outbreaks of acute respiratory infections, the study focuses on the U.S. Navy’s efforts in Ghana, Burkina Faso, and Côte d'Ivoire. The study analyzes surveillance systems currently in place in the aforementioned countries and highlights the possible effect of proximity to animal farms in the spread of disease. Army Medicine can highlight the US’ role as an international leader in public health campaigns.

**Military Medicine: Use of Sterile Pre-Fabricated Antibiotic Beads in the Combat Hospital Setting**

This study highlights the difficulty of administering antibiotic medication in a combat setting. Researchers set out to determine the sterility of 50 packs of antibiotic beads. Analyzed over a 6-week period, the beads saw an average shelf life of 9.3 days and the beads remained sterile, showing no growth of organisms from cultures. Army Medicine can utilize the results of the study to publicly discuss the efficacy of combat-related innovations such as antibiotic beads.

**Medical Protocol and Training**

**Military Medicine: Development of a Valid Simulation Assessment for a Military Dismounted Assault Task**

Australian researchers developed a simulation to assess Soldiers’ physical capacity to perform a variety of tasks under circumstances that varied depending on type of terrain, load carried, bound duration, and movement velocity. This simulation can assist leadership in determining the viability of physical requirements that can assist Army Medicine in addressing common physical ailments among infantry including lower back injury.

March 2013
Military Medicine: The Rush University Advanced Trauma Training Program, A Novel Approach for Military Trauma Training

Nearly 90 percent of combat deaths occur before the patient is able to reach a treatment facility. This statistic not only points to the importance of rapid transportation, but it underscores the import of exemplary training for early intervention. Researchers set out to create a comprehensive course to train medics to assess and treat various injuries, including PTSD and TBI. Thus far, the courses have been effective in enhancing early battlefield intervention.

Military Medicine: Increasing Access to Care and Reducing Mistrust: Important Considerations When Implementing the Patient-Centered Medical Home in Army Health Clinics

This study sought to determine which individual characteristics, including religious participation, mistrust, racism, spirituality, perceived access to care and continuity of care, might play a role in patient outcome. Results indicate that perceived access to care is the only individual characteristic that is positively linked with better mental health status. Researchers determined that higher levels of mistrust tend to have lower patient satisfaction and poorer health. Such research is timely given Army Medicine’s focus and current media attention surrounding behavioral health.

Military Medicine: Analyzing the Future of Army Aeromedical Evacuation Units and Equipment: A Mixed Methods, Requirements-Based Approach

This review of MEDEVAC and FVL programs seeks to determine parameters for improved use. Results confirm previous predications that travel faster than 250 knots and ranged longer than 300 nautical miles are best undertaken by FVL. This study recommends a specific engine bridging strategy based on altitude and endurance, and it suggests that FVL MEDEVAC aircraft become weaponized.

Military Medicine: Evaluation of Hemostatic Field Dressing for Bacteria, Mycobacteria, or Fungus Contamination

To determine best practices for field dressing and eradicating potential pathogen growth in wounds, Military Medicine studied 16 samples of QuikClot and CELOX gauze and found no contaminants, even after being subjected to field conditions. Knowing QuikClot and CELOX are compatible with combat scenarios allows Army Medicine to effectively use these products and message on their effectiveness and reliability.

Military Medicine: Utilization of Bedside Urogenital Ultrasound in an Austere Combat Setting: Enterovesicular Fistula Case Report
The case study of the use of ultrasound on a Marine highlights the unique and non-invasive role that ultrasound technology and experts can provide in a combat setting. Through this technology, medical professionals were able to transport the Marine to a “higher echelon of care,” where he was diagnosed with Crohn’s disease and an associated enterovesicular fistula.

**Military Medicine: Isolation of Leclercia adecarboxylata From an Infected War Wound in an Immune Competent Patient**

With the focus on a rare disease, leclercia adecarboxylata, this case study focuses on a Soldier in need of medical attention, specifically amputations, following an IED blast. Through follow-up, problems with the Soldier’s sciatic nerve prompt further investigation and discovery of the rare disease. Army Medicine can highlight the effective treatment and diagnosis even of extremely rare diseases.

**Military Medicine: Efficacy of Tourniquets Exposed to the Afghanistan Combat Environment Stored in Individual First Aid Kits Versus on the Exterior of Plate Carriers**

In order to determine the most effective way of carrying and transporting tourniquets in the Afghan environment, researchers study three primary experimental options: on the plate carrier, individual First-Aid Kits (IFAK) wrapped in manufacturer packaging, and IFAK with no manufacturer packaging. Determining best practices in terms of storage and transport for tourniquets allows Army Medicine to highlight highly detailed information related to combat care.

**New England Journal of Medicine: Family Presence during Cardiac Resuscitation**

In research conducted by French researchers, this journal article offers a case study of Roberta, an elderly woman with deteriorating health. The discussion follows her downturn in health but focuses on the presence of the family during cardiopulmonary resuscitation (CPR). The article features two opinions: one supports family presence during CPR while the other discourages the behavior. The pro-family perspective points to research that found increased anxiety, depression, and PTSD-related symptoms in instances where the family was not allowed to witness CPR. The potential for developing PTSD while witnessing life-saving techniques in near-death situations may offer Army Medicine insight into the potential relationship with combat and the disorder.

**Medscape: Loving Gaze: When Family Witness CPR at Home**

Building on research noted immediately above, the article extrapolates the relationship between CPR and anxiety, depression and potentially PTSD from the article in the New England Journal of Medicine.

**Physiological Injuries and Surgery**

March 2013
Military Medicine: Simultaneous Bilateral Anterior Shoulder Fracture Dislocation Following a Seizure: A Case Report

This case study examines a rare instance where a Soldier received a simultaneous, bilateral, anterior dislocation of the glenohumeral joint. These injuries are most common in cases of electrocution or seizures, and this investigation indicates that early reduction and immobilization produce the best long-term results.

Military Medicine: Contributors to the Overall Health of the War Fighter

This article seeks to point out the possible causes and conditions of common injuries including musculoskeletal injuries, mental health and overall physical health. The author specifically discusses aerobic and endurance training that does not directly enhance fitness in real-world scenarios. Military training and fitness requirements, in many cases, are strenuous and do not offer rest time that would prevent injury. In assessing poor health, the author specifically addresses the overuse of energy drinks and supplements, unhealthy diets, out-of-date physical training programs, tobacco use, and excessive alcohol consumption as having detrimental impacts on overall health.

Military Medicine: Concurrent Acute Motor and Sensory Axonal Neuropathy and Immune Thrombocytopenic Purpura

The prevalence of Guillain–Barré syndrome (GBS), acute motor and sensory axonal neuropathy (AMSAN) and immune thrombocytopenic purpura (ITP) is the focus of research in Military Medicine. The abstract notes GBS does not often occur simultaneously with other autoimmune diseases, so the existence of GBS, AMSAN, and/or ITP is of interest to researchers. With 11 previous cases of GBS and ITP, researchers offer the first case of AMSAN and ITP occurring concurrently. Army Medicine can build upon the discovery of AMSAN and ITP occurrence by detailing the rarity of the situation but also by pointing to the discovery of these rare incidences.

Military Medicine: It's Not a Tumor, It's a Cataract! Rapid Myopic Progression and Diplopia Secondary to the Formation of an Oil-Drop Cataract

In differentiating between a tumor and cataract, the article focuses on the early detection of oil-drop cataracts. Without early detection, reporting patients may see “unnecessary workups and referrals.” The case report of a 56-year-old male was referred to the clinic due to rapid, unexplained myopic progression. The patient returned to the clinic for three additional visits indicating a lack of expertise in the original diagnosis. Army Medicine can discuss comprehensive medical knowledge while highlighting medical professionals who are able to diagnose early and avoid costly referrals.
Military Medicine: Superior Mesenteric Artery Syndrome in a Young Military Basic Trainee

Further discussing early diagnosis, this article analyzes the case of a 19-year-old female patient who was transported to the emergency department following three weeks of abdominal pain. The initial assertion was intestinal angina, but several of her conditions indicated that intestinal angina was not the affliction. She suffered from superior mesenteric artery (SMA) syndrome. Again, the rare nature of the syndrome allows effective diagnoses and treatments to positively frame Army Medicine’s devotion to unique, patient-centered care.

Medscape: Combined Paravertebral and Intrathecal vs Thoracic Epidural Analgesia for Post-thoracotomy Pain Relief

With the assumption that thoracic epidural analgesia (TEA) is an effective pain reliever post-thoracotomy, researchers set out to determine whether thoracic paravertebral block (PVB) and intrathecal opioid (ITO) can be combined to match the efficacious nature of TEA. Results indicate slightly variant outcomes but no significant differences. Army Medicine can include messaging on “best practices” research when discussing hard-to-diagnose or -treat illnesses or injuries.

PTSD

Psychiatric Annals: Virtual Reality Applications to Address the Wounds of War

This review determines how and where virtual reality is being implemented to treat PTSD for Soldiers returning from the wars in Iraq and Afghanistan. Various simulations exist that allow Soldiers to relive their experiences on the ground as well as those that encourage them to operate easily in normal daily routines. A limited number of virtual reality programs allow Soldiers to interact with a virtual therapist, allowing them to overcome the stigma associated with therapy. Army Medicine can utilize research to determine the viability of virtual reality treatment for PTSD.

Annals of Surgery: Posttraumatic Stress Disorder (PTSD) Screening and Early Intervention After Physical Injury

This article discusses the exemplary care under a group of medical personnel at Harborview Injury Prevention and Research Center and their level 1 trauma center program. Their care is singled out because of the high-level of attention in treating the psychological impact of traumatic injuries. Harborview found that patients who developed PTSD are more likely to be female, less severely injured, intentionally injured, blood alcohol positive, younger and to have prolonged hospitalization.
Military Medicine: Participation in Outdoor Recreation Program Predicts Improved Psychosocial Well-Being Among Veterans With Post-Traumatic Stress Disorder: A Pilot Study

In seeking effective treatments for PTSD, researchers invited 74 veterans to a 2-day, 3-night excursion to explore fly-fishing as an alternative therapy. The veterans participated in numerous assessments over varied time periods in order to qualify for the trip. Fly-fishing results in improvements in attentiveness and positive mood, with significant reductions in negative mood, anxiety, depression, and somatic symptoms of stress. Common media coverage of fly-fishing as an alternative therapy can be coupled with Army messaging on the efficacy of the therapy.

PLOS Medicine: Adjunctive Atypical Antipsychotic Treatment for Major Depressive Disorder: A Meta-Analysis of Depression, Quality of Life, and Safety Outcomes

With the widespread prescription of antipsychotic medication as a treatment for depression, the study seeks to identify the risks and benefits of this tendency. The study findings urge caution for medical professionals in evaluating the cost-benefit analysis due to the slight benefit of reducing observer-rated depressive symptoms, the lack of benefit regarding quality of life, and the realization of potential treatment-related harm. Army Medicine is able to apply the same risk-benefit model in public messaging to discuss the possibility for severe and adverse effects related to antipsychotic drug treatments for depression.

Sleep

JAMA: Primary Care vs Specialist Sleep Center Management of Obstructive Sleep Apnea and Daytime Sleepiness and Quality of Life

Sleep apnea is a growing national problem that is affecting Soldier health, and researchers sought to determine the benefits and drawbacks of primary care when compared to specialist sleep center treatment. Both care facilities offered the same treatment options and outcomes were the same, suggesting treatment options and facilities are comparable. Such information is useful to Army medical personnel tasked with either treating or referring patients with sleep apnea.

Substance Abuse

JAMA: Improving Opioid Prescribing

In order to help set a precedent of guidelines that attempt to curb opioid analgesics, New York City Mayor Michael Bloomberg issued guidelines for patients discharged from the city’s emergency departments. These guidelines are unlikely to affect even a very significant portion of the public,
but they offer guidance for organizations hoping to curb opioid addiction. The guidelines encourage low doses of short-acting opioids rather than long-lasting slow-release products. The guidelines address the potential danger of mixing various prescriptions. This review is especially pertinent, as media has focused on the predominance of opioid abuse in the military and veteran communities.

**JAMA: Chronic Back Pain With Possible Prescription Opioid Misuse**

The prevalence of opioid misuse has led doctors to tighten restrictions on those who use the drug long-term. These restrictions ensure the patient is taking the prescribed amount at the correct time in order to prevent binging, drug sale or other forms of misuse. This interview discusses the complications in prescribing opioids long-term for chronic back pain including, inability to drink alcohol, addiction to other medications and illegal substances and unexpected physical response. Lessons learned can impact the medical community, which often suffers from back pain and utilizes prescriptions.

**Suicide**

**Neuropsychopharmacology: Connecting inflammation with glutamate agonism in suicidality**

Research on brain inflammation related to suicide points to the presence of two acids, quinolinic and kynurenic, an agonist and antagonist of NMDA receptor. Ketamine, similar to kynurenic acid, is an antagonist to NDMA receptors. The study analyzed the brain fluids of 64 suicide attempters with 36 control subjects, finding quinolinic acid is elevated in the fluids of attempters. Following lumbar punctures, the quinolinic acid levels significantly decrease. Results on factors that may contribute to the suicidality of patients allows Army Medicine to better understand the possible factors that link brain function and suicide and offer a space where Army leaders can destigmatize suicidal Soldiers.

**TBI**

**Military Medicine: AMPAR Peptide Values in Blood of Nonathletes and Club Sport Athletes With Concussions**

The prevalence of TBI and concussions in the military and its long-term implications can be lessened by early diagnosis and treatment. Researchers determined that AMPAR peptide assay combined with ImPACT and neuroimaging is a viable tool for diagnosing and assessing the severity of concussions.

**Neurology: Summary of evidence-based guideline update: Evaluation and management of concussion in sports**

March 2013
Researchers set out to update the 1997 American Academy of Neurology (AAN) practice parameter as relates to sports concussions. Their review of research and literature from 1995 to 2002 focused on concussion risk, diagnosis, post-concussion impairment and interventions to enhance recovery. Their findings indicate that concussion history and younger age are both predictors for concussion impairments, while data is insufficient to show any intervention enhances recovery.

Military Medicine: Development of a Measure to Inform Return-to-Duty Decision Making After Mild Traumatic Brain Injury

The lack of a measuring tool used to diagnose mTBI led researchers, stakeholders and end users to research literature and interviews in order to develop a tool to bridge the gaps in clinical feasibility, usability across facilities, military face validity, and mission-critical mTBI vulnerabilities. The coalition introduces the Assessment of Military, Multitasking Performance, a comprehensive tool used to diagnose mTBI especially as relates to a Soldier’s return to duty. Recent coverage of ineffective mTBI technology and approaches allows Army Medicine to point to this new assessment in discussing effective ways to categorize mTBI.

Military Medicine: Semi-Automated Trajectory Analysis of Deep Ballistic Penetrating Brain Injury

With the prevalence of penetrating head injuries (PHIs) in combat operations, researchers analyzed computed tomography (CT) to determine the efficacy of CTs versus manual methods. As CT provides support on the automation and quantification of penetrating TBI, the use of CT becomes invaluable with the increased likelihood of combat hospitals having limited expertise on staff. Army Medicine is able to highlight technical innovation such as the use of CTs in evaluating TBI or PHI especially in discussions of budget cuts that may relate to the lack of availability of civilian medical professionals.

Medscape: MRI Finds Possible Vascular Injury After Mild Head Injury

The article highlights the finding of primary injury to the vasculature early after mTBI. These lesions, according to researchers, may lead medical professionals to imaging-based biomarkers that may potentially differentiate various forms of TBI in order to effectively target medications. Army Medicine can utilize the research to show the complexity and variation in forms of TBI.

Other

Military Medicine: Recurrent Headache in Military-Dependent Children and the Impact of Parent Deployment
Recurrent headaches are common among all children, though rates increase among children who experience stressful life events including injury, bullying, or the absence of a parent from the home. Researchers sought to determine the rate at which military children experience recurring headaches and the potential link with their military parent's deployment. Results indicate that 30 percent of children interviewed experienced recurring headaches with more than half of those experiencing worsening symptoms during a 12-month period regardless of deployment. Researchers advise military parents to understand this link and to improve the child’s quality of life to facilitate proper diagnosis, support, and treatment.

The Lancet: Adverse health consequences of the Iraq War

The review of the health dangers brought about by the Iraq War highlights both the effects on the displaced Iraqi people, and the effect on the military and their families. For military personnel, the article focuses on TBI, PTSD, and other neuropsychological and psychosocial issues. The reporting focuses on "lessons learned" from the Iraq War, such as the impact on non-combatant Iraqi civilians, mental health disorders, environmental damage, and the possible prevention of the adverse health consequences.

Medical Journal Clips

Behavioral Health

When the violence of war comes home

The Lancet
David Forbes; Richard A Bryant
16 March 2013

There has been considerable focus on documenting the psychopathological sequelae of deployment-related trauma, but, despite much speculation, few data are available to ascertain the risk of violence arising from deployments. In The Lancet, Deirdre MacManus and colleagues extend the findings from self-report studies and use the data from criminal records to show for the first time the link between combat and interpersonal violence. The consequences of interpersonal violence are enormous in terms of human suffering, even greater than those caused by non-interpersonal trauma. These findings draw attention to an important public health issue arising after deployment.

The finding by MacManus and colleagues that combat increased the risk of violence leads to questions about the potential mechanisms underpinning this elevated risk. The data presented in this study show an association, rather than a specification of the actual mechanisms that could potentially be targeted in intervention programmes that might reduce violence in individuals who have had combat roles. Insights from the
The current study into possible directions for future research come from the findings that alcohol use and arousal both conferred an additional risk for violence. There is evidence that trauma and symptoms of post-traumatic stress disorder can lead to increased alcohol use, arguably as a means of self-medicating the distress arising from the symptoms. There is also much evidence that alcohol use contributes to temper outbursts and violence due to reduced inhibition. There is also evidence that elevated arousal heightens risk of temper outbursts, suggesting that the increased arousal in post-traumatic stress disorder might lower the threshold for loss of temper and engagement in violence.

Another possibility is the role of moral injury, a recently studied response in troops engaged in the current conflicts. Moral injury has been defined as “perpetrating, failing to prevent, bearing witness to, or learning about acts that transgress deeply held moral beliefs and expectations”. Military personnel are not only exposed to a high likelihood of direct contact with enemy combatants but are also at increased risk of being responsible for deaths of non-combatants. Participation in specific activities during combat, such as killing another individual or failing to protect a fellow soldier, might lead to distress that is characterised by shame, guilt, or anger that can be directed towards oneself or others. There are findings that suggest that killing during deployment in Iraq contributes to subsequent anger, even after controlling for combat exposure. The experiences during conflict might violate an individual’s core set of moral values to the point that they engage in violent and antisocial behaviours after deployment. Additionally, military training promotes use of aggression as an adaptive response to threat during combat. Individuals in combat roles with a history of combat exposure might therefore be likely to have often activated this aggression in response to perceived threats. Accordingly, level of combat exposure can be a contributory factor because of the perception of threat and the response pattern of aggression.

To maximise the value of the current findings, we need to better understand the potential interactions between these risk factors and the mechanisms underpinning violence. Addressing these risks or problems in isolation of each other could miss the underlying mechanisms. For example, how do combat exposure, post-traumatic stress disorder, hyperarousal, and substance abuse interact with each other? Further, what other factors that were not measured in MacManus and colleagues’ study contribute to violence after deployment? Post-deployment stressors, decompression procedures, family or social support systems, and an array of other factors could moderate the relation between combat and violence after deployment. These need to be studied with a multivariable framework to fully comprehend the roles of these potential risk factors in violence. Importantly, as the investigators noted, criminal tendency before military service was a risk factor for violence, suggesting that we need to understand how combat exposure interacts with pre-existing patterns in individuals who serve in conflict zones.

The investigators correctly note that the findings of this study do not suggest that we should screen for criminal history before selection of personnel who will be deployed for combat. Instead, the current findings draw attention to the need for a more concerted effort to understand the specific mechanisms that affect how the experiences of combat can enhance risk of violence after deployment. By understanding these factors, we might develop more informed prevention and intervention programmes for troops as they reintegrate into civilian life.

**Violent offending by UK military personnel deployed to Iraq and Afghanistan: a data linkage cohort study**
Summary

Background

Violent offending by veterans of the Iraq and Afghanistan conflicts is a cause for concern and there is much public debate about the proportion of ex-military personnel in the criminal justice system for violent offences. Although the psychological effects of conflict are well documented, the potential legacy of violent offending has yet to be ascertained. We describe our use of criminal records to investigate the effect of deployment, combat, and post-deployment mental health problems on violent offending among military personnel relative to pre-existing risk factors.

Methods

In this cohort study, we linked data from 13 856 randomly selected, serving and ex-serving UK military personnel with national criminal records stored on the Ministry of Justice Police National Computer database. We describe offending during the lifetime of the participants and assess the risk factors for violent offending.

Findings

2139 (weighted 17·0%) of 12,359 male UK military personnel had a criminal record for any offence during their lifetime. Violent offenders (1369 [11·0%]) were the most prevalent offender types; prevalence was highest in men aged 30 years or younger (521 [20·6%] of 2728) and fell with age (164 [4·7%] of 3027 at age >45 years). Deployment was not independently associated with increased risk of violent offending, but serving in a combat role conferred an additional risk, even after adjustment for confounders (violent offending in 137 [6·3%] of 2178 men deployed in a combat role vs 140 [2·4%] of 5797 deployed in a non-combat role; adjusted hazard ratio 1·53, 95% CI 1·15—2·03; p=0·003). Increased exposure to traumatic events during deployment also increased risk of violent offending (violent offending in 104 [4·1%] of 2753 men with exposure to two to four traumatic events vs 56 [1·6%] of 2944 with zero to one traumatic event, 1·77, 1·21—2·58, p=0·003; and violent offending in 122 [5·1%] of 2582 men with exposure to five to 16 traumatic events, 2·01, 1·50—2·70; p<0·0001).

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Interpretation

Alcohol misuse and aggressive behaviour might be appropriate targets for interventions, but any action must be evidence based. Post-traumatic stress disorder, though less prevalent, is also a risk factor for violence, especially hyperarousal symptoms, so if diagnosed it should be appropriately treated and associated risk monitored.

Introduction

Reporting of high profile cases of violence committed by veterans of the Iraq and Afghanistan conflicts within their home communities and families has intensified concerns about the consequences of deployment in this population of veterans and the wider society. The US Institute of Medicine reported that criminal justice involvement is one of the most significant problems for veterans of the Iraq and Afghanistan conflicts. There has been much public debate in both the USA and the UK about the proportion of prisoners in the criminal justice system, many with convictions for violent offending, who have served in the military, especially in operations in Iraq or Afghanistan. Violent behaviour is often assumed to directly result from the deployment experiences of military personnel. However, robust research into the pathways that might lead to military personnel committing violent offences and the effect of pre-military risk factors, deployment experiences, particularly combat exposure, and post-deployment mental health problems, are lacking.

Substantial evidence over the past 10 years of the conflicts in Iraq and Afghanistan has suggested adverse effects of combat on the mental health of military personnel. In addition to increased risks of post-traumatic stress disorder, anxiety, depression, and alcohol misuse, there is evidence to suggest that some military personnel are at increased risk of engaging in risky and violent behaviour on return from deployment. The results of some studies have also shown that the risk of violence might be partly related to pre-existing risk factors, including early antisocial behaviour and social adversity. Mental health problems after deployment, such as post-traumatic stress disorder, alcohol misuse, and anger management problems are often cited as potential mediators of the link between combat and subsequent violence. However, much of this research has been limited by self-report measures of violence and cross-sectional study design. A recent attempt to investigate involvement of US veterans with the criminal justice system relied on self-report of arrests.

In our study, we link data from an established cohort of UK military personnel with lifetime official criminal records to describe life-course offending in a sample of the UK Armed Forces; describe the sociodemographic and military factors associated with violent offending; assess the effect on violent offending of deployment, serving in a combat role, and exposure to traumatic events on deployment; and assess the role of mental health and behaviour problems and alcohol misuse in post-deployment violent offending.

Methods

Study design and participants
In our data linkage cohort study, we used a randomly selected sample of 13,856 UK military personnel who were actively serving in the UK Armed Forces at the time of recruitment into the study. The Defence Analytical Services and Advice, UK Ministry of Defence, did the sampling. The sampling was done by assigning each individual to a stratum with a random number, sorting them into ascending order, and selecting the first X individuals (X was the sample size for the stratum). The stratification variables were service and enlistment type (regular or reserve). Recruitment and data gathering were undertaken in two phases. The randomly selected sample of 17,689 participants in phase 1 (June, 2004, to March, 2005) were personnel who had been deployed to Iraq between Jan 18, and June 28, 2003, and those who had been trained but had not yet been deployed. In phase 2 (November, 2007, to September, 2009), an additional random sample of 6,628 personnel, who were newly recruited to the military after the beginning of the study (the replenishment sample) and thus had a chance of being deployed, was added to the sample to ensure that the demographic characteristics of the current UK Armed Forces were represented in the study. A further random sample of 1,789 personnel, who had been deployed to Afghanistan, was added in response to the UK commitment to the military operation in Afghanistan. Special Forces personnel were excluded. Full details of recruitment have been published previously.

13,856 participants completed a questionnaire at phase 1, phase 2, or both phases: 3,872 participants who responded at phase 1 (overall, 10,299 [58%] responded at phase 1) were not followed up at phase 2; 6,427 (68%) of 9,395 participants contacted at phase 2 completed a questionnaire at both phase 1 and phase 2; 2,663 (40%) of 6,628 respondents from the replenishment sample and 894 (50%) of 1,789 respondents from the Afghanistan sample completed a questionnaire at phase 2 only.

Ethics approval was provided by the National Research Ethics Service, King's College Hospital Research Ethics Committee, UK Ministry of Justice, UK Ministry of Defence, and the UK Criminal Records Office.

**Procedures**

Information was gathered by use of a self-report questionnaire about sociodemographics, experiences and behaviour before joining the military, experiences since joining the military (including deployments and combat exposure), and health and behaviour after deployment. The list of publications with data from this questionnaire can be accessed at the King's Centre for Military Health Research. Personnel were classed as deployed if they reported having served in Iraq or Afghanistan since the beginning of the Iraq conflict in 2003. Deployment was defined as combat or non-combat (eg, explosive ordnance disposal, signals, medical, and logistics) based on the reported main role in deployment. Questions were asked about a range of traumatic events during deployment (including, seeing personnel wounded or killed, landmine attacks, and coming under mortar or artillery fire), adapted from the combat experience scale.

Post-deployment mental health variables were defined as symptoms of common mental disorder in the past month with a cutoff score of four or above on the General Health Questionnaire-12 (GHQ-12); cases of post-traumatic stress disorder in the last month using a cutoff score of 50 or greater on the 17-item National Centre for Posttraumatic Stress Disorder Checklist (PCL-C) and 30—49 for subthreshold post-traumatic stress disorder; alcohol misuse in the past year with a score of 16 or greater on WHO’s Alcohol Use Disorders Identification Test (AUDIT). Additionally, the symptoms reported on the PCL-C were used to ascertain if an individual met the criteria for the four post-traumatic stress disorder symptom
clusters according to the operationalised criteria to be set out in the new Diagnostic and Statistical Manual, fifth edition (DSM-5): re-experiencing symptom cluster (one of five potential re-experiencing phenomena [B1—5 in DSM-IV]); avoidance symptom cluster (one of two potential active avoidance symptoms [C1—2 in DSM-IV]); emotional numbing cluster (two of five potential symptoms of emotional numbing [C3—7 in DSM-IV]); and hyperarousal symptom cluster (two of five potential hyperarousal symptoms [D1—5 in DSM-IV]).

At phase 2, a validated measure of aggressive behaviour was used to score frequency of reported verbal, property, or physical aggression or number of threats of violence in the past month (never, once, two to four, five or more) based on the stem "In the past month, how often did you": get angry at someone and yell or shout at them; get angry with someone and kick or smash something, slam the door, or punch the wall; get into a fight with someone and hit the person; and threaten someone with physical violence. The total of these scores for the responses was the aggression score for the past month.

The cohort data were linked to the Ministry of Justice Police National Computer (PNC) database, which is the UK national criminal offence database for recording the standard offences. Offences that are dealt with by military police are recorded in military criminal records and should be transferred to the PNC database if they are recordable offences—ie, any offence punishable by imprisonment and some non-imprisonable offences.

We linked the cohort database with the PNC database by using a matching process based on surnames, forenames, initials, sex, and date of birth. Only automatic matches were accepted. Linkage provided the date of charge for the offence, type of offence, and the outcome of the offence for each individual with a criminal record. Convictions, cautions, reprimands, and warnings were all deemed offences. The offences were classified according to their legal descriptions: interpersonal violence (further categorised into non-physical interpersonal violence such as threats, verbal abuse, and harassment; less serious physical interpersonal violence including common assault, battery, and affray; more serious physical interpersonal violence including actual bodily harm, grievous bodily harm, and homicide); other aggressive behaviours (including dangerous driving, criminal damage); sexual offences (violent, non-violent); drug-related and alcohol-related offences; and other offences (not included in other aggressive behaviours—eg, motoring offences). Sentencing was classified as custodial or non-custodial.

Statistical analyses

Participants’ offences are described from birth until the end of the follow-up (July 31, 2011). The observation period for the analyses began at the start of the study (Jan 23, 2003) or date of entry into the military if later and continued until the participant committed a violent offence, died, or follow-up ended (right censored). Variation in time at risk was accounted for with Cox regression modelling. Nelson Aalen plots were used to confirm that the data conformed to the assumption of proportional hazards. A number of potential confounding factors, such as sociodemographic and military characteristics and pre-military violent offending, were identified a priori. Factors independently associated with both exposure and outcome (at the 5% level) were included in the adjusted multivariable Cox regression models.
Because of the low numbers of women (n=1497) and the military policy that women should be deployed in non-combat roles mostly, they were included only in the initial descriptive analyses and analyses of the sociodemographic factors associated with violence but not subsequent analyses of the association between deployment, combat and combat-related trauma, and violent offending. The effect of deployment (as a time-varying exposure variable) on violent offending was analysed with multivariable Cox regression models to adjust for confounders simultaneously. Deployed participants were then followed up from completion of the study questionnaire until first subsequent violent offence, death by any cause, or end of follow-up. The effects of combat role, exposure to traumatic events on deployment and post-deployment mental health, and behaviour problems on the risk of violent offending were analysed. Potential confounders were included simultaneously in adjusted multivariable Cox regression models. The mediating role of each of the post-deployment mental health problems in the association between combat role and violent offending and traumatic experiences and violent offending was estimated by adding these variables to the unadjusted and adjusted Cox regression models.

Hazard ratios (HRs), 95% CIs, and two-sided p values are presented (significance defined as p<0.05). Weights were created to account for sampling fractions and response rates. All analyses were done in STATA MP (version 10.0) with survey commands.

Role of funding source

The UK Medical Research Council funded this project. The UK Ministry of Defence funded the data gathering. The authors’ work was independent of the UK Ministry of Defence, which had no role in the analysis, interpretation, or decision to submit this report. We disclosed the contents of the report to the Ministry of Defence at the point we submitted it for publication.

Results

The sample population consisted of 13 856 participants of predominantly regular (full-time military personnel) status (11 652 [weighted 92.7%] of 13 856), with a median age of 37 years (IQR 30.6–44.5) by the end of the follow-up. The sample was representative (ascertained by comparison with data from the UK Defence Statistics) of the deployable UK Armed Forces at the time of selection: predominantly men (12 359 [89.7%]), serving in the army (9049 [63.5%]) as opposed to the Royal Air Force (2644 [20.1%]) or the Royal Naval Service (including Royal Navy and Royal Marines, 2163 [16.5%]), and of non-officer rank (11 086 [80.3%]). 5980 (46.0%) participants had achieved an education level of up to high school equivalent. Median age of enlistment was 19.7 years (17.6–23.7) and median time spent in service was 12.2 years (7.5–21.3). 8443 (59.0%) participants were still in service by the end of the follow-up.

2197 (weighted 15.7%) of 13 856 participants—2139 (17.0%) of 12 359 men and 58 (3.9%) of 1497 women—committed one or more offences during their lifetime. 8753 (98.5%) of 8887 offences were committed by men. 1875 (85.3%) offences resulted in a conviction and 322 (14.6%) a caution, reprimand, or warning. Violent offenders (n=1398) were the most common type of offenders—64% of 2197 offenders in the sample and 10.1% (1369 [11.0%] men and 29 [1.9%] women) of the entire sample. 423 (29.9%) of 1398 violent offenders had committed an offence of more serious interpersonal violence—ie, of a severity of at least actual bodily harm. When the prevalence of men who had committed any offence in
their lifetime and the prevalence of men who had committed a violent offence in their lifetime was measured in the sample by age group, the prevalences of all offender types and violent offenders (29·8% and 20·6%, respectively) were much higher in men younger than 30 years than in the older age groups and fell with increasing age. 891 (6·4%) of the total study sample had committed an alcohol-related or drug-related offence and 834 (6·0%) had committed an offence classed as other. There were 72 (0·5%) sex offenders in the total sample. The peak (modal) age for first offence was 19 years (median 21 years, IQR 18—26). 214 (1·7%) of 13 856 participants and 139 (1·6%) of 9017 individuals deployed to Iraq or Afghanistan had a recorded custodial sentence at some point in their lifetime.

Following adjustment, the strongest predictors of violent offending, after sex and age, were rank and pre-service violent offending. By phase 2 of data gathering, 9095 participants (weighted 53·0%) had been deployed to Iraq or Afghanistan. More participants offended per 1000 person years at risk in the post-deployment period than in the pre-military and in-service pre-deployment periods for all types of offending. The number of participants who committed a violent or drug-related or alcohol-related offence per 1000 person years at risk increased from the pre-service to in-service periods and then increased further in the post-deployment period. By contrast, the number of participants who had committed other types of offences (eg, fraud and theft) per 1000 person years at risk decreased from the pre-service period to the in-service period and then increased after deployment.

Deployment of men to Iraq or Afghanistan was associated with an increase in subsequent violent offending compared with men who had not been deployed (553 [weighted 7·0%] of 8280 vs 220 [5·4%] of 4080; HR 1·21, 95% CI 1·03—1·42; p=0·018), but this association did not remain after adjustment for age, educational level, pre-service violent offending, rank, service, engagement status, and serving status (1·01, 0·85—1·20; p=0·893). However, for men who had been deployed in a combat role the risk of violent offending was significantly greater than the risk for those deployed in a non-combat role (violent offending in 137 [6·3%] of 2178 men deployed in a combat role vs 140 [2·4%] of 5797 deployed in a non-combat role). Pre-military violent offending was associated with being deployed in a combat role (160 [46·6%] of 373 men who had a history of pre-military violent offending were deployed in a combat role vs 2018 [27·5%] of 7602 men who did not have a history of pre-military violence; odds ratio 2·31, 95% CI 1·81—2·93, p<0·0001; adjusted odds ratio 1·79, 1·34—2·39, p=0·0001) and accounted for some of the association between combat role and violent offending. With adjustment for this and the other confounders in the multivariable analyses, a reduced but significant association between combat role and subsequent violent offending remained (adjusted HR 1·53, 95% CI 1·15—2·03; p=0·003). In the deployed group, exposure to two or more traumatic events was associated with a significantly increased risk of violent offending after adjustment for confounders (violent offending in 104 [4·1%] of 2753 men with exposure to two to four traumatic events vs 56 [1·6%] of 2944 with none to one traumatic event, 1·77, 1·21—2·58, p=0·003; and violent offending in 122 [5·1%] of 2582 men with exposure to five to 16 traumatic events, 1·65, 1·12—2·40, p=0·01) and the risk increased with increasing number of traumatic events (test for trend, p=0·032).

Effect of combat role and traumatic experiences during deployment on risk of violent offending in 8280 male military personnel on return from deployment

In the analysis of the post-deployment mental health and behaviour problems, alcohol misuse, post-traumatic stress disorder, and high levels of self-reported aggressive behaviour were all strong predictors of subsequent violent offending among those who had been deployed (violent
offending in 120 [weighted 9·0%] of 1363 men with alcohol misuse vs 155 [2·3%] of 6768 men with no alcohol misuse, adjusted HR 2·16, 1·62—2·90, p<0·0001; violent offending in 25 [8·6%] of 344 men with clinical post-traumatic stress disorder vs 221 [3·0%] of 7256 with no symptoms of post-traumatic stress disorder, 2·20, 1·36—3·55, p=0·001; violent offending in 56 [6·7%] of 856 men with an aggression score of six to 16 vs 22 [1·2%] of 1685 with an aggression score of zero, 2·47, 1·37—4·46, p=0·003. Symptoms of post-traumatic stress disorder showed a dose—response relation with risk for violent offending; the risk increased with increased burden of symptoms of post-traumatic stress disorder. We undertook further similar multivariable Cox regression analyses to assess each of the four post-traumatic stress disorder symptom clusters for prediction of violent offending after return from deployment and noted that the association with violent offending was stronger for the hyperarousal symptom cluster (96 [6·9%] of 1554 men with hyperarousal symptoms were convicted of a violent offence vs 177 [2·7%] of 6619 without hyperarousal symptoms; adjusted HR 2·01, 95% CI 1·50—2·70; p<0·0001) than symptoms of avoidance (65 [6·3%] of 1069 men with avoidance symptoms were convicted of a violent offence vs 209 [3·1%] of 7108 without avoidance symptoms; 1·49, 1·07—2·07; p=0·018), symptoms of emotional numbing (57 [5·7%] of 1046 men with symptoms of emotional numbing were convicted of a violent offence vs 217 [3·2%] of men without symptoms of emotional numbing; 1·50, 1·06—2·13; p=0·023), or re-experiencing symptoms (75 [5·6%] of 1450 men with re-experiencing symptoms were convicted of a violent offence vs 199 [3·0%] of 6727 without re-experiencing symptoms; 1·34, 0·98—1·83; p=0·065).

Post-deployment mental health and behaviour problems and violent offending

Each post-deployment mental health problem was added to the regression models for risk of violent offending associated with serving in a combat role and exposure to traumatic events to assess its role as a mediator. Addition of alcohol misuse to the unadjusted model slightly reduced the strength of the association between serving in a combat role and violent offending from an HR of 2·86 (95% CI 2·19—3·73; p<0·0001) to 2·52 (1·92—3·29; p<0·0001). Adjustment for post-traumatic stress disorder alone had less effect, reducing the unadjusted HR to 2·74 (2·09—3·61; p<0·0001); adjustment for symptoms of common mental disorder had a minimal effect (2·84, 2·16—3·72; p<0·0001). Adjustment for all three problems in the Cox regression model and all the confounding variables reduced the adjusted risk slightly from an HR of 1·53 (1·15—2·03, p=0·003; adjusted for confounders only) to 1·43 (1·07—1·91, p=0·017; adjusted for confounders and all three mental health problems). Post-deployment mental health problems seemed to have a greater mediating role in the association between exposure to traumatic events and violent offending. Addition of alcohol misuse to the unadjusted model reduced the HR for the risk associated with exposure to six or more traumatic events from 3·34 (2·33—4·77; p<0·0001) to 2·83 (CI 1·93—4·13; p<0·0001). Addition of post-traumatic stress disorder in the unadjusted model reduced the HR to 2·98 (2·05—4·43; p=0·001), and symptoms of common mental disorder again had less effect, reducing the HR to 3·26 (2·33—4·77; p<0·0001). When the model was adjusted for all three mental health problems and the other confounders, the association was reduced from 1·65 (1·12—2·40, p<0·0001; adjusted for confounders only) to 1·48 (0·99—2·22, p=0·057; adjusted for confounders and all three mental health problems).

Discussion

The results of our analyses show that violent offenders were the most common types of offenders and the rate of offending in the post-deployment period was greater than in the in-service pre-deployment and pre-military periods for all types of offending including violent offending. Pre-military
violent offending and lower military rank were some of the strongest predictors of violence. Deployment was not independently associated with increased risk of violent offending, but, among deployed personnel, serving in a combat role conferred an additional risk of violent offending after adjustment for pre-military violent offending and sociodemographic and military factors for violence (rank, service, engagement status, and serving status). More frequent exposure to traumatic events during deployment also increased the risk of violent offending. Post-deployment mental health problems and high levels of self-reported aggressive behaviours were important risk factors.

Panel
Research in context
Systematic review
We searched PsycINFO, PubMed, and Google Scholar for published articles using a combination of terms: “combat”, “deployment”, “Iraq”, “Afghanistan”, “military”, “aggression”, “violence”, “criminal”, “offending”, “posttraumatic stress disorder”, “alcohol misuse”, “anger”, and “aggression”. No date or language restrictions were applied. One author (DM) downloaded and read abstracts and identified the 40 most relevant studies. Additionally, we searched Google and Google Scholar and the UK Ministry of Justice website for reports and data about offending, incarceration, and criminal justice involvement in the military and general population. Much of the research literature is based on US military samples. Evidence suggests that some military personnel are at increased risk of engaging in risky and violent behaviour on return from deployment. Results of some studies have shown that the risk of offending in military populations is related more to pre-existing risk factors, including previous offending, than to combat exposure. Mental health problems, such as post-traumatic stress disorder, alcohol misuse, and anger have been shown to be associated with post-deployment violence. Only one UK study has been published in which the results suggested that serving in a combat role, deployment-related traumatic experiences, and post-deployment post-traumatic stress disorder, and alcohol misuse were associated with interpersonal violence on return home. Research so far has been restricted by cross-sectional data and the lack of an objective outcome measure of violence.

Interpretation
In this study, our analyses of objective data confirm findings based on self-reported data for violence by the UK military. Through the use of an objective measure of pre-military and post-deployment violent offending and longitudinal data, this study improves on the methods previously used to investigate pathways to violent behaviour in a military population. The findings provide information that can enable better violence risk assessment in serving and ex-serving military personnel. They draw attention to the role of mental health problems and the potential effect that appropriate management of alcohol misuse, post-traumatic stress disorder, especially hyperarousal symptoms, and aggressive behaviour could have in reducing the risk of violence.

17.0% of male military personnel had a criminal record. According to the Ministry of Justice data, an estimated 28.3% of men in England and Wales aged between 18 years and 52 years in 2006 had a criminal conviction. The lower prevalence of lifetime criminal records in the military population might be partly attributed to the time spent in military service (median 12.2 years). The peak age of both offending by men in the general population and enlistment in the military is 19 years. So the men are enlisting at an age when they are at highest risk of offending. Indeed
in men aged 40—45 years in this sample who were still serving at the time of recruitment into the study, the prevalence of lifetime offending had fallen to 11·7% compared with 29·8% for those younger than 30 years. The prevalence of lifetime offending should by definition rise with increasing age (although more slowly in the older age groups); therefore, the data suggests that many of the offenders in the younger age group leave the military earlier than do those in the older age groups, who have served longer in the military and offend less than do the younger groups. We also know that offending in service is recorded on a military police database and, until recent years, offences were less likely to be transferred to the national PNC database unless they were greater than a certain threshold of severity (eg, violent offences). This recording might explain the drop in the number of non-violent offences during the in-service period. Other interpretations could be that the military instils more ordered behaviour or is more tolerant of low-grade crime. The proportion of this sample (median age 37 years) who had served a custodial sentence (1·7%) was also less than in a similarly aged general population birth cohort (7·0%). However, the period of greatest risk of incarceration is after military service and in this study we only followed up ex-serving personnel for a restricted period. Further follow-up is necessary to investigate the issue of custodial sentences in ex-serving personnel.

Unlike the general population, which has a lower prevalence of male violent offenders than other types of offenders such as acquisitive-type offenders (ie, those with a record of offences such as theft), lifetime male violent offenders were the most common type of offenders in this sample of military personnel. Overall, 11·0% of men in the military sample had committed a violent offence in their lifetime compared with 8·7% of the general male population in England and Wales aged 46 years in 2001. The difference in the prevalence of lifetime violent offenders in the military compared with the general population is more striking in men younger than 30 years (20·6% in the military sample vs 6·7% of those aged up to 30 years in England and Wales in 2001). Similar to the pattern of change in prevalence of overall lifetime offenders in the military sample, the prevalence of lifetime violent offenders is lower in the older age groups—ie, those who have served longer in the military (6·4% in men aged 40—45 years). This pattern contrasts with that of the prevalence of lifetime violent offenders in the general population, rising with age (from 6·7% in men up to age 30 years to 8·7% in those up to age 46 years in England and Wales in 2001), suggesting that many of the violent offenders in the younger age group leave the military earlier, thus leaving a lower prevalence of lifetime violent offenders in the older age groups. So, by contrast with the apparent lower prevalence of all offenders in this military population, male violent offenders were more prevalent overall than in the general male population, but particularly so in the younger age groups.

That a greater proportion of the deployed military sample offended in the post-deployment period than in the rest of their in-service or pre-military periods for all types of offending, including violent offending, suggests that deployment or aspects of deployment act to increase offending and violent offending in the military. However, deployment to Iraq or Afghanistan in itself was not noted to be a significant risk factor for subsequent violent offending. This finding is not surprising because deployment to a conflict zone provides different experiences depending on an individual's role while there. Indeed, deployed personnel in combat roles were at increased risk of subsequent violent offending. Much of this risk is attributable to pre-existing risk factors such as pre-military violent offending, lower rank, and younger age, reinforcing the common perception that many of the individuals entering the military already have an excess of risk factors for violence. However, besides these risk factors, serving in a combat role and exposure to an increased number of traumatic events on deployment conferred an additional risk of subsequent violent offending. Numerous studies have found associations between combat exposure and violence, offending and incarceration in military personnel. Many studies so far have been hindered by the use of self-report measures of post-deployment behaviours, retrospective or cross-sectional study
design, or the confounding effect of previous antisocial and violent behaviour has not been accounted for. The results from our study reinforce our previous finding of an association between combat and self-reported violence, provide the temporal link between the exposure events and subsequent violence, and eliminate the potential for recall bias to affect the outcome measure of violence. Combat experiences might affect an individual's propensity to violent behaviour through various mechanisms including preparatory pre-deployment training to instil attitudes that enhance survival and ensure troops are able to commit targeted aggressive acts. However, deployment in a combat role is not a random process. Indeed, individuals who volunteer or are selected for a combat role are likely to have a propensity for risk taking and aggressive behaviour. In the UK, infantry units have traditionally promoted aggression as a desirable trait and such units frequently recruit individuals who are socially disadvantaged and are likely to have low educational attainment. Although in this study we accounted statistically for sociodemographic and military confounders and a previous tendency to violent offending, a residual confounding effect cannot be ruled out.

Most of the individuals who deploy readjust to life successfully after returning home. For individuals who do not, a better understanding is needed of the pathways to violent offending. The results of a longitudinal study of US Marines showed that a post-combat psychiatric diagnosis was one of the strongest predictors of antisocial behaviour by military personnel. We also noted a strong association between post-deployment mental health problems and subsequent violent offending, particularly alcohol misuse and post-traumatic stress disorder. Deployment has been shown to be associated with increased alcohol use. Alcohol misuse is a well known risk factor for violence in non-military populations. We noted that alcohol misuse was strongly associated with violent offending in our sample and that it was a mediator of the link between both serving in a combat role and exposure to traumatic events and violent offending.

The findings of several studies have suggested that combat exposure is associated with aggression primarily through its relation with post-traumatic stress disorder symptoms. We noted a strong link between post-traumatic stress disorder and violent offending in the deployed group. Post-traumatic stress disorder was shown to be a mediator of the link between traumatic events and violent offending. Individual presentations of post-traumatic stress disorder can vary according to the extent to which an individual presents with symptoms from each of the four clusters (as proposed in the new DSM-5): re-experiencing symptoms such as nightmares and flashbacks; hyperarousal symptoms such as irritability or outbursts of anger and alertness to threat; active avoidance symptoms (ie, avoidance of reminders of the trauma); and passive avoidance or emotional numbing such as diminished interest, restricted affect, and feelings of detachment. The results of recent research have suggested that the hyperarousal symptom cluster is most strongly associated with violent behaviour. Our results add further support to this finding. Combat veterans with post-traumatic stress disorder and other mental health concerns frequently present with comorbid problems of anger and aggression. Our results show that high levels of self-reported aggressive behaviour were also predictive of post-deployment violent offending.

To the best of our knowledge, this study is the first large scale epidemiological study in which criminal records were used to investigate offending behaviour in a national cohort of Armed Forces personnel. The use of criminal records eliminates the problem of recall bias associated with self-reported measures. Prospective follow-up allows better investigation of the pathway to post-deployment violence. The limitations inherent in the process of data linkage with official records must, however, be acknowledged. The matching process used only automatic matches to reduce the potential for false positives. This process is likely to have produced a higher rate of false negatives and hence underestimation of offending. The PNC database also underestimates the rate of known offending because it only records offences that come to the attention of the police.
Our results emphasise the importance of pre-existing risk factors for violence in military personnel. A simplistic response would be to suggest that the military cease to recruit young men with low levels of educational attainment or a previous criminal record. However, this suggestion is no more logical than saying that they should only recruit officers in the future. The military is composed of a range of individuals, some of whom have aggressive traits and who are trained to engage in targeted aggression. Screening for violence risk in a population in which the outcome is already prevalent is difficult. More research into the potential value of violence reduction interventions in individuals returning from combat to their home communities is needed because any inputs must be evidence based. Alcohol misuse treatment and interventions to reduce anger and aggressive behaviour might help to reduce violence risk. Although post-traumatic stress disorder is less prevalent than alcohol misuse, importantly, it should be appropriately treated when diagnosed and the risk to the individuals and others should be monitored. These results reinforce the potential benefit of targeting post-traumatic stress disorder hyperarousal symptoms for risk reduction of violent offending.

Contributors

DM secured funding for her role in this project; developed the analytical strategy; undertook the data analyses and interpretation; and wrote the report. KD was involved in the development of the analytical strategy, contributed to the interpretation of the results, provided advice about the forensic aspects, and commented on the report at several stages in its preparation. MJ was involved in the design of the study, participated in data gathering and some analyses, and commented on the report. LH was involved in the design and planning of the study, coordinated the project, and commented on the report. NG provided military assistance and advice about the design and undertaking of the study, and commented on the report. RJR is one of the principal investigators for this study; he was involved in the design and planning of the study, developing the analytical strategy for the report, and the interpretation of the results; and has commented on the report. TF was involved in the development of the analytical strategy for this report, provided advice about the forensic aspects, and commented on the report at several stages in its preparation. SW was the chief investigator for this study; he was responsible for securing funding for this study, led the design and planning of the study, was involved in developing the analytical strategy for the report, and has commented on the report extensively throughout its preparation. All authors have seen and approved the final version of the report.

Conflicts of interest

NG is a full-time member of the UK Armed Forces, and is currently seconded to King's College London. NTF and SW are employed by the Academic Centre for Defence Mental Health, based at King's College London, which receives funding from the UK Ministry of Defence. SW is also an honorary civilian consultant adviser in psychiatry to the British Army and a trustee of Combat Stress, a UK charity that provides service and support for veterans with mental health problems. The authors acknowledge financial support from the Department of Health through the National Institute for Health Research Comprehensive Biomedical Research Centre award to Guy's and St Thomas’ NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. DM is funded by a Medical Research Council Clinical Research Training Fellowship and undertook this project as part of her PhD studies with the King's Centre for Military Health Research. KD and TF are
employed by the Institute of Psychiatry and are forensic psychiatrists who provide supervision and advice about the project; they declare that they have no conflicts of interest.

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Driving-Related Anxiety in Recently Deployed Service Members: Cues, Mental Health Correlates, and Help-Seeking Behavior

Military Medicine
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Abstract

Recent military operations have involved repeated trauma exposure while driving vehicles. Combat deployment and post-traumatic stress disorder (PTSD) have been associated with risky driving practices, increasing the likelihood of fatalities and problems adjusting to civilian life. However, no studies have specifically examined the role of driving-related anxiety, including common cues and mental health correlates. This study conducted structured interviews with 46 recently deployed service members. Interviews assessed the prevalence of driving-related anxiety or hyperarousal (anger or irritation) in relation to civilian driving scenarios, combat exposure, post-traumatic stress symptoms, depression symptoms, and help-seeking behavior. The majority of participants reported high driving anxiety or hyperarousal in response to scenarios involving close proximity to other cars. Driving-related anxiety was positively correlated with PTSD and depression. Although PTSD and driving anxiety were positively associated with help seeking, only one-third of soldiers sought help for driving anxiety and most sought help from informal sources (i.e., friend and battle buddy). The findings underscore the need to address driving-related anxiety in combat-exposed service members with mental health symptoms, with a particular focus on specific anxiety-provoking situations. Furthermore, interventions that reduce stigma and improve access to formal care could improve help seeking and treatment for these problems.

Introduction

Recent military operations in Afghanistan and Iraq (Operation Enduring Freedom and Operation Iraqi Freedom [OEF/OIF]) frequently involved multiple deployments and high-intensity insurgent warfare, resulting in heightened exposure to traumatic events such as direct fire, witnessed violence, and physical injury. Combat exposure has been associated with a variety of psychiatric disorders, including post-traumatic stress
disorder (PTSD) and depression. Research with recently deployed soldiers has found that approximately 14% to 28% meet current or past year criteria for PTSD and 13% to 14% meet criteria for depression.

In comparison to prior conflicts, OEF/OIF deployments involve the chronic threat of roadside bombs and improvised explosive devices (IEDs). Many of these events take place during road patrols and convoys. Therefore, it is not surprising that many cues for PTSD symptoms arise while driving and that PTSD symptoms represent a significant predictor of risky driving practices among military personnel. Specifically, PTSD symptoms such as intrusive memories, avoidance of trauma-related cues, hyperarousal, and irritability can interfere with safe driving. Risk factors for trauma-related mental health symptoms, including deployment history and combat exposure, have also been associated with increased likelihood of risky driving behavior, as well as fatal motor vehicle accidents. A study of OEF/OIF veterans receiving residential treatment for PTSD found that this cohort was at greater risk for unsafe and aggressive driving practices in comparison to veterans of Persian Gulf and Vietnam wars.

Furthermore, one unpublished study found that deployed soldiers reported higher driving-related anxiety than a comparison group of never deployed Army cadets. Driving-related trauma exposure was significantly associated with driving-related anxiety. In sum, little research has been conducted on driving-related anxiety, and no studies have described the frequency of driving-related combat exposure or anxiety in OEF/OIF veterans. This information is needed to inform interventions and practices to reduce risky driving, mental health symptoms, and the public health burden associated with driving-related anxiety, injuries, and fatalities.

Despite high rates of mental health problems in returning military personnel, more than half of OEF/OIF veterans with mental health symptoms do not seek mental health services, often as a result of concerns about stigmatization. Although studies of trauma-exposed civilians indicate a greater likelihood of seeking help from informal sources (e.g., friends, family), as opposed to formal sources (e.g., mental health clinicians), studies have yet to examine these patterns in military service members. Understanding these patterns of help seeking will assist future efforts to develop accessible interventions that reduce driving-related anxiety and facilitate mental health treatment-seeking.

The primary purpose of this study was to explore the nature of driving-related anxiety and its association with driving-related combat exposure and common trauma-related mental health outcomes (i.e., PTSD and depression) in recently deployed service members. We furthermore assessed which civilian driving situations evoked the most anxiety in returning veterans. A secondary purpose of this study was to examine patterns of help-seeking behavior among service members with driving-related anxiety.

Methods

Participants and Procedure

A total of 46 recently deployed male service members completed structured interviews. Soldiers were recruited via e-mail through local and state service members and veterans’ organizations. Soldiers were also recruited during a battle assembly weekend for the Army Reserves. The study was approved by Clemson University Institutional Review Board. The average age of participants was 27.6 (SD = 6.2). Approximately 6% were
active duty, 6% were veterans, and the remainder were in the Reserves. The average time deployed during the past 2 years was 9.6 months (SD = 2.8). The average time since last deployment was 9.6 months (SD = 10.3). A total of 91% had most recently been deployed to Afghanistan and 9% to Iraq. On average, participants reported moderate to heavy combat exposure (M = 25.8, SD = 6.0 on the Combat Exposure Scale).  

Measures  

Combat Exposure  
The Combat Exposure Scale is a 7-item self-report measure that assesses wartime stressors ranging from going on combat patrols to witnessing injury and death. Items are rated on a 5-point scale assessing frequency, duration, and degree of loss. The total score (ranging from 0 to 41) is a sum of weighted scores based on “light” to “heavy” categories. The measure has shown good internal stability and test–retest reliability. To estimate prevalence of driving-related combat exposure, we also asked participants, “Did you experience an IED, enemy fire, direct injury, or did you witness injury or death while in a vehicle?”  

Post-Traumatic Stress Disorder  
We used the primary care self-report PTSD screen (PC-PTSD). This 4-item instrument has strong sensitivity (0.78) and specificity (0.87) when using a cutoff score of 3.5. Therefore, a cutoff score of 3 was used to categorize participants as screening positive for PTSD in this study.  

Depression  
We used the self-report PRIME-MD, a 2-item screener with strong sensitivity (0.86) and specificity (0.75) when using a cutoff score of 1. Therefore, a cutoff score of 1 was used to categorize participants as screening positive for depression.  

Driving Anxiety and Behaviors  
To assess changes in participants’ civilian driving behaviors, we included one item that asked participants if they drive differently than before combat. If they answered “yes,” an open-ended question prompted them to describe how they drive differently. Responses were grouped into 12 different categories by the 2 lead researchers of the study.  

We measured anxiety/hyperarousal during various civilian driving situations using 27 quantitative items adapted from an existing scale. Each item followed the prompt, “When driving on U.S. roads in the past 30 days, how frequently did you feel anxious, angry, or irritated when encountering the following situations?” Participants rated multiple situations using a 5-point scale ranging from “Never” to “Nearly Always or Always.” Items described civilian driving situations, such as “driving at dusk or night” and “another car is tailgating you.” One item also asked about “when driving
in general.” Participants endorsing a “4” or “5” were classified as having “frequent anxiety” for that item. A median score was created from the 27 items to represent average driving anxiety. Cronbach’s α for this scale was 0.94.

Help-Seeking Behavior

Participants who endorsed any of the driving anxiety items were asked if they had sought help for driving-related anxiety, anger, or irritation from any of 16 different sources. These included friends, family members, health care professionals, and counselors. They were also asked who they would be likely to go to for help in the future.

Results

Driving Anxiety and Behaviors

A significant majority of participants (96%) endorsed having experienced an IED, enemy fire, direct injury, witnessed injury or death while in a vehicle. A large majority (80%) also reported driving differently than before combat experience. For example, 52% reported being more anxious in response to various driving triggers, 48% reported engaging in more hypervigilance and cautious driving, and 37% were angrier and/or engaged in aggressive driving (Table I). Table II shows the prevalence of high anxiety/hyperarousal for each civilian driving situation. The driving situations that elicited the most frequent anxieties were being tailgated, being boxed in by other cars, and cars approaching quickly.

Forty-one percent of the participants screened positive for PTSD, 41% screened positive for depression, and 26% screened positive for both PTSD and depression. Participants who screened positive for PTSD were more likely to report that they drive differently after combat than those who screened negative (95% vs. 70%, χ² = 4.21, p < 0.05). Participants who screened positive for depression were also more likely to report that they drive differently after combat than those who screened negative (95% vs. 70%, χ² = 4.21, p < 0.05). Thirty-five percent of all participants reported often or always feeling “anxious, angry, or irritated” while driving in general. Similarly, participants who screened positive for PTSD were more than 4 times as likely to report frequent anxiety/hyperarousal while driving in general than those who screened negative (63% vs. 15%, χ² = 11.49, p < 0.01). Similarly, participants who screened positive for depression were more than twice as likely to report frequent anxiety/hyperarousal while driving in general than those who screened negative (53% vs. 22%, χ² = 4.55, p < 0.05). Screening positive for PTSD (r = 0.61, p < 0.01) and depression (r = 0.34, p < 0.05) was also positively correlated with median scores on the driving anxiety scale. Combat exposure was unrelated to driving differently after combat, to anxiety/hyperarousal while driving in general, or to median driving anxiety scores.

Help Seeking

Approximately one-third (34%) of all participants and 38% of participants with frequent anxiety/hyperarousal while driving in general had sought help for driving-related problems. Participants who screened positive for PTSD were more likely to report engaging in help seeking than those who screened negative (61% vs. 13%, χ² = 10.37, p < 0.01). Median driving anxiety scores were positively associated with help seeking (r = 0.34, p < 0.01)....

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Depression was not related to help seeking. Participants most frequently reported seeking help from informal sources, including friends, fellow soldiers, and family members (Table III). Most frequently identified sources of future help seeking were battle buddy (59%), friend (52%), wife/girlfriend (50%), parent (30%), counselor (28%), VA hotline (28%), religious advisor (28%), and sibling (26%). Only 53% of participants who screened positive for PTSD and 26% of participants who screened positive for depression sought help from a professional (e.g., psychologist, psychiatrist, counselor, medical doctor, occupational therapist).

Discussion

In our sample of recently deployed OIF/OEF service members, nearly all had experienced combat exposure while driving, and the majority reported driving differently as a result of these experiences. Over one-third of participants endorsed significant driving anxiety/hyperarousal while driving in general. Furthermore, a majority of participants reported anxiety/hyperarousal in response to described driving situations involving close proximity to other cars. Given the link between anxiety symptoms and risky driving behavior, these findings highlight the importance of reducing driving-related anxiety and hyperarousal in returning service members. In addition, we found that driving-related anxiety/hyperarousal was positively associated with PTSD and depression symptoms. Therefore, soldiers with trauma-related mental health diagnoses are likely at additional risk for driving-related anxiety/hyperarousal and associated problems adjusting to civilian driving.

Contrary to expectations, combat exposure was not related to driving-related behavior changes or to anxiety/hyperarousal. Restricted range on the combat exposure measure may have attenuated the correlation between these variables, given that most participants reported high levels of combat exposure, and the standard deviation of 6.0 was smaller than the standard deviation reported in previous studies (8.7–10.9). To better evaluate the relationship between combat exposure and driving anxiety, future research should include participants with a wider range of combat experiences (i.e., ranging from none to severe).

Although service members screening positive for PTSD were more likely to seek help for driving-related problems, possibly because of greater symptom severity or targeted screening for PTSD symptoms, the majority of participants reporting frequent driving anxiety did not seek help for these problems. Furthermore, depression was unrelated to help seeking. This is consistent with prior literature that has found depression to be associated with negative attitudes toward help seeking, with some studies finding no relationship between depression and help-seeking behavior.

In addition, it is possible that service members have received information on how to identify and seek help for PTSD symptoms, but there has been less of an emphasis on depression. One explanation for the gap between mental health needs and help-seeking behavior in the military is that social norms of traditional masculinity can inhibit professional help seeking. Therefore, it is not surprising that in this study, service members were most likely to seek help from informal sources (e.g., friend, spouse, battle buddy) as opposed to formal sources. Taken together, these findings suggest that improved screening and awareness of these problems, as well as interventions that target help-seeking attitudes and reduce stigma, could facilitate receipt of professional mental health services. Furthermore, support persons may benefit from education regarding how to assist returning service members and when to refer to formal treatment.
This study was limited by its use of a cross-sectional design and small, homogenous sample, restricting our conclusions regarding causality and limiting generalizability of the findings. It is possible that service members who chose to participate were more likely to have driving-related problems and that inclusion of a large number of recently deployed soldiers resulted in an increase in reported symptom levels in comparison to the larger military population. Future studies should use longitudinal designs and multivariate models that control for demographic variables and other significant mental health correlates. Research is also needed to replicate these findings in larger, more heterogenous samples.

Implications

Our findings suggest that treatments are needed to address driving-related anxiety and hyperarousal, particularly among returning service members presenting with trauma-related mental health problems such as PTSD and depression. The intervention that has received the most empirical support in reducing trauma-related anxiety is prolonged exposure therapy. In this treatment, individuals are repeatedly exposed to feared stimuli in either imaginal or in vivo fashion. Virtual reality devices have recently been used to create more realistic, cost-effective, and safer means of exposing individuals to anxiety-provoking situations. Driving simulators are already being used to rehabilitate wounded service members and veterans in occupational therapy and medical settings, where therapists are likely to encounter individuals with comorbid mental health problems. These devices could be adapted to present interactive scenarios representing the situations associated with the highest levels of anxiety and hyperarousal, as identified by this study. Given that many service members are more likely to visit medical health care professionals than mental health providers, such interventions could increase access to mental health services by allowing occupational therapists and medical professionals to address both physical and mental health problems. Furthermore, the integration of technology into health care settings can be presented as using “high-tech” tools for “reintegration training,” which may reduce stigma and appeal to a generation who grew up with gaming technology.
2003 to 2008 were significantly more likely to subsequently be screened for alcohol/substance abuse, test positive for illicit substances, or receive an Army separation for behavioral misconduct. These associations were highest among Soldiers granted waivers for nonlawful alcohol/drug violations. Soldiers granted waivers for felony offenses and serious nontraffic violations were significantly less likely to separate from the Army compared with Soldiers not granted enlistment waivers.

Introduction

When considering an applicant for service in the U.S. Army, recruiters examine several indicators, including Armed Forces Qualification Test scores, demographics, and criminal history. Enlistment waivers may be granted for applicants who fail to meet one or more criteria. Enlistment waivers are granted for a number of different reasons, including age at enlistment, married with two or more dependents, unmarried with dependents, medical concerns, misconduct (a single incident or pattern of behavior), or positive alcohol/drug tests at a Military Entrance Processing Station. Enlistment waivers for misconduct and/or positive alcohol/drug tests are referred to as “moral conduct” waivers. Because of the difficulties associated with keeping the force at strength during a time of war (i.e., reduced accessions and increased attrition), there is a perception the Army “relaxed standards” for enlistment and increased the number of waivers granted for medical and conduct/drug use problems.\(^1\) Changes in accession standards have been anecdotally implicated with the observed increased in previous negative behavioral health outcomes occurring among Soldiers, such as alcohol/drug use, domestic violence, and attrition related to misconduct, and most likely varies based on the types of waivers granted.

Although only one peer-reviewed study could be identified that has assessed the association between specific waivers and subsequent negative behavioral and/or social health outcomes, there are a number of nonpeer-reviewed studies (e.g., technical reports, postgraduate theses) that have examined this association. Service members granted specific enlistment waivers have been shown to be more likely to have negative outcomes, such as a medical evaluation board (MEB) or attrition for reasons related to poor moral character, but they also have been shown to be more likely to complete basic training, have lower rates of personality disorders, less likely to attrite from service early, and be more likely to reenlist. Previous population-wide enlistment waiver studies that examined recruits enlisting before 2001 were reviewed, but considered not comparable to the current study population. No previous studies were identified that examined the likelihood of negative behavioral and social health outcomes during military service, such as positive drug tests, interaction with substance abuse programs, or domestic violence.

The objective of this study was to evaluate whether Soldiers granted specific types of moral and medical enlistment waivers were more likely than other Soldiers to experience negative behavioral and social health outcomes during their military service and/or attrition from the Army. We hypothesized that Soldiers granted moral waivers would be associated with an increased likelihood of subsequent behavioral and social health outcomes during their military career and would be more likely to separate (attrite) from the Army for negative reasons.

Methods

Data and Procedures

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All Soldiers who enlisted in the Army between 2003 and 2008 and served in either of two brigade combat teams (BCTs) of interest (n = 8,843) were identified for this study by the Armed Forces Health Surveillance Center (AFHSC). Data were obtained from the AFHSC (demographics and military characteristics), U.S. Army Accessions (description of enlistment waivers and any subsequent attrition), Army Center for Substance Abuse Programs (ACSAP) (Army Substance Abuse Program (ASAP) screening for alcohol and/or drugs), Drug and Alcohol Management Information System (DAMIS) (positive illicit drug tests), and the Army Central Registry (ACR) (history of perpetrating domestic violence and/or child abuse/neglect). Data were then linked using a standardized nonidentifying study key developed by the AFHSC to ensure the data remained unidentified to the study team.

Measures

Accession waivers are considered by each service for applicants with a disqualifying medical or moral condition. Moral waivers for enlistment require documentation that a meritorious case exists to warrant an exception to the standards established (Army Regulation 601-210). Many factors are used to determine eligibility for waivers, including education, Armed Forces Services Vocational Aptitude Battery (ASVAB) scores, references, and involvement in the community, among others. The waiver process serves as a filter to screen for potential applicants, who have been rehabilitated; are good risks from a moral standpoint; and possess a documented, meritorious waiver request (Army Regulation 601-210).

For this study, in addition to examining Soldiers granted “any” type of waiver, four specific classes of waivers were examined: serious nontraffic violations, juvenile or adult felony violations, nonlawful violations involving alcohol or drugs (to include positive drug tests), and medical waivers for mental conditions (International Classification of Diseases, 9th Revision, Clinical Modification 290-319). Serious nontraffic violations can include, but are not limited to, conviction or adverse disposition for carrying of weapon on school grounds; an act of violence including threats against any school faculty members; domestic battery/violence not resulting in a qualifying Lautenberg conviction; conviction of other adverse disposition for driving while intoxicated, driving under the influence, or driving while impaired; and possession of marijuana or drug paraphernalia.

Subsequent to accession, negative behavioral and social health outcomes of interest were examined, including alcohol and/or drug problems, domestic abuse, and attrition. Soldiers were defined as having a problem with alcohol or drugs during their military career if they tested positive for an illicit substance or if they were screened at the ASAP clinic for the use of alcohol or drugs. Soldiers were defined as perpetrating domestic abuse if there was documented history of substantiated neglect and/or physical, sexual, or emotional abuse of a spouse or child. Attrition from the Army was also examined. Attrition was defined as any Soldier who separated from the Army for any reason (except death) and is categorized as: all causes, behavior, mental, and performance. Attrition for behavioral reasons was further defined for Soldiers who separated from the Army for behavioral misconduct or Unified Code of Military Justice (UCMJ) violations.

Data Analysis
Enlistment waivers granted to Soldiers in this population of two BCTs from 2003 to 2008 were examined to determine whether there was an increasing trend from 2003 to 2008. Adjusted odds ratios (AORs) (and 95% confidence intervals [CIs]) were calculated for the association between Soldiers granted waivers and subsequent negative behavioral or social health outcomes and/or attrition from the Army. Odds ratios were adjusted to account for the hierarchical nature of the data (Soldiers are nested within battalions, which are nested within brigades). Nested data are likely to be correlated, thus Soldiers in a specific battalion or brigade are more likely to behave like other Soldiers in the battalion or brigade than they are to act like Soldiers in another battalion or brigade. Thus, generalized linear mixed modeling (GLMM) was utilized to properly account for the intraclass correlation. The random effects in the model were battalions nested within brigades. Initially, the only fixed effect was the exposure variable (i.e., specific waivers), and the resulting odds ratios and CIs were adjusted for the correlated nested nature of the data. Additionally we added to the GLMM, demographic factors (gender, ethnicity [White, African-American, Hispanic, other], marital status while assigned to the BCT [single, married, divorced, other], age at entry into service [<21, 21–25, 26–30, 30+ years], home of record region at enlistment [midwest, northeast, south atlantic, south central, west, other]) and other potential covariates of interest (grade [enlisted, commissioned officer], time in service [<1, 1–2.99, 3–4.99, 5+ years]) to compute the covariate AORs and associated CIs for each specific waiver type. For each of the outcomes assessed, covariate-adjusted models to include all covariates with a plausible bivariate association (p < 0.15) were developed, backward deleting the least significant variable. Model building and variable selection procedure was based on a commonly used approach. If after removing the least significant variable, other covariate regression coefficients changed by more than 15%, the nonsignificant covariates were included in the model as a confounder. When all remaining covariates had a p-value less than 0.05 or had been identified as a confounder, a covariate-adjusted model resulted. All analyses were completed using SAS, v9.1 (Cary, North Carolina), GLMM procedures.

Results

The current study population consists of 8,943 Soldiers who joined the U.S. Army from 2003 to 2008 and were assigned to the two BCTs of interest. Upon enlistment, this population was primarily male, White, under 21 years of age, and from no particular region on the United States; while in the BCT, the majority of Soldiers were single (Table I). Comparatively, the study sample demographics were quite similar to all Army accessions from 2004 to 2008 (n = 714,679) with respect to gender, age, and race.

The percent of Soldiers in the current study population entering the Army from 2003 to 2008 who were granted medical and moral waivers increased significantly between 2003 (6.8% and 12.4%, respectively) and 2008 (9.2% and 19.7%, respectively), with the largest increase observed in the percent of moral conduct waivers. The increasing trend of moral waivers was driven by serious nontraffic violations, which increased significantly among Soldiers from 2003 (5.7%) to 2008 (14.2%). Overall, about 1 in 5 Soldiers (21.7%) in the current study population were granted some type of enlistment waiver; 7.5% were granted a waiver for a serious nontraffic violation (Table II).

The number of Soldiers in the current study population who had drug and/or alcohol concerns during their military career is indicated by the percent who were screened for alcohol and/or drug problems at ASAP (14.3%) and/or tested positive for illicit drugs (7.5%). Soldiers with a substantiated case of domestic abuse were rare (1.5%). Nearly a third of this population had separated from the Army at the time of the study (32.0%), a much smaller percent specifically for misconduct or behavioral problems (4.8%) (Table III).
Soldiers granted "any" type of enlistment waiver were significantly more likely to test positive for an illicit substance (AOR = 1.5, 95% CI 1.3–1.7), to be screened at ASAP for alcohol/drug abuse (AOR = 1.4, 95% CI 1.2–1.6), or to attrite from the Army for UCMJ violations or behavioral misconduct (AOR = 1.6, 95% CI 1.3–2.0). Soldiers granted waivers for nonlawful alcohol or drug violations or serious nontraffic offenses were significantly associated with the greatest likelihood of a positive test for an illicit substance (AOR = 3.3, 95% CI 2.2–4.9; AOR = 1.8, 95% CI 1.5–2.3, respectively) or being screened at ASAP for alcohol/drug abuse (AOR = 2.9, 95% CI 2.1–4.2; AOR = 1.6, 95% CI 1.4–1.9, respectively) during their military career. Soldiers who were granted waivers for nonlawful alcohol or drug violations were also more likely to leave the Army because of UCMJ violations or behavioral misconduct (AOR = 2.9, 95% CI 1.8–4.7) (Table IV).

Soldiers granted waivers for serious nontraffic violations and/or juvenile/adult felonies were significantly less likely to separate from the Army for UCMJ violations or behavioral misconduct (AOR = 0.8, 95% CI 0.7–0.9; AOR = 0.6, 95% CI 0.4–0.8, respectively). Enlistment waivers were not significantly associated with subsequent domestic abuse in this population.

Discussion

The percent of Soldiers enlisting in the current study population who were granted medical and conduct waivers increased significantly from 2003 to 2008, with the largest increase seen in the percent of moral conduct waivers. During this same time, there was an increase in the percent of Soldiers accessing into the overall Army with medical and moral waivers from 2003 (12%) to 2008 (20%) (US Army Recruiting Command Waivers [by Component] Briefing, Army G-1, Department of Military Personnel Management, EOM February 2009). Soldiers in the current population examined who were granted enlistment waivers were significantly more likely to subsequently be screened at ASAP, test positive for an illicit substance, or separate from the Army for misconduct behavior. These associations were highest among Soldiers granted specific moral waivers for nonlawful alcohol/drug violations. Soldiers granted waivers for felony offenses and serious nontraffic violations were significantly less likely to separate from the Army when compared with Soldiers who were not granted enlistment waivers. The results are similar to previous studies, which examined enlistment waivers for misconduct and drug/alcohol use.

The increase in subsequent ASAP screening, illicit drug tests, and attrition for misconduct/behavior among Soldiers granted waivers for alcohol/drug nonlawful violations was most striking. Other reports have also shown Soldiers granted waivers for drugs were significantly more likely to subsequently attrite within 36 to 48 months of accession. A population assessment of first-term attrition among all U.S. Army Soldiers who enlisted from 2000 to 2006 (n > 400,000) reported recruits granted waivers for drugs were twice as likely to attrite for substance use compared with nonwaivered recruits, though the absolute magnitude was relatively small since less than 7% of all attrition discharges were for drug/alcohol problems. An analysis comparing the likelihood of 48-month attrition and the average time to sergeant (E5) promotion determined that being granted a waiver for drugs/alcohol was associated with both relatively high 48-month attrition and lower probability of getting promoting “fast to Sergeant.” A study completed by the RAND Arroyo Center reported recruits with conduct or drug waivers had significantly increased patterns of misconduct, drug abuse, court martial, and commission of serious crimes.
As observed in other large population assessments, serious nontraffic waivers were the most common moral waiver granted to Soldiers in the current study population from 2003 to 2008. The largest increase in waivers observed in the current study population was also waivers for serious nontraffic violations. Soldiers granted a waiver for a serious nontraffic violation were associated with a significant increased likelihood of subsequent screening at ASAP and positive drug tests for an illicit substance. Soldiers granted serious nontraffic violation waivers were not significantly more likely to attrite from the Army for "any" reason or specifically for UCMJ violations or behavioral misconduct. With the exception of attrition for negative behavioral reasons, no previously published studies have assessed behavioral and social health outcomes subsequent to accession with waivers. Malone and Carey also observed a null association between waivers for serious nontraffic violation waivers and attrition for behavioral reasons, but observed that Soldiers with these waivers had faster promotion rates than Soldiers without waivers. Distifeno observed significantly lower early attrition rates (180 days), but significantly higher full-term attrition rates for "any" reason among Soldiers with serious nontraffic waivers.

Positive outcomes were not specifically examined in the current study; however, we did observe a significantly decreased likelihood of subsequent overall attrition among recruits granted waivers for felony offenses (−40%) or serious nontraffic violations (−20%) compared with recruits not granted enlistment waivers. Other studies have also showed that early attrition rates (i.e., within 1 year of accession) are typically lower among waivered recruits compared with nonwaivered recruits. RAND Arroyo Center (2009) reported that recruits with conduct or drug waivers had significantly higher success rates in basic training, better entry level performance/conduct, and were more likely to receive good conduct medals. A study commissioned by the House Armed Services Committee concluded that new recruits with moral, medical, or other waivers were less likely to drop out of basic training, had lower rates of personality disorders, reenlisted in higher numbers, were promoted to sergeant 4 months faster, and were more likely to receive medals of valor than new recruits not given waivers. Awareness of the lack of comparable job opportunities outside of the military for persons with criminal backgrounds may factor into a reduced likelihood for attrition for these Soldiers. Alternatively, it is possible that the factors that contributed to engaging in criminal behavior or misconduct have been impacted by the Army core values (i.e., duty, respect, selfless service, honor, integrity, personal courage) and/or camaraderie associated with being a Soldier.

In this population, medical enlistment waivers for mental health reasons were not associated with subsequent negative behavioral health outcomes or attrition from the Army. One previous study found that the relative risk of undergoing an MEB among U.S. Navy and Marine personnel receiving medical waivers for mental health reasons was the same as Sailors and Marines receiving any type of waiver, but MEBs specifically for mental health reasons were 5 times more likely. No other studies were identified which specifically examined mental health waivers and subsequent behavioral and social health outcomes or attrition.

Although few studies have directly explored the impact of moral conduct and mental health waivers, Soldiers themselves often report negative opinions about these waivers and Soldiers who receive these waivers. Previous studies have shown, during focus groups, that active duty Soldiers commonly report perceptions that recruitment standards have been reduced in recent years to sustain force strength for Operation Iraqi Freedom/Operation Enduring Freedom conflicts, and many believe the practice of granting enlistment waivers to recruits with mental health problems, criminal backgrounds, and substance abuse histories has led to a less qualified force with "weak-minded" or "bad" Soldiers. Soldiers believe that the consequences of increased enlistment waivers include an increase in discipline problems, behavioral health concerns, and
relationship problems. One study found that Soldiers believed relaxed recruitment standards, and the increase in enlistment waivers, particularly felony waivers, was contributing to acts of violence and aggression within Army populations. However, to date, there is no evidence (published or unpublished) to support the assertion that units with higher levels of risk have more high-risk "substandard" Soldiers than other units. The Army-wide percent of accessions with a moral conduct waiver decreased from fiscal year (FY) 2007 (15%) to FY 2008 (13%) (U.S. Army Recruiting Command Waivers [by Component] Briefing, Army G-1, Department of Military Personnel Management, EOM February 2009), and because of increased accession standards and requirements for new recruits starting in FY 2009, the percent of new recruits granted enlistment waivers should continue to decrease.

Limitations

The findings of this study should be considered in conjunction with the following limitations. This analysis based on data available for Soldiers assigned to 2 BCTs may not be representative of all Army Soldiers or all Soldiers with waivers. The time to follow-up for the current study population entering the Army from 2003 to 2008 differs by year of accession and thus, although we controlled for the year of accession in the analysis, Soldiers with less follow-up time are likely to bias the association observed between waivers and subsequent behavioral outcomes and attrition toward the null. This is important to note because previous studies have shown that recruits with waivers typically do well early in their first enlistment and also because in this population we observed a large increase in waivers (particularly serious nontraffic waivers) among recruits entering in 2007 to 2008. Behavioral outcomes among recruits entering the broader Army around this time with waivers may be similar or more likely than those observed in the current study. In this study, we were unable to ascertain data on combat medals, promotions, and details of basic training success, which might provide indicators of successful outcomes among recruits granted waivers. Likewise, our study population size did not lend itself to assessing rates of early attrition. Future studies should also consider other factors occurring before, or at the time of enlistment (e.g., undiagnosed mental health concerns, learning disabilities, body mass index), which may be associated with, or predictive of, the outcomes examined in this study.

Conclusions

The percent of Soldiers enlisting in the current study population who were granted medical and conduct waivers increased significantly from 2003 to 2008, with the largest increase seen in the percent of moral conduct waivers. Soldiers granted waivers for alcohol/drugs or serious nontraffic offenses were significantly more likely to test positive for an illicit substance or be screened at ASAP for alcohol/drugs during their military career, and Soldiers granted waivers for alcohol/drugs were also significantly more likely to attrite from the Army for misconduct/UCMJ violations. Accession policies that may have increased the number of Soldiers with waivers could have selected a population with more preexisting risk factors for negative behavioral health outcomes. Army leadership should consider these findings to inform decision making about changes to waiver policy and to anticipate the potential need for additional support services and other second-order effects associated with any such changes.

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Disease

Visceral Leishmaniasis With Associated Immune Dysregulation Leading to Lymphoma

Military Medicine
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ABSTRACT

Objective: We describe an atypical presentation of visceral leishmaniasis (VL) complicated by Epstein–Barr virus (EBV)-lymphoproliferative disorder and angioimmunoblastic T-cell lymphoma in a U.S. Government contractor recently deployed to Iraq and Afghanistan. Methods: We performed a search of PubMed (1966–2012) using the terms visceral, leishmaniasis, operation, iraqi, freedom, desert, storm, EBV, lymphoproliferative, angioimmunoblastic, and lymphoma. The purpose of the search was two-fold: to find reported cases of VL during U.S. military operations and to ascertain if lymphoproliferative disorder (specifically, because of EBV) was ever described as a sequelae of VL. Results: Case series of VL acquired in the Middle East between 1990 and 2012 showed that while fever, abdominal pain, and hepatosplenomegaly were common signs and symptoms of VL, diffuse lymphadenopathy (our patient's presentation) was rare. Moreover, VL in and of itself lends to profound immune dysregulation, leading to a myriad of complications to include EBV-lymphoproliferative diseases. Conclusions: Diffuse lymphadenopathy because of VL is a very atypical presentation for infection acquired in the Middle East. Clinicians must be mindful of the extreme immune dysfunction that occurs as a result of this potentially fatal infection and the associated complications to include EBV-related lymphoproliferative disorders and lymphoma.

INTRODUCTION

Visceral leishmaniasis (VL), also referred to as kala-azar, is a disseminated protozoan infection occurring primarily in the tropics and subtropics. The causative agents include Leishmania donovani and Leishmania infantum with infection transmitted by sand flies. Clinical presentation ranges from asymptomatic, self-resolving infections to insidious onset of fever, weight loss, weakness, fatigue, and hepatomegaly. Although lymphadenopathy is common in patients in Sudan, it is less common in other areas. The majority of cases of VL occur in India, Brazil, Sudan, and Bangladesh, though there have been scattered reports of VL and viscerotropic leishmaniasis in soldiers deployed to Afghanistan and Iraq. Delay in diagnosis and initiation of effective therapy is problematic as untreated infection can be fatal.

Immunologic dysfunction is a key component of disease because of VL. VL in and of itself can lead to immunosuppressant, specifically because of ensuing deficits in cell-mediated immunity. Patients with primary and secondary immunodeficiencies are prone to Epstein–Barr virus-related lymphoproliferative disease (EBV-LPD) and lymphoma. EBV can manifest in either a latent or replicative life cycle. Active viral replication may be
because of deficits in immunosurveillance, which then lead to lymphoproliferation. We hypothesize that progression of EBV-LPD led to development of angioimmunoblastic T-cell lymphoma.

Since World War II, U.S. military operations have had exposure to cutaneous and VL in the Middle East. During the first Gulf war, an unusually high rate of VL was reported among hospitalized soldiers. According to a report by the Army Medical Surveillance Activity Office in 2007, the U.S. Army received fewer reports of leishmaniasis in Iraq and Afghanistan. However, this may have been because of inadequate case reporting as opposed to fewer infections. This case is intended to raise awareness of continued exposure to VL in servicemen and the complications associated with resultant immune dysregulation from the infection itself.

CASE SUMMARY

The patient was a 50-year-old Caucasian male government contractor who presented with progressive, nontender lymphadenopathy involving his cervical, axillary, and inguinal lymph nodes, 6 months after returning from deployments to Iraq and Afghanistan. He had been in each country for 1 year starting with 6 months in Iraq immediately followed by 6 months in Afghanistan. He also endorsed fever, drenching night sweats, fatigue, and abdominal distension.

On examination, his temperature was 97.7°F (36.5°C), heart rate was 120 bpm, and respiratory rate was 17. Pertinent findings on examination included nontender cervical, axillary, and inguinal lymphadenopathy, a maculopapular rash on the chest and splenomegaly. Laboratory evaluation revealed a WBC count of 5.4 × 10^3/mcL, Hb count of 14.7 g/dL, platelet count of 146,000/mcL, AST 21 U/L, and ALT 83 U/L. A computed tomography (CT) of the neck, chest, abdomen, and pelvis confirmed generalized lymphadenopathy and splenomegaly. He was admitted to the inpatient internal medicine service for expedited workup for suspected malignancy.

Workup including an inguinal lymph node and bone marrow biopsy revealed a reactive process, noncaseating granulomas and no malignant cells with negative stains for acid fast baceria and fungal organisms. A recombinant antigen (rK39) assay for VL was positive. The patient was started on intravenous liposomal amphotericin B (AmBisome) 3 mg/kg daily and within 24 hours experienced resolution of fever. He completed a full course of therapy for VL, which entailed AmBisome 3 mg/kg/day on days 1 to 5 followed by 3 mg/kg/day on days 14 and 21 and experienced gradual resolution of splenomegaly and lymphadenopathy.

On the last day of AmBisome therapy, he underwent a CT of the neck to evaluate a postoperative seroma at his biopsy site. He was sent to the Emergency Department because of a diffuse rash that developed within minutes of receiving intravenous contrast for the CT. Within 24 hours of receiving corticosteroid therapy for possible allergic reaction to contrast dye, he experienced relapse of lymphadenopathy, splenomegaly, and rash. Despite a second course of AmBisome for presumed relapse of VL, his lymphadenopathy persisted. Repeat rK39 assay results returned as negative, however. At this juncture, a definitive diagnosis of EBV-positive B-cell LPD resembling polymorphic B-cell lymphoma was made based on multiple expert rereviews of previous biopsies. The patient was reevaluated in Medical Oncology and started on rituximab but experienced no relief in his symptoms. He was admitted to an outside institution because of ongoing fever and lymphadenopathy, where he underwent repeat
lymph node and bone marrow biopsies. The lymph node pathology showed angioimmunoblastic T-cell lymphoma and EBV-positive polyclonal B-cell LPD. Bone marrow pathology showed positive marrow involvement of T-cell lymphoma with lymphoma cells representing less than 20% of the marrow. He is currently undergoing chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone.

DISCUSSION

VL is a vector-borne disease that is transmitted by the female phlebotomine sand fly. The sand fly is typically most active at night and its bites may go unnoticed. The incubation period for VL is generally 2 to 6 months, though it can range from a few weeks to over 2 years. Onset is usually insidious and almost always starts with persistent fever followed by fatigue, anorexia, weight loss, and abdominal enlargement because of hepatosplenomegaly. Lymphadenopathy is frequently seen in Sudanese VL but is uncommon in other areas. When present, lymphadenopathy is generalized and can include epitrochlear, cervical, axillary, and inguinal lymph nodes. There have been cases of localized lymphadenopathy as the presenting finding in patients in Southern Europe and Latin America, though these cases lacked other systemic signs and symptoms. Extensive lymphadenopathy has also been reported in cases of cutaneous leishmaniasis in Northeast Brazil.

Laboratory studies are often significant for pancytopenia (anemia is typically present) and hypergammaglobulinemia. Leukopenia is prominent in these patients; however, this was not the case in our patient who had leukocytosis (the etiology remains unclear). Although mild glomerulonephritis has been described, renal failure is rare. Our patient had acute kidney injury, and this was thought to be secondary to hypoalbuminemia-induced third spacing of intracellular fluids. His kidney function returned to baseline with treatment.

The mainstay in diagnosis of VL is demonstration of parasites in tissue by direct visualization or culture. In specialized parasitology laboratories, a polymerase chain reaction test can be performed on these samples to detect Leishmania DNA. Several serological techniques that measure antibody levels have also been developed for the diagnosis of VL. These include a direct agglutination test, enzyme linked immunosorbent assay using antibody to native gp63, rK39 of Leishmania chagasi (that cross-reacts with L. donovani and L. infantum), and indirect immunofluorescence antibody test. Optimal results have been shown by antigen rK39 with sensitivity of 100% and specificity of 96%. In addition, antibody titers to rK39 correlate with parasite burden and may be used to monitor the response to treatment and assist in predicting clinical relapse. This finding is consistent with what was observed in our patient as VL was diagnosed using the rK39 assay and repeat testing following treatment with AmBisome was negative.

VL is of significant concern to the U.S. military since hundreds of thousands of troops have been stationed in endemic areas since the start of Operation Enduring Freedom and Operation Iraqi Freedom. Afghanistan has one of the highest incidences of cutaneous leishmaniasis in the world, but there had only been 23 reported cases of VL in the literature before the start of Operation Enduring Freedom. Since then, there have been an increasing number of reported cases of VL in U.S. military personnel. In fact, after Operation Desert Storm in 1991, a case series detailed eight soldiers who were found to have viscerotropic leishmaniasis in the setting of exposure in Saudi Arabia. Even though most of their symptoms paralleled the reported spectrum of VL, these eight patients had a myriad of nonspecific clinical signs and symptoms. Two patients had evidence of lymphadenopathy, one of whom had localized axillary lymphadenopathy. A more recent case series detailed VL in four soldiers with
deployments to Iraq and Afghanistan. All these patients presented with fever and splenomegaly along with various other nonspecific signs and symptoms. However, none was found to have diffuse lymphadenopathy.

Our patient had a very atypical presentation of VL. Although diffuse lymphadenopathy is common in infections acquired in the Sudan, it is unusual elsewhere. There was a high index of suspicion for lymphoma initially, in addition to infectious diseases such as infectious mononucleosis and resultant hemophagocytic lymphohistiocytosis, toxoplasmosis, acute retroviral syndrome because of HIV as well as rheumatologic etiologies such as rheumatoid arthritis, systemic lupus erythematosus, and Sjogrens syndrome. An extensive workup to include multiple serologies and lymph node biopsies and cultures were unrevealing for any of these etiologies. Inguinal lymph node and cervical lymph node biopsies along with bone marrow biopsy, while negative for malignancy, did not show intracellular amastigotes of Leishmania as expected, further complicating diagnosis. However, as previously noted, superior sensitivity and specificity of the rK39 assay helped to solidify his diagnosis and prompt immediate treatment.

This patient's case was further complicated by what was initially thought to be relapse of VL. Relapse following adequate treatment for VL is not infrequent. A U.S. Food and Drug Administration review of clinical trials to support approval of AmBisome for treatment of VL revealed a higher rate of relapse in immunosuppressed patients when compared to immunocompetent patients. VL is recognized as an opportunistic infection in patients who experience functional T-cell deficiency following treatment with corticosteroids, other immunosuppressive agents or because of advanced AIDS. Interestingly, it has been documented that immunologic dysfunction and depressed cell-mediated immunity are hallmarks of VL infection. Specifically, there is a decline in lymphocyte ability to proliferate in response to Leishmania antigen. One study that examined postmortem spleens and lymph nodes of cases of VL showed small lymphocyte depletion in thymus-dependent regions. Furthermore, another study by Carvalho et al showed that patients with active VL had significantly lower interleukin-2 and γ interferon levels that are important in mediating several lymphocyte functions. This inability to generate interleukin-2 and γ interferon to Leishmania antigens during VL infection lends itself to profound immune dysregulation.

Some of the major pathogenic etiologies important in the development of EBV-LPD/lymphoma in patients with immunodeficiency include the use of immunosuppressants in patients with transplantation or rheumatic disease and AIDS associated with HIV infection. Among transplant patients, EBV-LPD/lymphoma was described in patients who had been treated with corticosteroids and azathioprine. In addition, an increase in the incidence of EBV-LPD/lymphoma was documented with the introduction of calcineurin inhibitors. It is, therefore, not surprising that patients with secondary immunodeficiencies because of VL are prone to EBV-LPD/lymphoma. Decrease in immunosuppressive therapy sometimes led to regression of EBV-LPD, underscoring the possibility that reduction in immunosurveillance is associated with risk of EBV-LPD. Other treatment options for LPD include anti-B-cell monoclonal antibodies such as rituximab and chemotherapy. We hypothesize that EBV-LPD in our patient occurred because of reactivation of latent EBV due to profound immune dysregulation from VL. His profound immunosuppression because of VL coupled with added insult from corticosteroid therapy likely facilitated the development of progressive EBV-LPD to non-B-cell NHL. The fact that he responded dramatically to VL treatment initially argues against non-B-cell NHL as the primary process, although this remains possible.

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In conclusion, VL is a disseminated infection associated with high mortality left untreated. It holds particular relevance to health care workers caring for returning military and other Defense Department employees given recent reports of infection acquired during deployments to Iraq and Afghanistan. Many of these potential cases would be predicted to occur outside the military or Veterans Administration health care setting, raising the need to consider specific diagnostic testing for this potentially fatal infection in the context of a history of service in Iraq or Afghanistan. Although lymphadenopathy is an atypical presentation of infection acquired in the Middle East, VL should certainly remain in the differential in any patient with associated fever and splenomegaly. Furthermore, clinicians should not discount the profound immune dysregulation associated with widely disseminated infection and be vigilant in entertaining complications to include EBV-related lymphoproliferative disorders and lymphomas as a complication of infection.

Tuberculosis Among Nonimmigrant Visitors to U.S. Military Installations

Military Medicine
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ABSTRACT

Background: Nonimmigrant visitors are not required to be evaluated for tuberculosis (TB) before entering the country. Little literature exists describing the challenges of TB control among this demographic. This report reviews the challenges in managing TB in this population on U.S. military installations. Methods: Six cases were identified from reportable medical event reports. Information was obtained from public health personnel via phone interviews. Verified cases from 2004 to 2011 were included. Results: Challenges were congruent among locations including: lack of procedures to screen for infection and disease among individuals at time of entry allowing one case to be admitted with acquired immunodeficiency syndrome and another concurrently on treatment for active TB; delays in the diagnosis of active TB as median time from entry to diagnosis was 62 days; and the need to conduct an effective contact investigation as the mean contact index was 77 including 1 secondary case of active TB. Conclusions: These cases emphasize the need for screening for TB in visitors from high-risk countries at time of entry, prompt diagnosis and treatment if found, procedures for evaluation of contacts, and interjurisdictional cooperation in large contact investigations. These challenges are common to nonimmigrants in both military and civilian settings.

BACKGROUND

Birth or residence outside the United States is the strongest risk factor for both active and latent tuberculosis (TB) in the United States, and foreign-born persons now account for 60% of all active TB cases. The incidence of TB is high in many countries that are a source of both immigrant and nonimmigrant visitors to both the United States and Canada. However, TB control strategies have limited success in many foreign-
In the United States, those ≥15 years of age applying for permanent immigrant status require a medical history, physical examination, and chest X-ray (CXR). If an applicant has a CXR with findings suggestive of TB, has signs and symptoms of TB, or has human immunodeficiency virus (HIV) infection, the applicant should provide three sputum specimens to undergo microscopy for acid-fast bacilli (AFB), as well as culture for Mycobacteria and confirmation of the Mycobacterium species, at least to the Mycobacterium tuberculosis complex level. In the case of those applying for permanent immigrant status, there are many different categorizations. For instance, a Class A immigrant (“Abnormal,” CXR suggestive of active TB and positive smears) either must apply for a waiver signed by the local health department in their intended U.S. destination or complete TB therapy in their respective nation of origin until 3 serial sputum smears are negative. This case series, however, pertains to the nonimmigrant alien (as defined by the Immigration and Nationality Act) whose class of admission is designated “vocational student,” by the Department of Homeland Security. Unlike immigrants and refugees, nonimmigrant visitors are not required to be medically evaluated for TB before entering the country. In addition, only foreign students staying for a period of 6 months or greater require screening. Furthermore, since the U.S. government has an “open-door policy” for most nonimmigrant classes of admission, no restrictions exist on the total number of admissions each year. Little previous literature exists describing the challenges of TB control among these nonimmigrant visitors. This retrospective case series describes 6 active TB cases among nonimmigrant visitors at U.S. military installations from 2004 to 2011. We evaluate the effectiveness and timeliness of case detection, treatment, and CIs. We then review the issues and challenges in managing TB in this population, which impact the TB prevention and control programs in both military and nonmilitary settings. The limited examples presented here are by no means exhaustive and represent extreme cases along a continuum from LTBI to TB disease with or without concurrent pathology. They are intended to raise awareness and stimulate discussion as to how instances such as these can best be avoided in the future.

METHODS

Routine surveillance for active TB occurs through public health personnel assigned to U.S. military installations. These local public health personnel then notify the supporting local health department as well as the service-specific public health center: the U.S. Army Public Health Command, Navy or Marine Corps Public Health Center, and the U.S. Air Force Medical Operations. Cases were identified by the author(s) from routine surveillance reportable medical event databases, and further information was obtained from local public health personnel via phone interview and e-mail correspondence (occurring from April 2011 to April 2012), including labs, radiographs, and CIs. All diagnoses were verified according to the criteria provided by the Centers for Disease Control and Prevention (CDC): (1) isolation of M. tuberculosis from a clinical specimen; (2) demonstration of M. tuberculosis complex from a clinical specimen by nucleic acid amplification test (NAAT); (3) demonstration of AFB in a clinical specimen when a culture has not been or cannot be obtained or is falsely negative or contaminated; or (4) by meeting the clinical case criteria. Only verified cases among foreign nonimmigrant visitors at U.S. military installations from 2004 to 2011 were included in the case series. The infectious period was calculated utilizing the CDC guidelines.
CASE STUDIES

Case 1

This case arrived for training in 2006 from Swaziland and 24 days later was seen for nonspecific respiratory symptoms. He apparently appeared well and was prescribed standard therapy for presumed pneumonia based on CXR. Soon after he was seen with progression of cough to hemoptysis, night sweats, chills, and fevers. CXR revealed progression to diffuse opacities. That same day the service member (SM) was transferred to a civilian facility with a preliminary diagnosis of pulmonary TB based on symptoms and imaging results.

Pursuant to AFB stain positivity, he was started on standard multidrug treatment. Follow-up computed tomography (CT) of the chest revealed numerous small cavitations. He was discharged at the end of February after which there was no documentation and it is assumed that he returned to Swaziland. The plan was for exposed staff to be screened along with the subject’s classmates. Attempts were made to reach the 14 contacts that had since left the area, and a memo was sent out delineating requirements for screening; however, only 50% were reached. Although one secondary case of TB was identified, he had not been screened and in March 2007, he tested positive by tuberculin skin test (TST) during routine screening. Since he was asymptomatic, treatment was deferred and the connection to the source was not made. Then, while deployed in 2008, he developed symptoms and the case was later genetically linked to the source via spoligotyping.

According to those interviewed, the principle issue was ensuring all exposures were informed of their potential for infection. Although a substantial number of contacts were exposed in close proximity and for prolonged durations, there was incomplete contact information. Although there were multiple attempts to reach suspected contacts via Army Knowledge Online, there were many obstacles including full e-mail boxes, reservists who rarely check their accounts, and changes in duty status. In many cases, the various jurisdictions notified contacts in writing trusting that each would seek evaluation with their providers. It was later discovered that there had been delays in memoranda approval. Moreover, although there had been a search of community health investigation records, there had been a staff turnover and many files could not be recovered. Finally, there was often incomplete data for the determination of priorities and the CI required collaboration with administrators who were unfamiliar with TB.

Case 2

Before this asymptomatic subject arrived from Afghanistan for training in September 2009, a CXR was completed and interpreted as negative. Two months after arrival during routine screening, he was found to have a borderline abnormal CXR; however, he neglected to show for a public health follow-up appointment. When he presented for his initial flight physical in January 2010, his CXR had progressed and TB was considered a differential diagnosis. Subsequent CT chest revealed numerous nodules and further testing was pursued. Based on the sources’ negative AFB smear, no contacts were deemed high risk. There were 15 students and 8 instructors classified as intermediate risk. Three of the total 32 contacts were called back for retesting, as the other 29 had been initially tested after the window period had passed.

According to those interviewed, the main issue encountered was lack of supervision as the institute had no official Charge of Quarters or medical oversight. Thus, “foreign students were treated like graduate students at a university and they were pretty much given free reign.” Their experience
was that “no matter how important or how much they emphasized mask precautions, foreign nationals would not wear a mask.” This prompted the principle investigator to “ask the attending physician if he would be willing to do the equivalent of a social admit and keep the source on the ward for the first 2 weeks of directly observed therapy (DOT).” Finally, concern was magnified as the subject had been attending classes for a long period of time before diagnosis.

Case 3

This Cambodian SM arrived in the United States in 2010. Before his arrival, officials at Lackland Air Force Base had instituted a targeted TB screening program to evaluate students arriving from the WHO's top 22 high-risk countries. Under the auspices of this incipient program, new students from high-risk countries are processed into classes on day 1 and are sent for a screening CXR on day 2. The otherwise asymptomatic Lieutenant Commander's chest films were read as abnormal before the weekend; however, the patient could not be located and his command was advised to have him report to the public health clinic the following Monday. Preventive Medicine assessed the case that day, and he was hospitalized in a negative flow room. CT chest provided further evidence of active TB while hospitalized. It was later confirmed that the source had been in his fourth month of treatment for active TB before departing Cambodia. Regardless, the Cambodian Army physician had cleared him for travel to the United States. Public health officials immediately sent the subject home only 1 week after his arrival. Further, the State Department disqualified the Army physician from any further overseas clearances to the United States. After interviewing the source case and determining that he had in fact been initiated on treatment, it was decided that he had no contacts with the potential for infection. There were no records available after his departure date.

According to those interviewed, the main issue encountered for this case was significant communication difficulties between TB controllers and the subject as well as their counterparts in Cambodia. Although this subject had reported with no medical records, he had arrived with the results of his clearance screening examination. Crucially, it indicated that the subject's CXR had been normal and made no mention of the fact that he was receiving continuation phase chemotherapy for TB. It is worth pointing out that this example is unique among the other five as in that the receiving installation had already instituted an active screening program; thus, he was sent home only 8 days after arriving emphasizing how effective screening procedures can be when implemented in a systematic and standardized manner at our own borders.

Case 4

This African SM from Sierra Leone arrived in the United States for training on January 3, 2011. Three weeks later, he was seen in the on-post Emergency Room complaining of cough, fevers, chills, sore throat, odynophagia, dyspnea, headaches, pleuritic chest pain, and anorexia. Workup revealed a pericardial effusion, and he was transferred to a civilian hospital for in-house cardiology care. During this hospitalization, he was noted to have a significantly depressed CD-4 count consistent with acquired immunodeficiency syndrome (AIDS), methicillin-sensitive Staphylococcus aureus bacteremia progressing to sepsis, and a CT of the chest revealed diffuse bilateral nodules. Likely due to anergy, interferon-gamma release assay (IGRA) and TST were indeterminate. He was diagnosed with miliary TB based on previous cervical lymph node, lung, and pleural biopsy positivity via AFB stain as well as sputum culture. The last record available stated that the case was to be transferred back to Sierra Leone “in 1
week.” Since the SM (1) was diagnosed with miliary TB; (2) was smear negative by bronchoscopy; (3) exposed no one in a congregate setting; (4) had no cavities on chest films; and (5) had not been previously treated, an official CI was not initiated. This case had ongoing symptoms when he last received medical care in the United States. Since there was no CI undertaken, there were no significant obstacles associated with this case.

Case 5

This case is a native of Peru who arrived in the United States in 2003. He had been seen initially in October 2003 and treated for pneumonia. Subsequently, in March 2004, he had been afforded therapy for a “lower respiratory infection.” By August, his symptoms had progressed to a chronic productive cough, pleuritic chest pain, and weight loss. Further, a CXR revealed a large cavity that had not previously been noted. He was admitted to the hospital where further testing revealed active TB. Potential contacts were defined using Colorado State Health Department Guidelines and were identified through interviews, a cadet questionnaire, and class rosters. Follow-up screening was scheduled to correspond with influenza vaccinations and was completed for the entire class of 2009, regardless of whether they had initially been screened. This subject was in the country for a total of 4 years, completing his training at the Air Force Academy without further incident.

The most significant hurdle for this investigation was identification of potential contacts. Additionally, emphasizing the importance of a thorough and efficient contact tracing, the conversion rate was sufficient enough (among so many contacts) that there was a real concern of some progressing to active disease if prophylactic treatment was not given. However, there were significant staffing issues with only one preventive medicine physician assigned to screen the entire exposure cohort. Finally, Peru had no routine screening in place. According to the State Department, the only requirement was a statement that the students were free of infectious disease. This could be met simply by a signed letter of health from a physician; however, this had not been obtained. Nevertheless, subsequent to this event, all international students have been screened utilizing QuantiFERON blood testing and CXR upon arrival at the U.S. Air Force Academy. This example is unique among the other five as in this case policies and procedures were adopted that require screening of all international students reporting for training.

Case 6

This subject arrived for training in May 2009 and had been screened in Afghanistan with a “normal CXR.” After suspicious follow-up imaging on a routine flight screen, a CT of the chest revealed a cavitating nodule concerning for TB. Further testing was carried out resulting in a diagnosis of active pulmonary TB. At the time he was hospitalized, he revealed that he had been fatigued for 3 months, had decreased appetite, and had lost 4 kg of body weight. At discharge, he was instructed to stay confined to his quarters wearing a surgical mask. In addition, he was informed that he could not attend school for 2 weeks while on treatment. However, against medical orders, he attended classes unmasked only 3 days after discharge. The last available note stated that surveillance CXR revealed a persistent cavity. During the CI, IGRAs were utilized for screening the entire student cohort. One of the 2 who converted had severe and concurrent rheumatoid arthritis and had been previously prescribed methotrexate and Humera. This contact had been administered Bacille Calmette–Guerin vaccine and had always been of the belief that she would have false positive TSTs. Because of this, she had never completed treatment for LTBI.
According to those interviewed, the most serious issue during this investigation was supervision of the noncompliant and potentially infectious foreign student. Monitoring these subjects was described as a "systemic issue in that historically, there has not been a Charge of Quarters assigned and thus, no supervision."

RESULTS

All six of the cases (100%) were foreign born. One of the six cases (17%) was previously diagnosed with TB and was still undergoing treatment at the time of entry into the United States. Positive AFB smears were discovered in two (40%) of the five cases who had smears completed and all five of these (100%) had a positive culture for M. tuberculosis. There were no cases of multidrug-resistant or extensively drug-resistant TB. NAAT testing was positive in all three cases in which it was performed. Cavitary lesions were reported in two (40%) of the five cases who had smears completed and all five of these (100%) had a positive culture for M. tuberculosis. Testing for TB infection using a TST or IGRA was performed among five of the six cases (83%); three of the five (60%) cases had at least one positive test. Only one case (Case 3) had TB screening at entry into the United States and had a positive IGRA; the rest of the TSTs and IGRAs were performed as part of the diagnostic workup for clinical TB. One patient was previously coinfected with HIV that had progressed to AIDS and was diagnosed with miliary TB. Presenting symptoms are shown in Table II displays timelines for each of the six cases. The majority of the contacts were because of exposure in military congregate settings rather than family members or friends. For the four cases who were symptomatic, the median length of time from entry into the United States to date of symptom onset was 51.5 days (range: 21–105) and the median length from entry date to date of diagnosis was 62 days (7–417). Median period from symptom onset to initiation of treatment was 34.5 days (16–317). Median interval of time in country was 236 days (8–1278). Half of the cases remained in the United States until after the completion of treatment, and the other cases were repatriated during therapy.

The period from the date of diagnosis to the initiation of the CI was an average of 4 days (1–12). The median length of the infectious period was calculated to be 136 days (8–429), and the average percentage of time in United States during infectious period was 96%. A total of 460 contacts were identified, for a median contact index of 23 (mean: 77), but the number of contacts per case varied widely from 0 to 383. Two hundred two (44%) were identified as high-risk contacts, 232 (50%) as intermediate risk, and 26 (6%) as low risk. Four hundred eight (89%) were evaluated and 398 of those (98%) returned to have their TST read. There were 48 cases of LTBI for a conversion rate of 12%, and one case (0.2%) developed active TB. Three hundred seventeen of the remaining 412 at-risk contacts (77%) returned after the window period, and 11 of these converted (3.5%). All 48 cases with positive TSTs started and completed treatment.

On average, after being listed as the source, cases were interviewed within 6 business days. Potential sites for contact were visited within 2 to 3 business days after the initial interviews were completed. All high priority contacts exposed to a source case with positive AFB sputum smears or who had cavitary disease on CXR were contacted within 1 day of listing, and evaluations were completed within 3 days per CDC guidelines. For those high-priority contacts exposed to a source case that was AFB sputum smear negative, all were contacted within 7 days of listing, and evaluations were completed within 10 days.

DISCUSSION
Little previous literature exists describing the challenges of TB control among nonimmigrant visitors. This report describes a series of 6 cases of TB among nonimmigrant visitors at U.S. military installations. These cases reveal several challenges to TB control and prevention that are common in both military and nonmilitary settings. These challenges include developing procedures to screen for active and latent TB among foreign-born individuals at time of entry into the United States, avoiding delays in the diagnosis of active TB, and conducting an efficient and effective CI in a congregate setting.

Screen for Active and Latent TB at Time of Entry

Because of the low burden of disease, high cost, and high logistic burden, instituting screening procedures and requirements for these visitors before entry is not required. Since there is no entry requirement to do so, these cases were mostly unscreened for active or latent TB before entry into the United States. However, at the time of entry into the United States, one of these cases was receiving treatment for active TB, one had been previously infected with HIV that had progressed to AIDS, and the rest either developed TB or were being treated for TB before entry. This suggests a need for screening at some point, both to provide a health benefit for the entrant and to protect the health of U.S. citizens who come into contact with these individuals. Screening procedures for both active and latent TB are widely employed in university settings when foreign students enter the United States. Similar procedures should be employed by any organizations accepting nonimmigrant visitors.

Avoid Delays in the Diagnosis and Treatment of TB

Several of the cases in this report had significant delays in diagnosis and treatment, thus increasing the likelihood of complications and unnecessarily exposing their contacts to increased risk of infection. Settings in which nonimmigrant visitors enter the United States should also introduce policies and procedures that support the goal of prompt recognition, diagnosis, and treatment of TB disease. This includes educating both patients and providers, ensuring laboratory capacity, and establishing surveillance procedures.

Delays in the diagnosis and treatment of LTBI must be avoided. The one secondary case of TB disease had two missed opportunities. Initially, he was identified as a close contact of the source case but was not screened nor included as part of the CI. The second opportunity presented itself during his predeployment health screening 18 months later. He was found to have a 15-mm TST reaction but was deferred without evaluation until after his return from deployment to Iraq. When the patient developed symptoms of active TB, military health officials were concerned that the infection was deployment related. Subsequent spoligotyping by the Maryland State Health Department confirmed that transmission had in fact come from the foreign military exchange student. This case further highlights the need for policies and procedures that effectively diagnose and treat LTBI as well as active TB.

Perform Effective and Efficient Contact Investigations
CIs must be performed according to established procedures, and active and latent TB must be promptly diagnosed and treated in these contacts. Both variability in the conduct of CIs and difficulty with screening the contacts who are identified have been noted in previous studies. Several additional challenges in conducting CIs among nonimmigrant visitors were noted in this study. Although many of the source patients were available for interview, they were often poor historians with significant language barriers. CIs are logistically complicated activities, requiring collaboration of many interdependent agencies and jurisdictions, further complicated by the involvement of foreign national governments with additional cultural and language barriers. Information about and follow up of these contacts was sometimes incomplete. Even when contacts were successfully reached, the response rate was sometimes low. The overall proportion of contacts evaluated for TB infection, and disease (89%) was actually higher than the national average (79%). However, this did not meet the 2015 national performance target of 93%. At 100% each, the proportions of contacts that started and completed treatment were higher than both the national average and the national target. Resources devoted to training of ancillary staff and to ensure adherence to protocols are needed to continue to promote efficiency and effectiveness in CIs.

The findings of this report are subject to several limitations. In the interest of brevity, only six cases were included in this series. Additionally, data capture may have been incomplete and cases of TB among nonimmigrant visitors missed. There was very limited information available on the screening procedures and prior medical history of the cases before entry into or after departure from the United States. Misclassification is also possible for many of the variables, such as assessments of the levels and total duration of exposures, especially among workplace contacts. Moreover, the cases described were among nonimmigrant exchange students from a limited set of nations (each with their own sets of rules pertaining to screening procedures) studying or working on U.S. military installations, which may limit the generalizability of the findings to other populations and settings. Finally, we were unable to obtain data regarding the total number of nonimmigrant visitors who studied at U.S. military installation during the timeframe of this study limiting the context of the study.

The cases discussed in this report emphasize the need for screening nonimmigrant visitors at time of entry into the United States, prompt diagnosis and treatment of TB, and effective procedures for evaluation of contacts and interjurisdictional cooperation in congregate settings and large CIs. These challenges are common to nonimmigrant visitors in both military and nonmilitary settings. Policies and procedures should be put into place in any setting in which these visitors come into the United States, such as university settings and military exchange programs. These policies should emphasize: (1) proper screening for both active and latent TB using modalities such as symptom screen, TST or IGRA, and CXR, followed by immediate treatment; (2) awareness of the signs and symptoms of active TB at clinics where nonimmigrant visitors seek care, and the need for immediate treatment; and (3) adherence to and effective management of standard CI procedures in congregate settings.

BACK TO TOP

Building Military Influenza Surveillance Capacity in West Africa

Military Medicine

March 2013
Abstract

Militaries are especially susceptible to operationally important outbreaks of acute respiratory infections such as pandemic and seasonal influenza. In addition, militaries play important roles for State Parties working to meet International Health Regulations 2005, particularly in developing countries. In 2009, the U.S. Naval Medical Research Unit No. 3 joined with the Noguchi Memorial Institute for Medical Research and the armed forces of Ghana, Burkina Faso, and Côte d'Ivoire to create or improve influenza surveillance capacities within the militaries. This article describes the process undertaken to achieve this goal. In the Ghana Armed Forces, influenza surveillance for outpatients was instituted at seven medical stations throughout the country and for inpatients at the tertiary referral hospital in Accra. As a result, military sites now contribute around half of the influenza cases detected in Ghana and reported weekly to the World Health Organization. Samples were also collected by the militaries of Côte d'Ivoire and Burkina Faso, although political instability slowed progress. This effort is part of an ongoing strategy to build influenza surveillance capacity within West African militaries in support of military services, global outbreak investigations, International Health Regulations-2005, and the development of country-specific pandemic preparedness plans.

Introduction

In many developing countries, military members live in barracks in proximity to animal or poultry farms, increasing the risk of infection with zoonotic diseases. Military personnel may also work in limited spaces under stressful conditions, creating a situation favorable for the rapid spread of respiratory infections. Militaries have been affected by global pandemics as well as more focal outbreaks in military naval vessels. When the military is called on for peacekeeping, maintaining order, reestablishing stability, and implementing pandemic response plans, significant vulnerability and operational impact are expected. During the 1918 influenza pandemic, the U.S. military personnel had 40% morbidity rates because of influenza, and influenza mortalities exceeded those from battle wounds, dramatically impacting mobilization efforts. Even in nonpandemic years, hospitalization rates because of respiratory disease in military recruits have been three times higher than the rate in the general population. When significant numbers of personnel are unable to adequately perform their assigned duties because of illness, missions may fail.

Considerable changes to international law on public health have occurred as reflected in the International Health Regulations 2005 (IHR-2005) and these changes impact the role of militaries. Militaries need core capacities for disease surveillance and response, not only for their own force health protection but also as part of broader public health responsibilities, carried out in coordination with national and international civilian institutions. The U.S. military has established systems for disease surveillance and outbreak response in troops and requires influenza vaccination for all active duty military. Militaries with more experience and infrastructure, such as the U.S. Department of Defense, can also contribute by
helping other militaries build public health surveillance and response capacities. However, in West African countries, influenza surveillance systems are less well developed and sometimes nonexistent, especially in the militaries. In addition, influenza vaccination is not performed.

Since symptoms of respiratory infections are overlapping, molecular methods have been recommended for the rapid and accurate diagnosis of viral influenza. Such methods have been developed by the U.S. Centers for Disease Control and Prevention (U.S. CDC) and require special equipment, training, and biosafety measures. In 2009, the U.S. Naval Medical Research Unit No. 3 (NAMRU-3) partnered with the Ghana Armed Forces (GAF), the Burkina Faso Armed Forces (BFAF), and the Côte d’Ivoire Armed Forces (CIAF) to establish core capacity in militaries for influenza and respiratory disease surveillance. The purpose of this work was to develop strategies to (1) initiate collaboration between military and civilian institutions, (2) establish National Influenza Centers (NICs), (3) confirm the diagnosis of cases, (4) explore disease burden, (5) comply with the requirements of the IHR-2005 published by the World Health Organization (WHO), and (6) provide guidance for the development of country-specific pandemic preparedness plans. This article focuses on the process we undertook to achieve these goals and provides a brief overview of results with more detailed surveillance findings to be published separately.

Materials and Methods: Assessments and Implementation Strategies

In early 2007, the NAMRU-3 conducted training and provided $250,000 worth of supplies and equipment to the Noguchi Memorial Institute for Medical Research (NMIMR) in Ghana to establish an NIC capable of detecting H5N1 avian influenza (AI) and identifying pandemic outbreaks of viral respiratory disease. However, building capacity at the military sites was not started until 2009, when a team consisting of a U.S. military physician, a senior U.S. military medical service corps officer, a senior Ghanaian virologist, and a regional influenza surveillance coordinator for the NAMRU-3 visited with heads of medical services for the Ministry of Defense from each of the three countries to assess the current status of influenza surveillance, including laboratory capacity, and their desire to improve influenza surveillance. Visits to military health facilities and discussions with the military medical staff identified equipment and supplies needed for surveillance at the sites. In addition to understanding the current capacities and interest of host countries, the team needed to understand what other development aid was ongoing, especially United States Government (USG) activities. Coordinating through embassies, the team determined what activities were in process from other USG agencies such as the U.S. CDC and the U.S. Agency for International Development (USAID). All military-to-military capacity building also needed to be consistent with USG diplomatic activities, and therefore, all planned activities were coordinated through the DoD offices at the various embassies, particularly, the Offices of Security Cooperation.

Once equipment and supplies were purchased and delivered to the new sites (Table I), a workshop was held in Accra to provide training on sample collection and processing, filling epidemiologic data forms, and other influenza surveillance methodology (Fig. 1). Country meetings were organized to develop follow-up plans and implement three components of influenza surveillance: outpatient influenza-like illness (ILI) surveillance, inpatient severe acute respiratory infection (SARI) surveillance, and surveillance in birds. Each component was discussed for feasibility, timelines for initiation, and need for preliminary steps. Collaboration with the civilian Ministry of Health (MOH) in each country was recommended as an initial step for respiratory disease surveillance to gain quick momentum and avoid duplication. Though each component was integral to the understanding of influenza in a country, a stepwise approach was adopted to better identify and overcome challenges in establishing surveillance.
systems. In all three countries, initial ILI surveillance plans were for a laboratory-based system using nasopharyngeal or oropharyngeal samples collected from the first five patients meeting the case definition per day at each site. As these systems developed, a more rigorous epidemiologic approach involving collection of data on all patients seen at each sentinel site was implemented. Follow-up was made by representatives from the NAMRU-3 and the NMIMR, who visited individual sites to provide supplies and more on-site training (Fig. 2).

Country-Specific Influenza Surveillance Activities

Ghana

In 2007, an initial partnership was established between the NAMRU-3, the NMIMR and the Ghanaian MOH to develop the country's NIC. In May 2010, the NIC was formally recognized by the WHO and provided regular information to the Ghanaian MOH and international institutions. Military sentinel sites in regions where the MOH sites had not been effective were selected to make the overall influenza surveillance system more robust and reliable. Within 1 year (2009–2010), seven military sites from six different regions were added (Table II) after receiving appropriate training and supplies (Fig. 2). The addition of these sites to the civilian system added three regions of Ghana, not previously captured, and improved the geographic coverage of the country.

Since ILI surveillance was an ongoing public health activity of the Government of Ghana, samples were collected routinely from patients presenting at the sentinel sites with flulike symptoms and sent to the NIC. For SARI, a partnership was established between the GAF, the MOH, the WHO, and the U.S. CDC to develop an inpatient surveillance system in three hospitals in Ghana, including the 37th Military Hospital. Initially funded as a research protocol, SARI surveillance procedures were implemented by the collaborators aimed to support a sustainable inpatient surveillance system for the sites. Approvals were obtained from scientific and ethical review boards at the NMIMR, the NAMRU-3, and the Ghana Health Service. Review and approval were also obtained from the U.S. CDC, the Ghanaian MOH, and the Ghanaian Ministry of Defense. Samples from admitted patients showing severe respiratory signs and symptoms were tested for a variety of pathogens, and detailed epidemiologic data were collected. Like ILI samples, SARI samples were sent to the NIC for polymerase chain reaction (PCR) testing and positive results were reported to the WHO.

Burkina Faso

There was no preexisting influenza surveillance in either the civilian or military systems in Burkina Faso. The NAMRU-3 worked with the MOH under a separate program to develop civilian influenza surveillance by donating real-time PCR equipment and providing training to the MOH designated NIC in 2009. As in Ghana, it was decided that the military system should start by coordinating with the civilian NIC. ILI sentinel surveillance was initiated at three sites (two in Ouagadougou and one in Bobo Dioulasso). SARI surveillance was planned for implementation after the establishment of the ILI systems, in a stepwise approach to building capacity that would allow personnel to gain experience in surveillance methodology at an appropriate pace. It was also decided that sustainable and rigorous AI monitoring requires a dual approach: (1) surveying and
inventorying the poultry populations near military camps and (2) education of the owners of poultry about the signs of AI and the importance of surveillance.

Côte d'Ivoire

The country has been under United Nations sanctions since 2002. The conditions triggering these sanctions have made public health influenza surveillance programs more difficult to implement and sustain. The Institut Pasteur of Côte d'Ivoire has functioned as the country's influenza reference lab since 2003 and was officially recognized as an NIC by the WHO in 2008. Influenza sentinel surveillance has been supported by a U.S. CDC Cooperative Agreement since mid-2006. The military hospital in Abidjan originally participated in the surveillance system created by the Côte d'Ivoire MOH, but lapsed into dormancy. Some of the reported reasons included insufficient resources for the military site and poor communication of results between the NIC and the military hospital. The approach decided on for Côte d'Ivoire was to reestablish the existing military hospital site for both ILI and SARI and to add two additional military ILI sites in Abidjan.

Results and Discussion

Comprehensive influenza surveillance systems cannot easily be created from scratch, nor can they be implemented quickly in their entirety given the infrastructure challenges and resource constraints faced by developing nations. The stepwise approach taken in this collaborative project between the U.S. military and militaries of three West African countries has been to develop military public health systems in stages that could be continually improved on toward a desired end state. A thorough assessment formed the foundation for implementation strategies, allowing collaborators to identify the starting point and minimum needs for a basic system in each country (Table I). The collaborators determined that implementing what might be called a “laboratory-based” ILI surveillance system would be the best starting point for each country. In this system, each site was asked to collect samples from the first five patients to meet the ILI case definition each week. This strategy caused much less burden to the staff at each site than a system that requires tracking of all patients seen every week. It also allowed each site to identify strengths and weaknesses in the initial surveillance system and adapt accordingly, without overwhelming efforts.

More enhanced surveillance was initiated as experience was gained in laboratory-based surveillance. Training in case definition recognition and sample collection and handling techniques were the first needs identified. Further training and resources required for robust epidemiologic monitoring based on capturing all cases meeting case definitions for ILI with a laboratory sampling scheme were provided. SARI surveillance detected the severe cases, which had obvious benefits in identifying circulating influenza viruses of concern for increased virulence. The process started by tying in with a NAMRU-3 research project to establish an integrated hospital-based surveillance system in collaboration with the U.S. CDC, the NMIMR, and the GAF. This required designated teams from the public health department of the hospital to actively search for newly admitted patients meeting the SARI case definition daily. However, resources limited these teams to normal working hours. Although, the logistics of developing surveillance systems to capture all eligible cases (i.e., all admitted cases meeting SARI case definitions) were difficult to fulfill in understaffed hospitals, Ghana achieved significant progress, being the first country engaged by the NAMRU-3 and the initial focus of the plan.
In 2007, AI was detected in poultry farms in Ghana near Tema, where 12,811 birds died and 23,327 were culled. This marked Ghana as the eighth African country to confirm this disease. Two other infected farms in Ghana were also identified in other geographic regions. To reduce disease spread and minimize economic losses, poultry movement and sale was restricted and infected flocks were culled. Ghana's Ministries of Finance and Agriculture compensated farmers for culled birds. Although more than 60 farms around the country were assessed for sick and dying birds, no human AI infections were observed. To confirm disease diagnosis in birds, many virologists from NIC were trained at the NAMRU-3 on H5N1 virus detection by PCR subtyping and sequencing. Results showed a high similarity between the virus (>98.8%) and isolates from sub-Saharan African countries such as Côte d'Ivoire, Sudan, Burkina Faso, and Nigeria.

Although some passive AI surveillance has been done in Ghana, routine active surveillance requires continuous monitoring of domestic poultry. Military camps are located near areas of likely introduction of AI, including those mentioned earlier, and represent promising surveillance sites for identifying, testing, and reporting cases. However, there are not large poultry farms to serve as convenient surveillance sites, but instead small numbers of domestic poultry are owned by numerous persons in and around military camps. This decentralization made it difficult to know the exact numbers and locations of birds and to ensure owners knew signs and symptoms of AI in their birds. To raise awareness, troops and families from twelve military barracks were trained by veterinarians from the GAF, the NMIMR, and the NAMRU-3 on AI surveillance, prevention of emerging infections in humans and biosecurity. Of 1,028 participants who took part in the seminars, 668 (65%) showed good knowledge of AI and associated risks but biosafety practices were minimal. A questionnaire was also developed to collect information on animal and poultry flocks in 102 households in military barracks to direct public health policies. In addition, cloacal and tracheal samples were collected from 680 poultry and domesticated wild birds as an initial part of an active AI surveillance program. Analysis for influenza A using PCR showed that none of these samples were H5N1 positive.

After the emergence of pandemic influenza A H1N1 in April 2009, a patient in Accra tested positive for the new strain in August, making Ghana the third African country to report the disease. More cases were confirmed afterward by the enhanced sentinel sites. Of 2,810 children presenting at 22 health facilities across Ghana with ILI symptoms, 636 (23%) tested positive for influenza virus, with 60% of the strains belonging to pandemic H1N1. In 2010, over 1,238 samples were collected and tested from military sites in Ghana, with 164 (13%) testing positive for influenza. Of the 164 positive samples, 113 (69%) were identified as the 2009 strain of influenza A H1N1, 42 (26%) were influenza A H3N2, 7 (4%) were influenza B, and 2 were influenza A not subtyped. When the number of confirmed H1N1 cases from both military and civilian sites reached 513 in early 2010, the National Disaster Management Organization and the Ghana Health Service warned of a possible influenza outbreak in the country. Figure 3 shows the steady increase in samples received at NIC from military sites in Ghana over 2 fiscal years (FY). Results from tested samples were consistently provided to the GAF, the MOH, and the WHO every week. The GAF sites continue to form a significant component of the influenza sentinel surveillance system in Ghana. For the period January to June 2012, eight military reception stations provided 483 of 838 (58%) respiratory samples that matched case definitions for ILI and severe respiratory illness for this period from 17 sentinel sites nationwide.

The 37th Military Hospital in Accra along with other military sites created a more robust surveillance system, with military organization helping support sites that provided regular samples to the NIC, often in regions where civilian sites were less reliable. Samples collected from military sites constituted over 25% of the total cases reported weekly to the WHO through the Ghanaian MOH at the time of this writing. The Medical Services
of the GAF in partnership with the NAMRU-3 and the NMIMR launched an 8-day medical awareness campaign in 2011 to educate troops, their families, and civilian employees of the GAF on outbreaks of swine influenza and AI. Integration of the eight military sites into the nascent civilian surveillance program continued through coordination between the ministries of health and defense and provided more accurate surveillance results. Table II shows the timeline of capacity building for surveillance at the military sites.

In Burkina Faso, H5N1 was detected with the help of international partners in a poultry farm in Kadiogo province, just 10 km from the capital Ouagadougou in early 2006. This made it the fifth country to declare AI infection in West Africa. The disease was widespread, leading to the culling of thousands of birds during the outbreak (3.2% prevalence). It heavily impacted the economy of the country (gross domestic product per capita = $1,200, 19), where more than 76% of poultry (32 million) is raised traditionally in rural households. The virus was initially identified at the VLA Weybridge, United Kingdom (OIE/FAO Reference Laboratory for AI) and in Padova, Italy. Laboratory tests at the NAMRU-3 in Cairo showed that the virus was similar to those of Ghana, Côte d'Ivoire, Sudan, and Nigeria. However, avian samples were not consistently collected in Burkina Faso during this investigation, since most poultry owners were culling sick birds without notifying anyone from civilian or military veterinary services, and there was no internal testing capacity in the country at the time. More recently, the 2009 influenza A H1N1 virus has not been detected in Burkina Faso by the nascent sentinel sites (1 civilian and three military) established with support from the NAMRU-3 for ILI surveillance. Other influenza viruses (influenza A H3N2 and influenza B) have been detected and reported to the WHO in 2011. The apparent absence of the 2009 strain of influenza A H1N1 in Burkina Faso may be because of the establishment of these surveillance sites after the peak reported from neighboring countries such as Ghana, the relatively small numbers tested so far, or to other unknown factors. Burkina Faso is a landlocked country that has suffered from frequent public unrest, regional conflicts with the neighboring Côte d'Ivoire, weak infrastructure, and constraints on development, but a few dedicated public health professionals within the armed forces helped push the project described here despite these obstacles.

Côte d'Ivoire was the seventh African country to report infection with the highly pathogenic AI strains. The first outbreak appeared in March 2006 in the backyard of a traditional farm in Abidjan. Other outbreaks were further reported 500 km southwest of Abidjan. Military and civilian agencies coordinated for AI collection and testing, as in Ghana. Military veterinarians investigated dead birds reported in and around the capital city Abidjan and near borders with Ghana and submitted samples to civilian laboratories. Through this passive AI surveillance, highly pathogenic AI was reported as the cause of death in wild ravens in 2009. Detailed information on the infection of domestic poultry around the military facilities was not available. Between 2003 and 2004, nasal swabs were collected from 211 patients in Côte d'Ivoire to monitor human influenza viruses. The results showed that 12.8% of the samples were positive, mainly for A H3N2 followed by influenza B, and one seasonal A H1N1. In June 2009, the first cases of the 2009 H1N1 strain were confirmed from Côte d'Ivoire but the number of samples tested remained relatively low and sporadic. Although the number of newly added military sites has doubled during the project period (Table II), political unrest has affected many aspects of the surveillance and much information was lost.

By the time of this writing, all three countries had PCR capacity to detect and subtype influenza virus, while both Ghana and Cote d'Ivoire were also able to perform viral culture. In addition, human and logistical capacity to initiate and maintain sentinel surveillance sites has been expanded and strengthened. The internal ability to detect, subtype, and communicate results of human influenza infection as well as improved passive and
active AI surveillance helped each country to develop local preventive measures and strengthened the global influenza surveillance networks. This will also serve as a backbone for surveillance against other infectious diseases of pandemic nature. During the 2009 influenza pandemic, it was observed that the rate of spread of pandemic H1N1 virus to West African countries was delayed and virulence was low. The delay may be because of several factors, including environmental conditions in West Africa and patterns of global travel, and this delay may itself be responsible for the low virulence seen. However, the delay in reported cases was not because of lack of surveillance capacity, which predated the pandemic as shown in this article. The surveillance capacity developed in Ghana with the NAMRU-3 assistance resulted in consistent detection of influenza A H3N2 and B viruses for several months before the pandemic strain detection at a sentinel site. Since then, the surveillance capacity has been expanded as described here, and contributes significantly to fulfilling IHR-2005 requirements, a legally binding global agreement to protect public health by supporting national and international alert and response systems. Although the WHO announced in 2010 that H1N1 influenza virus has moved into the postpandemic period, it has been recommended that surveillance activities continue to monitor for the appearance of potential localized outbreaks and virus reassortment events.

Lessons Learned

Laboratory assessment of the three countries highlighted a number of technical challenges to develop successful surveillance systems in the region. For example, specimens collected from respiratory tract swabs of humans or birds for influenza surveillance must be placed in transport medium and transferred frozen or refrigerated to the reference laboratory. Many military sites were located in remote areas, with unreliable electrical power, inadequate refrigeration capacity, rotating personnel, and difficult transportation logistics. Sample processing at the reference laboratories necessitated capacity to conduct real-time PCR testing. Although results of testing in the laboratory were relayed to clinicians and both civilian and military public health officers, existing reporting systems were sometimes insufficient.

It may be worth mentioning that equipment necessary for PCR testing was expensive to install and maintain, especially in West Africa, where service providers are located out of the region and local conditions, such as power fluctuations, subject equipment to significant strain. Reagents were also expensive to procure in West Africa and shortages were frequent because of a variety of factors, including shipping delays, cold chain violations, inadequate resources, and poor laboratory inventory management systems. Additional challenges were faced while creating influenza surveillance capacity for militaries in West Africa, since influenza diagnostic capacity was not fully in place and some sites required the development of passive and active surveillance systems at sentinel sites. Computerized patient record systems were not available in health care settings in West Africa, including militaries, and paper records were poor. Developing systems under these conditions for syndromic monitoring of the numbers of ILI cases was challenging, partly because of a lack of standardization in charting and recording of diagnoses. Resource constraints often meant that military systems had to rely on centralized civilian public health reference labs, which led to communication challenges between civilian and military systems, not to mention the appropriate allocation of resources between different ministries of national governments.

In summary, significant progress has been made in building influenza surveillance systems in three West African militaries. To avoid redundancy, maximize resource utilization, and ensure inclusion of militaries, a coordinated system was established between ministries of health, defense, education, wildlife, and others. Although progress in Cote d'Ivoire and Burkina Faso has been slowed by political instability, Ghana has made
significant strides, with samples from military sites currently accounting for over half of specimens processed at the NIC. In 2012, over 3 years after influenza surveillance was started at military facilities in Ghana, significant data on circulating influenza strains in the country continues to be provided from these sites to the GAF, the MOH, and the WHO.

Use of Sterile Pre-Fabricated Antibiotic Beads in the Combat Hospital Setting

Military Medicine
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Abstract

Time and manpower constraints associated with acute combat casualty care can make antibiotic bead production at the point of care prohibitively difficult, if not impossible. The purpose of this study is to evaluate our technique for the sterile prefabrication of antibiotic-impregnated polymethylmethacrylate (PMMA) beads in the combat hospital environment by assessing their sterility at the time of use. This investigation is a prospective study of a consecutive series of specimens. Imipenem-impregnated antibiotic beads were sterilely prepared, threaded on a suture strand, and packaged. Over a 6-week period, 50 consecutive packages were evaluated for sterility with aerobic and anaerobic culture swabs performed at the time of opening. Culture results, as well as number of shelf days for each specimen, were then reviewed. Of the 50 packages of antibiotic-impregnated PMMA beads, the average number of days on the shelf before use was 9.3 (range: 2–17). None of the packages showed growth of organisms from the cultures, indicating that antibiotic-impregnated PMMA beads can be sterilely produced and maintained in their sterile state for future use in the combat hospital environment. This practice should be considered a safe adjunct in the management of contaminated, open traumatic injuries in this setting.

Introduction

Combat extremity injuries routinely present with large open wounds, and are often associated with extensive foreign contamination. These wounds also evolve over time and produce a large and progressive zone of injury. As a result, serial debridements are required to obtain a soft tissue envelope amenable to definitive fixation and wound closure. In addition, wound management adjuncts, such as antibiotic beads and negative pressure wound therapy (NPWT), are often used to help decrease the risk of deep wound infection. The primary indications for the use of antibiotic beads in the management of combat extremity injuries are (1) the management of dead space associated with cavitary defects, (2) local antibiotic delivery in the setting of known infection to assist with eradication of infection, and (3) local antibiotic delivery for infection prophylaxis in the setting of at-risk, complex, and contaminated traumatic wounds.
Infection rates in the treatment of combat casualty wounds have been reported between 35 and 89%. With such a high risk of infection, a multimodal approach to controlling bacterial contamination is used from the outset of care. Early and frequent surgical debridement with high volume irrigation is often augmented with the use of antibiotic beads with or without NPWT. Antibiotic beads, in particular, have the advantage of delivering a high concentration of antibiotics at the local level while systemic levels remain low. Their use is well documented in the management of combat extremity injuries, and in open fractures, antibiotic beads have been shown to decrease rates of infection when combined with contemporary debridement principles.

In a combat setting, surgical resources can become strained. Multiple casualties often present simultaneously, and require fracture stabilization and debridement of wounds. Given the inherently time-consuming process of generating polymethylmethacrylate (PMMA) antibiotic beads, time and manpower limitations often make their use untenable. Gentamicin- and tobramycin-impregnated antibiotic beads are commercially available; however, cost, limited antibiotic choices, and supply issues render them inappropriate for use in the combat hospital environment. Therefore, most patients initially receive systemic antibiotics and surgical debridement with irrigation alone. Use of local antibiotic delivery modalities is usually not initiated until the patient arrives at a higher echelon of care. This delay can be days to weeks later, thereby transitioning therapy from one of contamination eradication to early infection treatment.

One potential solution to this problem is the sterile prefabrication of antibiotic-impregnated PMMA beads during periods of lower tempo clinical operations, which can then be maintained on the shelf until needed. The purpose of our study was to describe an “all-sterile” technique to prefabricate and sterilely package PMMA antibiotic beads, as well as to validate this technique by confirming their sterility at the time of implantation. This is in contrast to previously described methods involving the production, and subsequent gas sterilization, of bead packages. Our hypothesis is that these bead strands remain sterile over the relatively short time interval expected before use in the combat hospital setting.

Materials and Methods

Over a 6-week period between December 2010 and January 2011, 50 sterile packages of PMMA antibiotic beads were produced and implanted in combat-related open wounds. All wounds were additionally treated with NPWT. Aerobic and anaerobic culture swabs were obtained from each set of beads at the time of opening the sterile package. The beads themselves, as well as their suture string, were cultured. Cultures were then incubated for 3 days and were considered negative if there was no bacterial growth after 72 hours of incubation. Documented outcome measures were the culture results, the number of shelf days before implantation, and number of patients, as well as the type of wounds treated. Statistical analysis was performed by χ2 test, using available historical controls for accepted contamination rates for surgical instrument trays.

Bead Preparation Technique

For each strand of beads, one 40-g package of Palacos PMMA cement (Zimmer; Warsaw, Indiana) was mixed with 1 g imipenem antibiotic powder. Imipenem was chosen on the recommendation of the infectious disease specialist at our institution based on the local antibiogram and the preponderance of Escherichia coli isolates in our facility as the dominant pathogen encountered. The cement was hand-mixed under sterile...
conditions in the operating room during periods of low casualty flow. The beads were prepared by individuals who had scrubbed their hands per standard technique, and who were masked, gowned, and gloved as is standard for the performance of sterile procedures. A sterile table was prepared, and the beads were produced using the same technique as is used when made intraoperatively. Approximately 1-cm-diameter beads were produced and strung onto a Number 1 Ethicon Prolene suture (Johnson & Johnson; New Brunswick, New Jersey). Approximately 15 to 20 bead packages were prepared at a time, as determined by the available supply of PMMA cement and antibiotic powder. The operating staff and surgeons involved in bead production were all familiar with producing antibiotic beads. The beads were then sealed into sterilized pouches. Each package was then marked with the date of production and an arbitrary expiration date 30 days after production (Fig. 1).

Results

The beads were implanted in 42 extremities in 23 patients with open wounds, all resultant from blast injuries. Some patients returned to the operating room for debridement and irrigation procedures on multiple occasions when antibiotic beads were implanted. Thirty-one of the wounds were residual limbs of combat-related traumatic amputations. The remainder of the wounds included six open fractures and five open wounds involving volumetric soft tissue loss without fracture.

Cultures were taken at the time of implantation of all bead strands. The average time between preparation and implantation of bead packages was 9.3 days (range: 2–17 days). None of the cultures taken from any of the 50 specimens showed any growth from the aerobic or anaerobic cultures. Based on the lowest reported value in prior investigations of the rate of contamination of surgical trays, a 4% positive culture rate was used as a historical acceptable value for the purpose of statistical analysis. The zero percent rate of positive cultures from our specimens could represent a random finding. Using the χ² test, however, we can be 87% confident that the culture-positive rate in this study is less than or equal to this historical control (p < 0.15). This finding is not statistically significant (Fig. 2).

Discussion

The use of antibiotic-impregnated PMMA beads in the management of open fractures and in combat extremity injury is well documented. They have been shown to effectively decrease the rate of osteomyelitis in open fracture management, and to be an effective adjunct in the treatment of chronic osteomyelitis. They have also been shown to be a cost-effective adjunct in the management of open fractures, with an average cost of $419. Antibiotic beads have also proven to be helpful in the management of extremity blast injuries, and have been used both in conjunction with NPWT and in bead pouches. In applying these two techniques, the method by which antibiotic beads are prepared and implanted is identical. When creating an antibiotic bead pouch, the wound is then sealed in an impervious dressing, which contains the wound effluent, and the wound remains bathed in a high concentration of antibiotics. When an NPWT is used, this effluent is drawn from the wound, along with much of the eluted antibiotic. Although there are other compelling reasons for the use of NPWT in open wounds associated with combat-related blast injury, there is evidence that the use of a bead pouch may result in decreased infection rates when compared to the use of NPWT alone. There is also recent evidence that the bead pouch is superior to antibiotic beads used in conjunction with NPWT. In a study at the U.S. Army Institute of Surgical Research, NPWT
decreased the effectiveness of antibiotic beads in a goat complex musculoskeletal wound model inoculated with Staphylococcus aureus. However, in that investigation, antibiotic beads used in conjunction with NPWT was more effective in decreasing bacterial burden than NPWT alone.

Prefabrication of antibiotic PMMA beads is not a new technique. The production of tobramycin-impregnated beads, and their “off-the-shelf” use, has been previously described by Cunningham et al, and others. Their technique used gas sterilization of nonsterilely prepared bead strands to avoid heat denaturation of the antibiotic during sterilization. Although effective, this method of ensuring sterility of the prefabricated beads is not possible in the combat hospital environment. It is for this reason that we decided to attempt an “all-sterile” prefabrication method, and decided to validate the sterility of this technique by culturing the beads at the time of implantation. Acceptable antibiotic release from prefabricated beads has also been previously shown. The antibiotic elution profile of tobramycin-impregnated beads undergoing gas sterilization remained unchanged at 1 year after production compared to the time of production. This shelf life interval is substantially longer than we would expect in the combat hospital environment.

To date, all investigations involving prefabricated beads have used tobramycin, whereas imipenem was used in this study. Imipenem is a heat-stable carbapenem antibiotic, which has a proven record of incorporation into PMMA beads. In our combat hospital, antibiotic-impregnated PMMA beads are used nearly exclusively in the management of blast injuries, as an adjunct in the prevention of infection. Multiple drug-resistant E. coli is the predominant pathogen infecting the wounds of blast-injured patients in our combat hospital. In accordance with local clinical practice guidelines, we chose to use imipenem-impregnated PMMA in this study in response to the local institutional antibiogram.

The sample size in our study was limited by the available resources of our combat hospital, both with respect to the supply of culture swabs themselves and to the laboratory resources available for incubation of culture specimens. Although no specimens in this investigation were culture positive at the time of implantation, the statistical significance of this finding depends on how this compares to historical controls.

Historical controls for an acceptable percentage of contaminated surgical instruments and implants are difficult to assess. In one study, the percentage of culture-positive surgical instrument trays was 4% at 30 minutes and 14% at 1 hour after opening. Another study showed positive cultures in 10% of wooden surfaces, and 33% of metal surfaces were culture positive at 90 minutes. The specimens in these studies were collected using appropriate sterile technique, and the same process of specimen collection was used in this investigation. These rates of culture positivity can be considered to be additive between the true rate of contamination and any false positives resultant from contamination of the cultures themselves. This rate of positive cultures taken from instruments is accepted in clinical practice. It remains despite modern infection control procedures, modern sterilization techniques, and with much more sophisticated air purification processes than exist in a combat surgical setting. Despite this, there were no positive cultures in this investigation, whereas there is a not insignificant rate of culture positivity historically shown from open instrument trays after just 1 hour of surgery. This is likely to be at least partially because of the inherently antibacterial nature of the beads when compared to surgical instruments. Secondary to the high rate of bead use at our combat hospital, the number of shelf days of the sterile bead packages was reasonably low.
The average number of bead packages used in each surgical case was greater than two. This shows the potential benefit of this technique, as it is applied to multiply injured patients in the combat hospital environment. In that clinical setting, multiple surgeons may be working on multiple limbs simultaneously, which places significant time pressure on the surgical technician assisting with the case. This is not only compounded by the potential need to fabricate antibiotic cement beads at the point of care, but further multiplied by the need shown in this study for multiple strands of antibiotic cement beads.

The sample size in this investigation is relatively small, and the average shelf life of our bead packages was short. It is possible that with either a larger number of specimens or a longer period of shelf time, that the rate of culture positivity could be significantly higher. Repeating this investigation with a longer period of shelf storage and increasing sample size could account for these limitations in potential future investigations. In addition, in the future, the use of calcium sulfate prefabricated antibiotic beads could be considered, as they have been shown to have superior antibiotic elution profiles over the short duration typically used in the management of combat extremity injuries. Production of antibiotic-impregnated PMMA beads at the point of care in the operating room is a time-intensive process. In the combat environment, casualty flow is seldom constant, with frequent periods of low clinical load, punctuated by intervals where a large number of severely injured patients present within a narrow window of time. In these instances, time and manpower resources can be significantly strained, making the time required to produce antibiotic beads prohibitive. We believe that antibiotic beads represent an important adjunct to surgical debridement and wound irrigation in the management of combat extremity blast injuries. In addition, the sterile prefabrication of antibiotic-impregnated PMMA beads during ebbs in casualty flow is a safe and effective way to expand the capability to use this adjunct even in cases of high casualty flow. We recommend that this technique of prefabrication of antibiotic beads be considered for use in blast-injured patients in the combat hospital setting.

Medical Protocol and Training

Development of a Valid Simulation Assessment for a Military Dismounted Assault Task

Military Medicine
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ABSTRACT

The Australian Defence Force is currently developing physical standards commensurate with job demands. Vital to this development process has been the accurate profiling of common military tasks. One such task required of all dismounted combat soldiers, an offensive assault on an enemy force, was the subject of in-depth profiling. In addition to overall assault performance, potential differences among patrol roles (scout, gunner, and flank) were investigated. Three different mock assaults of 100 to 150 m were performed by three patrols comprising qualified experienced infantry
soldiers. Each soldier was fitted with a heart rate monitor and wore a global positioning device. Average assault duration was 6.5 minutes and required nineteen 7-m bounds performed on a 22-seconds duty cycle at 75% heart rate reserve and a work to rest ratio 1:4. Assaults conducted in more densely vegetated terrain resulted in significantly reduced (p < 0.05) bound distance, bound duration, and movement velocity. Results indicated significant performance differences (p < 0.05) among patrol roles for external load carried, heart rate response, bound duration, and distance covered while movement velocity was not different (p > 0.05). As a result of profiling the assault task, a valid simulation capable of assessing soldiers’ physical capacity to perform this task was developed.

INTRODUCTION

Recently within the Australian military, there has been a large focus on the development of valid job-related employment standards. It is envisaged that the application of these standards will ensure personnel have the physical capacity commensurate with the performance of critical duties and tasks required of soldiers in their unique and often demanding working environment. Failure to perform such tasks to a minimum acceptable standard could put the individuals, their colleagues, and ultimately the full complement of personnel involved in an activity at increased hazard. These physical employment standards have also been aimed at providing a safer workplace by ensuring each soldier is physically capable of performing all necessary duties without risk of injury as a result of inadequate and/or non-job-related physical conditioning. Profiling the physical demands of common and essential military tasks is therefore an essential and logical part of establishing bona fide operational requirements. A review of the training processes within the Australian Army and consultation with military staff indicated that the key tactical movement tasks required of the dismounted combatant included a defensive withdrawal under fire and an offensive assault. The withdrawal under fire is achieved using a break contact drill, a maneuver that is employed for withdrawing from an enemy when engagement is not desired. Breaking contact requires soldiers to alternate between providing covering fire and sprinting down a corridor of section members, with this rotation continuing until a safe separation distance has been achieved. The characterization of this task has previously been reported along with the development of a valid task simulation test.1 However, the characterization of an offensive assault has not previously been reported in the literature. In its most basic sense, this task requires a group of soldiers to advance on, and assault an enemy position, while being engaged in a firefight, with the objective being the neutralization of the enemy threat. An offensive assault is achieved using coordinated fire and movement, which is characterized by repeated short sprints known as “bounds” where a soldier advances from one point of cover to the next, with subsequent bounds being separated by periods of relative rest where they apply fire onto the enemy position.

To accurately replicate the physiological demands of an activity such as fire and movement, it is imperative that one first understands and quantifies performance parameters and characteristics. In a team-sport environment, performance analysis may include such variables as distance covered during a match, the number of sprints above a given velocity, time spent within differing modes of movement, and rest durations. The information generated from these investigations can then be used to guide the physical conditioning programs and the development of activity-specific fitness testing procedures.2–4 The technique and technology used to analyze performance are varied and have recently moved away from the traditional video-based player tracking and subsequent replay analysis to athlete-worn global positioning system (GPS) units as a more convenient and equally valid method to categorize movement during field-based sports.5–7 The latter technique forms the basis of the current research.
Global positioning technology and equipment have evolved significantly over recent years, progressing from units capable of sampling at 1 Hz (one sample per second) to those claiming 15 Hz sampling. Although player-worn GPS devices have displayed valid and reliable results when tracking longer duration, continuous and low-intensity movements, their validity when analyzing high-intensity, short-duration activities and repeated sprint situations has been questioned. Validity of GPS-derived measures appears to be dependent on the speed of movement, the distance traveled during that movement, and the sampling rate of the device used. Certainly, it appears that although GPS devices sampling at 1 Hz possess acceptable validity during continuous movement, they have very limited applicability within short-duration, high-intensity or repeat sprint activities. In previous work characterizing a break contact maneuver, video data were relied on to determine work to rest ratios and thus calculate time spent sprinting and resting, because of limitations in sampling rate (1 Hz) of the GPS equipment used. The use of GPS devices with more frequent sampling rates has been shown to vastly improve measurement precision during activities consisting of high movement speeds and short durations. This evolution in technology has provided greater confidence in captured data and given rise to a much more detailed understanding as to the nature of intermittent, short-duration, high-intensity sprint activities.

The purpose of this investigation was to establish the movement characteristics, activity parameters, and physiological demands of an offensive assault task (comprising fire and movement) performed by the dismounted combatant using a soldier-worn 10 Hz GPS technology. The outcomes of this task characterization will be used to guide the development of a suitable assessment capable of simulating the demands of the assault task. A test based on the movement characteristics and physiological demands of fire and movement within an assault would provide confidence that the minimum capacity commensurate with the performance of this common and critical dismounted combat task is assessed.

METHOD

Experimental procedures were approved by the Australian Defence Human Research Ethics Committee. All participants were fully briefed and provided written and informed consent. Twenty-three active service infantry soldiers (male) participated in the study (age [years] 22.8 [SD 3.1]; body mass [kg] 83.9 [SD 12.2]; height [m] 1.81 [SD 0.10]; estimated aerobic power from 20-m multistage shuttle test [mL•kg⁻¹•min⁻¹] 49.6 [SD 3.8]).

Offensive Assault: Task Description

The process applied to characterize the assault task occurred over two stages. First, subject matter experts of various ranks were consulted to determine the tactical requirements of the task according to standard operating procedures to define a realistic operational scenario under which the task would be performed. Second, a series of staged, in-field observations of fire and movement were conducted. In evaluating the tactical requirements of the task, it was determined that a dismounted patrol will adopt a formation that is appropriate for the given terrain, vegetation, and enemy threat. Patrol members are positioned within these formations in accordance with their responsibilities, and this role-specific positioning necessitates differing requirements in the event that the patrol comes into contact with an enemy force. Scouts are positioned at the front of the patrol and are responsible for relaying information. Centrally located within the patrol are gunners, responsible for...
carrying the automatic machine guns. Positioned at the back of the patrol are flank soldiers tasked with providing rear security. If the patrol contacts or is contacted by an enemy force, they will shift formation to one known as extended line. Typically, scouts will hold position while the other patrol members move to realize this shift. The end result sees the patrol is seen in a single line perpendicular to the enemy position.

To advance in this extended line formation, movement is performed in a staggered manner, with only a portion of the group (approximately 40%) moving at any one time while the remainder waits in place and engages the enemy. Movement consists of getting up from a prone firing position, sprinting forward a short distance, and then readopting a prone firing position. For the purposes of this article, this will be referred to as a “bound.” Closing on the enemy position is controlled so that alternate subgroups move to maintain a relatively straight assault line. Once the enemy position has been captured, a further distance of typically 20 m (depending on the terrain and vegetation) will be cleared to ensure no more enemy soldiers remain. This final piece of the assault is commonly referred to as the “fight through” and is conducted using a low crawl movement.

Procedures

Three patrols each consisting of seven to eight soldiers conducted three staged, mock assaults (herein referred to as “assault”) on an enemy force under the instruction of their respective patrol commanders. The three assaults were performed within a 3-hour session with 30- to 40-minutes rest in between. Assault distances were advised by subject matter experts, were determined to accurately reflect typical engagement distances, and were presented to the patrols in a varied order and included the following: (1) 100-m flat terrain with sparse vegetation (100S), (2) 100-m flat terrain with medium-density vegetation (100M), and (3) 150-m flat terrain with sparse vegetation (150S). Patrol members wore fighting order, which was comprised of webbing, weapon, body armor, and helmet. Mean fighting order load was 24.4 (SD 4.9) kg, which approximated 28.9 (SD 4.9) % of body mass. External loads for scout and flank were not different to one another (p > 0.05). Gunners carried a significantly heavier (p < 0.05) absolute external load (31.9 [SD 4.5] kg) when compared to both scout (22.2 [SD 1.3] kg) and flank (21.9 [SD 2.1] kg). This significant difference (p < 0.05) remained when external load was expressed as percentage of body mass (gunner, 35.3 [SD 5.1] %; scout, 27.0 [SD 3.2] %; flank, 26.9 [SD 1.8] %).

To achieve a more valid representation of the task, patrol commanders were not constrained during the performance of the assault (i.e., allowing them to dictate the response they deemed appropriate) and each assault was conducted against a two-man enemy party and blank ammunition was used. The behavior of the enemy party was controlled to ensure parity between patrols regarding engagement distance, aggression shown, and enemy activity cessation. Although all care was taken to ensure consistent engagement distances, it was noted that contact was not initiated with each patrol at exactly the same point on the ground as each patrol was in a slightly different formation when it was engaged by the enemy, adding to the variability of assault parameters. However, although these variations affected reproducibility, they did add the element of realism to the assault.

Assault duration was defined from when the first weapon discharged through to the completion of the fight through. Variables of interest during the assaults included the following: (1) duration of assault, (2) distance covered during assault, (3) number of bounds performed, (4) distance covered during each bound, (5) duration of each bound, (6) rest interval between bounds, and (7) heart rate response.
Measurements

Before the conduct of the assaults, each participant was fitted with a GPS device (minimax S4, Catapult Sports, Melbourne, Australia) and a heart rate monitor (Polar Team2 Pro, Polar Electro Oy, Kempele, Finland). The GPS device is a small, lightweight unit worn on the upper back, between the shoulder blades, in a custom garment. The unit captures and records data from numerous sensors, including a 10-Hz GPS and a triaxial accelerometer.

An automated bound recognition feature was developed and incorporated into the proprietary software program (LoganPlus, Catapult Sports). The identification of a bound occurred if the following conditions were met: (1) bound entry velocity threshold ≥ 1 m•s\(^{-1}\), (2) bound exit velocity ≤ 0.2 m•s\(^{-1}\), (3) duration within that velocity band ≥ 2 seconds, and (4) minimum interbound rest duration ≥ 2 seconds.

Analysis

Comparisons between variables of interest were performed using one-way analysis of variance and corrected for multiple comparisons (Bonferroni correction). These comparisons were conducted between assault types (100S, 100M, and 150S) and patrol roles (scout, gunner, and flank). Level of significance was set at 0.05. Data are presented as means and SDs of the means, unless otherwise stated.

RESULTS

Mean assault durations were 6.6 (0.6) minutes (range 6.0–7.2 minutes), 4.6 (1.3) minutes (range 3.8–6.2 minutes), and 8.7 (2.4) minutes (range 6.2–11.0 minutes) for the 100S, 100M, and 150S, respectively. When all assaults were combined, the mean duration was 6.6 (2.3) minutes, performed at a mean movement rate of 23 (5) m•min\(^{-1}\). Mean bound cycle duration (inclusive of bound duration and interbound rest) was between 20 and 25 seconds for each of the assault types and the patrol roles. Although bound duration was observed to increase from scout to gunner to flank, only the comparison between scout and flank was found to be significantly different (p < 0.05). Although no significant difference was observed, the interbound rest interval was observed to decrease across the patrol roles from scout to gunner to flank. Bound velocity was found to be significantly greater in sparse vegetation compared to medium (p < 0.05) but not different between patrol roles (p > 0.05). Assault data are presented in Table I

There was no difference observed in heart rate response among the assault types (p > 0.05). However, significant differences between patrol roles were present. For instance, the scout role was found to elicit a significantly lesser response than both gunner and flank (p < 0.05) while heart rate responses of gunner and flank were not different (p > 0.05). Heart rate data for the three patrol roles are shown in Figure 1

Heart rate responses of each patrol role during three dismounted military assault types (100S, 100-m sparse vegetation; 100M, 100-m medium-density vegetation; 150S, 150-m sparse vegetation) and the three assaults combined. Results are presented as mean percentages of heart rate
reserve with error bars indicating the SE of the means. Statistical analysis was only conducted on the “combined” assaults. Columns sharing the same symbol are significantly different from one another (p < 0.05).

To elucidate the nature and magnitude of inter-role performance differences observed during this study, total bound time, total interbound rest, and heart rate response were analyzed further. Total bound time was considered to be the product of the number of bounds and the mean bound duration, whereas total interbound rest was equal to the number of bounds minus one multiplied by mean interbound rest duration. Resulting from this analysis was the finding that while the flank soldier spent 50% more time than the scout and 26% more time than the gunner engaged in bounding, the interbound rest remained relatively similar, with only a 5% between-role variation observed. This between-role difference is also reflected in the resulting work to rest ratios, which were 1:5, 1:4, and 1:3 for scout, gunner, and flank, respectively. Even though soldiers in the role of flank had a higher work to rest ratio and spent more time bounding than the gunner, the heart rate response was observed not to be different. This can be explained with the fact that gunners carried a significantly heavier external load. Given the flank role was found to carry an equivalent external load relative to the scout, but have a higher work to rest ratio and greater total bound duration, there was a significantly greater heart rate response observed for this role (p < 0.05).

Recalling that a typical fight through covers approximately 20 m, results support the validity of the engagement distance within the 100S and 150S assaults but highlights a shorter than expected distance for the 100M. This shortfall within the 100M assault is proposed to result from a difficulty in visual recognition by the enemy party (because of vegetation) and the abbreviated fight through observed. The positioning of the scout role also provided further insight into the assault movement rate because of the fact that on initial enemy contact, this role remains relatively fixed while other patrol members maneuver to form the extended line. Subsequent to extended line formation, the movement rate of an assault averaged approximately 20 m•min−1 during the fire and movement advance.

DISCUSSION

All military forces are trained to perform a dismounted assault of some variety, and there is much training literature and doctrine regarding the conduct of these assaults accessible to personnel. However, until the availability of suitable technology to analyze and describe task performance, this information has been based on the opinions and experiences of subject matter experts. To the best of our knowledge, this is the first time the movement characteristics and physiological demand of a dismounted assault on an enemy force have been explored using high-fidelity GPS technology. It was found that a typical 100-m dismounted assault took approximately 6 minutes to conduct and required the performance of a 6- to 7-m bound every 20 to 25 seconds at a work to rest ratio of approximately 1:4 and was completed using a low crawl over a short distance. This resulted in the task being performed at an average intensity of 75% heart rate reserve with efforts at over 85% observed. Differences regarding task performance between patrol roles have also been highlighted with a strong indication that the roles of flank and gunner are more physically demanding than scout.

A current U.S. Army Field Manual detailing soldier combat skills describes an individual movement technique that is performed during enemy contact which is the fastest method of movement from one point of cover to the next. The Field Manual terms this movement “rushing,” and it is
essentially the same as the “bounding” movement described in this study. Although there is no definitive distance or number of steps prescribed, it states that a “rush” should be limited to 3 to 5 seconds in duration to prevent enemy machine gunners or riflemen from tracking a moving soldier. The findings of this study support this.

The majority of military physical fitness assessment batteries used to establish employment/deployment suitability test only aerobic power and local muscle endurance, with assessments such as distance runs with no external load and body mass resisted exercises (e.g., push-ups and sit-ups) commonly being used for this purpose. Noticeably missing from these testing batteries is an assessment of short-duration, high-intensity repeat sprint performance. In addition to this, the majority of fitness assessments are conducted in lightweight clothing (shorts, t-shirt, and running shoes), which is not reflective of the considerable external load typically carried during the performance of dismounted soldiering tasks. Given that the successful performance of the assault task characterized in this study is fundamental to the role of dismounted soldiers, physical conditioning and assessments should emphasize this attribute. Therefore, the failure to include a repeated, short-duration, high-intensity component to physical fitness testing regimes and replicate external load carriage requirements is of concern particularly if establishing a soldier's fitness for duty is deemed paramount.

Using task characterization results identified in this study and advice received from subject matter experts, a fire and movement simulation was developed. The development process took into consideration a number of factors, including assault duration, engagement distance and assault movement rate, and the role(s) on which to model the simulation. It was critical that the simulation possessed a high degree of validity, was safe for soldiers to perform, and could be easily implemented.

To realize service-wide acceptability and satisfy scientific integrity and defensibility, it was critical that the simulation appear logical and accurately predict task performance. Thus, during the formulation of the simulation, four forms of validity were considered: content validity, the degree to which the simulation represents the physiological characteristics of the task; criterion validity, a demonstrated relationship between the simulation and a direct measure of task performance; construct validity, the simulation measures attributes necessary for successful task performance; and face validity, the appearance that the simulation reflects the task.

Subject matter experts advised an engagement distance of 100 m as a minimum standard, and this was used as a base on which to develop the simulation. From the six 100-m assaults conducted, the average duration was 5.6 minutes and comprised 16 bounds of approximately 6.5 m at a movement rate 20 m•min−1. As dismounted combatants may be required to perform each of the roles within a patrol, it was decided to use gunner and flank as the performance standard because of their higher overall demand.

The resulting simulation comprises sixteen 6-m bounds (for a total of 96 m) followed by an 18-m leopard crawl (to simulate the fight through). Considering the observed movement rate and work to rest ratio, bounds were to be performed on a 20-s cycle, with each bound to be completed within 5 s, with the leopard crawl to be completed within 35 s. The simulation has a total duration of 5.9 minutes. Although each bound is commenced from a prone firing position, as is the case during task performance, the finish position has been altered for reasons of safety. During task performance, each bound normally ends with soldiers diving to the ground to assume their new fire position. However, within the simulation,
each bound will finish in a kneeling firing position before adopting the prone position ready for the next bound. For ease of implementation and standardization, the assessment should be performed on a level grassed area, use a 24-m layout (constituting 4 × 6-m bounds), be controlled by a custom-made digital cadence, and require an external load equivalent to fighting order to be worn. The result is a task simulation possessing high degrees of content, criterion, construct, and face validity and is safe for participants.

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The Rush University Advanced Trauma Training Program, A Novel Approach for Military Trauma Training

Military Medicine
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ABSTRACT

Nearly 90% of combat deaths occur on the battlefield before the casualty reaches a treatment facility. It has been shown that early intervention in trauma patients improves morbidity and mortality. Hence, the training of military health care providers in lifesaving measures is imperative to saving lives on the battlefield. To date, few courses exist to provide skills in combat-zone trauma stabilization and treatment. Even fewer offer training in the identification and treatment of post-traumatic stress disorders and traumatic brain injury. We set out to develop a multidisciplinary, comprehensive course to include didactic lectures as well as hands-on training and observational modules. Ten courses have been delivered to date. Thus far, feedback from military personnel and course participants has revealed the positive impact of the training program. In this manuscript, we present the layout of the program and its contents.

INTRODUCTION

Since the tragic events of 9/11, over one million soldiers have been deployed to Iraq and Afghanistan. Nearly 90% of U.S. combat deaths occur on the battlefield before the casualty ever reaches a treatment facility. In general, early intervention in the trauma patient has been shown to improve mortality. Therefore, training army medics in essential lifesaving procedures can reduce battlefield mortality rates as well as permanent disability from injuries during combat.

Currently, military personnel have a limited number of options in courses that offer training in combat casualty care, for example, the Tactical Combat Care Course and Tactical Medics International.6,7 These courses provide participants with skills in the early treatment of combat-related trauma injuries. However, there are few courses offered to military personnel that combine training in the aforementioned skills with the early identification and treatment of post-traumatic stress disorder (PTSD) and traumatic brain injuries (TBIs). Therefore, a group of emergency
physicians at Rush University Medical Center (RUMC) in Chicago developed a comprehensive Advanced Trauma Training Program (ATTP) for military personnel. This multidisciplinary program incorporates didactic, observational, and hands-on practical training to equip army medics, nurses, physician assistants, and physicians with the knowledge and skills necessary to render them more effective in the initial triage, evaluation, and treatment of battlefield trauma.

The mission of this program is to provide participants with a comprehensive set of skills that will reduce battlefield mortality rates. The aim of this program is to exceed industry standards by offering advanced trauma resuscitation and stabilization skills. Board-certified emergency medicine physicians utilize both didactic sessions and hands-on practical training modalities. The program is designed to enhance the military health care provider's ability to identify, treat, and stabilize wounded warriors before transport to forward surgical teams, combat support hospitals, or area medical facilities. Finally, nationally renowned experts in the field of combat stress disorders and TBIs instruct course participants on the necessary tools to identify and manage mild TBI and PTSD.

Each ATTP course takes place over a 6-day period at RUMC, a large urban tertiary care facility in Chicago. Course administrators and instructors are board-certified emergency physicians with certification in International Trauma Life Support (ITLS), Basic Disaster Life Support (BDLS), and Advanced Disaster Life Support (ADLS), and Hazmat. In addition, experts in the fields of PTSD and TBI work closely with course instructors to offer specific modules in these topics. Thus far, twelve courses have been completed between May 2007 and September 2012, with a total of 850 participants.

DIDACTIC MODULE

Course participants receive a total of 18.25 hours of lectures. The lectures are based on ITLS9 and BDLS10 material. The ITLS framework is a global standard that enables participants to master the most up-to-date techniques in rapid assessment and appropriate intervention and identification of immediate life-threatening injuries in the prehospital setting for both adult and pediatric cases. The ITLS Military edition is a "stand-alone military edition text, edited by a military surgeon." which is utilized during the didactic training for its military-based scenarios. Upon completion of the course, each soldier is certified in ITLS—Advanced.

The BDLS10 component is a review of the all-hazards approach to managing various man-made and natural events that have the capacity to cause multiple casualties, including chemical, biological, radiological, nuclear, and explosive events.

In addition to ITLS and BDLS course material, participants receive didactics in blast injuries, laboratory procedures for hands-on modules, and mass casualty (MASCAL) triage.

TBIS AND COMBAT STRESS DISORDERS MODULE

Our course offers 5.5 hours of training in TBIs and combat stress disorders.
"...early data shows that the treatments that have worked well in Veterans with PTSD alone, such as cognitive processing therapy, prolonged exposure or SSRI's, can also work well for Veterans who have suffered a mild traumatic brain injury as well as emotional trauma."11

This combat stress disorders module is delivered in two segments: first as a 2-hour large-group lecture, the "Early Identification and Prevention of Traumatic Stress Disorder." The second segment is 2.5 hours of small-group sessions during which course participants learn to identify early and midcourse signs of traumatic stress reactions to combat. Participants practice preventive techniques including relaxation training, breathing retraining, and use of imagery. Mastery and practice of these skills under stressful conditions limits their own stress disorder risk. Furthermore, trainees can apply the skills to treat other soldiers with early and midlevel stress reactions.

The content includes:
- Identification of acute stress disorder and PTSD
- Breathing retraining
- Relaxation and stress reduction techniques in the field
- Use of imagery to increase motivation and mastery
- Applications of relaxation techniques and imagery for sleep hygiene and counteracting impact of nightmares
- Applications of breathing retraining, relaxation, and stress reduction techniques in treatment of wounded combatants
- Understanding the role of professional mental health treatment for self and others who develop PTSD

TBI module is delivered through a 1-hour small-group session. Course participants are introduced to this complicated medical condition by field experts and undergo a pilot testing process to quickly and more completely identify injuries, both in and out of military theater. Participants learn that because of the complexity of the brain, every injury is different and dangerous. Since brain swelling peaks between 1 and 3 days after the injury, a delay in the presentation of symptoms underscores the imperative to identify possible victims to reduce the risks to themselves and their fellow soldiers.

Participants learn the principles of TBI and to:
- Identify the cognitive aspects of the TBI (loss and/or difficulties with memory, attention span, orientation, and concentration)
- Identify the physical components of TBI (loss and/or difficulties with balance, coordination, and the bilateral use of the extremities)
- Use the components of the pilot testing process to quickly and completely identify injuries

LIVE TISSUE LABORATORY MODULE

The live tissue laboratory is a 4-hour module during which participants gain, or enhance, their competence in critical and lifesaving procedures.

The live tissue laboratory experience includes:
- Surgical cricothyroidotomy
- Needle decompression
— Chest tube insertion
— Emergency thoracotomy
— Pericardiocentesis
— Intraosseous lines
— Suturing

Board-certified emergency physicians skilled in the above procedures show and teach course participants in small groups of 4 to 5 to allow for maximum exposure and practice.

CADAVER LABORATORY MODULE

The 4-hour cadaver laboratory is conducted in the Rush University Anatomy Laboratory. All participants are trained on advanced procedures such as vascular access techniques and advanced airway management. Participants study the relationship of certain interventional procedures to the corresponding human anatomy.

The cadaver laboratory experience includes:
— Basic airway management
— Airway visualization with Glide Scope
— Intubation
— Surgical cricothyroidotomy
— Venous cutdown
— Intraosseous access
— Needle decompression
— Chest tube insertion
— Emergency thoracotomy
— Pericardiocentesis
— Suturing

The cadaver laboratory module is taught by board-certified emergency physicians skilled in the above listed procedures.

TRAUMA LANE/MASS CASUALTY EVENT MODULE

The MASCAL segment is a 2.5-hour module delivered in three consecutive sessions to smaller group of 10 to 15 participants at a time. This module offers participants the opportunity to practice advanced lifesaving procedures in various critical scenarios. Participants are exposed to
victims who are highly technical, life-size, computerized mannequins, and well-moulaged volunteers and professional actors, simulating real-life injuries. The module is directed and supervised by emergency physicians and experts in simulation techniques.

The simulation laboratory scenarios include:
- Head trauma with respiratory failure: intubation with in-line stabilization
- Blast lung injury with tension pneumothorax: needle decompression
- Penetrating chest injury with sucking chest wound: chest dressing
- Blunt abdominal trauma with hemorrhagic shock: IV access
- Impaled abdominal object with hemorrhagic shock: interosseous line access, foreign body stabilization
- Smoke inhalation with burn: intubation and wound care
- Extremity trauma with exsanguination: pressure control and tourniquet
- Stress-induced psychologically unstable patients: appropriate patient restraining techniques

Each MASCAL scenario is executed in two parts. During the first part, participants arrive at the mocked-up scene of an improvised explosive device explosion with civilian and military casualties. Rough terrain, extreme weather conditions, background artillery fire, and general chaos produced by “live” patients create a challenging environment under which participants must triage and treat their patients. The second part of the MASCAL scenario begins with patient transport from scene 1 to a “mock” mobile army surgical hospital unit in the RUMC Simulation Laboratory. Participants must continue to stabilize and treat the transported casualties while taking on new patients in the mobile army surgical hospital unit with limited resources and supplies.

AMBULANCE RIDE-ALONG MODULE

Each course participant spends one 6-hour shift with Chicago Fire Department paramedics to observe real-life emergency situations and care in the prehospital setting. All firehouses are specially selected by RUMC’s Emergency Medical Systems director for their urban locations and demanding call schedules.

TRAUMA CENTER OBSERVATION MODULE

RUMC has partnered with four local Level I Trauma Centers in Chicago to provide participants with one 6-hour observational experience proctored by emergency department staff members. This module offers participants the opportunity to observe the spectrum of trauma care from the initial stabilization all the way through to the surgical intervention.

SKILLS STATIONS MODULE
The skills stations serve to augment lecture material in a small-group environment with one-on-one attention from emergency physicians, paramedics, and simulation experts. The small-group environment fosters advancement of skills and improves understanding of procedure techniques and indications.

Participants rotate through the following skill stations:
- Cardio-pulmonary resuscitation: performed on simulation mannequins
- Airway: intubation performed on a trainer mannequin
- Spine motion restriction: performed on volunteers or co-participants

TESTING AND COURSE EVALUATION

At the end of the week-long course, all participants take multiple-choice ITLS- and BDLS-standardized examinations and patient assessment skills exam. The exams are delivered and proctored by emergency physicians.

Course evaluations are conducted through course assessment surveys and an after action review. Course evaluations are reviewed thoroughly by course instructors; participants’ suggestions are often incorporated into subsequent courses for improvement. The after action review is conducted by military personnel in a private environment to promote open feedback from the participants. The feedback is synthesized and provided back to course instructors for further development of the training program.

COURSE FEEDBACK

The course has received significant feedback from participants. Most of the feedback has been overwhelmingly positive. Many students remarked on the benefit of being directly trained by emergency physicians in an academic environment where interaction between teachers and students and group discussions are encouraged. Students also note the benefit of being taught procedures and then being able to practice those skills repeatedly in multiple settings during the course. In fact, the procedure labs were met with great approval by course participants and were typically cited as their favorite part of the course: “This course is very beneficial to all of us who are deploying or have deployed. We see it (procedures) on screen and here we actually do them live…”

Participants offered suggestions for course improvement. Many commented on needing more time practicing suturing skills. Some also suggested more exposure to venous cutdowns, hemostatic agents, and basic and advanced airway techniques. Trainees further requested more ride time with the Chicago Fire Department and, possibly, extending the course to a 7 day to accommodate additional time allotments. Most of the negative feedback we received focused on increasing hands-on sessions in place of didactic lecture times. This feedback has been addressed in subsequent courses. Course instructors have streamlined the ITLS and BDLS lectures to ensure completion of the curriculum without redundancy to make more time for hands-on modules.
COURSE LIMITATIONS

The authors recognize that the only objective way of quantifying the success of such a training program would be by collecting the morbidity and mortality data and outcomes of the casualties under the care of program graduates. Such data is not readily available for review. We base some of our assessment of the utility and uniqueness of our course on the feedback we receive from course participants, military liaisons, and visiting military personnel. Furthermore, we have collected the data on trainees’ feedback upon return from deployment and will address it in our future manuscript.

CONCLUSION

ATTP is a comprehensive multidisciplinary training program for military personnel. To date, 850 military health care providers have participated in the ATTP course. It has been well received as a complementary program to the overall predeployment training for military personnel. The program offers prehospital assessment management skills based on internationally accepted standards established by ITLS and BDLS. It emphasizes rapid triage, stabilization, and transport to a higher level of care and provides hands-on skills training for lifesaving procedures. Furthermore, it addresses PTSDs and mild TBI. The course is unique in that it is taught by board-certified emergency physicians collaborating with military advisors with combat experience.

BACK TO TOP

Increasing Access to Care and Reducing Mistrust: Important Considerations When Implementing the Patient-Centered Medical Home in Army Health Clinics

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ABSTRACT

Objective: To determine which individual characteristics (religious participation, mistrust, racism/discrimination, spirituality, perceived access to care, and continuity of care) were predictors of patient outcomes (patient satisfaction, physical health, and mental health status) for an Army health care clinic transitioning to the Patient-Centered Medical Home (PCMH). Method: A descriptive, correlational design using stepwise multivariate regression analyses to assess the effect of individual characteristics on patient outcomes for 200 Army Soldiers and family members receiving health care services. Results: Perceived access to care was positively and mistrust was negatively related to patient satisfaction (p < 0.001 for both variables). Participants who reported more support from God and more mistrust also reported poorer physical health status (p < 0.008 and p March 2013
< 0.003, respectively). Perceived access to care was the only individual characteristic that showed a significant (p < 0.019) positive association with a better mental health status. Conclusion: This study suggests that better access to care improves patient satisfaction and mental health status; however, those with higher levels of mistrust tend to have lower patient satisfaction and poorer health. Participants with poorer health also tend to rely on more support from God. These important individual characteristics should be the considered when implementing the PCMH.

INTRODUCTION

In 2010, a course was set for the U.S. Army Medical Command to transition from a “health care system” to a “system of care.” This transition was to be facilitated with the implementation of the Patient-Centered Medical Home (PCMH), including recognition from the National Committee for Quality Assurance (NCQA) as a PCMH. In addition, the NCQA states that the PCMH is a health care setting that facilitates partnerships between individual patients, their personal physicians, and the patients’ family to assure patients get the indicated care when and where needed in a culturally and linguistically appropriate manner.

The military health care system has processes in place to deliver care; however, the challenges of implementing the PCMH with regards to a military population with constraints of existing regulations, laws, and financial budgets are unique. A key component to be considered in implementing any successful health care program is the patient and family members who will be the end users. There is evidence that suggests individual characteristics of patients (e.g., predisposing values, attitudes, beliefs, culture, and biological or demographic markers) have an impact on their health status and perception of the care received. The individual characteristics are important factors in creating a patient-centered approach to care because they affect interactions between the patient and the provider, patient and the health care system, and the patient's perception of health care services received. Therefore, individual patient characteristics should be considered when implementing the PCMH.

In addition, the effects of religious activities and spirituality on physical and mental health are gaining attention in the military because of the stresses experienced by military members and their families after a decade of war. Religious activities and spirituality have been associated with improved health outcomes and greater patient satisfaction, and those with higher levels of religious participation have lower rates of depression, alcohol and drug use, and suicide rates. Conceptually, religiosity is distinguished from spirituality. Religiosity or religious participation refers to beliefs and behaviors related to organized religious institutions, whereas spirituality occurs on a more personal level and refers to a search for meaning in life or a personal relationship with God that may or may not be associated with religious institutions. Few research studies, however, address types of support gained directly from having a personal relationship with God, especially in military populations. This personal relationship with God may be an important aspect of the culture of members of the military, particularly when they encounter life-threatening situations.

Another factor that affects patient satisfaction, physical health, and mental health relates to culture, and members of the military also bring their personal heritage and cultures with them. Cultural factors are beliefs, patterns, and attitudes learned from previous generations or personal experiences. A key cultural factor concerns trust, particularly trust between patients and the health care system. Trust in health care providers has a strong influence on health behaviors of patients and is built over time with repeated interactions. Conversely, mistrust in the health care system negatively influences patient satisfaction and health status, especially among minorities. Mistrust is defined as the lack of integrity, competence,
trust, and ability or willingness to function as the patient's advocate. In a study with 234 military beneficiaries, 89% of the participants reported that they trusted their health care provider and 76% reported that their health care provider was the most influential person in their seeking screening. Racism/discrimination in the military negatively affects patient satisfaction and health outcomes. Racism/discrimination refers to the patient's perceived differences in treatment by health care providers based on race or ethnicity. Discrimination has led to higher delays in seeking medical care and nonadherence to treatment recommendations. In a study focused on the discriminatory experiences of minority veterans, the investigators found that more than 50% of the African American veterans (n = 768) reported experiencing discrimination during their military career, and this racial discrimination was significantly associated with lower physical health. This is significant as the Institute of Medicine has recommended further research to determine if racial or ethnic discrimination has an effect on physical and mental health of minorities in the military.

Access to health care is another important aspect of patient outcomes since individuals with adequate access to health care are more likely to have continuity of care. Many individuals tend to equate having health insurance with access to health care services; nevertheless, others have demonstrated one must have the knowledge of how and when to access health services. Hence, there is a need to evaluate access to care in a population of active duty (AD) Army Soldiers and family members who have health insurance. Access to care greatly affects patient satisfaction and health outcomes. Establishing partnerships and trusting relationships requires repeated interactions such as those that occur with continuity of care when patients see the same health care personnel (nurses and primary care providers).

A unique factor within military populations is that all AD personnel are reassigned to new geographical locations every 3 to 4 years. This relocation process involves both health care personnel and patients, thereby limiting the amount of continuity from any one provider. Although AD Soldiers and their family members are generally able to access care when needed, continuity with the same health care provider is a harder goal to realize and affects patient satisfaction. The PCMH model provides continuity of care in addition to the traditional view of just access to care. Patient satisfaction is a measure of quality of care. New health policies and existing credentialing organizations now require health care facilities to measure patient satisfaction, which may shift greater health care decision-making to the patient. In this study, patient satisfaction refers to the patient's perception or attitude about the health care received based on their values, beliefs, and interactions with health care providers. Although most health care organizations use Healthcare Effectiveness Data and Information Set (HEDIS) to measure patient satisfaction, HEDIS measures were designed for use by employers to make insurance choices among multiple health care plans. HEDIS measures do not take into consideration individual patient's beliefs, culture, and resources, or how they affect the patient's perception of care received.

In addition to patient satisfaction, being in good health is extremely important for maintaining a fit and ready military force. Health status refers to the state of physical, mental, and social well-being as determined by the individual's goals and expectations, and not necessarily the absence of illness or disease. The perspective of being healthy or not is subjective and based on experiences and culture; therefore, it is important to determine which individual characteristics are important and affect health outcomes. There have been discussions describing the process of implementing the PCMH; however, there are few empirical research studies describing the patient's perspective of health before implementing the PCMH.
Therefore, the purpose of this study was to address current gaps in knowledge by taking a multifactorial approach to determine which individual characteristics are predictors of patient satisfaction and health status in Army AD Soldiers and their family members receiving health care services in a typical health care clinic. In addition, the knowledge gained will inform the clinic leadership and others as they prepare to transition from the typical health clinic to the PCMH model.

METHODS

A descriptive, correlation design was used in this study to examine relationships of individual characteristics that predict patient satisfaction and health status (physical and mental health). A modified version of Andersen's Behavioral Model for Health Services Use was used to guide this study. Andersen's model looks at multiple dimensions of conditions that impede or facilitate the use of health care services.

Sample

The inclusion criteria for participation in this study were the following: (1) AD Army Soldiers or family members, (2) at least 18 years old, (3) ability to speak English, (4) no apparent cognitive impairment, (5) not under the influence of alcohol, and (6) eligible to receive care at a particular military health care site in Hawaii. The clinic selected to recruit participants represents a typical Army health clinic population, and the clinic was close to an adjacent shopping center which allowed for greater access to the population. Participants were recruited by the research team in person inside the clinic where they received their care or the shopping center adjacent to the clinic. After gaining informed consent, participants were given the study questionnaire and a $20 gift card on completion. The study protocol was approved by the Human Use Committee at Tripler Army Medical Center. Investigators adhered to the policies for protection of human subjects as prescribed in 45 Code of Federal Regulation 46.

Measures

Data were collected using self-administered questionnaires. The questionnaires consisted of measures to assess concepts related to individual characteristics (religious participation, mistrust, racism/discrimination, spirituality, perceived access to care, and continuity of care) and patient outcomes (patient satisfaction, physical health status, and mental health status).

Individual Characteristics

Religious participation was measured using the Participation in Religious Activities scale, which assessed the frequency of participation in a variety of religious activities. The scale contained 11 items with 5 responses ranging from 1 (never) to 5 (very often). All items were summed with higher scores indicating a higher degree of religious participation. Cronbach's alpha in this study was 0.95.

Spirituality was measured using the Perceived Support from God scale consisting of a 15-item scale composed of two subscales. The Support from God subscale is a 9-item subscale that measures the individuals' perception of receiving help and support through their relationship with God,
and the God's Purpose for Me subscale is a 6-item subscale that reflects the level of help and comfort the individuals receive from the belief that a loving God is in control and has plans for their life. Items for both scales had 5 responses ranging from 0 (not at all) for those items that are not relevant to 4 (all of the time). All items were summed with higher scores reflecting stronger religious beliefs. Cronbach's alphas in this study were 0.95 and 0.90, respectively with a total scale reliability of 0.96.

Mistrust was measured using a 12-item scale composed of two subscales: a 7-item Trust subscale from the Primary Care Assessment Survey (PCAS) and a 5-item Medical Mistrust Index subscale. All items had 5 responses ranging from 1 (strongly agree) to 5 (strongly disagree). Several items were reverse coded, and all items from both scales were summed with higher scores indicating a higher degree of mistrust. Cronbach's alphas in this study were 0.80 and 0.75 with a total scale reliability of 0.86.

Racism/Discrimination was measured using the Racism Within Healthcare Settings scale, which assessed the individual patient's perceived differences in treatment by health care providers by race. The scale contains 4 items with 5 responses ranging from 1 (strongly agree) to 5 (strongly disagree). Three items were reverse coded, and all items were summed with higher scores indicating a higher degree of racism. Cronbach's alpha in this study was 0.85.

Perceived access to care was measured using the Perceived Access to Health Services scale, which assessed the individual's ability to access medical care in respect to cost, convenience, and feasibility. The 10-item scale had 5 responses ranging from 1 (strongly disagree) to 5 (strongly agree). Several items were reverse coded, and all items were summed with higher scores indicating a higher degree of perceived access to care. Cronbach's alpha in this study was 0.76.

Continuity of care was measured using the Visit-based Continuity subscale of the PCAS, which assessed how often patients saw their assigned primary care manager. This 2-item subscale had 5 responses ranging from 1 (always) to 5 (never). Both items were reverse coded and summed with higher scores indicating more continuity. Cronbach's alpha in this study was 0.86.

Outcome Measures

Patient satisfaction was measured using a 15-item Patient Satisfaction Within the Healthcare System scale, which assessed satisfaction with wait times, time spent with providers, information received, quality of care, and cost of care. This scale had 5 responses ranging from 1 (very dissatisfied) to 5 (very satisfied). All items were summed with higher scores indicating a greater degree of patient satisfaction. Cronbach's alpha for this sample was 0.93.

Health status was measured using the 12-item SF-12v2, which assessed physical and mental health status. Ten items in this instrument have 5 responses ranging from 1 (all of the time) to 5 (none of the time), and the remaining 2 items have 3 responses ranging from 1 (yes, limited a lot) to 3 (no, not limited at all). QualityMetric software was used to score the instrument and generate two summary scores—physical composite score (PCS) and mental composite score (MCS). Cronbach's alphas in this study were 0.86 for PCS and 0.83 for MCS.
Data Analysis

Descriptive statistics, using means and SDs for continuous variables and percentages for categorical variables, were used to summarize the demographic characteristics. A series of regression models, using a two-step modeling process consisting of univariate and stepwise multivariable models, were used to examine the relationship between individual characteristics and patient outcomes (patient satisfaction, physical health, and mental health). First, a series of simple linear regression analyses modeling patient satisfaction, PCS, and MCS independently were used to assess the effect of each individual characteristic. The following individual characteristics were considered for inclusion as independent variables in the univariable models: religious participation, mistrust, racism/discrimination, spirituality, perceived access to care, and continuity of care.

Distribution of Individual Characteristics Scales in a Sample of 200 Participants

In the second step of modeling, we included a multivariable model of all individual patient characteristics from the single-predictor models with a Wald test p-value ≤0.10. Stepwise regression was used for the final model selection. The global F test and the statistic were used to assess each model's goodness-of-fit, and assumptions for each multiple linear regression model was evaluated graphically. We applied a 0.05 criterion for significance in the final model. Statistical programming and analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

In total, 200 participants provided the required informed consent and completed questionnaires for the study. The participants' mean age was 29 years with 77% of the sample falling in the 18- to 34-year age range. The majority (86%) of the female sample (n = 122) were family members, and the majority (81%) of the male sample (n = 78) were Army AD Soldiers. The majority of participants were Caucasian (59%) followed by African American (18%). On average, these participants completed 13.6 years of education, and the junior enlisted (E1-4) represented 59% of the AD sample (n = 91).

Estimates of the Coefficients, Standard Errors, and Probability Values from Final Stepwise Multiple Linear Regression Models for Patient Satisfaction, Physical Health, and Mental Health Univariate modeling results showed that the following variables were independent predictors for poorer physical health: religious participation (p = 0.04), support from God (p = 0.008), and mistrust (p = 0.003). Perceived access to care was the only individual patient characteristic that was independently associated with a better physical health status. Results of stepwise multivariable regression identified only 2 of these 5 characteristics, as significant predictors of physical health: support from God and mistrust. The parameter estimates for both significant predictors were negative, suggesting that, after adjustment for other characteristics, participants who relied on a greater level of support from God and reported more mistrust were also those with poor physical health.

Individual Characteristics to Mental Health
Of the individual characteristics, mistrust and racism/discrimination were negatively associated while perceived access to care was positively associated with mental health in the univariable models. After adjusting for mistrust and racism/discrimination in a stepwise multivariable model, perceived access to care maintained its statistically significant association with MCS. The positive parameter estimate obtained for perceived access to care indicates that, when holding other variables constant in the model constant, patients with greater perceived access to care on average tend to display better mental health status.

DISCUSSION

To our knowledge, this is the first study to evaluate the predictive ability of individual characteristics to patient outcome variables for patient satisfaction, physical health status, and mental health status in Army AD Soldiers and their family members. Particularly, this study examined individual characteristics of religious participation, mistrust, racism/discrimination, and spirituality that can be attributable to the “whole-person” concept for patients.

One of the most important findings show that access to care is predictive of higher levels of patient satisfaction and better mental health status, and this is consistent with other studies showing that access to care positively influences patient satisfaction. Efforts to enhance access for military populations should be maintained. All members of this population have more health insurance than most Americans; however, access to care was still an issue. This finding demonstrates that having health care insurance does not equate to having adequate access to needed health care services.

Our second most important finding relates to the influence of mistrust and racism/discrimination to patient outcomes. Racism/discrimination and mistrust had a significant negative impact on patient satisfaction, physical health, and mental health in univariate models. This is a finding consistent with other studies that demonstrate the negative influence that racism/discrimination and mistrust have on patient satisfaction as well as other patient outcomes. However, racism/discrimination lost significance after placed in the multivariable models.

The Army Medical Department is currently involved in a campaign to create a “Culture of Trust.” This study provides the impetus for creating an environment and health care system where patients trust their health care providers. Mistrust in health care providers decreases the likelihood that patients will seek care and follow recommended treatments and therapies, which worsens health conditions. With the long period and exposure to war, Soldiers and family members need to feel comfortable in seeking behavioral health services. Behavioral health service is a component of the PCMH; therefore, trust will be needed in order for these services to be adequately utilized.

Continuity of care is considered an important aspect of access of care. In this study, continuity of care had a significant positive relationship with patient satisfaction in the univariate regression model; however, the significance was lost when included in the model with access to care. This finding demonstrates that the ability to access proper care when needed was more influential than continuity with primary care providers. A plausible explanation for this finding may be the nomadic nature associated with AD Army Soldiers, their family members, and AD health care providers. Interventions are being developed to improve continuity of care by targeting Soldiers and their family members to consistently see the
same provider care manager (PCM-by-name). Given the transient-nature among AD Army health care providers, Soldiers, and their family members, they may be more accepting of a lack of continuity. Therefore, efforts and interventions to achieve PCM-by-name may not provide the anticipated return of investment for these nomadic populations.

This study provides insight on the relationship of religious participation and spirituality to patient outcomes. Contrary to other published studies, participating in religious activities was not associated with improved patient satisfaction, physical health, or mental health when all individual characteristics were examined. This was an unexpected finding, given that participation in religious activities tend to have better physical and mental health. The finding that this relatively young military population had low religious participation may be similar to the current trend of more Americans transitioning from traditional religious denominations to nondenominational or interdenominational religious participation. In a previous study with a group of African American men (n = 505) using the same instrument to measure participation in religious activities, they had a mean score of 40.6 compared to the participants in this study (n = 200) who had a mean score of 28.8. The finding that religious participation did not predict patient outcomes in this study is likely attributed to a decreased participation in religious activities and spirituality secondary to decreased commitment to church affiliation among this highly nomadic population. Nevertheless, spirituality (conceptualized as a personal relationship with God) was significantly related to poorer physical health. This is consistent with other studies where sicker patients with chronic health conditions tend to rely more on support from God to help them cope with their physical ailments.

There are limitations associated with this study. The sample included in this study is representative of only one AD Army Health Clinic in the Pacific region of the United States; therefore, the result of this study may not be generalizable to other populations located in different geographical regions. Some of the participants completed study questionnaires in the same clinic where they receive care. As a result of the proximity and structure of the military, some participants may not be as truthful with responses in fear of retributions from their responses to items on the questionnaire. The study was cross-sectional with data collected only at one point in time; therefore, causality cannot be determined.

IMPLICATIONS

Patient outcomes, such as patient satisfaction, physical health, and mental health, in this study are relevant to the success of the PCMH and ultimately Soldiers' and family members' medical readiness. One of the joint principles of the PCMH is enhanced access to care, and if the PCMH model is implemented appropriately, an expected outcome would be improved patient satisfaction. As leaders decide on which interventions to incorporate into the PCMH, careful understanding of patients’ perspectives should be considered as they are the end users of health care services. Rather than focusing on PCM-by-name or team, efforts and interventions should address having adequate access to health care services for Soldiers and their family members when they need it. For a population of individuals who have more health insurance and health care services available than the majority of Americans, findings from this study reinforces that health insurance does not equate to having access to care. The Army Medical Department has acknowledged the importance of establishing a “Culture of Trust” among medical facility staff and initiated training; however, findings from this study illustrate the negative ramifications of mistrust on specific patient outcomes. The importance of spirituality needs more attention and incorporated in the “Whole-Person” concept; therefore, efforts to incorporate the involvement of spiritual leaders (Chaplains, Pastors, Ministers, Priests, and other religious leaders) in health care should be sought.
CONCLUSION

The results of this study offer Army leadership beginning information from the patient's perspective that can be used to assist in the development and modification of interventions and processes for the transition to the PCMH. Access to care is associated with higher levels of patient satisfaction and better mental health status; therefore, access to care should be one of the top priorities. Continuity of care was not viewed as important as access to care for patient outcomes for the nomadic-type AD populations. Improving trust in health care personnel may increase patient satisfaction and improve the patient satisfaction and health status for this population. Those with poor physical health should have spiritual leaders available as needed. Psychosocial and sociocultural factors described as individual characteristics are important social determinates of health.

Analyzing the Future of Army Aeromedical Evacuation Units and Equipment: A Mixed Methods, Requirements-Based Approach

Military Medicine
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ABSTRACT

We utilize a mixed methods approach to provide three new, separate analyses as part of the development of the next aeromedical evacuation (MEDEVAC) platform of the Future of Vertical Lift (FVL) program. The research questions follow: RQ1) What are the optimal capabilities of a FVL MEDEVAC platform given an Afghanistan-like scenario and parameters associated with the treatment/ground evacuation capabilities in that theater?; RQ2) What are the MEDEVAC trade-off considerations associated with different aircraft engines operating under variable conditions?; RQ3) How does the additional weight of weaponizing the current MEDEVAC fleet affect range, coverage radius, and response time? We address RQ1 using discrete-event simulation based partially on qualitative assessments from the field, while RQ2 and RQ3 are based on deterministic analysis. Our results confirm previous findings that travel speeds in excess of 250 knots and ranges in excess of 300 nautical miles are advisable for the FVL platform design, thereby reducing the medical footprint in stability operations. We recommend a specific course of action regarding a potential engine bridging strategy based on deterministic analysis of endurance and altitude, and we suggest that the weaponization of the FVL MEDEVAC aircraft will have an adverse effect on coverage capability.
INTRODUCTION

The Medical Evacuation Proponent Directorate (MEPD) Futures Study Team of the U.S. Army Medical Department (AMEDD) continues to analyze current shortfalls and future requirements to support the aeromedical evacuation (MEDEVAC) mission and specifically the Future of Vertical Lift (FVL). The FVL is a futures program focused on replacement of the aging military helicopter fleet. As such, it represents the future of Army MEDEVAC capability. This article discusses the relevant, previous findings of the MEPD study team (including existing capability shortfalls, data acquisition, and agnostic capability requirements). This study also details a discrete-event simulation (DES) of Afghanistan, provides additional insight regarding aircraft engine requirements based on proposed engine solutions (interim and future), assesses the notion of weaponizing MEDEVAC platforms, and discusses the future way ahead for cabin design and major combat operations. The study, funded by MEPD, begins with a review of the existing knowledge about the MEDEVAC fleet and the implications for FVL planning.

Study Background

In a 2009 study, MEPD evaluated the total number of Army MEDEVAC aircraft authorized as part of the total army analysis process. Conclusions from this study indicated that estimating the number of MEDEVAC platforms requires both workload and geographic analysis. In addition, the study identified the distribution of patients by evacuation category for two aeromedical evacuation units with complete data (31% urgent, 21% priority, 48% routine), the distribution of the number of intratheater movements by patients (85% = 1 movement, 13% = 2 movements, 2% > 2 movements), and the number of patients per evacuation (57% = 1 patient, 43% > 1 patient). The importance of this study is that it not only provided an initial basis for future geographic and workload-based simulations, but also underscored the necessity to evaluate unique medical assets separately from grouped units (in this case aviation units). This finding underscores the need for medical involvement in the development of the FVL platform.

Linked to distributions and data of the 2009 study, MEPD developed a two-stage stochastic optimization model using realistic, historical data that allocated both treatment and evacuation (ground and air) assets across a mock operating area to minimize patient transport time in 2010. This study provided a few important components necessary for simulating future scenarios in support of the FVL project, two of which were the stochastic casualty generator used by similar research and the distribution of injury severity scores (ISS) based on real-world data. In addition, the study showed that the complexity of the problem would require more wide-scale use of simulation.

Beginning in 2011, MEPD began evaluating the design of the current MEDEVAC company based on doctrine, organization, training, maintenance, leadership, personnel, and facilities (DOTMLPF). Results of this study identified widespread concurrence from 100 survey respondents of the shortages in enlisted personnel, maintainers, and maintenance equipment. All of these results were statistically significant (α = 0.05). Aviation branch officers and enlisted were asked to estimate the number of geographically dispersed sites the General Support Aviation Battalion could reasonably support with maintenance given its current structure. Previously deployed MEDEVAC experts were asked to report on the number of remote sites their organization occupied on their last or current deployment. The difference in the distribution between the 2 response sets is shown.
The number of separate, geographically dispersed MEDEVAC sites supportable by the maintenance component of Army aviation, the General Support Aviation Battalion, is estimated to be different than the self-reported number of sites a MEDEVAC unit occupies in ongoing stability operations, resulting in shortages of capabilities. This finding was identical to separate analysis conducted by the Army Aviation Center and is important to the development of the FVL platform. Aircraft with increased range and speed might be able to reduce the number of geographically separate locations required of MEDEVAC units. Such a reduction in geographic locations would reduce the maintenance footprint required. The study provided a basis for understanding the current MEDEVAC organization, as the Army plans the redesign of the Army helicopter fleet. Also from this survey, comments from the field were collected and analyzed qualitatively for each DOTMLPF area. Analyzing these comments was more than revealing, as relevant themes emerged. These qualitative themes mirrored the statistical findings in that there was widespread discussion of maintenance issues associated with geographic dispersion.

In a separate 2011 survey and Monte Carlo simulation of daily operational readiness rates (percentage of the time aircraft are operational), the MEPD study team assessed the impact that contractors currently have on operational readiness in theaters of operation. One of the considerations was that the development and adoption of more capable aircraft might reduce the maintenance footprint by eliminating geographic dispersion requirements and/or reducing maintenance exposure by shortening mission time, eliminating the need for many contractors. Understanding the current contribution of contractors would help with future analysis of any potential cost savings associated with design and development of the FVL platform. Survey responses (n = 90) garnered from 600 aviators indicated that contractors had a significant effect on operational readiness rates.

In 2012, MEPD deterministically analyzed requirements for speed and range based on specifications of the future brigade operating area and Secretary of Defense requirements for response time. Findings associated with this study informed decision makers about the speed and range requirements for the future MEDEVAC platform along with possible doctrinal employment. The findings follow: (1) aircraft with ground speed capability of 350 knots can provide 100% coverage of the future brigade operating space (300 km2) given simplifying assumptions; (2) aircraft with ground speed capability of 260 knots provide 100% coverage for future brigades projecting power in a circle of radius 150 km; (3) Colocating MEDEVAC assets and surgical elements when casualty distributions are uncertain (uniformly distributed over a circle) optimizes the one-hour coverage directed by the Secretary of Defense.

By 2011 and throughout 2012, the FVL project came to the forefront for MEPD, and the study team began looking at the problem using a variety of stochastic and deterministic techniques. A DES emerged as a reasonable solution to assessing future capabilities (platform agnostic) based on modeling an Afghanistan-like, stability operations scenario. The advantage of the DES is that it allows for flexible modeling of multiple parameters associated with aircraft design, unit employment, etc. Once a baseline model has been verified and validated, then excursions are readily conducted over an array of parameters, often using design of experiments (DOE) methods.

Through 2012, several other requirements for analysis emerged, including the need to address specific engine considerations. The YT706 General Electric (GE) Aviation engine adopted by the Special Forces community was of interest to the aviation community as a potential bridging
strategy to the FVL, and the Army’s Improved Turbine Engine Program (ITEP engine) established capabilities for future engines important to analyze. The ITEP engine is supposed to achieve a 50% increase in power (3000 shaft horsepower [SHP]), a 25% reduction in fuel for a given SHP, and a 35% reduction in maintenance costs. Although still in the Science and Technology phase (expected to emerge for request for proposals in 2013), both GE Aviation and a 50/50 venture between Honeywell and Pratt & Whitney are actively seeking to build an engine with these capabilities.7 The question important to the FVL MEDEVAC variant was the utility of acquiring the ITEP or YT-706 for the UH-60 Black Hawk before the fielding of the FVL platform as a bridging strategy for the current UH-60 fleet or waiting for the FVL with the proposed ITEP. Another question that emerged during 2011 and 2012 was the possibility of arming current and future MEDEVAC aircraft, which made national news. This issue ostensibly arose after delays in launch time, whereas MEDEVAC assets awaited armed escort to provide aerial security at the landing zone. Aside from the “con” arguments regarding the Geneva Convention and the use of unarmed aircraft emblazoned with the Red Cross to designate noncombatant status, other arguments against arming MEDEVAC platforms have included the negative effects of increased aircraft gross weight as well as the remaining MEDEVAC chase aircraft requirement (i.e., MEDEVAC aircraft must launch with a second escort aircraft). The MEPD Capabilities Study Team was asked to look at the weight factor directly.

Study Purpose and Research Questions

Given what the study team found in previous work, we had a reasonable basis and background to address three additional research questions for 2012. The first research question dealt with a capabilities assessment of the effects of speed and range on force structure in theater. The second research question surrounded engine capability for the bridging strategy to the FVL platform, adopt the YT706, or wait for the ITEP. The third research question addressed an analysis weaponizing the FVL platform. The research questions (RQs) follow:

— RQ1: What are the optimal capabilities of an FVL MEDEVAC platform given an Afghanistan-like scenario and parameters associated with the treatment/ground evacuation capabilities in that theater? Answering this question for Afghanistan provides a basis for modeling the FVL platform across multiple geographies, as different regions of the country vary in altitude, environmental conditions, and terrain.
— RQ2: What are the MEDEVAC trade-off considerations (range, endurance, altitude, etc.) associated with different aircraft engines operating under variable conditions? Answering this question is foundational to the FVL study, as it provides an assessment of bridging strategies before fielding of the FVL.
— RQ3: How does the additional weight of weaponizing the current MEDEVAC fleet affect range, coverage radius, and response time? Answering this question is important for both current operations and the FVL configuration.

RQ1: METHODS, RESULTS, AND DISCUSSION

Discrete Event Simulation of Afghanistan

For RQ1, the published studies to date provided the necessary framework for the development of a DES focused initially on Afghanistan. The problems with questions of this nature involve both the scenario and the definition of capabilities. The study team evaluated the nature of the
problem and determined that flexible simulation (with the capability to change scenarios relatively rapidly) with post hoc optimization (design of experiments with a goal-programming optimization approach) would yield results suitable for analysis of the future, especially given the increasing complexity of analyzing a yet-to-be designed future aircraft. Unfortunately, scenarios are restricted often by what we know (the present) versus what we do not know (the future), at least for validating that the simulation is producing results congruent with the known. To address this issue, the study team selected an Afghanistan-like scenario to help with the validation process.

Selected capabilities of importance to the study team included the following: range of aircraft in nautical miles (NM), speed of aircraft in knots, altitude capability of aircraft (as estimated by path network), and cost of aircraft as a function of speed (estimated). These variables have a significant effect on the requirement for medical assets such as intensive care units (ICUs) and operating tables as well as the ability to move a patient from the point of injury to surgical treatment within the allotted time. Further, changing aircraft capability has an effect on maintenance (consider exposure to $\beta$-distributed downtime) as well as aircraft utilization (opportunity cost). As part of the simulation, the study team conducted post hoc analysis using DOE factors. By manipulating variables of interest, we were able to optimize objective functions in a goal-programming fashion based on weights of key decision makers.

Modeling Environment

MedModel was the primary programming and simulation environment for the simulation. MedModel allows for flexible, rapid development of complex simulation problems. Although many simulation platforms exist, MedModel has been used by the military for various applications including unit rotation planning and medical planning. The Center for AMEDD Strategic Studies (CASS) retains the site license associated with this simulation.

The Scenario

Understanding that the primary mission set for analysis was the collection of patients, the treatment of patients, and the evacuation of patients, the study team determined that an initial analysis of the Afghanistan Theater of Operations (which has a known casualty stream, real data, and concrete distances) would provide a reasonable scenario for initial evaluation. To set up the problem in an unclassified way, the team resorted to using open-source data for casualties and distributing these casualties around population centers.

The Locations and Time Frame

The number of population centers selected was 24, throughout the country, as these population centers were of sufficient size to receive geographic attention from publicly available mapping sources (i.e., Google Maps). The time for the study was set to May 2009 to April 2011, 730 days. This period reflected a period of increased casualties.

The Entities
The primary entity in this simulation was the patient. Given the focus on evacuation times, all other objects were considered resources that the patient could demand. Even the FVL platform was considered a resource rather than an entity. The differentiation between entities and resources is important only to the coding available in MedModel. The primary resources in the model include the use of ground evacuation resources (medics and vehicles), fuel, mechanics, intensive care units (ICUs), operating rooms, and the FVL platform itself. The fuel and mechanic distributions are underdeveloped but exist to provide future refinement.

The total number of casualties estimated to be moved during this time was 9,293, which included 8,369 wounded-in-action (WIA), 889 killed-in-action (KIA), and an additional 35 disease nonbattle injury (e.g., heart attack victims). The WIA and KIA derived from an open-source database. According to Karen Bagg, an operations research analyst and statistician at CASS, this source matches closely with the Department of Defense reports. These last 35 were calculated using a rate of 1.83 disease nonbattle injury admissions per 100,000 troops (provided by CASS) with the number of troops deriving from the Brooking's Institute Afghanistan Index.

Patient Arrivals

Although exact locations of casualties are known, using these distributions would potentially classify this study. Instead, the study team chose to scatter the casualties randomly around the geographic casualty centers. The scenario selected included only two hospitals: one in Kandahar and one in Kabul. These locations currently provide out-of-theater evacuation capability, and so this site selection was logical. The team chose not to place any far-forward support for the initial analysis to test the robustness of the simulation and post hoc optimization for challenging scenarios. Distributing the casualties appropriately was a function of using a Compound Poisson Process. In this process, patient groups arrived in Poisson distribution fashion with a fixed arrival rate. The number in the group was based on a triangular distribution derived from a previous MEDEVAC study. The daily arrival rate was set to 1 every 70 hours for each of the 24 locations. This rate of arrival mimicked the number of daily casualties experienced during the time frame of May 2009 to April 2011. Initial arrival time was randomized uniformly over time using a $\beta (1, 1)$ distribution. The patient priority for the MEDEVAC queuing process was determined by an empirically generated ISS, a measure of patient severity that is widely tracked by the U.S. military. The ISS effectively weighs the severity of a patient from 0 to 75, with higher numbers equating to more severe casualties. The queuing priority was based on this patient attribute.

Patient Processing

Because the simulation was designed to evaluate an entire health care evacuation and treatment system, the flow through the system was important to understand. Specifically, the study team wanted to establish a parsimonious model that captured the essential flowchart elements. Each patient arrival was triaged by a medic with treatment time distributed exponentially with a wait parameter of 15 minutes. Patients were initially categorized as a KIA (8% from CASS), a return to duty (RTD) (9% based on National Trauma Data Bank 2010 analysis), a died of wounds (2.5% from CASS), or a non-RTD evacuee survivor requiring medical treatment (80.5%). Patients were also assigned to either litter or nonlitter status, $\sim$Bernoulli(0.5), associated with a previous study.

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ISS for evacuated survivors were assigned based on the National Trauma Data Bank 2010 distributions. Higher ISS scores indicate more severely injured patients with survival rates dropping rapidly.

ISS Distribution is Shown Along With Associated Probabilities of Surgery (S) and ICU Visit Along With ICU Visit Given No Surgery. Patients Having Surgery Are Assumed to Visit the ICU. Some Patients May Not Have Surgery But Still Visit the ICU (e.g., Heart Attacks)

The FVL platform, as the most important resource, had special processing logic worth discussion. Processing logic for movement, downtime, repair, and refueling provided the basis for comparative analysis. Repair and refuel logic allowed for flexible macros (future DOE analysis), while downtime was modeled as an exponential distribution with rate parameter of one event per 24 hours. At a minimum, aircraft are expected to have a daily inspection. The expected downtime for this inspection was initially set to 72 minutes but was adjustable by the macro.

Path Networks

Aircraft travel path networks were modeled to reflect feasible paths for 200 NM, 250 NM, 300 NM, 350 NM, and 400 NM aircraft ranges. The 350 NM and 400 NM paths were considered “high altitude,” as they traversed terrain in excess of 10,000 feet mean sea level.

Verification and Validation

Decision makers agreed that the model was reasonable for use in the FVL analysis. CASS verified that the model inputs and outputs were reasonable. Certain design characteristics were evaluated to make sure that the model's outputs were appropriate based on the input parameters. The initial casualty stream of 9,293 was replicated in an initial 30 replicates with no statistical difference (sign test). (The first five observed casualty streams were 9295, 9287, 9361, 9186, and 9268.) After several runs and modifications, the model appeared to perform as expected.

DES Results and Implications for FVL

Results from all runs suggested that aircraft with speeds greater or equal to 250 knots would reduce the average wait for patients in the queue below 60 minutes, the standard set by the former Secretary of Defense. One should note that expected wait does not ensure all patients would be evaluated within 60 minutes at the nearest medical treatment facility in-theater.

As indicated by Fulton et al, analyzing both workload and geographic factors is important to understanding the requirements for any specific MEDEVAC mission set. What is interesting in this scenario is that geography trumps workload: aircraft with sufficient capability would allow consideration of having fewer medical treatment and evacuation locations in the theater of Afghanistan. For this scenario, highly capable, all-weather MEDEVAC assets would allow the establishment of only two surgical hospitals to support U.S. casualties. In addition, highly capable, all-weather MEDEVAC assets allow the reduction of the number of evacuation locations, which are dictated currently by geographic dispersion rather
RQ2: METHODS, RESULTS, AND DISCUSSION

Analysis of Proposed Engines

The importance of RQ2 is simple: any bridging strategy is associated with this analysis. Addressing this research question required a few simplifying assumptions. First, we used the existing UH-60 fleet and specifically the operator's manual dated September 25, 2009. We compared the GE 701-C engine, the GE 701-D engine, the YT706-700R engine, and the proposed ITEP engine. The first three engines are currently in use for the UH-60.

Facts and Assumptions

Certain facts and assumptions were important to this analysis. First, one should note that fuel burn is a linear function of SHP over most of the relevant range. Second, torque required is linearly related to fuel burn. Third, we had to make the assumption that the ratio of SHPs between engines provides a reasonable but imperfect method for estimating torque requirements. In other words, if an engine with 2000 SHP requires 1,000 SHP for a specific airspeed and altitude, then an engine with 3,000 SHP would require (2/3) × 1000 = 667 SHP. Since the ITEP engine is not yet developed, this assumption was necessary, as no test data exist. We also had to assume that fuel burn rates from GE are accurate.

Aeromedical Evacuation Coverage

After comparing the engines descriptively, the study team evaluated the performance using a real-world environment, Afghanistan. At high altitude and hot conditions, the one-hour MEDEVAC coverage circles—circles which depict an “out and back” one-hour travel time—change very little, as the aircraft airspeed is often limited by the main transmission (or engine limits occur near simultaneously with the transmission limit). In other words, sprint speed is limited based on other than just engine considerations, so all engines will be able to meet the one-hour response time window. That said, the ITEP is expected to burn 25% less fuel throughout this relevant range.
In high altitude and hot conditions, the coverage capability in terms of hovering altitude will change. At 30°C surface temperature and calculating a 2°C drop per 1,000 feet, we estimate that an 18,000 pound UH-60 can hover OGE with 701D engines at about 7,000 feet or 2,134 m (interpolated maximum torque available of about 90%). We applied a ratio of SHP to determine the additional altitude that the YT706 and ITEP might provide. We estimate that the YT706 can produce enough power to hover OGE at approximately 11,000 feet or 3,353 m using a proportional power calculation. Specifically, if the maximum power for the 701D is 76%, then the YT706 should be able to produce nearly 76% × 2638 SHP/1994 SHP = 100% power. The ITEP should be expected to allow hover OGE at 14,000 feet or 4,267 m. The estimated maximum power is shown as 73%. Given the ratio of SHP and assuming a proportional engine “bleed” rate, the ITEP is estimated to be able to produce 73% × 3000 SHP/1994 SHP = 110% power, which is less than the UH-60L transmission limit. The limitation in these estimates is such that we assume engine performance curves of the ITEP and YT706 will mimic those of the 701C/D series.

Results of Engine Analysis and Implications for the FVL

The engine comparison for the current fleet was revealing as six major findings emerged: (1) Hour coverage circles are restricted by transmission limits rather than engine considerations at altitudes up to 8,000 and temperatures near 30°C (clean), as the transmission cannot accept additional torque from improved engines. No change in MEDEVAC area coverage occurs for these areas. When engine limits begin in the 701C and 701D, the coverage capability diminishes rapidly; (2) Altitude and torque availability increase with the adoption of either the YT706 or the ITEP; (3) The GE-reported fuel consumption for the YT706 (pounds per SHP per hour) shows only nominal differences between engines except for the planned ITEP, which necessarily must show a 25% decrease in consumption along the relevant range of operation; (4) The YT706 altitude improvement in comparison to both the current 701D and the ITEP is 4,000 feet in terms of hover OGE. Such an increase might be relevant in some situations; however, the cost–benefit may not be sufficient to justify its acquisition as a bridging strategy; (5) Given reasonable planning assumptions for high altitude/hot temperatures and using maximum range airspeeds, the ITEP variant will provide nearly 100 NM additional range for the UH-60; (6) In the end, it may be cheaper to procure new FVL airframes than attempt to retrofit the fleet with new transmissions and other components necessary to handle the capability of the ITEP. This hypothesis needs to be evaluated carefully.

RQ3: METHODS, RESULTS, AND DISCUSSION

Analysis of Fleet Weaponization

As a final research question, the study looked at the effects of weaponizing the MEDEVAC platform. Answering RQ3 is important for both current operations and the FVL configuration. The approach to answering this problem was performance planning.

Comparisons

To see the effects of weaponization, we chose to compare the “clean” UH-60L typically configured for MEDEVAC at various weights versus against a “dirty” UH-60L configured with M-60 machine guns mounted (an increase in flat plate drag of 0.6 and weight with ammunition of 250.6
pounds). For consistency, we used 6,000 feet pressure altitude and 30°C. Calculations were based on travel at maximum range airspeed with a 20-minute reserve at maximum endurance airspeed and a 20-minute run-up, launch, load, and land cycle.

Implications for the FVL

Although it is possible to weaponize the MEDEVAC aircraft of the future, the geographic advantage is reduced depending on the weight and drag associated with the weaponization. Specifically, that reduction on the UH-60 might be as much as 14%. Although the exact effect for the FVL is not known, it is known that increasing weight and flat plate drag reduce response time. Given the requirement for two ships per mission that currently limits launch time, leaders will have to assess whether planning for quick launches is a better solution than arming MEDEVAC aircraft.

CONCLUDING REMARKS

In this study, we showed the techniques for developing the future MEDEVAC force. These methods are based on both qualitative and quantitative approach, employing mixed methods and soliciting input from the field. We recognize multiple and infinite limitations in attempting to use the current state of knowledge to forecast the future; however, we also recognize that all Bayesian methods require prior distributions and yet form the basis for artificial intelligence. In this case, we believe our analysis is reasonable, and it will be refined over the next decade, as more information becomes available.

The analysis provided here has specific implications for decision makers. First, we confirm previous findings that travel speeds in excess of 250 knots are advisable for the FVL design. Second, capable FVL platforms will reduce the medical footprint in stability operations. (NOTE: this finding is not related to major combat operations, which directly require a workload component.) Third, if the AMEDD must choose between a bridging strategy in the YT706 engine versus waiting for the ITEP, the study team recommends waiting for the ITEP. The YT706 adds some altitude capability, but other aircraft limits will be problematic. Fourth, the weaponization of FVL will have an adverse effect on coverage capability and the potential reduction of force structure possible in stability operations.

Currently, the study team has shifted its attention to the cabin design considerations for the future MEDEVAC variant. We have designed a preliminary survey, which links to three-dimensional, interactive computer-assisted design models. Soldiers in the field will have the opportunity to walk through the proposed cabin designs virtually and provide feedback throughout the development cycle. This work is ongoing and the results are forthcoming.

BACK TO TOP

Evaluation of Hemostatic Field Dressing for Bacteria, Mycobacteria, or Fungus Contamination

Military Medicine
Infectious complications have a major impact on wounded warriors. Pathogens causing infections include multidrug-resistant bacteria, fungi, and mycobacteria. The potential sources for these pathogens include nosocomial transmission, the environment (e.g., dirt), or the patients (skin flora) themselves. The purpose of this pilot study was to explore the possibility that hemostatic field dressings might act as an inoculation source of pathogens into wounds. To accomplish this, hemostatic field dressings were assessed for the presence of bacterial, fungal, or mycobacterial contamination. We evaluated two samples of QuikClot Combat Gauze and two samples of CELOX Gauze subjected to normal stresses associated with storage after receipt from the manufacturer. We then evaluated 16 samples of QuikClot Combat Gauze that were collected from personnel deployed in Afghanistan and had undergone routine mechanical stress. Samples underwent screening with Trypticase Soy Broth, blood agar plates, MacConkey agar plates, CHROMagar Staphylococcus aureus plates, chocolate agar plates, Potato Flake agar, Lowenstein–Jensen media, and Middlebrook 7H11 media. No bacteria, fungi, or mycobacteria were recovered from the dressings. It does not appear that hemostatic field dressings are contaminated, even after subjected to field conditions. Further research is needed to identify inoculation sources of fungi and mycobacteria, which cause infections.

Introduction

Approximately 25% of wounded warriors develop a combat-related injury infection, with percentages rising to as high as 50% if casualties are injured severely enough to be admitted to an intensive care unit. The vast majority of these infections are due to multidrug-resistant bacteria including methicillin-resistant Staphylococcus aureus, Acinetobacter baumannii, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae. Extensive work has been undertaken to determine the source of the bacteria, with the majority of the studies supporting nosocomial transmission over colonization of the casualty before injury or inoculation of bacteria into the wound at the time of injury from environmental contamination (e.g., the wounded warrior's clothes or the dirt). Less commonly seen pathogens leading to infections have included invasive fungal infections (IFIs) of skin and soft tissue wounds. These pathogens typically have been recognized in trauma patients in settings associated with agriculture injuries, motor vehicle accidents, and blunt crush injuries when material from the environment is directly inoculated into the wound. Recently, the Joplin tornado was associated with local IFIs of a single mould species, Apophysomyces trapeziformis (family: Mucoraceae), resulting in a high rate of amputations (31%) and 25% mortality. The British military has dealt with IFIs during their deployments to Afghanistan, especially in the Helmand province, when casualties suffered severe lower extremity amputation with perineal/pelvic injury during dismounted patrols, and when these injuries were associated with high blood product support because of excessive blood loss. The U.S. military has noted increasing rates of IFI over the last few years with similar risk factors as described by the British military. In addition to fungal infections, there have also been reports of mycobacterial infections complicating the care of trauma patients and wounded warriors; however, the only published combat associated case is pulmonary disease in a burn patient.

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Limited studies have been done to assess the possible sources of fungi and mycobacteria that are associated with wound infections. The primary hypothesis is that these pathogens are directly inoculated into wounds at the time of injury because of environmental contamination associated with the lush vegetation in southeastern Afghanistan. The premise of environmental contamination was also a commonly held belief for Acinetobacter infections before extensive research showing that those infections were primarily caused by nosocomial transmission of the organisms and not their presence in the dirt. Another possible source could be hemostatic field dressings, as they are increasingly being used on the battlefield. There have been solitary reports of contaminated battlefield gauze and a Food and Drug Administration (FDA) investigation because of complaints against the manufacturer of QuikClot Combat Gauze (http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm203960.htm); however, we were unable to find systematic evaluations, publications, or reports to the manufacturer or the FDA of hemostatic field dressing contamination with pathogens. It is possible that packages could be contaminated at the time of manufacturing because of packaging problems, or later, because of mechanical stresses on the packaging (e.g., wear and tear within a rucksack), atmospheric pressure changes, or temperature extremes when military personnel carry the packages while deployed or normal storage of the packages in the United States. IFIs and bacterial infections have not been caused by a single species of bacteria or mould, which limits the likelihood that there is a common source contamination of the dressings at the manufacturer. In addition, manufacturers systematically test their lots for contamination per rigorous guidelines to ensure contamination is not occurring at the time of manufacturing and packaging of the dressings. The packaging itself also undergoes testing to ensure there are no leaks, which might allow for the introduction of contaminants. These safety procedures by the manufacturer do not reduce the possibility that packaging might develop microtears during mechanically stressful storage by military personnel in the deployed setting. To the best of our knowledge, no studies have systematically assessed hemostatic field dressings for contamination rates. As such, we obtained hemostatic field dressings (QuikClot Combat Gauze and CELOX Gauze) directly from the manufacturer (i.e., before exposure to the stresses associated with a deployment) to perform an independent study to establish if there is potential contamination within unstressed packages stored in the United States. We also obtained unused hemostatic field dressings (QuikClot Combat Gauze) directly from personnel in a deployed setting to determine if the dressings were contaminated with bacteria, fungi, and/or mycobacteria after exposure to stress in extreme environments. The purpose of this pilot study was to explore the possibility of microbial contamination of hemostatic field dressings and, if any existed, to estimate the contamination rate of packages carried by deployed warfighters.

Materials and Methods

Samples

We collected hemostatic field dressings to assess them for the presence of bacterial, fungal, or mycobacterial colonization before use. One set of dressings was obtained directly from the manufacturer, which was stored on a shelf inside a temperature-controlled room in the United States without undergoing any physical stress associated with the deployed environment. This included two samples of QuikClot Combat Gauze (Z-Medica Corporation, Wallington, Connecticut) (expiration dates 4/2014 and 4/2013) and two samples of CELOX Gauze (Medtrade Products Limited, Crewe, United Kingdom) (expiration date 11/2012). These samples were screened for contamination during March to April of 2012. The
second set of samples included only QuikClot Combat Gauze collected from personnel in Afghanistan. No CELOX Gauze was used in the combat zone at the time of this study. The obtained gauze packages underwent the normal wear and tear of a deployed environment. There were nine lots among the 16 packages (expiration dates were 4/2014 [5], 9/2014 [1], 10/2013 [1], 1/2013 [1], 7/2012 [5], 8/2012 [2], and 9/2012 [1]), and they were screened for contamination during June to July of 2012.

Culture Techniques

For this study, we elected to follow clinical microbiological techniques and to use adequate media, which are being used for the recovery of pathogens observed in our wounded warriors.

The first set of samples (that had not deployed) underwent cultures for gram-positive and gram-negative bacteria, mycobacteria, and fungal pathogens. Primary bacterial media included Trypticase Soy Broth (TSB), blood agar plates (BAPs), MacConkey agar plates, CHROMagar S. aureus plates, and chocolate agar plates. Primary mycobacterial cultures included chocolate agar plates, Lowenstein–Jensen media slants, and Middlebrook 7H11 media slants. BAP and Potato Flake agar (PFA) were used to evaluate for mould and yeast cultures. The gauze was aseptically taken out of the packages and soaked in TSB. Then the dressings were compressed to express the TSB. The TSB culture was filtered using Nalgene CN analytical filter units (Thermo Scientific, Rochester, NY) designed for microbial analysis and sterility testing. The filters were then cut in pieces, and one piece each was placed onto the agar plates, and several smaller pieces were placed into the slants. All cultures were incubated at 37°C except PFA and chocolate agar, which were incubated at 30°C. Plates were reviewed at 24 and 48 hours, then weekly for 6 weeks for fungal and mycobacterial cultures. The TSB cultures were kept for more than a week to determine if longer incubation might have yielded in growth.

The second set of samples (collected from Afghanistan) underwent a modification of the prior technique to ensure that all internal aspects of the packaging were sampled and to allow for a screening method that was more reflective of the single hemostatic field dressing we obtained. The products were visually evaluated for wear and tear on their external surface and intact vacuum. Initially, 125 mL of TSB were added to the gauze in the original package and squeezed to ensure adequate mixture. Because of absorption of the liquid by the gauze, only 80 mL TSB culture was recovered from each package. The TSB culture was then passed through two filters using the Nalgene CN analytical filter units. Two drops of each recovered culture was also added to 5 mL TSB. The filters were cut into pieces, and one piece each was placed on BAP, MacConkey agar, CHROMagar S. aureus, chocolate agar, and PFA plates. Furthermore, several smaller pieces were added to Lowenstein–Jensen media and Middlebrook 7H11 media slants. TSB, BAP, MacConkey agar plates, CHROMagar S. aureus plates, and the slants were incubated at 37°C. Chocolate agar and PFA plates were incubated at 30°C. All plates were read after 24 and 48 hours according to standard clinical microbiology protocols. Longer incubation times cause the degradation of certain bacterial media and have not been shown to substantially enhance the growth of the aerobic bacteria often associated with wound infections. However, the TSB cultures were kept for more than a week to determine if longer incubation might have yielded in growth. The fungal and mycobacteria plates and slants were held for 6 weeks with weekly readings for growth.

Quality Control

March 2013
As a sterility control (negative control) for the test procedure, 80 mL of plain TSB was filtered through two filters (40 mL each) and filter pieces were cut and placed on the same media as used above. The samples were incubated as described above. Positive controls were performed to ensure the test procedure was appropriate to recover microorganisms from the gauze and the media that were used to support the growth of the recovered organisms. Four clinical isolates were used: 1 methicillin-resistant S. aureus, 1 multidrug-resistant A. baumannii-calcoaceticus complex, 1 Mycobacterium fortuitum, and 1 Aspergillus flavus isolate. The gauze was spiked with 108 CFU/mL bacteria or mycobacteria suspension or with 2.5 × 10⁴ CFU/mL mould conidia/hyphae suspension. TSB was added and the samples were processed as described above. No growth was detected on any media inoculated with samples collected from the four hemostatic field dressings, which were obtained directly from the manufacturer and stored in a relatively controlled environment in the United States. In addition, there was no growth observed for the 16 QuikClot Combat Gauze field dressings, which had undergone the stresses associated with deployment. It is notable that none of the hemostatic field dressing packages showed any evidence of tears, and the vacuum seals were not broken, but the external surfaces of QuikClot Combat Gauze packages obtained from Afghanistan were dirty and showed visible evidence of wear and tear. The sterility (negative) control plates and slants were negative for any growth. All positive control plates and slants showed growth of the corresponding microorganism.

Results

No growth was detected on any media inoculated with samples collected from the four hemostatic field dressings, which were obtained directly from the manufacturer and stored in a relatively controlled environment in the United States. In addition, there was no growth observed for the 16 QuikClot Combat Gauze field dressings, which had undergone the stresses associated with deployment. It is notable that none of the hemostatic field dressing packages showed any evidence of tears, and the vacuum seals were not broken, but the external surfaces of QuikClot Combat Gauze packages obtained from Afghanistan were dirty and showed visible evidence of wear and tear. The sterility (negative) control plates and slants were negative for any growth. All positive control plates and slants showed growth of the corresponding microorganism.

Discussion

Infections of combat-related injury wounds are associated with substantial morbidity and mortality. To improve outcomes, an understanding of the source of the pathogens infecting casualty wounds is essential. This pilot study suggests that hemostatic field dressings, which are applied to wounds by the medics and corpsmen at the time of injury, are not contaminated with bacteria, fungi, or mycobacteria. This evaluation included a limited number of products that were not subjected to field environment stresses, as well as samples that were exposed to the mechanical stress and extreme temperatures of Afghanistan.

Efforts to understand the epidemiology of infections have primarily focused on bacteria since they have carried the greatest burden of disease in the wounded warriors. These evaluations have included healthy personnel before deployment, healthy personnel while deployed, cultures of fresh wounds at the time of injury, non-U.S. personnel admitted to U.S. deployed medical facilities, and the environment itself. At this time, the majority of this work has revealed that non-U.S. personnel introduced bacteria into the U.S. deployed military facility, and then nosocomial transmission further propagated the bacteria, especially A. baumannii. However, this systematic approach has not been carried out for other
bacteria, and no work has been undertaken to evaluate potential sources for fungi and mycobacteria. Currently, mycobacterial infections are very rare and likely reflect contamination from the environment. Routine surgical intervention should eradicate these pathogens. IFIs are likely reflective of the extreme nature of the injuries with difficulties to adequately remove the foreign debris that were inoculated into the wounds at the time of injury. One hypothesis, as to why substantial IFIs have not been seen previously in wounded U.S. military members, is that the U.S. military was not operating in environments with lush vegetations known to harbor fungus. Even though there have been major U.S. military conflicts in the past (e.g., in Vietnam, in Korea), there is no data available on IFIs during those operations. It is notable that the British military has wrestled with these infections during their deployments, and as the U.S. military increasingly became involved in conflicts in the same area (previously under the control of the British military), increasing IFIs were noted for U.S. military personnel with similar catastrophic injuries.10,14

Field dressing manufacturers are required to assess their products for contamination and leakage with well outlined processes for culture, sample sizes, package integrity, etc. In addition, manufacturers undergo FDA evaluation if complaints have been made about their products. An FDA investigation and appropriate responses occurred in 2009 with the manufacturers of QuikClot Combat Gauze quickly following complaints about their product (http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm203960.htm 14 Aug 2012). However, these processes do not include screening for the various pathogens that have been recovered from wounds of combat casualties. In addition, field dressing manufacturers are not required to have their devices undergo testing that represents stresses of the deployed environment. The U.S. military should continually assess their medical materiel for safety, suitability, and efficacy within the environments encountered by warfighters.

This pilot study suggests that there is no contamination of hemostatic field dressings when they are stored in controlled environments in the United States or when they have been deployed to Afghanistan. However, since only 20 samples were studied, it might be possible that a larger study of hemostatic field dressings would reveal contamination. In addition, other field dressings are used in the combat zone (e.g., sterile cotton gauze) and it might be prudent to evaluate them for contamination, as well.

Further environmental studies are also needed, especially in areas of Afghanistan associated with the highest concentration of injuries with IFIs. These studies should focus on the vegetative areas that might likely harbor the fungal pathogens. In addition, studies of the dirt, for the detection of possible mycobacteria, should be considered if increasing rates of mycobacteria infections are noted. However, such studies might not be feasible because of limited resources and capabilities in theater and U.S. Customs restrictions to import dirt.

Given the screening of the hemostatic field dressings by the manufacture, the goal of the study was not to compare lots of the field dressings before and during deployment but to only compare contamination in general before and during the stresses of deployment. Lot-specific testing should be pursued if there appears to be a single pathogen species infecting wounded warriors.

Conclusions
This pilot study suggests that hemostatic field dressings are free from contamination by bacteria, fungi, or mycobacteria, even after being subjected to the extreme conditions encountered by warfighters in Afghanistan as long as there is no breach in the package. Further research is needed, however, for sources of fungi and mycobacteria, which lead to infections in our wounded warriors.

Utilization of Bedside Urogenital Ultrasound in an Austere Combat Setting: Enterovesicular Fistula Case Report

Military Medicine
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March 2013

Abstract

The role of bedside ultrasound by physicians with advanced ultrasound training, such as emergency medicine providers, has been clearly established in the austere setting of combat medicine. This highly mobile, noninvasive, and versatile imaging modality has a role in evaluating battle- and nonbattle-related presentations. This case report describes a U.S. Marine reporting to an austere medical facility with the chief complaint of abdominal pain. An ultrasound of the patient's urinary tract revealed abnormalities that suggested right bladder wall thickening and an echo dense layer of sediment as the potential source of his discomfort. These findings supported patient transfer to a higher echelon of care. Further diagnostic testing revealed Crohn's disease with an associated enterovesicular fistula.

Introduction

Abdominal pain accounts for 6.5% of chief complaints presenting to the emergency department, and can be a diagnostic challenge for emergency physicians. Despite advances in diagnostic radiology, 21% of patients still receive the diagnosis of undifferentiated abdominal pain. In combat environments, the complaint of abdominal pain becomes an even greater challenge attributable to the lack of diagnostic modalities. However, the utilization of portable ultrasonography by a credentialed provider has been shown to be helpful in isolated settings such as the international space station or forward-deployed medical facilities.

The increased availability of ultrasonography in austere environments has shown to be effective in narrowing the differential of abdominal pain, aiding in patient diagnosis, and providing supportive information to justify transfer to a higher level of care. When used by a skilled provider, ultrasound provides a noninvasive and repeatable modality that can visualize the urogenital system. The kidneys, ureters, and bladder can be
visualized to evaluate for hydronephrosis, urinary tract calculi, masses, and infectious or inflammatory conditions of the bladder. This case report presents a U.S. Marine who was evaluated at a Role 2 medical facility in Helmand Province, Afghanistan with subacute abdominal pain. Bedside urogenital ultrasound provided images consistent with abnormal bladder pathology and thus supported the need to expedite this patient's transfer to a higher echelon of care, where eventually the diagnosis of Crohn's disease (CD) with enterovesicuclar fistula was established.

Case Report

A 26-year-old male U.S. Marine presented to a Role 2 medical facility, Shock Trauma Platoon/Forward Resuscitative Surgical System (STP/FRSS), with subacute abdominal pain. He complained of 3 weeks of intermittent, right lower quadrant abdominal pain that worsened the morning of presentation. He reported associated right testicular pain, subjective fevers, and dysuria that led to several near-syncopal episodes. The abdominal pain occurred immediately after every meal and would last for 3 to 4 minutes and then subside. In addition, he reported having blood in his stool on at least three occasions during this period and one episode of blood in his urine. Before presentation at the STP, the patient was seen by his battalion medical officer and was diagnosed with urethritis. He was prescribed a course of antibiotics that did not alleviate his symptoms. He denied any testicular trauma, history of sexually transmitted disease, or abdominal surgeries. Patient did endorse an unintentional weight loss of 15 to 20 lb over a period of 6 months. His medical history was significant for an episode of testicular torsion at the age of 2 and an episode of nephrolithiasis 3 months before. He was taking doxycycline for malaria prophylaxis. His social history and family history were unremarkable. He had no known drug allergies.

Physical Examination

His vital signs were the following: oral temperature of 99.2°F, blood pressure of 123/76, heart rate of 99, and O2 saturation of 99% on room air. Examination revealed a well- appearing, physically fit white male in moderate distress secondary to abdominal pain. He was oriented to person, place, and time. Head, eyes, ear, nose, and throat examinations were all normal. The respiratory examination was normal with clear bilateral breath sounds. Examination of the heart showed a regular rate with no rubs, murmurs, or gallops. Femoral and radial pulses were normal bilaterally. Inspection of the abdomen revealed normal contour and lack of surgical scars; no abnormal pulsations, distension, masses, or ecchymosis were noted. Auscultation of bowel sounds was normal in all four quadrants. The patient had no tenderness, guarding, rebound, or masses during palpation of the upper quadrants of the abdomen. Diffuse tenderness to palpation in the lower quadrants was noted, right greater than that in the left. The patient had no guarding, rebound tenderness, or masses that were appreciated in the lower quadrants. The genitourinary examination was normal. No blood was seen at the urethral meatus. The testes were palpated and no abnormal masses or varicosities were felt. Prehn's sign was negative and the cremasteric reflex was present. No hernias were palpated during the examination. Bilateral inguinal lymphadenopathy was appreciated. There was no costovertebral angle tenderness. Rectal examination revealed no frank blood, hemorrhoids, or fissures. Stool was present in vault. Rectal tone was normal and the prostate was normal in size and texture and was not painful on examination. No rashes, petechiae, or ecchymosis were observed on examination of the skin.

Clinical Course
The patient's vital signs and physical examination findings were noted as above. To further differentiate his abdominal pain, additional testing was obtained, which included a complete blood count, comprehensive metabolic panel, stool guaiac, and a dipstick urinalysis. Complete blood count showed a white blood cell count of 8.5 × 10^3/uL, with a mildly elevated granulocyte percentage of 82%, hemoglobin and hematocrit of 13.5 g/dL and 43.7%, respectively, and an elevated platelet count of 624 × 10^3/uL. Comprehensive metabolic panel was normal, and the stool guaiac test was negative for occult blood. The patient's urine was grossly cloudy and dipstick urinalysis revealed large amounts of leukocyte esterase, positive for nitrate, and a large amount of nonhemolyzed blood. Because of the patient's history of nephrolithiasis coupled with the pyuria and hematuria, a bedside kidney and bladder ultrasound study was performed. A residency trained emergency medicine physician performed the study. Urogenital ultrasound training is a standard part of curriculum in emergency medicine residencies, and this utilization of bedside ultrasound is within the scope of practice for emergency medicine physicians. Ultrasonography revealed grossly normal-appearing kidney parenchyma with mild hydronephrosis on dynamic bedside imaging (Figs. 1 and 2). The coronal and sagittal scans of the bladder showed echo dense sediment that layered at the base of the bladder (Figs. 3 and 4). Based on the patient's laboratory and ultrasound findings, he was started on a course of ciprofloxacin, 500 mg twice a day, and flagyl, 500 mg three times a day, each for 10 days. Oxycodone/acetaminophen 5 mg/325 mg was also prescribed as needed for pain. The patient's presentation of pyuria, hematuria with unilateral pain, and bedside ultrasound images suggestive of urogenital pathology performed by a credentialed provider warranted medical evacuation to a higher level of care. Thus, he was evacuated to the regional Role 3 medical facility and then on to Landstuhl Regional Medical Center (LRMC). A CT scan at LRMC noted intravesicular air, layering debris, and focal bladder wall thickening in the right posterolateral region (Fig. 5). The patient underwent colonoscopy, which noted bowel wall changes consistent with CD (Fig. 6). Laparoscopy was performed to evaluate bladder wall hypertrophy. Pathology revealed inflammatory changes consistent with an enterovesicular fistula secondary to inflammatory bowel disease. These findings correlated with the initial ultrasound images obtained in the austere setting of the STP/FRSS.

Discussion

The use of ultrasound in the modern combat setting has been well described. In addition to applications in trauma, this imaging modality can be used to increase the efficiency of procedures and the evaluation of abdominal pain. One of the specific techniques for evaluating acute abdominal pain is ultrasound of the urogenital system. The specific indication for portable ultrasound has been well described and used since the late 1960s. Ultrasonography of the urogenital system has proved to aid in the screening and eventual diagnosis of bladder cancers, identification of urinary tract calculi, and in the evaluation of cystitis. When using ultrasound to evaluate the bladder and kidneys, expected findings of a normal bladder scan should show that a normal full bladder is a fully transonic, empty-looking area with well-defined smooth contours. The transverse ultrasound of a normal bladder should show flattening of lateral walls. Ultrasound of normal kidneys should have an ovoid shape in longitudinal section and a near-circular contour in transverse section.

Any alterations of these shapes should be regarded with suspicion concerning specific pathology. Ultrasound findings of hydronephrosis can be found well described in the medical literature since the 1970s. Hydronephrosis is classically described in three different grades ranging from mild hydronephrosis with mild dilation of the renal pelvis and calyces to severe hydronephrosis with marked dilation and almost total absence of normal March 2013
renal tissue. In the patient with pelvic trauma, bladder rupture should be suspected when the urinary bladder is contracted or an irregular appearing bladder dome is seen. Cystitis can lead to ultrasonographic findings of bladder wall thickening, intravesicular or intramural air, and a fluid–fluid interface from sediment that arises from inflammation, infection, or hemorrhage. Bladder or ureteral stones will often attenuate the ultrasound beam leading to an acoustic shadow not unlike the appearance of gallstones.

In this patient, ultrasound images showed abnormalities of intravesicular sediment, suggesting infection. This patient's constitutional symptoms of subacute abdominal pain, weight loss, and bloody stools suggested another diagnosis aside from simply cystitis. In the young active duty population, it is important to consider CD in patients with bloody stool and weight loss. CD is largely diagnosed in patients 15 to 30 years of age. Fistula formation has been reported in as many as 35% of patients who suffer form CD. Enterovesicular fistulas are an uncommon form of bladder pathology, and only found in 2 to 8% of patients with CD. These fistulas can lead to ultrasound findings of focal bladder wall abnormality and diffuse bladder wall thickening related to infection. The ultrasound images of the patient in this case report showed cystitis in addition to enterovesicular fistula. The CT, laparoscopy, and colonoscopy performed at a higher echelon of care ultimately confirmed a diagnosis of CD.

This case shows the utility of portable ultrasound for the evaluation of abdominal pain in the austere environment when performed by a skilled and credentialed provider with ultrasound training. Furthermore, it shows ultrasound's ability to detect abnormalities of the urogenital system including condition of the bladder, an evaluation that falls within the scope of practice of emergency medicine providers trained in ultrasound. In addition, skilled, credentialed providers have the advantage of having scanned multiple patients and thus have the ability to differentiate between normal and abnormal findings. It should, therefore, be stressed that ultrasound should not be used as a means for making medical decisions and dispositions unless one is specifically credentialed to perform a specific ultrasound examination. Ultrasound should be used as an aid to gather more information about a patient's clinical presentation. This patient's abnormal portable ultrasonography findings of the urogenital system gave additional necessary information that supported the immediate transfer of this patient to a higher level of care and aided in his early diagnosis and treatment of CD with enterovesicular fistula.

**Isolation of Leclercia adecarboxylata From an Infected War Wound in an Immune Competent Patient**

Military Medicine
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March 2013

Abstract
We describe the case of a wounded soldier with a gluteus infection from which Leclercia adecarboxylata was cultured. To our knowledge, this is only the second report of this unusual pathogen being isolated from an abscess and the first report of L. adecarboxylata as the etiology of a war wound infection.

Case Study

A 25-year-old soldier was admitted to our orthopedic surgery service for planned excision of right leg heterotrophic ossification (HO). Seven months earlier, while on dismounted patrol in Afghanistan, he was severely wounded by an improvised explosive device and sustained a right open elbow fracture; traumatic left below the knee amputation; left index finger amputation; and soft tissue trauma of the abdomen, perineum, and right buttock. He had a prolonged hospital course after his injury and underwent multiple surgical procedures including colectomy and revision of his left below the knee amputation, was fitted for prosthesis, and eventually discharged for outpatient physical rehabilitation. However, subsequent HO formation impinged on his right sciatic nerve causing both neuropathy and limited right hip range of motion, necessitating his readmission. Intraoperatively, the patient was found to have not only HO but also a focal collection of purulence and necrosis in the right buttock as well as retained foreign matter (boot eyelet and leather), which was debrided. Gram stain of the pus and necrotic tissue showed gram-negative bacteria, which produced a homogeneous (i.e., monomicrobial) culture, and were subsequently identified as Leclercia adecarboxylata by automated testing (BD Phoenix Automated Microbiology System, Becton Dickinson, Franklin Lakes, NJ). The identity of the bacterium was confirmed by 16s ribosomal sequencing in which the 16s rRNA gene was first amplified by polymerase chain reaction using a universal 16s rRNA primer pair. Amplicons were then sequenced (Macrogen, Rockville, MD) and assembled (DNASTar, Madison, WI) in triplicate from four different DNA preparations. Escherichia coli ATCC 35354, Enterobacter cloacae ATCC 13047, and Enterobacter aerogenes ATCC 13048 were used as controls. The isolate showed in vitro resistance to amoxicillin-clavulanate, ampicillin-sulbactam, and cefazolin but was otherwise susceptible to antibiotics tested including fluoroquinolones. Debridement of deeper gluteus tissue 11 days later grew Pseudomonas aeruginosa, which was also susceptible to fluoroquinolone antibiotics. The patient was subsequently discharged on a 10-day course of oral ciprofloxacin, 750 mg twice daily, with full recovery.

Extremity blast trauma is a signature injury associated with the conflicts in Iraq and Afghanistan, which creates a milieu that predisposes to infection. Resultant to the blast from an explosive device, environmental and skin flora is inoculated along with foreign material deep into muscle and bone, which may become necrotic and ischemic. The types of pathogens causing these infections have been described in detail previously; but early on, they typically consist of antibiotic-susceptible environmental and skin flora that, with prolonged patient hospitalizations and exposure to antibiotics, becomes increasingly drug resistant, either by selective pressure or by nosocomial acquisition. In our experience, the organisms most commonly isolated from war wound infections include Staphylococcus aureus, P. aeruginosa, Acinetobacter baumannii-calcoaceticus, and members of the Enterobacteriaceae (especially, Enterobacter sp., Klebsiella sp., and Escherichia coli).

First described by Leclerc in 1962, L. adecarboxylata (formerly Escherichia adecarboxylata) is a motile gram-negative member of the family Enterobacteriaceae that is phenotypically similar to Escherichia coli. It is part of the gut flora of some animals and has also been isolated from...
such diverse sources as the blood of an asymptomatic platelet donor, sludge contaminated soil, the rhizosphere of wild legumes, egg shells, and the mouths of sharks. Despite its apparent ubiquity, L. adecarboxylata is very rarely reported as a human pathogen (Table I). However, the paucity of case reports may derive in part from the inability of automated diagnostic systems to reliably distinguish L. adecarboxylata from other closely related genera and misidentification of isolates as Escherichia or Enterobacter species. When infection caused by L. adecarboxylata is reported, it is usually in the setting of polymicrobial infections and immune deficiency. A PubMed literature review using the search term “Leclercia adecarboxylata” (http://www.ncbi.nlm.nih.gov/pubmed; accessed August 21, 2012) yielded 26 case reports (32 patients) of infection with L. adecarboxylata. Only nine prior case reports describe the isolation of L. adecarboxylata from wounds (two of which occurred in patients with poorly controlled diabetes, one in a patient with a chemical burn, and one in a patient who sustained trauma from a motor vehicle accident), and only one prior case report describes the isolation of L. adecarboxylata from an abscess. In that report, the speculated source of the infection was a public swimming pool, and the portal of entry was an inadvertent nick in the foot during a pedicure 4 weeks previously. Our case report is noteworthy not only because it describes isolation of this unlikely bacterium from an abscess in an immune competent patient but also because, to our knowledge, it is the first description of L. adecarboxylata as the etiology of a war wound infection. There is much that still needs to be elucidated about this unusual pathogen, including its correlations with immune suppression and polymicrobial infections. However, as the ability of diagnostic assays to distinguish L. adecarboxylata from other closely related Enterobacteriaceae improves, it is likely that this bacterium will be increasingly recognized as a potential human pathogen.

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Efficacy of Tourniquets Exposed to the Afghanistan Combat Environment Stored in Individual First Aid Kits Versus on the Exterior of Plate Carriers

Military Medicine
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March 2013

Abstract

Between February and May 2010, 1st Battalion, 6th Marines reported a 10% (10/92) breakage rate for tourniquets. One theory suggested was that tourniquets were weakened by exposure to the Afghan environment. Our study was designed to compare three groups of Afghanistan-exposed tourniquets to unexposed tourniquets. The three experimental arms were: (1) Afghan-exposed tourniquets worn on the plate carrier, (2) Afghan-exposed tourniquets carried in the Individual First Aid Kit (IFAK) and wrapped in manufacturer plastic wrapping, and (3) Afghan-exposed tourniquets carried in the IFAK with the manufacturer plastic wrapping removed. The outcome measures of this study were efficacy, breakage, and number of turns required to successfully stop the distal pulse. Tourniquets worn on the plate carrier had an efficacy of 57%, which was significantly lower than the control efficacy rate of 95.2%. When compared to the control arm, there were no significant differences in efficacy between the
tourniquets stored in the IFAK with or without manufacturing packaging. No control tourniquets or tourniquets stored in IFAKs broke; however, 46 (12%) of the plate carrier-exposed tourniquets did break. No statistically significant differences were found between the four groups with regard to the median number of turns required to stop the distal pulse.

Background

It is estimated that 7 in 100 combat deaths could be prevented by correctly applied tourniquets. Data from recent conflicts involving U.S. military personnel confirm the continued importance of hemorrhage control. Hemorrhage from injured limbs is a leading cause of battlefield death, and emergency tourniquet use during the current war has improved survival rates for patients enduring major limb trauma. All military personnel in theater carry tourniquets, and tourniquets are commonplace on the battlefield in Afghanistan with medical and nonmedical personnel. The U.S. military's primary tourniquet is the Combat Application Tourniquet (CAT). Each Marine and Corpsman is issued two CATs in their Individual First Aid Kit (IFAK) before deployment in support of Operation Enduring Freedom. The CAT is a self-adhering band that wraps around the extremity; a windlass is turned to constrict an inner strap, which slides within the band to tighten the tourniquet (Fig. 1).

A 14% (7/49) CAT breakage rate was reported by Marine Combat Team 3 in support of Operation Enduring Freedom between May and October 2009. During an internal review conducted between February and May 2010, 1st Battalion, 6th Marines reported a 10% (10/92) breakage rate for CATs during application. The review noted that 9 out of 10 breakages occurred in a single company whose protocol was to wear tourniquets on the outside of their plate carriers. Lower extremity efficacy rates for CATs directly exposed to the Afghanistan environment have been reported as low as 59%, compared with a 91% efficacy rate for unexposed CATs. Several theories have been considered to determine why the breakages occurred, including the possibility that tourniquets are weakened by exposure to hostile environments or excessive force during application. Although published results suggest that direct environmental exposure may increase susceptibility of tourniquets to breakage, further investigation is warranted to determine whether storing tourniquets in IFAKs preserves their efficacy.

The primary objective of this study was to compare the effectiveness of three groups of CATs exposed to the Afghanistan environment: (1) those worn on plate carriers, (2) those stored in IFAKs without manufacturer packaging, and (3) those stored in IFAKs with manufacturer packaging. A secondary end point was to determine the average number of turns, up to 4, of the tourniquet windlass needed to stop the distal pulse.

Methods

The protocol for this study was approved by our institutional review board and was conducted in compliance with all federal regulations governing the protection of human subjects in research.

Our study was designed to compare three groups of Afghanistan-exposed CATs to unexposed CATs on healthy volunteers in a controlled environment. The three experimental arms were: (1) Afghan-exposed CATs worn on the plate carrier vest, (2) Afghan-exposed CATs carried in the IFAK and wrapped in manufacturer plastic wrapping, and (3) Afghan-exposed CATs carried in the IFAK with the manufacturer plastic wrapping
removed. The outcome measures of this study were efficacy, breakage, and number of turns required to successfully stop the distal pulse for these three experimental groups and a control group.

We numbered 1,600 generation-6 CATs, manufactured between 90 and 120 days before deployment, and randomized the CATs to four study arms, each of which received 400 tourniquets. Eight hundred healthy volunteers from the same Marine Infantry Battalion were enrolled and assigned to one of the four study arms. Volunteer subjects provided informed written consent. In the three experimental groups, each volunteer was randomly issued two CATs. Per protocol, the experimental tourniquets were not to be used for treating combat injuries or for training purposes. Three arm-specific instructional periods were given on proper carrying of the tourniquets in Afghanistan. The date of landing in Afghanistan on deployment and departing Afghanistan on redeployment were recorded for each participant. Each month, an associate investigator inspected each volunteer's tourniquets for location and compliance with the study protocol. The 400 control tourniquets were stored in the manufacturer plastic wrapping in the locked, climate-controlled, Battalion Headquarters at Camp Lejeune, North Carolina.

Subjects were excluded if they had a history of clotting disorder, absence of a dorsalis pedis pulse, deep vein thrombosis, diabetes mellitus, hypertension requiring treatment, or other vascular disorder. Of 800 original participants, 23 participants and their tourniquets were lost to combat injury or death, 3 were excluded after they used their tourniquets to treat wounded coalition forces, and 1 was excluded when a participant lost his tourniquets on patrol. The final study group consisted of 773 male active duty Marines and 1,546 tourniquets.

Following the 7-month deployment, each volunteer's two CATs were randomly assigned to one of the participant's thighs. Before CAT application, the subject's age, height, weight, heart rate, blood pressure, and thigh circumference were noted. Doppler signal of the distal dorsalis pedis pulse was detected, and the location was marked on the skin. An investigator applied the CAT over the Desert Marine Corps Camouflage Utility Uniform, parallel to and approximately 2 cm inferior to the inguinal ligament. After ensuring a tight fit of the tourniquet, the windlass was turned by the participant until either: the CAT successfully eliminated the dorsalis pedis pulse for 30 seconds, the CAT broke in a way that prevented further turns, pain from the CAT became unbearable, or four turns had been completed without eliminating the distal pulse. Once the first CAT was tested, the procedure was completed on the opposite leg with the second CAT. To ensure consistency, the same evaluator conducted all CAT testing.

Breakage was defined as any part of the tourniquet breaking during application of the CAT over the Desert Marine Corps Camouflage Utility Uniform. If a CAT broke, we recorded the specific area of breakage and the number of turns completed before breakage. Efficacy was defined as successful elimination of the dorsalis pedis pulse for at least 30 seconds without causing unbearable pain, regardless of tourniquet breakage. The distal pulse was measured using a Doppler stethoscope (Huntleigh Healthcare, Eatontown, New Jersey). One turn was defined as a 180° arc, as described by the displacement of full supination or pronation of the wrist without regripping, plus an additional 90° to fasten the windlass into the clip. We recorded the number of turns, up to a maximum of four, required to stop the distal pulse for 30 seconds.

Results
Study group characteristics are shown in Table I. Thigh circumferences ranged from 49 to 77 cm (1–99.9 percentile of U.S. soldiers). An independent sample t-test, using a 99.9% confidence level, was used to compare each study characteristic across the four groups. There were no statistically significant differences in physical characteristics between the four groups.

The tourniquet mean age at the time of testing was 11.3 ± 0.46 months. The mean time that each tourniquet was exposed to the Afghan environment was 212 ± 12 days for plate carrier, 211 ± 11 days for IFAK with manufacturer packaging, and 212 days ± 12 for IFAK without manufacturer packaging. Tourniquets worn on the plate carrier had an efficacy of 57%, which was significantly lower than the control efficacy rate of 95.2% (Z = 3.3; p < 0.0005). When compared to the control arm, there were no significant differences in efficacy between the tourniquets stored in the IFAK with manufacturing packaging and those stored in the IFAK without manufacturer packaging (Z = 3.3; p < 0.0005). No control tourniquets or tourniquets stored in IFAKs broke; however, 46 (12%) of the plate carrier–exposed tourniquets did break (Z = 3.3, p < 0.0005). Of the 46 tourniquets that broke, 40 broke at the stabilization plate slot and 6 broke at the friction adaptor. None of the 46 tourniquets that broke were able to stop the distal pulse.

Of the 1,320 CATs that were efficacious, 9% required one turn, 26% required two turns, 60% required three turns, and 5% required four turns to successfully eliminate the pedal pulse (Table II). No statistically significant differences were found between the four groups with regard to the median number of turns required to stop the distal pulse. The group medians were as follows: control median 3.0 (mean 2.6 ± 0.747), plate carrier median 3.0 (mean 2.7 ± 0.635), IFAK with manufacturer packaging median 3.0 (mean 2.6 ± 0.729), and IFAK without manufacturer packaging median 3.0 (mean 2.6 ± 0.741).

Discussion

Currently, the CAT manufacturer recommends keeping the tourniquet in the plastic packaging until needed to protect the tourniquet from the elements. However, to prevent critical delays in tourniquet application, many units prefer to remove the manufacturer packaging before storage on the plate carrier or in the IFAK. This study was primarily designed to evaluate the effectiveness and breakage rates of tourniquets directly exposed to the combat environment and those stored in IFAKs with and without manufacturer packaging. The results indicate that, in the controlled testing environment, CATs directly exposed to the Afghan environment broke more often and were less efficacious at stopping the distal pulse than unexposed CATs. We found no reduction in the efficacy of CATs exposed to the Afghan environment and stored in IFAKs, with and without manufacturer packaging. Moreover, our results support previous reports that most CATs require 3 turns to be efficacious.

Although occlusive plethysmography has been reported to be more accurate than Doppler auscultation to detect distal blood flow, we used Doppler auscultation because it is the most accepted method to determine the presence or absence of the distal pulse. The 2010 Tourniquet Summit at Quantico, Virginia, reached consensus that testing should be performed by Doppler auscultation, and a review of the current tourniquet literature reveals Doppler as the primary method for testing efficacy.
Four windlass turns was chosen as the upper limit before study implementation because the first author's unpublished data indicated that more than four turns increases the risk of tourniquet breakage. Newer data indicate that the turn limit may be closer to six before breakage is common. The study had several procedural limitations. Tourniquets were only applied to the lower limb. As limb circumference increases, the percentage of tourniquet pressure reflected in the underlying soft tissues varies inversely. Hence, cessation of arterial flow in the upper limb is easier to achieve and would have a higher efficacy rate than the lower extremity. However, 68% of injuries requiring a tourniquet occur in the lower limbs. The study was also limited by investigators and participants not being blinded to the type of tourniquet (plate carrier, IFAK with or without manufacturer packaging, control) that was used on each leg. However, the lack of blinding is unlikely to affect our objective end points of efficacy and breakage. The results of our study can be generalized to a 7-month deployment to Afghanistan and may not extrapolate to longer deployments or different theaters of operation.

Conclusions

The results of our study indicate that exposing tourniquets directly to the Afghan environment decreases tourniquet efficacy and increases breakage rates. We recommend that commanding officers ensure that tourniquets are not worn externally on plate carriers or on other gear which would decrease their efficacy. There was no decreased efficacy of the CATs exposed to the Afghan environment stored in IFAKs with or without manufacturer packaging. We recommend that the Commanding Officer ensure the storage of CATs in IFAKs. Although no differences were observed between tourniquets stored in IFAKs with and IFAKs without manufacturer packaging, the Commanding Officer should carefully weigh the advantage of quickly applying the unwrapped tourniquet versus not following the manufacturer recommendation of keeping the tourniquet sealed until use. Service members should be trained that most CATs may routinely require three turns to be effective. Further investigation is warranted to evaluate the maximum number of turns that can be applied to CATs without increasing breakage rates and the exact variables that increase the risk for failure.

Family Presence during Cardiac Resuscitation

New England Journal of Medicine
James Downar, M.D., C.M., M.H.Sc., Patricia A. Kritek, M.D.
14 March 2013

Case Vignette

Roberta is a 72-year-old woman with hypertension and chronic obstructive pulmonary disease who has smoked for the past 50 years. She is admitted to the inpatient medical service after 3 days of progressively worsening fever, chills, and productive cough. On presentation to the emergency department, her temperature is 38.4°C (101.2°F), her heart rate is 110 beats per minute, and her blood pressure is 105/62 mm Hg.
The respiratory rate is 26 breaths per minute, and the oxygen saturation while she is breathing ambient air is 86%. Chest radiography reveals an infiltrate at the right lung base consistent with pneumonia. She receives ceftriaxone and azithromycin, an intravenous saline solution, and supplemental oxygen through a nasal cannula. By the time she arrives at the inpatient unit, her heart rate has slowed to 86 beats per minute, the respiratory rate is 20 breaths per minute, and the oxygen saturation is 96% while she is breathing 4 liters of supplemental oxygen. As her attending physician, you confirm with the patient that she wants to receive aggressive medical therapies, including cardiopulmonary resuscitation, if her medical condition deteriorates.

The following morning, Roberta's nurse notices that the pulse-oximetry readings have declined abruptly to 70%. When she enters Roberta's room, the nurse is unable to arouse the patient in response to verbal stimulus or sternal rub. She cannot detect a radial or carotid pulse. She calls loudly for help and activates the cardiac-arrest alert system. Chest compressions are initiated, and within 60 seconds the medical response team has arrived. At this moment, the patient's husband and two children enter the inpatient unit. Verifying that the code team has sufficient personnel for the moment, you step out of the patient's room and inform the family that Roberta's condition has deteriorated rapidly and that she is currently receiving cardiopulmonary resuscitation.

Treatment Options

After conveying this information to the family, you consider whether to ask the family members to remain with a social worker in the family waiting room, where they will be given frequent clinical updates from the care team, or to invite the family into Roberta's room to observe the resuscitation. Which one of these approaches to the broader issue do you find appropriate? Base your choice on the published literature, your own experience, and other sources of information.

To aid in your decision making, each of these approaches is defended in the following short essays by experts in the field. Given your knowledge of the patient and the points made by the experts, which option would you choose? Make your choice and offer your comments at NEJM.org.

Option 1: Recommend against Family Presence during Resuscitation
Option 2: Recommend Family Presence during Resuscitation

Option 1

Recommend against Family Presence during Resuscitation

James Downar, M.D., C.M., M.H.Sc.

I do not routinely invite family members to be present during resuscitations. My opposition stems from personal experience as a participant in resuscitation teams, when the presence of family members has interfered with the resuscitation efforts. I am concerned that family presence
during resuscitation may increase the risk of death for the patient and may also have physical, psychological, or legal repercussions for members of the resuscitation team. Most of all, I am worried about the psychological trauma to a family member witnessing the resuscitation efforts.

At first glance, the study by Jabre et al., which is reported elsewhere in this issue of the Journal, 1 seems to address these concerns. In a cluster-randomized, controlled trial of family presence during resuscitation in a home setting, family members who were invited by emergency medical services (EMS) personnel to witness resuscitation efforts had lower rates of post-traumatic stress disorder (PTSD)–related symptoms than did controls who were not invited. There were no significant between-group differences in the level of emotional distress in the medical team or in the outcomes of resuscitation, and there were no medicolegal claims in either group.

I hesitate to apply these findings to inpatient resuscitations because cardiac arrests that occur at home are different in that family members actually “invite” EMS to be present for the resuscitation, rather than the reverse. In the study by Jabre et al., all the cardiac arrests took place at home, and 73% were witnessed (presumably by family members). Moreover, almost half the family members in the control group witnessed cardiopulmonary resuscitation (CPR), and 20% actually performed CPR on their loved one before the arrival of EMS. In contrast, most inpatient cardiac arrests are discovered by nurses who then call for the resuscitation team to respond, and family members learn of the event only once the resuscitation is ongoing.

Before generalizing the results of the study by Jabre et al. to the inpatient setting, we need to know more about the mechanisms of harm and benefit that apply when family members are present during resuscitation efforts. Do family members benefit from being present at the resuscitation, or is family presence during resuscitation actually a harm that is mitigated by the presence of a resuscitation team member who provides support during and after the resuscitation? Social supports are known to protect against the development of PTSD,2 and they are a feature in many studies of family presence during resuscitation in the emergency department and pediatric setting (as well as in the study by Jabre et al.). But these social supports are not usually available in the case of inpatient arrests in adults, and family members who are present could experience severe psychological trauma if they are not given adequate support. Inpatient resuscitations are also more likely to feature interventions that cause visible bleeding, such as the insertion of a central venous catheter, and witnessing such interventions may be particularly traumatic to family members.

We must also remember that not all people react to a given psychological trauma in the same way. In the study by Jabre et al., family members who witnessed CPR were 11% less likely than controls to have symptoms of depression, but all five relatives (1%) who attempted suicide during the follow-up period had witnessed CPR. This suggests that there may be a subgroup of the population that is at risk for a severe adverse reaction to witnessing a resuscitation. We need to be careful whom we invite, since some persons may have a predisposition to PTSD after a traumatic event.4 At the time of the event we would have no way to predict which persons are most at risk for PTSD. The results of the study by Jabre et al. should prompt further investigation into the effects of family presence during resuscitation in the inpatient hospital setting. But until these investigations are complete, I will not routinely invite family members to be present during resuscitation efforts.

Option 2
Recommend Family Presence during Resuscitation

Patricia A. Kritek, M.D.

Although incorporating family presence into resuscitation events can be challenging, Roberta's family deserves the opportunity to be in the room in what may be the last minutes of her life. Small observational studies in the 1990s raised concerns that watching a loved one undergo CPR might result in immediate distress and lingering psychological impact. More recent studies, including the large, randomized, controlled trial reported in this issue of the Journal, show the opposite; in the study by Jabre et al., relatives who did not witness resuscitation efforts were more likely to have anxiety, depression, and PTSD-related symptoms afterwards.

We must provide guidance, explanation, and support to family members who decide to remain in the room during resuscitation efforts. Patients and families often express a desire to “do everything” but do not have an appreciation of what that really means. CPR and defibrillation can be brutal both to perform and to watch. It is not appropriate to invite family members into a patient's room unless the resources are available to have a family liaison present whose role is to guide them through the process as well as to counsel them about the outcome, particularly if the resuscitation is not successful. For some families, observing resuscitation efforts may help clarify the goals of care, reinforcing that what is happening is “too much.” Being in the room during an unsuccessful resuscitation effort may also help provide closure for the family by showing that everyone tried as hard as possible to save their loved one's life. Perhaps most important, family presence can allow for a final goodbye by a spouse, sibling, adult child, or parent who can't fathom being separated at the moment of death.

Many providers have expressed concern that the presence of family members in the room will alter the performance of the resuscitation team. Although early studies suggested that family presence altered decision making, more recent research, including the study by Jabre et al., shows that providers can perform equally well and feel equally comfortable with or without the family present. Having a dedicated liaison as part of the resuscitation team can also help ensure that the family does not impede the function of the team. Implementation of a guideline for family presence, coupled with training of the resuscitation team through simulation, has been shown to improve the comfort and performance of the health care team when family members are observing resuscitation efforts. As with all changes in practice, incorporating family presence into resuscitation will become easier as providers gain experience with the practice.

Keeping relatives out of a patient's room during what may be the last minutes of life can be quite painful for doctors, nurses, and other allied health providers. Part of our job as physicians is to help patients and families establish goals of care, process life-threatening events, and, at times, orchestrate the best death possible. We need to embrace this role to the end, allowing relatives the chance to be with a loved one in the last minutes of life, if that is what they desire.
Loving Gaze: When Family Witness CPR at Home

Medscape
Marlene Busko
14 March 2013

It's a nightmare situation that no one would want to witness: efforts to resuscitate a loved one who has collapsed at home. A new study, however, suggests that close relatives who were specifically invited to witness cardiopulmonary-resuscitation (CPR) efforts on an adult patient with cardiac arrest in the home were much less likely to have posttraumatic stress disorder (PTSD)–related symptoms than those who were not given the choice to be present.

Similarly, family members who actually witnessed the medical team's efforts were also much less likely to have symptoms of PTSD, anxiety, or depression than those did not witness the CPR.

Having a family member in the room did not hinder the resuscitation efforts, increase the stress levels in the health team members, or result in any lawsuit, Dr Patricia Jabre (Hôpital Avicenne, Bobigny, France) and colleagues also report.

The study, a randomized controlled trial of 570 relatives of patients with in-home cardiac arrest in France, is published in the March 13, 2013 issue of the New England Journal of Medicine

Commenting to heartwire, study author Dr Stephen Borron (Texas Tech University Health Sciences Centre, El Paso, Texas) said that "it is difficult to directly extrapolate the results to the US hospital care system, because of differences in training and staffing of the ambulances" and their more intense triage system. "I do think the findings suggest that family presence during CPR in the out-of-hospital setting can be beneficial, but additional studies need to be done to see if it transmits to the prehospital system that we have in the US."

Witnessed CPR, a Contentious Topic

Whether or not family members should watch while an emergency team tries to revive a loved one remains controversial. Some say that inviting a family member into the room will mean that they see their relative undergoing brutal manipulations that could cause lingering psychological trauma or even lead them to lash out at members of the medical team. On the other hand, being present during what is often an unsuccessful resuscitation may help give family members who want to be there a sense of closure by allowing them to see that every effort has been made and allowing them to say goodbye.
The researchers conducted a randomized controlled trial that enrolled relatives of adults with in-home cardiac arrest who received CPR during 2009 through 2011 from 15 prehospital emergency-service units in cities in France. Each unit was equipped with one or more ambulances staffed with at least an ambulance driver, a nurse, and a senior emergency physician.

For each patient, the researchers enrolled a first-degree adult relative—a spouse, parent, child, or sibling, selected in that order. The emergency-medical units were randomly assigned to either specifically offer the relative the opportunity to observe CPR (intervention group) or to follow standard practice regarding family presence (control group). In standard practice, relatives were not routinely offered the opportunity to observe, but they might ask for it and be granted this chance. In the intervention group, a medical team member followed a script to introduce the relative to the resuscitation scene, based on published guidelines.

Ninety days after the resuscitation, psychologists phoned the relatives to ask them to reply to an impact-event-scale telephone survey that evaluated PTSD symptoms (the primary outcome) and another survey that evaluated depression and anxiety.

In the intervention group, 211 of 266 relatives (79%) witnessed the resuscitation compared with 131 of 304 relatives (43%) in the control group. A total of 95 relatives did not complete the questionnaires. Only 20 patients (4%) were alive at 28 days.

In the intention-to-treat population, family members in the control group were much more likely to have PTSD symptoms than those in the intervention group (adjusted odds ratio 1.7, 95%CI 1.2–2.5; p=0.004) as were relatives who did not witness CPR compared with those who did (adjusted OR 1.6, 95% CI 1.1-2.5; p=0.02).

Study Helps Advance the Debate

AHA guidelines offer a "cautious endorsement" that "in the absence of data documenting harm and in light of data suggesting that it may be helpful, offering select family members the opportunity to be present during a resuscitation is reasonable and desirable," Drs Daniel B Kramer and Susan L. Mitchell (Harvard Medical School, Boston, MA) write in an accompanying editorial.

The study helps to advance the debate, they note, since "when offered the choice to witness resuscitative efforts, most relatives opted to do so," which resulted in improved mental-health outcomes without any apparent drawbacks.

"Future studies should aim to improve our understanding of why this choice may reduce the suffering of family members and whether such an approach could be implemented in practice in a safe and cost-effective manner," they conclude.

In-Patient CPR Case
An in-hospital cardiac-arrest case that accompanied the article highlights the importance of having a family liaison and being selective when offering family members the opportunity to be present.

Dr James Downar (University Health Network, Toronto, ON), arguing against family presence for this case, points out that, unlike in the study by Jabre et al, "cardiac arrests that occur at home are different in that family members actually 'invite' emergency medical services to be present for the resuscitation, rather than the reverse." Also, hospitals do not usually have a resuscitation team member to provide social support. It is important to be selective when inviting a relative to watch, he notes.

Similarly, Borron said "We have had limited experience in allowing family members to participate in family resuscitation; it's generally gone well, but we're very selective about when we offer that; it's not done routinely."

Dr Patricia A Kritek (University of Washington Medical Center, Seattle, WA), arguing for family presence, writes that being in the room "may . . . help provide closure" and "perhaps more important . . . can allow for a final goodbye." The study by Jabre et al "shows that providers can perform equally well and feel equally comfortable with or without the family present," she notes. However, like Downer, she writes that it is "not appropriate" to invite family members to witness the resuscitation unless there is a family liaison to explain the process to and counsel family members.

**Physiological Injuries and Surgery**

**Simultaneous Bilateral Anterior Shoulder Fracture Dislocation Following a Seizure: A Case Report**

Military Medicine

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ABSTRACT

Simultaneous, bilateral, anterior dislocations of the glenohumeral joint are rare, most attributable to major trauma. Seizure disorders and electrocution are a common cause of glenohumeral and fracture dislocations although these are most commonly posterior injuries. We present an interesting case report of diagnosis and treatment of an active duty sailor with bilateral anterior shoulder fracture dislocations following a seizure.
INTRODUCTION

Although unilateral dislocations of the shoulder are the most frequently encountered dislocation seen in orthopedics, the bilateral variant is rare. When present, bilateral glenohumeral dislocations more commonly occur in the posterior direction, usually secondary to violent muscle contraction in patients experiencing seizures or electric shock. Simultaneous bilateral anterior dislocations are extremely rare, with the majority attributable to trauma. A review of the literature by Sharma et al. yielded only approximately 30 cases with even fewer cases of fracture dislocations. We report the case of a 28-year-old active duty sailor with bilateral anterior shoulder fracture dislocations sustained during a first-time seizure episode.

CLINICAL CASE

A 28-year-old active duty U.S. Navy male with a past medical history significant only for hypertension presented to the emergency department following a first-time, witnessed, tonic-clonic seizure while aboard his ship. The seizure was attributed to an excessive dose of oral tramadol hydrochloride combined with nortriptyline; a known reported cause of seizures. During evaluation in the emergency department, he reported no recollection of the episode and denied any prior history of similar events. Internal medicine was consulted for evaluation of his seizure. During their examination, the patient complained of fatigue and diffuse cramping pain in his neck, upper back, shoulders, and arms. Radiographic evaluation included a computed tomography (CT) scan of his head and cervical spine, both were normal. At the time of admission, no shoulder images were obtained. The patient was admitted to the internal medicine service for seizure workup.

By hospital day 2, the patient's pain had localized to his shoulders bilaterally. In light of his continued symptoms, bilateral shoulder radiographs were obtained, showing bilateral anterior-inferior glenohumeral fracture dislocations.

A modified transverse U-type incision was utilized to access the shoulder joint, reflecting the posterior deltoid before entering the joint capsule. The greater tuberosity fracture was in two large, yet comminuted pieces representing the footprints of the supraspinatus and infraspinatus tendons with a Hill–Sachs lesion that composed 35% of the posterior humeral head and engaged the glenoid resulting in dislocation with physiologic motion. The supraspinatus and infraspinatus rotator cuff tendons were avulsed off the bone fragments and were incompetent. Because of the large Hill–Sachs and impaction injuries, a combination of frozen allograft humeral head, cancellous allograft chips, osteoinductive putty, and autograft cancellous bone was utilized for restoration of bone stock and subsequent rotator cuff repair.

He later required an arthroscopic subacromial bursectomy, with a mini open hardware removal for prominent screws causing impingement symptoms. The contralateral right shoulder was treated nonoperatively because he maintained a stable, concentric, and well-functioning shoulder following a comprehensive physical therapy program. At 18 months postinjury, both shoulders showed full flexion, abduction, abducted external rotation, and abducted internal rotation without instability findings.

DISCUSSION
Simultaneous bilateral anterior shoulder dislocations are a rare entity, with fracture dislocations even more uncommon. The simultaneous bilateral posterior variant, first described over 100 years ago, is more commonly described. A comprehensive search of the literature produces few cases of simultaneous bilateral anterior fracture dislocations caused by a seizure. The unique aspects of this case are the simultaneous anterior dislocations, causing bilateral greater tuberosity fractures (left greater than right), with one side requiring operative intervention for a displaced greater tuberosity and multiple recurrent dislocations. The cause of his seizure activity was attributed to the combination of tramadol hydrochloride and nortriptyline, lowering the seizure threshold, a known side effect of this medication. Since his initial hospitalization, he has experienced no additional seizure activity and has been seizure-free since this initial episode at age 28.

Typically, in the setting of a seizure, the weak external rotators are overwhelmed by the internal rotators, causing an exaggerated adduction and internal rotation, resulting in posterior dislocation. Anterior dislocations are more commonly the result of trauma, with positioning of the shoulder in extension, abduction, and external rotation during a fall. The resultant impingement of the greater tuberosity on the acromion causes the dislocation. They are typically unilateral as one extremity usually takes the brunt of the force. It is in only about 15% of anterior dislocations that a displaced fracture of the tuberosity occurs. A displaced greater tuberosity fracture almost certainly represents an incompetent rotator cuff, and long-term instability and disability can ensue. This patient had instability because of the fracture pattern and injuries, necessitating an open reduction and fixation with allograft augmentation to provide stability. An increased risk of fracture with glenohumeral dislocations is noted to occur in the setting of advanced age, first time dislocations, and high-energy mechanisms. The combination of these factors makes bilateral anterior shoulder fracture dislocations rare. In this case of a young patient with a low energy mechanism, the severity of the greater tuberosity fracture is quite impressive. It is not known why some dislocations occur anteriorly during seizure activity, since the majority of shoulder dislocations associated with seizures are posterior, though, may be due to the position of the shoulders during the seizure.

Whether the dislocation occurs anterior or posterior, the same initial management principles apply—early reduction and immobilization. Early fixation of this patient's left shoulder was performed in the setting of recurrent instability showing early failure of nonoperative management.

Contributors to the Overall Health of the War Fighter

After 11 years of fighting, U.S. service men and women are struggling with multiple health issues. Musculoskeletal injuries are among the highest percentage of injuries seen in the Veterans Administration hospitals. Other problems include mental health and overall physical health. This article seeks to point out the possible causes of these conditions.
Kraemer and Szivak stated that military physical fitness programs are out of date. They also stated that “Historically, and even today, the focus of conditioning in the military has been on aerobic type endurance training. Part of this arises out of the ease of implementation of such programs and the simplicity of the exercise prescription when training large numbers of soldiers during a physical training period. Additionally, physical training has often been geared toward performance on aerobic components of annual physical fitness tests, rather than on real-world mission requirements.” Service members run long distances in boots and utilities. Some exercise programs consist of push-ups, pull-ups, and abdominal exercises to exhaustion. Some of these programs include exercises day after day with few light days to allow for recovery. Baechle and Earle stated that overuse injuries result from repeated abnormal stress, applied to a tissue by continuous training or training with too little recovery time. Running everyday for long periods at a time with few recovery days and doing multiple rounds of exercises until exhaustion may contribute to musculoskeletal injuries. Kraemer and Szivak also stated that “Sequencing of workouts to limit overreaching and development of overtraining syndromes that end in loss of duty time and injury are paramount to long-term success. Allowing adequate time for rest and recovery and recognizing the negative influences of extreme exercise programs and excessive endurance training will be vital in moving physical training programs into a more modern perspective as used by elite strength-power anaerobic athletes in sports today. Because the war fighter is an elite athlete, it is time that training approaches that are scientifically based are updated within the military to match the functional demands of modern warfare and are given greater credence and value at the command levels.”

Marines carry gear that ranges in weight from 97 to 135 lbs per individual. For some service members, this represents a very arduous task and no doubt contributes to a percentage of the musculoskeletal injuries seen during and after deployment. Aerobic physical fitness programs do not train for strength, and therefore service members may not be building the strength required to carry this gear.

Sleep is often a rare commodity for a majority of service members whether they are stationed stateside or in a combat zone. Service members may not sleep well or sleep is inadequate because of job-related tasks. This creates a problem when the member is required to work the next day. Focusing on job-specific duties is difficult after sleeping poorly over long periods of time. As a consequence of poor quality sleep, the service member may take an energy supplement in an effort to function better at work the next day. Energy drinks are available on most military installations and in combat zones. Some service members even take energy supplements or energy drinks while deployed or at home in an effort to feel stimulated. Of more concern is that service members may take more than the prescribed dosage in an effort to feel more stimulated. After taking the same dosage for a period of time, the stimulatory effects decrease causing the service member to progressively increase the dose to maintain the effect, even when at home after deployment.

Tobacco use in the military is very common. Cigarettes and smokeless tobacco are sold on almost all bases. Cigarette smoking is associated with increases in exercise-related injuries. According to Baechle and Earle, “Smoking, in theory, could have these negative effects such as increased airway resistance due to nicotine-related bronchiole constriction or increased fluid secretion and swelling in the bronchial tree due to the irritation of smoke; and the paralysis of the cilia on the surfaces of the respiratory tract by nicotine, which limits the ability to remove excess fluids and foreign particles, causing debris to accumulate in the respiratory passageways and adding to the difficulty of breathing.” This partnered with the
constant inhalation of smoke from burn pits and dust from dust storms can affect lung capacity making it difficult to do everyday activities. Thus, tobacco use may contribute to the tired feeling that many service members experience, even when they return home.

Alcohol consumption is common in the military. It has a negative effect on athletic performance. Alcohol and cigarette smoking together have an even larger negative impact on physical fitness and overall health.

Individuals may experience anxiety when they are exposed to a different environment or a new group. Although a service member who is having problems within the unit in which he is deployed may be given consideration, a new unit might be less tolerant and even administer a punishment for minor infractions. This would be perceived as an unfriendly environment and would add to the stressors the service member is already experiencing. The transition period from deployment to home is particularly difficult for reservists who return to civilian life at the same time they return from deployment. Not surprisingly, reservists have a higher rate of mental health challenges.

There is a social component to these mental health symptoms. If an individual perceives their environment as unstable or poor, this perception adds to the stressors they may experience during their time in the military. Just as some university students experience homesickness when they go off college, young military members, who are often far from home, may experience the same feelings, even though they may not be deployed. Deployments are not easy. Depending on your military occupational specialty, a deployment can be extremely stressful or extremely boring. Trying to dodge a mortar attack, avoiding driving over an improvised explosive device, attacking the enemy, and dealing with issues at home create a large amount of stress. Sitting behind a desk for 40 hours a week and having access to Internet, telephones, and communication devices can transform problems at home into problems in a combat zone. Although some of these stressors go away when the service member arrives home, other stressors such as reintegrating to a family environment, accepting household chores, and communicating with civilians may substitute for the stressors of combat. With the deployment cycles being what they are, it may be difficult for a service member to switch out of combat mode into an at-home mode and then back into a combat mode so rapidly.

Although individually, these stressors may have little effect on the individual service member, collectively they possibly could have a large impact. Out-of-date physical training programs, poor sleeping habits, overuse of energy drinks, overuse of supplements, unhealthy diets, tobacco use, excessive alcohol consumption, and pushing one's body past its ability to recover clearly have detrimental impacts on the overall health of the war fighter. Efforts to address these modifiable risk factors are essential for maintaining the health and performance of U.S. service members during deployment as well as their overall quality of life once they return home.

BACK TO TOP

**Concurrent Acute Motor and Sensory Axonal Neuropathy and Immune Thrombocytopenic Purpura**
Abstract

Background: Guillain–Barré syndrome (GBS) is a potentially life-threatening autoimmune disease causing demyelination of peripheral nerves. Multiple variants of GBS exist, with acute motor and sensory axonal neuropathy (AMSAN) being the most severe. GBS typically does not occur in the setting of other autoimmune diseases; however, few case reports do exist describing the occurrence. Methods: We describe a patient with acute motor and sensory deficits and thrombocytopenia, ultimately diagnosed with concurrent AMSAN and immune thrombocytopenic purpura (ITP). Results: A 75-year-old woman presented with new onset diplopia and gait instability, however, was found to have a severe thrombocytopenia. Corticosteroids were initiated for ITP and intravenous immunoglobulin for apparent GBS. Nerve conduction studies and her clinical course indicated that she likely had AMSAN. Although her platelet count recovered, her neurologic status remained poor, prompting therapy with plasmapheresis with subsequent mild improvement. Conclusion: A review of the literature revealed eleven previous cases of concurrent GBS and ITP; however, we report the first case of concurrent AMSAN and ITP. Among these cases, trends were noted to include sex, preceding infections, and cranial nerve involvement.

Introduction

Guillain–Barré syndrome (GBS) is a well-described autoimmune disease affecting the peripheral nerves, presenting as an acute neuropathy characterized by muscular weakness, diminished or absent reflexes, and occasionally sensory disturbances. Several variants of the disease exist with the most common form being acute inflammatory demyelinating polyradiculoneuropathy, a T-cell-mediated macrophage-induced demyelination of peripheral nerves. Accounting for less than 5% of all GBS cases, the other variants are characterized by B-cell-mediated macrophage-induced destruction of the nodes of Ranvier, causing complete denervation and block of nerve conduction.1 The most severe variant is acute motor and sensory axonal neuropathy (AMSAN), distinguished by fulminant and rapid onset of quadriparesis within 7 days of onset of symptoms, usually requiring prolonged respiratory support.2 Unlike many other autoimmune diseases, GBS tends to develop in patients without other concurrent autoimmune diseases. Despite the rare occurrence of simultaneous GBS and other autoimmune diseases, we report a patient with rapid onset neurologic dysfunction and impending respiratory failure with a severe thrombocytopenia, ultimately diagnosed with AMSAN and concurrent immune thrombocytopenic purpura (ITP).

Case Report

A 75-year-old Caucasian woman presented to our institution complaining of a 10-day history of upper respiratory symptoms and new onset double vision. She likewise reported malaise and mild gait instability of several days, prompting use of her husband's walker. The patient was afebrile, in no acute distress, with a respiratory rate of 20 and an oxygen saturation of 99% on room air. Her initial examination revealed multiple neurologic...
findings to include a bilateral cranial nerve VI (abducens) palsy, gait instability, areflexia, and decreased vibratory sensation in the lower extremities. No motor deficits or weakness were noted on the initial neurologic examination. A complete blood count showed a normal hematocrit, hemoglobin, and white blood cell count; however, the platelet count was decreased at 20,000/mm. Electrolytes, renal function, thyroid function, and hepatic function studies were all within normal limits. Both the erythrocyte sedimentation rate and the C-reactive protein level were elevated at 73 mm/s and 14.5, respectively. A computed tomography scan of the head was unremarkable without hemorrhage or mass lesion.

She was admitted to the medical intensive care unit because of the presence of severe thrombocytopenia and neurologic dysfunction. Subsequent examinations over the next 12 hours showed progression with development of complete ophthalmoparesis, dysarthria, bilateral upper and lower extremity paresthesias, and diffuse motor weakness. Because of a negative inspiratory force of −10 cm H2O, she was intubated and placed on mechanical ventilation. Based on the clinical findings of progressive neurologic dysfunction and recent respiratory illness, her clinical presentation was consistent with GBS. As a practicing Jehovah's Witness, the patient and her family initially declined both plasmapheresis and intravenous immunoglobulin (IVIG) for religious reasons. Repeat complete blood count continued to show a severe thrombocytopenia with the platelet count decreasing to 9,000/mm. Review of the peripheral smear was consistent with a true thrombocytopenia without platelet clumping, schistocytes, or other abnormal cells. Methylprednisolone 1 g every 24 hours was initiated for treatment of ITP with planned therapy for 5 days. After further discussions with the family about her GBS and treatment options, the patient and family agreed to the use of IVIG, which began at 400 mg/kg/day on hospital day 2. They continued to object to plasmapheresis due to the requirement for albumin that was strictly forbidden because of their religious beliefs.

Test results for Lyme, rapid plasma reagin, human immunodeficiency virus, mycoplasma, West Nile, and botulinism titers were negative, as were titers for neurologic conditions to include myasthenia gravis, Eaton–Lambert, and paraneoplastic and anti-ganglioside antibodies. Result for rapid influenza A enzyme-linked assay was positive. Further test results for Campylobacter jejuni, Helicobacter pylori, cytomegalovirus, and Epstein–Barr virus were also positive, but these studies were acquired after initiation of IVIG. A nerve conduction study (NCS) was performed on hospital day 4 (Fig. 1), showing electrically unexcitable motor and sensory nerves, suggesting a rare variant of GBS termed AMSAN (Tables I). Because of the continued low platelet count of the patient, lumbar puncture was deferred until hospital day 8, at which time it was performed with fluoroscopic guidance. The cerebrospinal fluid revealed an albumin/cytologic disassociation, with a leukocyte count of 1 cell per high-powered field and a protein level of 101 mg/dL, providing further evidence supporting the diagnosis of GBS (Fig. 1).

The platelet count of the patient recovered during the next 2 weeks after a 5-day treatment with IVIG and tapering doses of methylprednisolone. However, there was no improvement in her neurologic function beyond maintaining motor function of her left great toe. Electromyography was performed on hospital day 15, which exhibited complete loss of motor unit stimulation diffusely, consistent with an axonal polyneuropathy, specifically AMSAN. Because of lack of clinical response, she was transferred on hospital day 27 to a nearby military treatment unit with the facility to perform plasmapheresis using hetastarch as a volume expander and avoid using human blood products. She underwent ten plasmapheresis treatments; by hospital day 36, she began to have mild neurologic recovery, regaining some motor function of her left foot, ankle, ocular muscles, and sensation to face and upper extremities. With completion of her plasmapheresis, mild neurologic improvement, and stable platelet count, she was transferred to a long-term acute care facility for further management and rehabilitation.

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Discussion

AMSAN is the most severe variant of GBS as it causes axonal denervation of both the ventral and the dorsal nerve roots and carries the worst recovery prognosis. Like the other GBS variants, AMSAN is a B-cell-mediated macrophage-induced demyelinating disease that affects both the ventral and the dorsal horns, thereby causing both motor and sensory deficits. Cases of AMSAN are rare, and no previous cases have been reported of both AMSAN and another concurrent autoimmune disease. The patient we described had a very typical presentation for AMSAN, but was also noted to have thrombocytopenia, ultimately diagnosed as ITP. Characterized by autoimmune destruction of platelets, ITP is diagnosed by a platelet count less than 100,000/mm3 in the absence of other processes that could lead to a thrombocytopenia. The diagnosis is made by excluding other causes of thrombocytopenia as no diagnostic test exists to confirm ITP.

As with many autoimmune phenomena, it is believed that an immune response prompted by a preceding infection cross-reacts with self-antigens, leading to the development of the autoimmune response damaging the peripheral nerves. The antibodies associated with the variants of GBS are directed against gangliosides specifically found in the makeup of myelin. Gangliosides are also found in platelets; however, those gangliosides do not correlate with the gangliosides found in the nervous system. Instead, ITP is characterized by an autoimmune reaction against the glycoproteins GPIIa-IIIb or GPIb-IX. Although the autoimmune reaction is usually targeting the glycoproteins of platelets in circulation, an autoimmune process also occurs in the bone marrow, causing decreased production of platelets by the megakaryocytes. No overlapping antigen has been discovered between GBS and ITP. Many different inciting infections have been described as causing both GBS and ITP, with the most common being Epstein–Barr virus, cytomegalovirus virus, influenza, Mycoplasma pneumoniae, and human immunodeficiency virus. In particular, C. jejuni has been associated with GBS, whereas H. pylori has been implicated in ITP. In this patient, it was noted during her workup that she had previous upper respiratory symptoms and was found to be influenza A positive, possibly providing the inciting insult that lead to the development of her diseases.

Management of all variants of GBS includes either IVIG or plasmapheresis; treatment is supported by a Cochrane Review showing no difference between the two therapies in improvement of disability after 4 weeks. The American Academy of Neurology practice parameter affirmed the results of the Cochrane Review stating that either IVIG or plasmapheresis were acceptable first-line therapies for GBS. Corticosteroids had no role in treating GBS. Of note, despite the proposed B-cell-mediated pathogenesis of AMSAN and the other GBS variants, rituximab is not part of the recommended first- or second-line therapies in the treatment of acute GBS. Close surveillance is needed in patients with GBS as respiratory depression and failure can occur as a result of diaphragmatic paralysis. A forced vital capacity less than 15 to 20 mL/kg, negative inspiratory force less than −30 cm H2O, and/or maximal expiratory pressure less than 40 cm H2O are considered criteria for elective intubation as the patient is nearing respiratory failure. Immune thrombocytopenia, as recommended by the American Society of Hematology, should be treated with either corticosteroids or IVIG, both as first-line therapies. However, treatment is not always needed as some cases may spontaneously remit. Therapy is generally reserved for patients with platelet counts less than 30,000/mm3.

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GBS and ITP are both relatively common autoimmune conditions, each occurring at a rate of less than five cases per 100,000 patients annually. Autoimmune conditions often appear to occur concurrently, and ITP often occurs with other autoimmune diseases; however, GBS typically does not occur with other autoimmune diseases and the concomitant occurrence of GBS and ITP is extremely rare. Sato et al reported in 2005 a compilation of seven published cases in addition to their case of concurrent GBS and ITP. Our updated review of the literature revealed that eleven previous cases of concurrent GBS and ITP have been reported (Table III). Of these eleven, seven were the acute inflammatory demyelinating polyradiculoneuropathy variants of GBS, three had unreported variants of GBS, and one was the Miller–Fisher variant. No NCS proven AMSAN variants have been reported to occur concurrently with ITP to date, making this potentially the first such case. A review of the cases showed multiple trends among the patients. The majority (73%) were female, had a preceding upper respiratory infection reported (73%), and had early cranial nerve involvement (64%). None of these patients had a preceding gastrointestinal infection, which is the classic preceding infection for GBS. Our patient followed the pattern of patients with concurrent GBS and ITP, as manifested by an elderly female with early cranial nerve involvement, recent upper respiratory infection, and no preceding diarrheal illness. These associations may provide a clue in determining a linking antigen that predisposes to developing concurrent GBS and ITP.

This patient's diagnosis of AMSAN carried a poor prognosis for recovery despite the multiple medical interventions made during her hospitalization to treat the autoimmune process. Our review of the literature supports that this case is unique as the first reported case of a GBS variant, AMSAN, with ITP. The previously reported cases of GBS and ITP exhibited several similarities to our patient, underlining the conclusion that each of these previous patients likely developed cross-reactivity against both platelet and neurogenic glycoproteins following an antecedent infection. This case emphasizes the treatment decisions related to the finding of concurrent GBS and ITP.

BACK TO TOP

It's Not a Tumor, It's a Cataract! Rapid Myopic Progression and Diplopia Secondary to the Formation of an Oil-Drop Cataract

Military Medicine
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Abstract

Oil-drop cataracts are detrimental to patients because of their capacity to cause rapid, and often unexplained, myopic progression with concomitant diplopia complaints. When not properly identified, they can lead to costly and unnecessary workups and referrals. Early diagnosis is important but unfortunately is often difficult because of the subtle nature in which these cataracts present, resulting in under-recognition by
clinicians. This case report and discussion will focus on ways to assist the practitioner in diagnosing oil-drop cataracts to ensure appropriate management of the troublesome symptoms affected patients confront.

Introduction

Myopic progression in a patient typically brings to mind changes in the human lens from either nuclear sclerotic cataracts or swelling secondary to diabetes. But if the progression itself is rapid and significant in nature, there is another lenticular manifestation that warrants investigation. Oil-drop cataracts are specifically known to cause large, swift increases in myopia, as well as secondary complaints of diplopia. Because of their insidious nature, practitioners may misdiagnose patients with neurological or binocular abnormalities, ordering extraneous testing including MRIs, CTs, and visual-evoked potential resulting in significant financial waste.

The following case report involves a patient who was referred to our clinic for further assessment because of a history of dramatic myopic progression. He subsequently developed diplopia. The patient was eventually diagnosed with oil-drop cataracts and cataract surgery was performed. The discussion that follows will explain the etiology and methods of detecting oil-drop cataracts, as well as systemic conditions with which they may be associated.

Case Report

A 56-year-old white man initially presented to our clinic after being referred by another practitioner for rapid, unexplained myopic progression. On this visit, his visual acuity with his habitual glasses was found to be reduced especially in the right eye, which was 20/150 and improved to 20/60 OD with pinhole, and 20/40 OS. With refraction, it was found that he had developed a 2.00 D myopic shift in the right eye and no change in the left eye (Table I). Besides a small amount of nuclear and posterior subcapsular cataracts, no etiology was determined for this shift. The patient was dilated and extensive peripapillary atrophy was noted along with previous barrier laser scars for lattice degeneration OU. New glasses were issued.

The patient returned 6 months later, now with a complaint of intermittent diplopia in addition to blurred vision. Visual acuity with his newest glasses was again reduced, but as with the previous examination, pinhole showed improvement. The patient's spherical equivalent refraction had begun at −2.75 OD and −5.25 OS at the baseline examination but had increased to −9.00 OD and −8.25 OS (Table I). No changes were found on anterior and posterior segment evaluation when compared to the initial examination. No binocular vision testing was performed at this visit.

Two months later, the patient returned to the clinic with a chief complaint of severe horizontal and vertical diplopia. Binocular testing was performed and a large deviation became evident. The patient was given a pair of trial frame glasses that included 10 prism diopter base-up prism and 10 prism diopter base-in prism to wear for an hour to determine whether the diplopia lessened or resolved. After this period of time, the patient noted an improvement in, but not complete absolution of, his diplopia, and stated it was becoming difficult to fuse. Intraocular pressure was found to be 24 mm Hg OD and 31 mm Hg OS by Goldmann tonometry. The patient was dilated and appeared to have an unchanged fundus compared

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to the initial examination; however, on slit lamp examination, an oil-drop cataract was identified (Fig. 1). Intraocular pressure elevation was then suspected to be of a phacomorphic etiology. Subsequent gonioscopy confirmed this suspicion by revealing an impressive convex iris approach. Cataract surgery was discussed and arranged. The patient underwent cataract surgery of his right eye initially, followed by his left eye a few weeks afterward with resulting visual acuity of 20/30-2 OD and 20/20 OS with resolution of monocular diplopia. Intraocular pressure also normalized to 16 mm Hg OD and 15 mm Hg OS postoperatively.

Discussion

For many decades, oil-drop cataracts have created diagnostic dilemmas for optometrists and ophthalmologists alike. Despite this fact, there is a relative scarcity in the literature regarding these lenticular trouble makers. As far back as 1946, Cordes described a type of cataract in which a small central zone, separated from the adult nucleus by a clear zone, developed an increased index of refraction resulting in a marked myopic shift and a “double focus.” A couple of decades later, Dr. Melvin Rubin described a devious type of cataract that, although unimpressive in appearance, caused significant myopic shift, and again a few years later, published a second case report describing a patient with monocular diplopia and an early cataract, the initially unsuspected but appropriate culprit. Since then, a small group of authors have described variously termed cataracts (“opalescent cataracts,” “multirefractile cataracts,” “mild nuclear sclerotic cataracts,” and “oil-drop cataracts”) sharing distinctive but often overlooked clinical features and characteristic symptoms. It is believed that although these authors used varying terminology, based on the description of signs and symptoms of affected patients, they were probably all describing the same clinical entity.

Patients having oil-drop cataracts characteristically present with complaints of blurred vision as well as monocular diplopia. The blurred vision is typically because of a myopic shift, which can be rather substantial. Interestingly, it has been found that even small changes in the index of refraction of the lens can cause large changes in the patient's refractive error. In their study, Brown and Hill demonstrated that a myopic shift precedes the visible signs of cataract by about 4 years, and that cataracts, specifically nuclear sclerotic cataracts, were indeed causative in the development of myopia. Marked astigmatism, often with minimal slit lamp evidence of cataract, has also been reported. Fortunately, patients with such shifts can experience at least partial symptomatic relief simply by the provision of new spectacles or contact lenses.

Special attention to such refractive shifts is especially important for the pre- or postoperative LASIK patient. Soong et al described five cases in which postoperative LASIK patients were erroneously thought to have developed myopic regression when, in fact, they had oil-drop cataracts causing their refractive shifts. Many of these patients underwent unnecessary LASIK enhancements when cataract surgery would have been the most suitable treatment. Patients who have had refractive surgery and either subsequently develop or concomitantly have oil-drop cataract may unfortunately undergo inappropriate corneal surgery, putting them at undue risk for associated complications, and creating a potential game of cat and mouse as the myopia continues to worsen. It is therefore very important that lenticular causes of myopic shifts be considered in all refractive surgery patients. Specifically, clinicians must keep a level of suspicion for the presence of oil-drop cataracts in the setting of apparent myopic regression.
Monocular diplopia is another frequently reported symptom of oil-drop cataracts. Such a symptom should be differentiated from distortion or metamorphopsia, the condition in which straight lines appear crooked. Metamorphopsia is typically associated with retinal or preretinal pathology and does not represent true diplopia. Also, it is common for uncorrected astigmatic patients to complain of double vision when in fact they only see a fringe around the edge of objects. True monocular diplopia is optical, and in the case of oil-drop cataracts, it is because of a double focus, occurring through both the central lens, which has one index of refraction, and the surrounding lens, which has another. O'Donnell and Maumenee4 reported on three patients in which “unexplained” visual loss was ultimately attributed to “mild nuclear sclerotic cataracts.” In their series, they highlighted the symptoms of monocular diplopia as a cardinal symptom to alert the clinician to the possibility of a lenticular cause of the vision loss.

The clinical features of oil-drop cataracts may be subtle, and are often overlooked. One of the most important distinguishing features that these cataracts manifest is a scissor-like reflex with retinoscopy, resembling a typical keratoconic retinoscopic reflex. The observant clinician will notice that the center of the light band will move at a different rate than the peripheral part of it with the central portion appearing more myopic.1 Just as in other diseases that create optical distortions, the retinoscopy reflex may reveal abnormalities before any obvious slit lamp evidence of pathology, and so can serve as a very important tool in evaluating such patients.

Slit lamp biomicroscopy also can provide clues to the presence of an oil-drop cataract. Perhaps the simplest method is to view the lens with a narrowed parallelepiped beam on a dilated pupil. A cloudy, white-appearing nucleus with a surrounding clear ring will be evident. This effect has been illustrated experimentally by examination of a compound lens, including one part with a different refractive index, in a slit lamp. A dark line becomes observable at the junction between the two dissimilar lens parts, much the same as what is apparent when viewing the oil-drop cataract. Another way is to use retroillumination. The central oil-drop will appear demarcated from the neighboring lens material.

Oil-drop cataracts are unique in that they may present in infants as well as in adults. If an infant is affected, the cataracts are present at birth and are thought to be because of an accompanying comorbidity, galactosemia. The oil-drop cataracts in an infant are initially transparent and are easily missed. In all instances of galactosemia, an enzyme deficiency of galactose-1-phosphate uridylyltransferase, galactose-1-phosphate epimerase, or galactokinase exists. This deficiency results in metabolic by-products that cause water influx with the ultimate characteristic lenticular changes. Fortunately, galactosemia is routinely screened and treated for at birth in the United States.

In adults, oil-drop cataracts develop because of the hardening of and formation of new refractile areas within the nucleus. The affected patient's visual degradation does not stem from a lenticular opacity as most cataracts do, but rather from an abrupt change in indices of refraction between the various layers of the human lens. The main reason oil-drop cataracts are often missed by even experienced clinicians is because of their subtlety. Using the aforementioned techniques, and evaluating for their unique clinical features, can help to confirm the diagnosis.

Besides these clinical objective methods, certain demographic trends can be noted in patients who exhibit oil-drop cataracts. Seven patients with oil-drop cataracts were referred to a neuro-ophthalmology practice for unexplained vision loss and myopic shift, six by ophthalmologists and one by an optometrist. They had all undergone extensive additional testing before referral, including fluorescein angiography, MRI, CT, and visual-
evoked potential testing. Some similarities are apparent when looking at their demographic data. A striking factor is that the referring practitioners had no firm diagnosis as to the cause of visual changes.

Another apparent trend is quite reassuring; that all of the cases in this series demonstrated normal results on neurological testing. Therefore, results of such testing can help practitioners either eliminate or support the diagnosis of oil-drop cataracts.

As the etiology of oil-drop cataracts differs in pediatric and adult patients, so do the treatments. In affected children, it has been found that strict dietary restrictions of galactose, an already essential part of a young galactosemic patient's lifestyle, can actually reverse the lenticular changes. In an adult patient, as with most lenticular abnormalities, cataract extraction seems to be the best method of treatment. A study was conducted that assessed seven eyes with oil-drop cataracts that underwent cataract extraction by phacoemulsification. After the cataract extraction and postoperative care was completed, the patients' postsurgical refractive error became typical and stable. Also of note was the complete resolution of diplopia in these eyes.

Conclusion

Oil-drop cataracts are a lenticular manifestation that can negatively affect a patient's quality of life. It is important for these cataracts to be diagnosed early so that appropriate management and treatment can be initiated. If the cataracts are not identified, the patient may indeed have visual complications such as decreased vision and diplopia, as well as the inconvenience and financial burden of multiple referrals and superfluous testing. Through simple measures such as a careful slit lamp examination on a dilated pupil, the patient can be directed to the correct specialist for appropriate surgical care.
diagnosed with SMA syndrome and received additional evaluation and treatment by her gastroenterologist and surgeon. SMA syndrome is rare and can cause bowel obstruction, perforation, gastric wall pneumatosis, and portal venous gas formation. Computed tomography angiography can be used to promptly diagnose this syndrome in the emergency department.

Introduction

Superior mesenteric artery (SMA) syndrome is a rare disease with only 400 documented cases in the English literature since 1980. In most individuals, the SMA branches from the abdominal aorta at an angle of 38° to 56°. The third portion of the duodenum passes between the SMA and the abdominal aorta. The angle of SMA takeoff can be decreased by loss of retroperitoneal fat, resulting in obstruction at the level of the third portion of duodenum as it is distended by food. It most commonly occurs in young, thin individuals. There have been few reports of this syndrome in the emergency department (ED), and if undiagnosed, weight loss, loss of appetite, vomiting, abdominal pain, loss of activity, bowel obstruction, and possible perforation can happen. There appears to be very few reports of SMA syndrome diagnosed in the ED, and only 3 cases were reported in military trainees. We report the case of a young military trainee with SMA syndrome diagnosed in the ED.

Case Report

A 19-year-old female military trainee was presented to the ED with intermittent dull, diffuse (although lower quadrants greater than upper), postprandial abdominal pain onset 1 hour after meals and lasting approximately 30 to 60 minutes per episode for the preceding 2 to 3 weeks that had acutely worsened and become associated with nausea and vomiting during physical training. She lived a sedentary lifestyle before entering basic training. During the initial 2 weeks of training, she had a 20-lb weight loss. She then developed postprandial pain, which progressively led to an additional 15-lb weight loss. She had previously attempted several over-the-counter antacid therapies. A recent gall bladder ultrasound was normal. On arrival to the ED, her vital signs were normal and she was not having acute distress. On physical examination, she had tenderness to palpation of the epigastric and periumbilical regions. The rest of her physical examination was normal. She was administered oral liquid aluminum hydroxide/magnesium hydroxide/simethicone mixed with viscous lidocaine and oral ranitidine, which did not relieve her nausea or pain.

Her serum renal function panel, complete blood count, and liver enzymes were normal. Her chest radiograph was interpreted as normal. Her clinical history of discomfort out of proportion to exam was concerning for intestinal angina. We obtained a computed tomography (CT) angiogram of the abdomen and surgical consultation. The CT demonstrated a narrow aortomesenteric angle (Fig. 1) and occlusion of the third portion of the duodenum, with proximal gastric and duodenal dilatation consistent with SMA syndrome.

On re-examination, she was improved and in consultation with the surgeon, she was discharged from the ED with nutritional supplementation. She was instructed to consume meals in the prone position to offload pressure from the SMA. Gastroenterology performed an esophagogastroduodenoscopy with no notable findings. However, she continued to experience pain, food avoidance, and weight loss and was referred to both bariatric and vascular surgery specialists for consideration of operative repair. She declined operative intervention and was discharged from the military after 6 months.

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Discussion

SMA syndrome is often misdiagnosed, and delays in diagnosis can lead to significant morbidity. One case report noted severe bowel obstruction, bezoar formation, gastric wall pneumatosis, and portal venous gas formation because of delay in diagnosis. Our patient demonstrated morbidity associated with delays in diagnosis including continued weight loss, loss of appetite, vomiting, abdominal pain, loss of activity tolerance, and removal from training. Multiple evaluations by primary care providers with continued worsening of symptoms coupled with improper therapy led to further cycles of food avoidance, weight loss, and increased discomfort. SMA syndrome has an unknown incidence. It most commonly appears in young, thin individuals. The lack of retroperitoneal fat leads to an abnormally acute angle of takeoff of the SMA from the aorta, resulting in compression and obstruction of the duodenum between the SMA and the abdominal aorta because of distention by food after eating. The normal aortomesenteric angle is 38° to 56°; our patient was noted to have a takeoff of <15°, likely caused by her recent, sudden weight loss. Transient cases of SMA syndrome occur in patients with severe anorexia nervosa. Severe cases may require surgery or parenteral feeding because of food avoidance leading to further loss of retroperitoneal fat. Treatment is usually conservative, via nutritional supplementation. Positional eating techniques may be effective and include eating food in the prone, knee-chest, or lateral decubitus position to offload pressure of the SMA from the duodenum. Some case studies describe improvement of symptoms with promotility agents, such as metoclopramide.

Limitations are that of a typical case report. Our patient's pain may have been because of another, undiagnosed disease. However, we obtained the diagnosis by CT scan, her symptoms were consistent with SMA syndrome, and after several months no other disorder was diagnosed.

In conclusion, SMA syndrome is rare and should be considered in the ED patients with recent rapid weight loss (including basic military trainees), who present with postprandial abdominal pain. Abdominal CT angiography is useful to diagnose this disorder.

Abstract and Introduction

combined Paravertebral and Intrathecal vs Thoracic Epidural Analgesia for Post-thoracotomy Pain Relief

Medscape
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Abstract
Background Although thoracic epidural analgesia (TEA) is considered the gold standard for post-thoracotomy pain relief, thoracic paravertebral block (PVB) and intrathecal opioid (ITO) administration have also been shown to be efficacious. We hypothesized that the combination of PVB and ITO provides analgesia comparable with that of TEA.

Methods After local ethics committee approval, 84 consecutive patients undergoing open thoracic procedures were randomized to the TEA (ropivacaine 0.2%+sufentanil) or the PVB (ropivacaine 0.5%)+ITO (sufentanil+morphine) group. The primary endpoints were pain intensities at rest and during coughing/movement at 1, 2, 4, 8, 12, 24, 48, and 72 h after operation assessed by visual analogue scale (VAS) score. Data were analysed by multivariate analysis (anova; \( P<0.05 \)).

Results Patient and surgical characteristics were comparable between the groups. The mean and maximal VAS scores were lower in the TEA (n=43) than in the PVB+ITO group (n=37) at several time points at rest (\( P<0.026 \)) and during coughing/movement (\( P<0.021 \)). However, in the PVB+ITO group, the mean VAS scores never exceeded 1.9 and 3.5 at rest and during coughing/movement, respectively; and the maximal differences between the groups (TEA vs PVB+ITO) in the maximal VAS scores were only 1.2 (3.4 vs 4.6) at rest, and 1.3 (4.4 vs 5.7) during coughing/movement.

Conclusions Although VAS scores were statistically lower in the TEA compared with the PVB+ITO group at some observation points, the differences were small and of questionable clinical relevance. Thus, combined PVB and ITO can be considered a satisfactory alternative to TEA for post-thoracotomy pain relief.

Introduction

Post-thoracotomy pain is frequent and associated with considerable complications. Severe postoperative pain, in general, impairs postoperative patient mobilization, increases perioperative morbidity, and may trigger a chronic pain syndrome. Post-thoracotomy pain, in particular, will adversely affect pulmonary function by impairing deep breathing and effective coughing, resulting in retention of secretions, atelectasis, and pneumonia.

Various regional techniques (e.g. intercostal, paravertebral, interpleural, and epidural blocks with local anaesthetics and opioids) have been used to provide pain relief after thoracotomy. Thoracic epidural anaesthesia (TEA) has emerged as the gold standard for post-thoracotomy pain control. However, this method is not suitable for all patients and is associated with numerous risks (e.g. dural perforation, spinal cord damage by formation of haematoma, infection and abscess; hypotension; urinary retention). Thoracic paravertebral nerve block (PVB) produces unilateral analgesia over several thoracic segments and has been shown to provide effective post-thoracotomy pain control. PVB was as effective as TEA in controlling post-thoracotomy pain and associated with less haemodynamic side-effects.
Single injection of an opioid into the subarachnoid space is a long-established but infrequently used analgesic technique in thoracic surgery. Both sufentanil and morphine have been used for this purpose. Related to their different lipid solubility, intrathecal (IT) sufentanil has a rapid onset (peak effect <5 min after injection) and relatively short duration of action (~1 h), whereas IT morphine has delayed onset (peak effect 6–7 h after injection) and long duration (~24 h). Thus, the combination of IT sufentanil and morphine provides rapid onset and long-lasting analgesia. Based on the various findings, we hypothesized that the combination of thoracic PVB with local anaesthetic and IT sufentanil and morphine would provide post-thoracotomy pain relief comparable with that of TEA with local anaesthetic and sufentanil.

Methods

The study was approved by the local ethics committee and registered (AZ: 35/07) (ClinicalTrials.gov number: NCT00493909). Inclusion criteria were age between 18 and 75 yr, and lung resection via open thoracotomy. Exclusion criteria were additional chest wall resection, emergency surgery, pregnancy, and contraindications to regional techniques (i.e. allergy to local anaesthetics, infection around the site of catheter insertion, evidence of systemic inflammation, coagulation disorder) (Fig. 1).

Patients were recruited between June 2007 and August 2008. After written informed consent had been obtained, patients were randomly allocated by computer-generated randomization to one of the following two groups: Group I: TEA with ropivacaine and sufentanil; Group II: combined thoracic PVB with ropivacaine and IT administration of opioids (ITO) sufentanil and morphine (PVB+ITO). Before operation, forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and peak expiratory flow (PEF) were measured.

All patients were pre-medicated with midazolam (3.75–7.5 mg p.o.) shortly before transfer to the operating theatre area. All thoracic epidural and paravertebral catheters were placed by one of the two investigators (S.H., T.L.) in the anaesthetic pre-induction room before induction of anaesthesia. In patients randomized to the TEA group, an epidural catheter was placed in the sitting position at interspaces T4/5, T5/6, or T6/7 (depending on the site of surgery) via an 18 G Tuohy needle (Pajunk, Geisingen, Germany) using the midline approach and hanging drop technique. A test dose of 2 ml of mepivacaine 1% (20 mg) with epinephrine (10 µg) was administered through the catheter to rule out inadvertent IT or intravascular placement. Epidural analgesia was induced by slow injection of a total of 10 ml of ropivacaine 0.2% and sufentanil (0.2–0.3 µg kg⁻¹ maximally 25 µg), followed by a continuous epidural infusion of ropivacaine 0.2% and sufentanil 0.5 µg ml⁻¹ at 8 ml h⁻¹ during surgery and until 72 h after operation.

In patients randomized to the PVB+ITO group, the paravertebral space ipsilateral to the thoracotomy (T4–8) was located as described by Richardson and Lonnqvist. The catheter was introduced through an 18 G Tuohy needle and advanced 3 cm into the paravertebral space. After gentle aspiration, a test dose of 3 ml of ropivacaine 0.5% with 15 µg epinephrine (5 µg ml⁻¹) was administered through the catheter to rule out inadvertent IT or intravascular placement. Thoracic PVB was induced with 30 ml ropivacaine 0.5% with epinephrine (5 µg ml⁻¹) followed by continuous paravertebral infusion of ropivacaine 0.2% at 8 ml h⁻¹ intraoperatively and until 72 h after operation.
For IT opioid (ITO) injection, the skin overlying the area of the L3/4 or L4/5 interspaces was disinfected, draped, and infiltrated with 2–3 ml of 1% lidocaine for local anaesthesia. The subarachnoid space was punctured with a 25 G pencil-point spinal needle (Pencant; Braun, Melsungen, Germany). After return of clear, free-flowing cerebrospinal fluid, preservative-free sufentanil 0.2–0.3 µg kg−1 (maximally 25 µg) (Sufenta®; Janssen-Cilag, Neuss, Germany) and morphine 4–5 µg kg−1 (maximally 500 µg) were intrathecally injected over 5–10 s in two separate syringes. After verification of correct needle placement by successful aspiration of cerebrospinal fluid after injection of opioids, the spinal needle was removed.

Subsequently, anaesthesia was induced with i.v. sufentanil 0.4–0.6 µg kg−1 and target-controlled infusion (TCI) of propofol (Propofol 1% MCT and Injectomat® TIVA Agilia, Fresenius-Kabi GmbH, Bad Homburg, Germany) at plasma concentrations of 2–4 µg ml−1. Anaesthesia was maintained with propofol TCI at plasma concentrations of 2–4 µg ml−1 and additional bolus doses of sufentanil 0.1–0.2 µg kg−1 to avoid arterial pressure values above 20% of baseline. The depth of anaesthesia was monitored by the bispectral index of the EEG (BIS) (BIS® A-2000 monitor, averaging time=30 s; Aspect Medical Systems, Newton, MA, USA). If the BIS value decreased below 30, the propofol TCI plasma concentration was decreased to minimal 2.2 µg ml−1.

An i.v. bolus of cisatracurium 0.1 mg kg−1 (Nimbex®, GlaxoSmithKline, Munich, Germany) was given to facilitate tracheal intubation with a double-lumen endobronchial tube. Correct position of the double-lumen tube after tracheal intubation and after patient positioning for surgery was verified by flexible fibreoptic bronchoscopy. During two-lung ventilation, patients were ventilated in a pressure-controlled mode (Zeus®, Draeger, Luebeck, Germany) at tidal volumes of 6–8 ml kg−1, at respiratory rates to maintain end-tidal carbon dioxide concentration between 4.9–5.7 and 5.3–5.9 kPa, with a positive end-expiratory pressure of 5 mbar, and an inspired oxygen fraction (FIO 2) of 0.6. During one-lung ventilation, tidal volume was decreased to 6 ml kg−1, respiratory rates were increased to maintain end-tidal carbon dioxide concentration between 5.3 and 5.9 kPa, and FIO 2 was increased to 0.8–1.0.

Catheters were inserted into the radial artery for invasive arterial pressure and blood gas monitoring, and into the subclavian vein for central venous pressure monitoring. The bladder was catheterized for measurement of urinary output. Core temperature was maintained above 36.0°C by a forced-air warming system. At the end of surgery, two chest tubes (anterior 21 Ch and posterior 24 Ch, silicon chest tubes, Redax Company, Mirandola, Italy) were placed before chest closure. The chest tubes were connected to a water seal chest drainage collection device. Continuous suction of −10 cm H2O was applied until the absence of an air leak for 24 h. After reversal of neuromuscular blocking agent and response to verbal command, patients were extubated in the operating theatre. They were then transferred to the intermediate care unit. Criteria for discharge from the intermediate care unit were VAS score ≤2 and removed chest tubes.

Postoperative Pain Management

The day before surgery, patients were instructed in the use of a patient-controlled analgesia (PCA) device (Graseby PCA 3300; Smiths Medical International Ltd, Hythe, Kent, UK) and in the visual analogue scale (VAS) score. The VAS score consisted of an unmarked 100 mm line, with 0 mm representing no pain and 100 mm the worst imaginable pain. Patients were asked to score pain on the VAS before operation.
After operation, all patients received i.v. infusions of paracetamol or metamizol (15 mg kg⁻¹ administered over 20 min every 6 h for 3 days). When sufficiently awake for pain assessment after operation, patients were asked by investigators blinded to the group assignment (E.H., K.O.) to score their pain on the VAS. This observation point was defined as T0. When the VAS score exceeded 30 mm, i.v. piritramide 3 mg (equivalent to 2 mg morphine) was administered and repeated at 5 min intervals until the VAS score decreased to <30 mm at rest. Patients whose VAS pain score at T0 was <30 mm (effective analgesia by definition) were directly connected to the i.v. PCA device, which was programmed to deliver bolus doses of piritramide 1.5 mg, with a lockout time of 5 min and a total dose of 40 mg per 4 h. VAS pain scores at rest and during coughing/movement, and PCA piritramide consumption were recorded hourly until 12 h (T12), 2 hourly until 24 h (T24), and 8 hourly until 48 h after operation (T48).

Postoperative Non-pain Management

Respiratory rate, heart rate, and arterial pressure were recorded hourly in the intermediate care unit and 8 hourly after discharge to the ward. Respiratory depression was defined as respiratory rate <8 bpm, and hypotension as a decrease in mean arterial pressure by 20% of baseline value and/or in systolic arterial pressure to <10.6 kPa for more than 3 min. Hypotension was treated by i.v. bolus doses of 10 µg norepinephrine. Arterial blood gases were measured 1 h after tracheal extubation and on the morning of postoperative day (POD) 1 with the patients breathing 3 litre min⁻¹ of oxygen via a nasal cannula. Twelve-lead ECGs were recorded on PODs 0 and 1, and additionally, if cardiac arrhythmias, a heart rate >100 beats min⁻¹, or signs and symptoms of myocardial ischaemia were observed.

Patient sedation was assessed 4 hourly by investigators blinded to the group assignment on a five-point sedation score (1, wide awake; 2, drowsy or dozing intermittently; 3, mostly sleeping but easily awakened; 4, asleep, difficulty responding to verbal commands; 5, awakened only by shaking). Over-sedation was defined as sedation score >4 combined with a respiratory rate <8 bpm, and was treated with i.v. naloxone.

Chest radiographs were obtained on PODs 0, 1, and 3. FVC, FEV₁, and PEF were measured daily during PODs 0–3, and at hospital discharge after chest physiotherapy using a portable spirometer (FlowScreen®, Viasys Healthcare GmbH, Hoechberg, Germany). Between T0 and T48, patients were assessed twice daily for sensory and motor function, nausea, vomiting, pruritus, and urinary retention.

Outcome Measures

The primary outcome measures were pain intensities at rest and during coughing/movement assessed by VAS score. The quality of effective analgesia was expressed as VAS values derived from the VAS pain score <30 mm at rest and during coughing during each assessment period (T0–12, T12–24, T24–48). Secondary outcome measures included respiratory function, pulmonary complications, nausea and vomiting, degree of sedation, hypotension, pruritus, urinary retention, consumption of i.v. piritramide, surgical revisions, time to chest tube removal, and length of hospital stay.

Statistical Analyses
The a priori power calculation was based on the assumption of ~30% incidence of severe post-thoracotomy pain as defined as VAS >60 mm. The aim was to detect a clinical relevant reduction in VAS score by 30 mm. To be able to detect a difference of 20 cm h\(^{-1}\) in the area under the curve of the VAS score during coughing with an expected standard deviation of 50 cm h\(^{-1}\), and \(\alpha\) - and \(\beta\)-errors of 0.05 (two-sided hypothesis) at a power of 0.8, the calculated sample size was 60 patients. To compensate for unforeseen drop-outs and a possibly higher variability than expected, we a priori planned to study 80 patients. Patient characteristic data (age, height, weight, lung function) were compared by analysis of variance (anova) using the Kruskal–Wallis test. Comparisons of serial measurements (VAS for pain) were performed with repeated-measures anova. Ranked data were analysed with the Kruskal–Wallis and Mann–Whitney U-tests when appropriate. Categorical data were examined by Fisher's exact test. Probability values under 0.05 were considered significant.

Results

Four patients were excluded from analysis because of surgical revision for postoperative bleeding (Group TEA; n=2) and accidental premature removal of the paravertebral catheter (Group PVB+ITO; n=2). They were randomly replaced by consecutive patients fulfilling the inclusion criteria, resulting in data from 80 patients for analysis (TEA group, n=43; PVB+ITO, n=37). Patient and surgical characteristics were comparable between the groups (Table 1). On the day of surgery (T0), and on PODs 2 (T24) and 3 (T48), pain scores in the TEA group were lower at rest (P<0.026) and during coughing/movement (P<0.021) than in the PVB+ITO group (Figs 2 and 3). However, at the various time points, (i) mean VAS scores never exceeded 1.9 at rest, and 3.5 during coughing/movement in the PVB+ITO group; (ii) the differences between groups in the mean VAS scores varied by only 0.1–0.8 at rest, and 0.4–1.3 during coughing/movement; and (iii) the maximal differences between the TEA and the PVB+ITO groups in the maximal VAS scores were only 1.2 (3.4 vs 4.6) at rest, and 1.3 (4.4 vs 5.7) during coughing/movement.

There were no significant differences (all P>0.05) between the groups in cardiovascular, respiratory, and renal complications; postoperative nausea and/or vomiting; fever; sedation; piritramide consumption; blood loss and blood transfusions; intermediate care readmission; length of hospital stay; mortality (Table 2). Over-sedation requiring treatment developed in two patients (~5%) of each group (Table 2) and occurred on POD 1. Postoperative FVC, FEV1, and PEF were lower than baseline values in both groups (all P<0.05; data not shown). However, PEFs were comparable between the groups at POD 2 and hospital discharge (P<0.05; Fig. 4).

Discussion

This prospective randomized clinical study compares TEA with the combination of PVB and ITO for postoperative pain control in patients undergoing open lung resection. The main findings can be summarized as follows: (i) TEA provided statistically better acute postoperative pain relief than a combination of PVB and ITO administration at rest and during coughing/movement; (ii) the differences between the groups in the mean and maximal VAS scores varied by maximally 1.3; (iii) in the PVB+ITO group, the mean VAS scores never exceeded 3.5; and (iv) secondary outcome measures did not differ between the groups. As TEA provided statistically better pain relief than the combination of PVB and in ITO, these findings do not entirely support our hypothesis that both methods would provide comparable pain relief. However, the differences in VAS

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scores at rest and during coughing/movement were small, not observed at all observation points, and of questionable clinical relevance. Furthermore, the statistically higher pain scores in the PVB+ITO group were not associated with worse postoperative outcome (e.g. pulmonary function, morbidity, length of intermediate care unit and hospital stay). Our findings thus indicate that the combination of thoracic PVB and IT administration of opioids is an acceptable alternative to TEA for post-thoracotomy pain relief. This is of special clinical relevance whenever TEA is not an option.

For two main reasons, good post-thoracotomy pain relief is essential for postoperative recovery. First, uncontrolled pain is one of the major risk factors for the quite common post-thoracotomy syndrome which is associated with a significant decrease in quality of life and need for chronic pain medication. With the exception of limb amputation, thoracotomy is associated with the highest incidence of chronic pain syndrome (up to 50%). Intercostal nerve injury (by incision, rib retraction, sutures) and pleural irritation (e.g. by chest tube placement) promote pain transmission to the central nervous system causing a pain memory. Effective block of neural afferents reduces acute post-thoracotomy pain and may thereby blunt the development of pain consciousness.

Secondly, patient satisfaction and successful surgical 'fast-tracking' largely depend on good post-thoracotomy pain relief. Preferably, good pain relief is achieved with as little as possible systemic administration of opioids because this will improve patient satisfaction and fast-tracking by reducing the debilitating opioid-related side-effects (e.g. nausea and vomiting, sedation), thereby facilitating early mobilization and oral nutrition, effective physiotherapy, and early discharge. This is the rationale for using regional anaesthetic techniques and IT administration of opioids.

Until recently, TEA has been considered the gold standard and method of choice for post-thoracotomy pain relief. The role of thoracic paravertebral block in this context has not been as clear. A meta-analysis of 10 randomized, non-blinded trials including 520 thoracic surgical patients compared PVB and TEA. There were considerable differences between studies in the use of drugs for TEA and PVB, the technique of PVB, type of additional postoperative analgesia, and study endpoints. In the TEA groups, opioids were infused together with local anaesthetics via epidural catheter in four of the 10 included studies (including 254 patients), but in the PVB groups only one of them (including 50 patients). This should have favoured pain outcome in the TEA group because the combination of local anaesthetic and opioid provides superior analgesia compared with the use of local anaesthetic alone. However, the meta-analysis did not find a significant difference in postoperative pain scores between the PVB and the TEA groups. Furthermore, PVB was associated with a lower failure rate, less pulmonary complications, and other side-effects (e.g. urinary retention, nausea and vomiting, and hypotension). Because of the better side-effect profile, the authors recommended PVB for pain relief after major thoracic surgery.

In contrast to all studies included in the meta-analysis, we did not compare TEA with PVB alone but with PVB plus IT administration of opioids. This was to compensate for the administration of local anaesthetic and opioid in the TEA group. As IT administration of opioids (i.e. morphine and/or sufentanil) provided pain relief after thoracic surgery, it is thus likely that the additional IT administration of opioids resulted in pain relief in our PVB+ITO group comparable with that in the TEA group.
Over-sedation and respiratory depression requiring treatment is a possible complication of epidural and IT administration of opioids. This occurred in two patients (~5%) of each group. This finding indicates that patients managed as described require postoperative monitoring of sedation and respiration. We ensured that the investigators assessing pain and sedation were unaware of group assignment.

Our study has several limitations. First, the study was underpowered to evaluate the secondary outcomes of respiratory function, pulmonary complications, nausea and vomiting, degree of sedation, hypotension, and pruritus. Secondly, gas diffusion was not investigated which limits the interpretation of the spirometric results. Thirdly, we do not know the failure rate of the TEA and PVB because we did not assess the level of sensory block in either study group after placement of the respective catheters before inducing general anaesthesia. The failure rate of mostly (~95%) non-catheter-induced, single-shot, nerve stimulator-guided PVB in adults for thoracic, abdominal, and orthopaedic surgery has been reported as 6.1%. Based on the anatomy of the paravertebral space, it is conceivable that a continuous infusion of a combination of local anaesthetic and opioid via a paravertebral catheter reduces the failure rate. It might be argued that the combination of a central block (i.e. PVB) and IT injection of opioids carries a higher risk of injury than TEA alone. Complications after PVB (accidental vascular puncture, pneumothorax, nerve damage, and Horner syndrome) vary between 0.5% and 6.8%, and those after IT injection of opioids (nausea, vomitus, respiratory depression) between 0.8% and 6.7%. This compares favourably with the rate of complications of 0.004% and 5.3% after TEA.

In conclusion, in this prospective randomized clinical trial, TEA provided statistically better acute pain relief after open thoracotomy than a combination of PVB and ITO administration. However, as the differences in VAS scores between the groups were small and of questionable clinical relevance, our findings indicate that combined PVB and ITO is a satisfactory alternative for post-thoracotomy pain relief.

**PTSD**

**Virtual Reality Applications to Address the Wounds of War**

Psychiatric Annals
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Numerous reports indicate that the incidence of posttraumatic stress disorder (PTSD) in returning Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) military personnel is creating a significant behavioral health care challenge. These findings have served to motivate research on how to better develop and disseminate evidence-based treatments for PTSD. This article details how virtual reality applications are being designed and implemented across various points in the military deployment cycle to prevent, identify, and treat combat-related PTSD in OEF/OIF service members and veterans.
The summarized projects in these areas have been developed at the University of Southern California Institute for Creative Technologies (USC ICT), a US Army University Affiliated Research Center, and will detail efforts to use virtual reality to deliver exposure therapy and provide stress resilience training prior to deployment. A brief discussion will follow that details work developing and evaluating virtual human agents in the role of virtual patients that represent military personnel for training the next generation of clinical providers. As well, research and development creating virtual humans serving in the role of online health care guides that can be used to support anonymous access to military-relevant behavioral health care information will be discussed.

Introduction to Clinical Virtual Reality

The US Department of Defense (DoD) continues to make a significant investment in research and development of virtual reality (VR) technology for a wide range of training applications. This investment, along with rapid advances in the underlying engineering enabling technology, also has supported the development of innovative VR clinical assessment and intervention tools in both the military and civilian sectors. By its nature, VR applications can be designed to simulate naturalistic environments. Within these virtual environments, researchers and clinicians can present ecologically relevant stimuli embedded in a meaningful and familiar simulated context.

VR simulation technology also offers the potential to create systematic human testing, training and treatment environments that allow for the precise control of complex, immersive, dynamic 3-D stimulus presentations, within which sophisticated interaction, behavioral tracking, user response, and performance recording is possible. When combining these assets within the context of functionally relevant, ecologically enhanced VR scenarios, a fundamental advancement emerges in how human assessment and intervention can be addressed in many clinical and research disciplines. VR-based testing, training, and treatment approaches that would be difficult, if not impossible, to deliver using traditional methods are now being developed, taking advantage of the assets available with VR technology.

This unique match between VR technology assets and the needs of various clinical application areas has been recognized by a determined and expanding group of researchers and clinicians who not only understand the potential impact of VR technology, but have also now generated a significant literature that documents the many clinical and research targets where VR can add value over traditional assessment and intervention methods.

More specifically, a short list of areas where clinical VR has been usefully applied includes fear reduction in persons with specific phobias; treatment for PTSD stress management in patients with cancer; acute pain reduction during wound care; physical therapy with burn patients and others undergoing painful procedures; body image disturbances in patients with eating disorders; navigation and spatial training in children and adults with motor impairments; functional skill training and motor rehabilitation with patients having central nervous system dysfunction (eg, stroke, traumatic brain injury, spinal cord injury, cerebral palsy, multiple sclerosis, etc); and for the assessment and rehabilitation of attention, memory, spatial skills, and other cognitive functions in both clinical and unimpaired populations.
To do this, VR scientists have constructed virtual airplanes, skyscrapers, spiders, battlefields, social settings, beaches, fantasy worlds, and the mundane (but highly relevant) functional environments of the schoolroom, office, home, street, and supermarket. Emerging research and development also is producing artificially intelligent virtual human patients that are being used to train clinical skills to health professionals and to serve as anonymously accessible, online health care guides. Based on these parallel advances in research and technology, VR has now emerged as a promising tool in many domains of clinical care and research.

Virtual Reality Definitions and Technology

Virtual reality has been very generally defined as "... a way for humans to visualize, manipulate, and interact with computers and extremely complex data." From this baseline perspective, VR can be seen as an advanced form of human-computer interface that allows the user to "interact" with computers and digital content in a more natural or sophisticated fashion relative to what is afforded by standard mouse and keyboard input devices.

In some cases, with the aid of specialized VR display devices, users can become "immersed" within a computer-generated simulated environment that changes in a natural/intuitive way with user interaction. VR sensory stimuli can be delivered by using various forms of visual display technology that can present real-time computer graphics and/or photographic images/video along with a variety of other sensory display devices that can present audio, "force-feedback" touch sensations, and even olfactory content to the user.

However, VR is not defined or limited by any one technological approach or hardware set-up. The creation of an engaged VR user experience can be accomplished using combinations of a wide variety of interaction devices, sensory display systems, and in the design of content presented in a computer-generated graphic world.

For example, "Immersive VR" can be produced by combining computers, head-mounted displays (HMDs), body tracking sensors, specialized interface devices, and real-time graphics to immerse a participant in a computer-generated simulated world that changes in a natural way with head and body motion. Thus, an engaged immersive virtual experience can be supported by employing specialized tracking technology that senses the user's position and movement and uses that information to update the sensory stimuli presented to the user to create the illusion of being immersed "in" a virtual space where they can interact.

One common configuration employs a combination of an HMD and head tracking system that allows delivery of real-time computer-generated images and sounds of a simulated virtual scene rendered in relationship to user movements that correspond to what the individual would see, hear, and feel if the scene were real. In these immersive systems, one of the key aims is to perceptually replace the outside world with that of the simulated environment to create a specific user experience.

Immersive HMD VR has been most commonly employed in applications where a controlled stimulus environment is desirable for constraining a user's perceptual experience within a specific synthetic world. This format has been often used in clinical VR applications for anxiety disorder...
exposure therapy, analgesic distraction for patients suffering from acutely painful medical procedures, and in the cognitive assessment of users with central nervous system dysfunction to measure performance under a range of systematically delivered task challenges and distractions. By contrast, “non-immersive VR” is commonly experienced using modern computer and console games systems (as well as in non-game research lab generated systems). This format presents a 3-D graphic environment on a flat screen monitor, projection system, or television (no real world occlusion) within which the user can navigate and interact.

Albeit delivered on a less immersive display, such graphic worlds are still essentially a VR environment, presented on these widely available commodity display systems have the capacity to provide the user with significant options for interaction with dynamic digital content using traditional computer and game interface devices (eg, keyboard, mouse, game pads, joysticks, etc). This is in addition to more complex interaction devices that can track more natural user activity (eg, data gloves, 3-D mice, treadmills and some high-end “force feedback” exoskeleton devices). Recently, off-the-shelf systems, such as the Microsoft Kinect, are now being shown to provide a novel way for users to interact with virtual environments (VEs) using natural body interaction via low-cost 3-D camera-based sensing of full body movement.

This article will illustrate how VR has been used to enhance the delivery of prolonged exposure therapy, provide stress resilience training, and to enhance clinical interactions with virtual human representations.

Virtual Reality Prolonged Exposure for PTSD

Among the many approaches that have been used to treat persons with PTSD, prolonged exposure (PE) therapy appears to have the best-documented therapeutic efficacy. Such treatment typically involves the graded and repeated imaginal reliving and narrative recounting of the traumatic event within the therapeutic setting. This approach is believed to provide a low-threat context where the client can begin to confront and therapeutically process the emotions that are relevant to a traumatic event as well as decondition the learning cycle of the disorder via a habituation/extinction process.

While the efficacy of imaginal exposure has been established in multiple studies with diverse trauma populations, many patients are unwilling or unable to effectively visualize the traumatic event. In fact, avoidance of reminders of the trauma is inherent in PTSD and is one of the cardinal symptoms of the disorder.

Virtual Reality Exposure Therapy

To address this problem, researchers have recently turned to the use of VR to deliver exposure therapy (VRET) by immersing users in simulations of trauma-relevant environments in which the emotional intensity of the scenes can be precisely controlled by the clinician, in collaboration with the patients’ wishes. In this fashion, VRET offers a way to circumvent the patient’s natural avoidance tendency by directly delivering multi-sensory and context-relevant cues that aid in the confrontation and processing of traumatic memories, without demanding that the patient actively try to access his/her experience through effortful memory retrieval.
Within a VR environment, the hidden world of the patient’s imagination is not exclusively relied upon and VRET may also offer an appealing treatment option that is perceived with less stigma by “digital generation” service members (SMs) and veterans who may be more reluctant to seek out what they perceive as traditional talk therapies. These ideas have been supported by three reports in which patients with PTSD were unresponsive to previous imaginal exposure treatments, but went on to respond successfully to VRET. As well, VR provides an objective and consistent format for documenting the sensory stimuli that the patient is exposed to that is not possible when operating within the unseen world of the patient’s imagination.

Virtual Iraq/Afghanistan

Based on this rationale and previous research, the USC ICT developed a “Virtual Iraq/Afghanistan” simulation that is being used in a variety of clinical trials to investigate the potential for this form of treatment. The treatment environment consists of a series of virtual scenarios designed to represent relevant contexts for VRET, including city and desert road environments. In addition to the visual stimuli presented in the VR HMD, directional 3-D audio, vibro-tactile, and olfactory stimuli of relevance can be delivered. Stimulus presentation is controlled by the clinician via a separate “Wizard of Oz” (where the subject interacts with what he or she believes to be an autonomous program, but one that is instead operated by an unseen person) interface, with the clinician in full audio contact with the patient. The design of the system was enhanced by feedback derived from user-centered tests with the application that were conducted at Fort Lewis, Washington, and within an Army Combat Stress Control Team in Iraq.

This feedback from nondiagnosed personnel provided information on the content and usability of our application that fed an iterative design process leading to the creation of the current clinical scenarios. A detailed description of the Virtual Iraq/Afghanistan system and the methodology for a standard VRET clinical protocol can be found elsewhere.

Initial clinical tests of the system have produced promising results. In the first open clinical trial, analyses of 20 active duty treatment completers (19 male, 1 female, mean age = 28 years; age range: 21 to 51 years) produced positive clinical outcomes. For this sample, mean pre/post PTSD military checklist (PCL-M) scores decreased in a statistical and clinically meaningful fashion: 54.4 (SD = 9.7) to 35.6 (SD = 17.4). Paired pre/post t-test analysis showed these differences to be significant (t = 5.99, df = 19, P < .001).

Correcting for the PCL-M, no-symptom baseline of 17 indicated a greater than 50% decrease in symptoms; 16 of the 20 completers no longer met PCL-M criteria for PTSD at post-treatment follow-up. Five participants in this group with PTSD diagnoses had pre-treatment baseline scores below the conservative cutoff value of 50 (pre-scores = 49, 46, 42, 36, 38) and reported decreased values at post treatment (post-scores = 23, 19, 22, 22, 24, respectively). Mean Beck Anxiety Inventory scores significantly decreased 33% from 18.6 (SD = 9.5) to 11.9 (SD = 13.6), (t = 3.37, df=19, P < .003) and mean PHQ-9 (depression) scores decreased 49% from 13.3 (SD = 5.4) to 7.1 (SD = 6.7), (t = 3.68, df = 19, P < .002).
The average number of sessions for this sample was just less than 11. Positive results from uncontrolled open trials are difficult to generalize from and we have been cautious not to make excessive claims based on these early results. However, using an accepted military-relevant diagnostic screening measure (PCL-M), 80% of the treatment completers in the initial VRET sample showed both statistically and clinically meaningful reductions in PTSD, anxiety and depression symptoms, and anecdotal evidence from patient reports suggested that they saw improvements in their everyday life. These improvements were also maintained at 3-month post-treatment follow-up.

Additional VRET Studies

Other studies also have reported positive outcomes. Two early case studies reported positive results using this system. Following those, another open clinical trial with active duty soldiers (n=24) produced significant pre/post reductions in PCL-M scores and a large treatment effect size (Cohen’s d = 1.17). After an average of seven sessions, 45% of those treated no longer screened positive for PTSD and 62% had reliably improved.

In a small preliminary quasi-randomized controlled trial, seven of 10 participants with PTSD showed a 30% or greater improvement with VR, whereas only one of nine participants in a “treatment as usual” group showed similar improvement. The results are limited by small size, lack of blinding, a single therapist, and comparison to a set relatively uncontrolled usual care conditions, but it did add to the incremental evidence suggesting VR to be a safe and effective treatment for combat-related PTSD.

At the 2012 American Psychiatric Association annual meeting, McLay presented data from a comparison of VRET with the traditional, evidence-based prolonged exposure approach in active duty SMs. The results showed significantly better maintenance of positive treatment outcomes at 3-month follow-up for Virtual Iraq/Afghanistan system compared with traditional PE. The overall trend of these positive findings (in the absence of any reports of negative findings) is encouraging for the view that VRET is safe and may be an effective approach for delivering an evidence-based treatment (prolonged exposure) for PTSD.

Four randomized controlled trials (RCTs) are ongoing with the Virtual Iraq/Afghanistan system with active duty and veteran populations. Two RCTs are focusing on comparisons of treatment efficacy between VRET and PE, and another is testing VRET compared with VRET and a supplemental care approach.

A fourth RCT is investigating the additive value of supplementing VRET and imaginal PE with a cognitive enhancer called D-Cycloserine (DCS). DCS, an N-methyl-d-aspartate partial agonist, has been shown to facilitate extinction learning in laboratory animals when infused bilaterally within the amygdala prior to extinction training. The first clinical test in humans that combined orally administered DCS with VRET was performed by Ressler et al with participants diagnosed with acrophobia (n = 28). Participants who received DCS plus VRET experienced significant decreases in fear within the virtual environment at 1 week and at 3 months post-treatment, and reported significantly more improvement than the placebo group in their overall acrophobic symptoms at 3-month follow-up.
The DCS group also achieved lower scores on a psychophysiological measure of anxiety than the placebo group. The current multi-site PTSD RCT (National Intrepid Center of Excellence, Cornell-Weill, and the Long Beach Veterans Affairs Medical Center) is testing the effect of DCS vs. placebo when added to VRET and PE with active duty and veteran samples (n = 300). DoD funding support for these RCTs underscore the interest that the DOD/Veterans Affairs (VA) has in exploring this innovative approach for delivering exposure therapy using VR.

Evidence-Based Nature of VRET

While RCTs are the gold standard for emerging treatment approaches to gain wide acceptance by the scientific community, it should be noted that at its core, the therapeutic model/principle that underlies VRET (cognitive-behavior therapy [CBT] with exposure) is in fact evidence-based. VRET is simply the delivery of this evidence-based treatment in a format that may serve to engage a wider range of patients in the necessary confrontation and processing of traumatic memories or “fear-structures” needed for positive clinical outcomes. Thus, even equivalent positive results with PE in these RCTs would validate its use as another safe and evidence-based therapeutic option.

The VRET approach also could serve to draw SMs and veterans into treatment, many of whom have grown up “digital” and may be more likely to seek care in this format compared with what they perceive as traditional talk therapy. This is important since numerous reports from both military and civilian blue ribbon panels underscore the importance of breaking down “barriers to care” for improving the awareness, availability, accessibility, and acceptance of behavioral health care in the military, Institute of Medicine, Dole-Shalala Commission Report, the Rand Report, and American Psychological Association.

Virtual Reality Resilience Training

Resilience is the dynamic process by which individuals exhibit positive adaptation when they encounter significant adversity, trauma, tragedy, threats, or other sources of stress. The core aim of resilience training is to promote psychological fitness and better prepare service members for the psychological stressors that they may experience during a combat deployment. There is a powerful rationale for developing methods that promote SM resilience and psychological fitness prior to a combat deployment.

Shift in Military Policy

The current urgency to address the psychological wounds of war in SMs and veterans also has driven an emerging focus within the military on emphasizing a proactive approach for better preparing service members for the emotional challenges they may face during a combat deployment to reduce the potential for later adverse psychological reactions such as PTSD and depression. This focus on resilience training prior to deployment represents no less than a quantum shift in military culture and can now be seen emanating from the highest levels of command in the military. For example, in an American Psychologist article, Army General George Casey states that “… soldiers can ‘be’ better before deploying to combat so they will not have to ‘get’ better after they return.” He then calls for a shift in the military “… to a culture in which psychological fitness is recognized as every bit as important as physical fitness.”
Connection between Thinking and Feeling

This level of endorsement can be seen in practice by way of the significant funding and resources applied to a variety of resilience training programs across all branches of the US military. Perhaps the program that is attempting to influence the largest number of service members is the Comprehensive Soldier Fitness (CSF) program. This project has created and disseminated training that aims to improve emotional coping skills and ultimate resilience across all Army SMs. One element of this program draws input from principles of cognitive-behavioral science, which generally advances the view that it is not the event that causes an emotion, but rather how a person appraises the event (based on how they think about the event) that leads to the emotion.

From this theoretical base, it then follows that internal thinking or appraisals about combat events can be “taught” in a way that leads to more healthy and resilient reactions to stress. This approach does not imply that people with effective coping skills do not feel some level of “rational” emotional pain when confronted with an event that would be challenging emotionally and mentally to any individual. Instead, the aim is to teach skills that may assist soldiers to cope with traumatic stressors more successfully.

The core motive with such efforts is to provide resilience training that would promote psychological fitness and reduce the later incidence of PTSD and other psychological health conditions upon redeployment home (eg, depression, suicide, substance use). A recent study on the CFS program reported results from a longitudinal study over 18 months with 22,000 soldiers indicating positive outcomes, but this report has been criticized for its exclusive reliance on self-report data and on other methodological grounds. Regardless of those academic “battles,” the post-deployment psychological health statistics are alarming and provide a compelling justification for continued efforts to better prepare SMs for the onslaught of emotional challenges that they may face during a combat deployment.

‘Stress Resilience in Virtual Environments’

Recently, the USC ICT has begun development of the STress Resilience In Virtual Environments (STRIVE) project, which expands on the Virtual Iraq/Afghanistan simulations developed for VRET. The STRIVE project aims to foster stress resilience by creating a set of combat simulations that can be used as contexts for SMs to experientially learn stress reduction tactics and cognitive-behavioral emotional coping strategies prior to deployment.

This approach involves immersing and engaging SMs within a variety of virtual “mission” episodes where they are confronted with emotionally challenging situations that are inherent to the OEF/OIF combat environment. Interaction by SMs within such emotionally challenging scenarios aims to provide a more meaningful context in which to engage with psychoeducational information and to learn and practice stress-reduction tactics and cognitive coping strategies that are believed to better prepare a SM for the psychological challenges that may occur during a combat deployment.
To accomplish this, STRIVE is being designed as a 30-episode interactive narrative in VR, akin to being immersed within a “Band of Brothers” type storyline that spans a typical deployment cycle. Within these episodes, SMs will get to know the distinct personalities of the virtual human characters in their squad and interact within an immersive digital narrative that employs cinematic strategies for enhancing engagement with the evolving storyline (eg, strategic use of narration, montage shots, dynamic camera direction).

At the end of each of the graded 10-minute episodes, an emotionally challenging event occurs, designed in part from feedback provided by SMs undergoing PTSD treatment (eg, seeing/handling human remains, death/injury of a squad member, killing someone, the death/injury of a civilian child). At that point in the episode, the virtual world “freezes in place” and a virtual human “mentor” character emerges from the midst of the chaotic VR scenario to guide the user through stress-reduction psychoeducational and self-management tactics, as well as providing rational restructuring exercises for appraising and processing the virtual experience. The resilience training component is drawing on evidence-based content that has been endorsed as part of standard classroom-delivered DoD stress resilience training programs, as well as content that has been successfully applied in nonmilitary contexts (eg, humanitarian aid worker training, sports psychology).

‘Context-Relevant Learning’

In this fashion, STRIVE provides a digital “emotional obstacle course” that can be used as a tool for providing context-relevant learning of emotional coping strategies under very tightly controlled and scripted simulated conditions. Training in this format is hypothesized to improve generalization to real world situations via a state-dependent learning component, and further support resilience by leveraging the learning theory process of “latent inhibition,” which is defined as delayed learning that occurs as a result of pre-exposure to a stimulus without a consequence. Thus, the exposure to a simulated combat context is believed to decrease the likelihood of fear conditioning during the real event.

The STRIVE project also incorporates a novel basic science protocol. While other stress resilience research efforts typically incorporate one or two biomarkers of stress and or resilience, the STRIVE projects will measure what we refer to as the “physiological fingerprint of stress,” commonly called allostatic load (AL). The theoretical construct of AL, initially developed by one of the STRIVE collaborators, Bruce McEwen, is a measure of cumulative wear and tear on physiological symptoms due to chronic stress. As a theoretical construct, it is a preliminary attempt to formulate the relationship between environmental stressors and disease, by hypothesizing mechanisms whereby multiple kinds of stressors confer risk simultaneously in multiple physiological systems.

Allostasis, Equilibrium, and Homeostasis

The construct of AL is based on the widely accepted response called allostasis. Sterling and Eyer defined allostasis as the body’s set points for various physiological mechanisms, such as blood pressure or heart rate, which vary to meet specific external demands, eg, emotional stress. McEwen and Stellar furthered our understanding of allostasis by broadening its scope. Rather than discuss allostasis in terms of a single set point that changed in response to a stressor, they described allostasis as the combination of all physiological coping mechanisms that are required to
maintain equilibrium of the entire system. Thus, allostasis is the reaction and adaptation to stressors by multiple physiological systems that brings the system back to equilibrium.

The related concept of homeostasis refers specifically to system parameters essential for survival. To place AL into the context of allostasis requires the view that allostasis does not always proceed in a normal manner. Any of the major physiological systems (e.g., inflammatory, metabolic, immune, neuroendocrine, cardiovascular, respiratory) in the process of responding to stress can exact a cost, or an AL, that can result in some form of physiological or psychological disturbance.

McEwen identified four types of AL: frequent activation of allostatic systems; a prolonged failure to shut off allostatic activity after stress; a lack of adaptation to stress; and an inadequate response of allostatic systems leading to elevated activity of other, normally counter-regulated allostatic systems after stress (e.g., inadequate secretion of glucocorticoid resulting in increased cytokines normally countered by glucocorticoids). Any of these types of AL intervene with the normal stress response of allostasis, thus increasing the negative health impact from stress. This will increase one’s risk for disease in the long-term and may preclude the short-term development of physical hardiness and psychological resilience.

In a first study of its kind, the STRIVE project will determine if AL can predict acute response to stress (e.g., electroencephalogram, galvanic skin response, electrocardiogram, pupil dilation, etc) when participants are exposed to the stressful simulated VR missions. Further analyses will determine if AL can predict participants’ responses to virtual mentor instructions on how the participants can cope with stress through resilience training. If we find that AL is capable of predicting either short-term response to stress or the ability to learn stress resilience, there would be numerous implications for the future use of AL, including identification of leadership profiles and for informing the development of appropriate training systems for all SMs.

Pilot research on this project is ongoing at the Immersive Infantry Training center at Marine Corps Base Camp Pendleton. This project is noteworthy in that it represents a direct application development effort (resilience training) while also serving as an “ultimate Skinner Box” for the scientific study of stress reactions using objective physiological assessment measures.

Use of ‘Virtual Humans’

Recent shifts in the social and scientific landscape have now set the stage for the next major movement in clinical VR with the “birth” of intelligent virtual humans. With advances in the enabling technologies allowing the design of ever more believable context-relevant “structural” VR environments (e.g., combat scenes, homes, classrooms, offices, markets), the next important challenge will involve populating these environments with virtual human (VH) representations that are capable of fostering believable interaction with real VR users.

This is not to say that representations of human forms have not usefully appeared in previous clinical VR scenarios. In fact, since the mid-1990s, VR applications have routinely employed VHs to serve as stimulus elements to enhance the realism of a virtual world simply by their static presence. However, seminal research and development has appeared in the creation of highly interactive, artificially intelligent and natural
language-capable VH agents that can engage real human users in a credible fashion. No longer at the level of a prop to add context or minimal faux interaction in a virtual world, VH representations can be designed to perceive and act in a 3-D VR world, engage in face-to-face spoken dialogues with real users (and other virtual humans), and in some cases they are capable of exhibiting human-like emotional reactions. Both in appearance and behavior, VHs have now evolved to the point where they can become usable components for a variety of clinical and research applications.

These advances in VH technology have now supported developments for military behavioral health in two key domains: the creation of virtual patients that can be used for training novice clinician care providers in areas that are relevant for working with military populations; and virtual human support agents to serve as online guides for promoting anonymous access to psychological health care information, and for assisting military personnel and family members in breaking down barriers to initiating care.

Virtual Patients vs. Human Standardized Patients

Since 1963, when Howard Barrows, MD, at the University of Southern California, trained the first human standardized patient, this approach using live actors has long been considered to be the gold standard medical education experience for both learning and evaluation purposes. Human standardized patients (HSPs) are paid actors who pretend to be patients for educational interviews and provide the most realistic and challenging experience for those learning the practice of medicine because they most closely approximate a genuine patient encounter. HSPs are also a key component in medical licensing examinations. For example, HSPs are used on the United States Medical Licensing Examination (USMLE) Step 2 Clinical Skills exam, which is mandatory for obtaining medical licensure in the US.

HSP encounters engage a number of clinical skill domains, including social, communication, judgment, and diagnostic acumen in a real time setting. All other kinds of practice encounters fall short of this because they either do not force the learner to combine clinical skill domains or they “spoon feed” data to the student with the practice case that turns the learning more into a pattern recognition exercise, rather than a realistic clinical problem-solving experience. The HSP is the only type of encounter where it is up to the learner to naturalistically pose questions to obtain data and information about the case that then needs to be integrated for the formulation of a diagnostic hypothesis and/or treatment plan.

Limitations of Human Standardized Patients

Despite the well-known superiority of HSPs to other instructional methods, they are employed sparingly. The reason for this limited use is primarily due to the very high costs to hire, train, and maintain a diverse group of patient actors. Moreover, despite the expense of HSP programs, the standardized patients themselves are typically low-skilled actors and administrators face constant turnover resulting in considerable challenges for maintaining the consistency of diverse patient portrayals for training students. This limits the value of this approach for producing realistic and valid interactions needed for the reliable evaluation and training of novice clinicians. Thus, the diversity of clinical conditions that HSP can characterize is limited by availability of human actors and their skills. HSPs that are hired may provide suboptimal variation control and are limited to healthy
appearing adult encounters. This is even a greater problem when the actor needs to be a child, adolescent, elder, person with a disability or in the portrayal of nuanced or complex symptom presentations.

The situation is even more challenging in the training of psychology/social work and other allied health professional students. Rarely are live standardized patients used in such clinical training. Most direct patient interaction skills are acquired via role-playing with supervising clinicians and fellow graduate students, with closely supervised “on-the-job” training providing the brunt of experiential training. While one-way mirrors provide a window for the direct observation of trainees, audio and video recordings are a more common method of providing supervisors with information on the clinical skills of trainees.

However, the imposition of recording has been reported to have demonstrable effects on the therapeutic process that may confound the end goal of clinical training and the supervisor review of raw recordings is a time-consuming process that imposes a significant drain on resources.

Virtual Patients

The development and implementation of computer-generated virtual patients (VPs) could address these limitations by providing diverse varieties of digital clinical presentations with a high degree of consistency and sufficient realism.
In this regard, VPs can fulfill the role of human standardized patients by simulating diverse varieties of clinical presentations with a high degree of consistency, and sufficient realism, as well as being always available for anytime-anywhere training. Similar to the compelling case made over the years for clinical VR generally, VP applications can likewise enable the precise stimulus presentation and control (dynamic behavior, conversational dialogue, and interaction) needed for rigorous laboratory research, yet embedded within the context of an ecologically relevant simulated environment.

Virtual Patient with Conduct Disorder

The USC ICT began work in this area in 2007 with an initial project that involved the creation of a VP, named “Justin.” Justin portrayed a 16-year-old male with a conduct disorder forced by his family to participate in therapy. The system was designed to allow novice clinicians to practice asking interview questions, to attempt to create a positive therapeutic alliance and to gather clinical information from this very challenging and resistant VP. Justin was designed as a first step in our research.

At the time, the project was unfunded and thus required our lab to take the economically inspired route of recycling a virtual character from a military negotiation-training scenario to play the part of Justin. The research group agreed that this sort of patient was one that could be convincingly created within the limits of the technology (and funding) available to us at the time. For example, such resistant patients typically respond slowly to therapist questions and often use a limited and highly stereotyped vocabulary. This allowed us to create a believable VP within limited resources for dialogue development. As well, novice clinicians have been typically observed to have a difficult time learning the value of “waiting out” periods of silence and nonparticipation with these patients.
We initially collected user interaction and dialogue data from a small sample of psychiatric residents and psychology graduate students as part of our iterative design process to evolve this application area. The project produced a successful proof of concept demonstrator, which then led to the acquisition of funding that currently supports our research in this area.

Sexual Assault Virtual Patient

Following our successful Justin proof of concept, our second VP project involved the creation of a female sexual assault victim, “Justina.” The aim of this work was twofold: explore the potential for creating a system for use as a clinical interview trainer for promoting sensitive and effective clinical interviewing skills with a VP that had experienced significant personal trauma; and create a system whereby the dialogue content could be manipulated to create multiple versions of Justina. This was to provide a test of whether novice clinicians would ask the appropriate questions to assess whether Justina met the criteria for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnosis of PTSD based on symptoms reported during the clinical interview.

For the PTSD content domain, 459 questions were created that mapped roughly 4-to-1 to a set of 116 responses. The aim was to build an initial language domain corpus generated from subject matter experts and then capture novel questions from a pilot group of users (psychiatry residents) during interviews with Justina. The novel questions that were generated could then be fed into the system to iteratively build the language corpus. We also focused on how well subjects asked questions that covered the six major symptom clusters that can characterize PTSD following a traumatic event.

While this approach did not give the Justina character a lot of depth, it did provide more breadth for PTSD-related responses, which for initial testing seemed prudent for generating a wide variety of questions for the next Justina iteration.

In the initial test, a total of 15 psychiatry residents (six females, nine males; mean age = 29.80 years, SD 3.67) participated in the study and were asked to perform a 15-minute interaction with the VP to take an initial history and determine a preliminary diagnosis based on this brief interaction with the character. The participants were asked to speak normally, as they would to a standardized patient, but were informed that the system was a research prototype that uses an experimental speech recognition system that would sometimes not understand them. They were instructed that they were free to ask any kind of question and the system would try to respond appropriately, but if it did not, they could ask the same question in a different way.

From post-questionnaire ratings on a 7-point Likert scale, the average subject rating for believability of the system was 4.5. Subjects reported their ability to understand the patient at an average of 5.1, but rated the system at 5.3 as frustrating to talk to due to speech recognition problems, out-of-domain answers, or inappropriate responses. However, most of the participants left favorable comments that they thought this technology will be useful in the future, and that they enjoyed the experience of trying different ways to talk to the character to elicit an relevant response to a complex question.
When the patient responded back appropriately to a question, test subjects informally reported that the experience was very satisfying. Analysis of concordance between user questions and VP response pairs indicated moderate effects sizes for trauma inquiries (r = 0.45), re-experiencing symptoms (r = 0.55), avoidance (r = 0.35), and in the non-PTSD general communication category (r = 0.56), but only small effects were found for arousal/hypervigilance (r = 0.13) and life impact (r = 0.13). These relationships between questions asked by a novice clinician and concordant replies from the VP suggest that a fluid interaction was sometimes present in terms of rapport, discussion of the traumatic event, the experience of intrusive recollections, and discussion related to the issue of avoidance.

Low concordance rates on the arousal and life impact criteria indicated that a larger domain of possible questions and answers for these areas was not adequately modeled in this pilot effort and this is now being addressed in our next generation VH research and development. We are currently collaborating with the USC School of Social Work, Center for Innovation in Research (CIR), which essentially is a master of social work degree program with an emphasis on military social work. The current project with CIR focuses on the creation of military VPs that will allow social work trainees to gain practical training experiences with VHs that portray behavior more relevant to military culture and common clinical conditions. A sample video of the military VPs being interviewed by a social work trainee (conducting a suicide assessment) can be found at: www.youtube.com/watch?v=CQTEcJJ_RhY.

Follow-on work to these VP projects has been funded to develop a tool-kit that allows clinical educators to author VPs for clinical training. One of the aims of the system is to build an interface that allows clinical educators to create a VP with the same ease as creating a Powerpoint presentation. Such VPs, authored by clinical professionals, would then become available to an open source community to broaden the opportunities for diverse clinical training experiences.

Online Virtual Human Health Care Guide

Research suggests that there is an urgent need to reduce the stigma of seeking mental health treatment in SM and veteran populations. One of the more foreboding findings in an early report by Hoge et al76 was the observation that among Iraq/Afghanistan War veterans, "...those whose responses were positive for a mental disorder, only 23% to 40% sought mental health care. Those whose responses were positive for a mental disorder were twice as likely as those whose responses were negative to report concern about possible stigmatization and other barriers to seeking mental health care."

While US military training methodology has better prepared soldiers for combat in recent years, such hesitancy to seek treatment for difficulties that emerge upon return from combat, especially by those who may need it most, suggests an area of military mental health care that is in need of attention. Moreover, the dissemination of health care information to military SMs, veterans and their significant others is a persistent and growing challenge. Although medical information is increasingly available over the Internet, users can find the process of accessing it to be overwhelming, contradictory and impersonal.
Challenges to Providing Military Mental Health Services

Despite a Herculean effort on the part of the DoD to produce and disseminate behavioral health programs for military personnel and their families, the complexity of the issues involved continue to challenge the best efforts of military mental health care experts, administrators, and providers. Since 2004, numerous blue ribbon panels of experts have attempted to assess the current DoD and VA health care delivery system and provide recommendations for improvement, including the National Academies of Science Institute of Medicine, Dole-Shalala Commission Report, the Rand Report, and the American Psychological Association. Most of these reports cite two major areas in need of improvement:

Support for RCTs that test the efficacy of treatment methodologies, leading to wider dissemination of evidenced based approaches.

Identification and implementation of ways to enhance the health care dissemination/delivery system for military personnel and their families in a fashion that provides better awareness and access to care, while reducing the stigma of help-seeking.

For example, the American Psychological Association Presidential Task Force on Military Deployment Services for Youth, Families and Service Members stated in 2007 that they were, "… not able to find any evidence of a well-coordinated or well-disseminated approach to providing behavioral health care to service members and their families." The APA report also went on to describe three primary barriers to military mental health treatment: availability, acceptability, and accessibility. More specifically:

Well-trained mental health specialists are not in adequate supply (availability).

The military culture needs to be modified so that mental health services are more accepted and less stigmatized.

Even if providers were available and seeking treatment was deemed acceptable, appropriate mental health services are often not readily accessible due to a variety of factors (eg, long waiting lists, limited clinic hours, a poor referral process and geographical location). The overarching goal reported from this and other reports is to provide better awareness and access to existing care while concurrently reducing the complexity and stigma in seeking psychological help. In essence, new methods are needed to reduce such barriers to care.

SimCoach Created to Improve Military Mental Health Service Usage

The SimCoach project aims to address this challenge by supporting users in their efforts to anonymously seek health care information and advice by way of online interaction with an intelligent, interactive, embodied virtual human health care guide. The primary goal of the SimCoach project is to break down barriers to care (eg, stigma, unawareness, complexity) by providing military SM, veterans, and their significant others with confidential help in exploring and accessing health care content and, if needed, for encouraging and supporting the initiation of care with a live provider.

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Rather than being a traditional Web portal, SimCoach allow users to initiate and engage in a dialogue about their health care concerns with an interactive VH. Generally, these intelligent graphical characters are designed to use speech, gesture, and emotion to introduce the capabilities of the system, solicit basic anonymous background information about the user's history and clinical/psychosocial concerns, provide advice and support, present the user with relevant online content, and potentially facilitate the process of seeking appropriate care with a live clinical provider.

An implicit motive of the SimCoach project is that of supporting users who are determined to be in need, to make the decision to take the first step toward initiating psychological or medical care with a live provider.

It is not the goal of SimCoach to breakdown all of the barriers to care or to provide diagnostic or therapeutic services that are best delivered by a live clinical provider. Rather, SimCoach was designed to foster comfort and confidence by promoting users' private and anonymous efforts to understand their situations better, to explore available options, and initiate treatment when appropriate. Coordinating this experience is a VH SimCoach, selected by the user from a variety of archetypical character options (see Figure 1), who can answer direct questions and/or guide the user through a sequence of user-specific questions, exercises, and assessments.

This interaction between the VH and the user provides the system with the information needed to guide users to the appropriate next step of engagement with the system or with encouragement to initiate contact with a live provider.

Again, the SimCoach project is not conceived as a replacement for human clinical providers and experts. Instead, SimCoach aims to start the process of engaging the user by providing support and encouragement, increasing awareness of their situation and treatment options, and in assisting individuals who may otherwise be initially uncomfortable talking to a live care provider.

Users can flexibly interact with a SimCoach character by typing text and clicking on character-generated menu options. Since SimCoach was designed to be an easily accessible Web-based application that requires no downloadable software, it was believed that voice recognition was not at a state where it could be reliably used at the start of the project in 2010. The feasibility of providing the option for spoken, natural language dialogue interaction is currently being explored to determine if off-the-shelf voice recognition programs are sufficiently accurate to maintain an engaged interaction between a SimCoach and a user.

The options for a SimCoach’s appearance, behavior and dialogue has been designed to maximize user comfort and satisfaction, but also to facilitate fluid and truthful disclosure of clinically relevant information. Focus groups, “Wizard of OZ” studies, and iterative formative tests of the system were employed with a diverse cross section of our targeted user group to create options for SimCoach interaction that would be both engaging and useful for this population’s needs. Results from these user tests indicated some key areas that were determined to be important, including user-choice of character archetypes across gender and age ranges, informal dialogue interaction, and interestingly, a preference for characters that were not in uniform.
Also, interspersed within the program are options that allow the user to respond to simple screening instruments, such as the PCL-M that are delivered in a conversational format with results fed back to the user in a supportive fashion. These screening results serve to inform the SimCoach’s creation of a model of the user to enhance the reliability and accuracy of the SimCoach output to the user, to support user self-awareness via feedback and to better guide the delivery of relevant information based on this self-report data. Moreover, an enhancement in user engagement with a SimCoach may be produced if a more accurate assessment of the user’s needs is derived from this process to inform the relevancy of the interaction.

Focus on Privacy Protection

Engagement also is supported by ensuring that the specific health care content that a SimCoach can deliver to users is relevant to persons with a military background (and of course, to their significant others). This was addressed by leveraging content assets that were originally created for established DoD and VA websites specifically designed to address the needs of this user group (eg, after deployment, Military OneSource, National Center for PTSD). Our early research with this user group indicated a hesitancy to directly access these sites when users sought behavioral health information with a common complaint being that there was a fear that their use of those sites may be monitored and might jeopardize advancement in their military careers or later applications for disability benefits.

Despite significant efforts by the DoD and VA to dispel the idea that user tracking was employed on these sites, the prevailing suspicion led many of the users in our samples to conduct such health care queries using Google, Yahoo and Medscape. To address this user concern, supplemental content presented by the SimCoach (eg, video, self-assessment questionnaires, resource links) are typically “pulled” into the site, rather than directing users away “to” those sites.

‘Go-to Relationship’

As the system evolves, it is our view that engagement would be enhanced if the user was able to interact with the SimCoach repeatedly over time. Ideally, users could progress at their own pace over days or even weeks as they perhaps develop a “relationship” with a SimCoach character as a “go-to” source of health care information and feedback. However, this option for evolving the SimCoach comfort zone with users over time would require significant database resources to render the SimCoach capable of “remembering” the information acquired from previous visits and to build on that information in similar fashion to that of a growing human relationship.

Moreover, the persistence of a SimCoach memory for previous sessions would also require the user to sign into the system with a user name and password. This would necessitate the SimCoach system to “reside” on a high security server, such that content from previous visits could be stored and accessed with subsequent visits.
Such functionality might be a double-edged sword, as anonymity is a hallmark feature to draw in users who may be hesitant to know that their interactions are being stored, even if it resulted in a more relevant, less redundant, and perhaps more meaningful interaction with a SimCoach over time. Likely, this would necessarily have to be a clearly stated “opt-in” function, as the technology may support this in the future.

Users also have the option to print out a PDF summary of the SimCoach session. This is important for later personal review and for the access to links that the SimCoach provided in the session to relevant Web content or to bring with them when seeking clinical care to enhance their comfort level, armed with knowledge, when dealing with human clinical care providers and experts. We have also created software authoring tools that allows other clinical professionals to create SimCoach content to enhance the likelihood that the program will evolve based on other care perspectives and emerging needs in the future.

The current version of SimCoach is undergoing beta-testing with a limited group of test-site users. Results from this user-centered testing will serve to advance the development of a SimCoach system that is expected to undergo a wider release in 2013. Although this project represents an early effort in this area, it is our view that the clinical aims selected can still be usefully addressed within the limits of current technology. However, we expect that SimCoach will continue to evolve over time based on data collected from ongoing user interactions with the system and advances in technology, particularly with improved voice recognition.

Along the way, this work will afford many research opportunities for investigating the functional and ethical issues involved in the process of creating and interacting with VHs in a clinical or health care support context. While the ethical challenges may be more intuitively appreciated, the functional technology challenges also are significant. As advances in computing power, graphics and animation, artificial intelligence, speech recognition, and natural language processing continue to develop at current rates, we expect that the creation of highly interactive, intelligent VHs for such clinical purposes is not only possible, but probable.

Conclusions

This article detailed a range of applications that illustrate the current use of clinical VR to address the behavioral health care needs of those suffering from the wounds of war. If one reviews the history of the impact of war on advances in clinical care, it could be suggested that clinical VR may be an idea whose time has come. For example, during WW I, the Army Alpha/Beta Classification Test emerged from the need for better cognitive ability assessment; that development later set the stage for the civilian intelligence testing movement during the mid-20th century. As well, the birth of clinical psychology as a treatment-oriented profession was borne from the need to provide care to the many veterans returning from WW II with “shell shock.” The Vietnam War then later drove the recognition of PTSD as a definable and treatable clinical disorder. In similar fashion, one of the clinical “game changing” outcomes of the OEF/OIF conflicts could derive from the military’s support for research and development in the area of clinical VR that could potentially drive increased recognition and adoption within the civilian sector.

As we have seen throughout history, innovations that emerge in military health care, driven by the urgency of war, typically have a lasting influence on civilian health care long after the last shot is fired.

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However, such impact will only occur if positive efficacy and cost-benefit outcomes are generated from research with these military-based VR applications. As in all areas of new technology design and development, it is easy for one to get caught up in the excitement that surrounds the potential for innovative clinical opportunities, while casting a blind eye to the pragmatic challenges that exist for building and disseminating useful and usable applications. Thus far, rational minds have prevailed among clinical VR developers and clinicians, most of whom have approached this area with an honest measure of enthusiastic vision, good science, and healthy skepticism. This has led to a growing interest in VR within the health care community as clinical tests are incrementally demonstrating that VR can be implemented safely, at a reasonable cost, and that it has now begun to yield clinical outcomes that are at the least equivalent to, and sometimes more effective than, the more traditional approaches. Thus, any rush to adopt VR should not disregard principles of evidence-based and ethical clinical practice.

In the end, technology is really no more than a tool. The technology in and of itself, does not “fix” anybody. Rather, these systems are designed to either train or extend the skills of a well-trained clinician, and in the case of SimCoach, to help a person to anonymously find the treatment they may benefit from with a live human provider.

These systems, while providing treatment options not possible until recently, will most likely produce therapeutic benefits when administered within the context of appropriate care via a thoughtful and professional appreciation of the complexity of these important behavioral health care challenges.

Note: Space limitations preclude the presentation of rich visual imagery of the work described in this article. The reader is invited to access Internet links provided in the Sidebar to view approximately 60 videos that are available for learning more about these projects.

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**Posttraumatic Stress Disorder (PTSD) Screening and Early Intervention After Physical Injury**

Annals of Surgery
Raul Coimbra, MD, PhD
March 2013

Dr Zatzick and the group from the Harborview Injury Prevention and Research Center and their level 1 trauma center program at the University of Washington are to be congratulated for their excellent work on the screening and management of posttraumatic stress disorder (PTSD) in surgically hospitalized injury survivors.

This article will be highly cited in future research projects and will be mandatory reading for all of us working in trauma settings and dealing with survivors of severe injury.
Trauma is a disease. As such, it must be approached in a multidisciplinary fashion. It is unacceptable to consider that the consequences of the initial injury will become nonexistent at the moment that the body heals. The late and long-term consequences of this devastating disease include, but are not limited to, impairment in physical functioning, psychological disturbances, social disintegration, destruction of families, lack of productivity, and high social costs.

The unavailability of proven screening and treatment strategies during or immediately after the acute phase of care suggests not only lack of knowledge and understanding of the "hidden" consequences of traumatic injury but also the complete failure of the health care system in providing support mechanisms to care for mental health care issues.

The study by Zatzick et al attempted to fill some of those gaps. During a 3.5-year period, the authors screened 207 trauma patients for PTSD symptoms, once during their initial hospitalization and then early after discharge from the hospital. After the screening process, patients were randomized to a stepped collaborative care intervention or usual care control. The interventions included care management, pharmacotherapy, and cognitive behavioral therapy (CBT), which lasted for 12 months and were delivered both in the hospital and in the outpatient clinics. Behavioral activation psychotherapy and motivational interviewing were delivered early on by the care management team. Pharmacotherapy included a serotonin-specific reuptake inhibitor (SSRI) and antidepressant agent in addition to medications targeting insomnia. CBT included psychoeducation, muscle relaxation, cognitive restructuring, and graded exposure.

The authors used 2 measures to assess PTSD: Clinician-Administered PTSD Scale (CAPS) and PTSD Checklist–Civilian Version (PCL-C). The PCL-C was used as the screening tool to enroll patients in the study. Patients who scored high on the PCL-C while in the hospital were screened again, and those who scored high for a second time were randomized into the study. In addition, the authors used the Patient Health Questionnaire to assess for depressive symptoms, the AUDIT-C for alcohol use, and the Medical Outcomes Study 36-Item Short Form Health Survey, Physical Component Summary, to assess physical health and function.

They found that study patients were more likely to be female, less severely injured, intentionally injured, blood alcohol positive, younger, and had prolonged hospitalization. They reached the remarkably high rate of 75% follow-up.

From a design point of view, the authors have taught us that even when including complex stepped treatment strategies, it is possible to carry out well-designed studies. Care managers spent approximately 13 hours per year providing care to individual patients, and the intensity of care provided decreased over the course of the 12-month period. Medication compliance was more than 60%, and 77% received more than 1 session of motivational interviewing targeting alcohol use and other high-risk behaviors, a definite indirect benefit of the study, which are certainly important components in the development of a comprehensive program. Perhaps, as important, patients participating in the collaborative care program component were more likely to receive pharmacotherapy, an adequate dosage of antidepressant medication, and a medication for insomnia. With such structured treatment strategy, it is not surprising that intervention patients were very satisfied with their general health and emotional care.
PTSD researchers who oppose or have criticisms to early screening and intervention state that in many cases, early PTSD symptoms resolve or disappear over time and therefore one should wait several days or weeks to use screening tools to effectively diagnose significant PTSD symptoms. Obviously, those who believe in early screening propose it in an attempt to mitigate symptoms and the development of the disease by implementing early intervention. Although the authors have not provided us with a clear denominator in their study, which would allow them to define the baseline rate of significant early PTSD after injury, they have clearly shown that symptoms "do not go away" as many investigators, who oppose to early screening, think. In fact, in the observation group at 6 months, mean CAPS and PCL-C scores remain close to baseline (immediately postinjury) values. At 12 months, mean CAPS scores remained above 50 and mean PCL-C were approximately 45 points.

The authors showed that patients in the intervention group demonstrated marked reductions in the symptoms of PTSD over a 12-month period. More importantly, differences were also demonstrated in the intervention group regarding treatment response criteria, PTSD remission criteria, and improvements in physical function, a novel finding in studies of patients receiving stepped collaborative care intervention. The study also emphasizes that CBT, which is more labor-intensive to deliver, might be reserved for PTSD patients with more long-term and recurrent symptoms and that "easier to apply" measures should be indicated early and might reach a sustainable level of resolution, avoiding the "shotgun" approach that may not serve all.

The findings of the study by Zatzick et al are very comprehensive and conclusive. Others have also studied issues related to early screening of PTSD in the posttraumatic period, although in smaller scales. Browne et al examined the clinical utility of screening and early intervention in reducing the disability (chronic pain, PTSD, and depression) after traumatic injury. They studied 142 severely injured patients (excluded patients with traumatic brain injury) within 4 weeks postinjury. They randomized patients to a multidisciplinary intervention (received care at 1 and 3 months for pain, rehabilitation, occupational therapy, and psychological services) or usual care. They found that acute pain, posttraumatic adjustment, depression, acute trauma symptoms, and alcohol use predicted depressive symptoms and PTSD severity at 6 months. Interestingly, 24% patients of the usual care group were initially below the cutoff mark for being at risk for PTSD or depression but had a diagnosis of these diseases at 6 months. Therefore, it seems that although early intervention is useful and is associated with a decreased incidence of significant PTSD or depression symptoms at 6 months after injuries, some patients will screen negative early on and will convert to a positive screening at a later time. This observation begs the question of when early is too early to screen. Future studies should be designed to answer this important question.

The question related to which component of the stepped intervention was the most effective in reducing PTSD symptoms still remains unanswered in the study of Zatzick et al. CBT and SSRIs are recommended for the treatment of PTSD. SSRIs, such as sertraline, paroxetine, and fluoxetine, have been used effectively in randomized clinical trials with favorable results. However, the choice of treatment is arbitrary and unclear to clinicians due to the lack of specific guidelines determining when therapy escalation is appropriate. It is possible that pharmacological therapy predominates in clinical practice because of the lack of availability and accessibility of CBT for the trauma patient population as stated by Polak et al.

One meta-analysis specifically attempted to compare the effects of pharmacological approach with psychotherapeutic treatment options for PTSD. A small advantage was found in favor of CBT compared with medications. One study found higher relapse rates at 6-month follow-up in patients...
treated with paroxetine than with CBT, whereas another study found that patients treated with psychotherapy were markedly more asymptomatic at 6 months (58%) than patients treated with a pharmacological approach. None of these studies included a significant number of patients compared with the present study. The duration of pharmacological treatment with SSRIs (12 weeks vs 24 weeks) has also been studied. It seems that a prolonged course of pharmacological therapy is more beneficial than a shorter course, although others have found otherwise.

Another early intervention that may be added to the current treatment strategies for patients with early, severe PTSD symptoms aims at modifying memory to prevent the development of PTSD before memory consolidation. To that end, Rothbaun et al randomly assigned patients to 3 sessions of a very early intervention beginning in the emergency department and compared this to an observation-only group. They assessed posttraumatic stress reactions (PTSRs) at 4 and 12 weeks postinjury and depression at 4 weeks. They were able to assess trauma patients at 11.8 hours postinjury, on average. Patients in the intervention group had lower PTSRs at 4 and 12 weeks and lower depressive symptoms at 4 weeks. They concluded that the modified exposure intervention initiated in the emergency department within hours postinjury is a successful, safe, and feasible strategy in reducing PTSRs and depression symptoms.

Recently, Reese et al used the Primary Care PTSD screening tool on trauma patients on clinic visits after hospital discharges post–acute traumatic event. Although no intervention was planned in the study, the authors concluded that the simplified screening tool is easy to use and can be used with both, patients and families of patients.

Another unanswered question is related to the cost-effectiveness of such an intense screening and treatment approach, as proposed by the Harborview group. Until we know which components are most effective early on, proposing broad screening and a multifaceted treatment approach may be too costly for trauma centers, which are already facing too many unfunded mandates.

Finally, the experience in the current military conflict has demonstrated that mild traumatic brain injury and PTSD combined is a disease complex that needs attention, investigation, and well-defined diagnostic and treatment strategies. We hope that investigators will consider well-designed multi-institutional studies to evaluate larger number of trauma patients, which will provide us with enough information about the natural history of mild traumatic brain injury and PTSD.

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**Participation in Outdoor Recreation Program Predicts Improved Psychosocial Well-Being Among Veterans With Post-Traumatic Stress Disorder: A Pilot Study**

Elizabeth Jane Vella, PhD; Briana Milligan, BA; Jessie Lynn Bennett, MS

March 2013
Abstract

Purpose: Evaluate the effectiveness of a 2-day, 3-night outdoor recreation intervention involving fly-fishing in reducing the psychological concomitants of stress among 74 veterans (M = 47.27, SD = 14.55 years) with post-traumatic stress disorder (PTSD). Methods: Participants completed repeated assessments of attentiveness, mood, depression, anxiety, and somatic stress across 3 time periods, corresponding to 2 weeks before the trip (baseline), the last day of the trip, and a 6-week follow-up. Assessments of perceptual stress, PTSD symptoms, and sleep quality were also administered during the baseline and follow-up periods. Results: Acute effects were observed for improvements in attentiveness and positive mood states, coupled with significant and sustained reductions in negative mood states, anxiety, depression, and somatic symptoms of stress. Comparisons between the baseline and follow-up periods revealed significant improvements in sleep quality and reductions in perceptual stress and PTSD symptoms. Conclusions: The current findings suggest that combat veterans with PTSD may benefit from participation in group-based outdoor recreation as a means to improve psychosocial well-being.

Introduction

A debilitating condition, post-traumatic stress disorder (PTSD), afflicts an estimated 7.7 million American adults, according to the National Institutes of Health. Amid this population are those who acquired the disorder in combat. Current estimates from the U.S. Department of Veterans Affairs state that PTSD affects about 30% of Vietnam veterans, 10% of Gulf War veterans, 11% of Afghanistan veterans, and 20% of veterans returning from Iraq. PTSD is characterized by symptoms resulting from traumatic event experience. These symptoms include recurring and distressing memories of trauma, hyperarousal, and avoidance of stimuli that trigger traumatic memories. Due in part to this clustering of symptoms, PTSD has high comorbidities with anxiety disorders, major depressive disorder, and sleep disturbances. Consequently, those with PTSD have been known to engage in avoidant coping strategies, such as alcohol and drug abuse, to ameliorate the symptomatology associated with the condition.

In addition to the symptoms and pathologies noted above, the effects of PTSD run deep below the surface at the physiological level, resulting from the wear and tear of a heightened stress system. The detrimental effects of stress on health are well documented. Chronic activation of the sympathetic nervous system can lead to high blood pressure and proinflammatory responses predictive of cardiovascular and immune dysfunction. Both prospective and archival research has found that veterans with PTSD are more likely to report health problems than those without PTSD. A 50-year prospective study suggests that combat-induced trauma predicts mortality rates by the age of 65. Moreover, a recent prospective study of approximately 2,000 initially healthy combat veterans revealed PTSD to predict coronary heart disease morbidity and mortality.

Common PTSD treatments run the full gamut of pharmacologic interventions, cognitive behavioral therapies, exposure therapy, and supportive psychotherapy. Psychotropic medication has been used to address PTSD symptoms as well as comorbid disorders, such as depression and anxiety. The most frequently administered drugs include antidepressants, anxiolytics, sedative hypnotics, and in some cases antipsychotics.
Despite the demonstrated efficacies of these various therapeutic approaches, a substantive proportion of patients with PTSD remain symptomatic following treatment.

Therapies designed to address stress symptoms at the psychosocial level may incur benefit by improving quality of life among patients with PTSD. Alternative therapies, such as outdoor therapeutic recreation, have promising implications for use among populations with PTSD, but have not been adequately examined within this target population. However, leisure and recreation activities have been found to reduce self-reported levels of stress and contribute to both physical and mental health in a variety of settings and among a host of demographic samples. Moreover, recent cross-sectional evidence has found significant associations between tendencies to engage in leisure activities and a variety of psychological and physical well-being assessments. Individuals reporting higher levels of leisure activity participation were found to display lower depression, negative affect (NA), resting blood pressure, daily cortisol production, waist circumference, body mass index, and higher levels of positive affect (PA). Indeed, experimental evidence has found spending time in natural environmental settings to increase PA, attentional capacity, and ability to reflect on a life problem.

Theoretical models designed to interpret the health-promoting effects of leisure activity participation have proposed attention restoration and leisure-related social support as potential mechanisms that may facilitate a shift toward improved psychosocial well-being among participants. Attention restoration theory posits that spending time in natural environments confer restorative effects on cognitive abilities. The theory has garnered support through research indicating that natural environmental stimuli modestly elicit involuntary attention mechanisms, thereby enabling directed attention mechanisms an opportunity to replenish, whereas urban environmental stimuli exerts a comparatively intense impact upon attention resources and as such are not restorative. An experimental intervention has provided supportive evidence, revealing an hour-long stroll through an arboretum to predict significant improvements on directed attention tasks relative to an hour-long walk through an urban area. Another theoretical orientation in the therapeutic recreation literature concerns the stress-buffering influence of leisure-related social support on health, suggesting that the presence of social support fostered via leisure activities enhances coping resources for daily stress. A longstanding history in health psychology research has focused attention on the salubrious effects of social support. Individuals in integrated social networks display lower disease morbidity and mortality rates relative to the socially isolated. Leisure activities often include a social companionship element serving as a critical component for predicting improved physical and mental health outcomes. Leisure-engendered social support may moderate the effects of stress on health by working as an instrumental agent in reducing depression and physical illness symptoms.

The focus of the current research is to evaluate the effectiveness of a group-based outdoor recreation program involving fly-fishing in reducing the psychological concomitants of stress among a sample of veterans with PTSD. The primary hypothesis under investigation is that the fly-fishing retreat will predict acute elevations in attentiveness and sustained improvements in psychosocial well-being and sleep quality, in addition to reductions in PTSD symptomatology. An exploratory ancillary hypothesis concerns the strength and direction of association between particular dependent variables, whereby reductions in PTSD symptoms will predict improvements in sleep quality.

Methods
Participants

The participants included 74 veterans (69 men, 5 women; $M = 47.27, SD = 14.55$ years; range: 22–64 years) who participated in one of the 19 fly-fishing retreats for veterans with PTSD at the Rivers of Recovery (ROR) residential facility, located off the Green River in northern Utah, which took place in summer to early fall of 2009 and 2010. ROR is a nonprofit organization dedicated to improving quality of life for veterans with disabilities through fly-fishing excursions along the Green River, a body of water stocked with rainbow and brown trout; the activity of fly-fishing was selected by the ROR organization because the sport has been regarded to induce a calm alertness in a pristine natural environment that may enhance the ability to focus and reduce perceptual stress levels. Inclusionary criteria for participation involved being a veteran who has served in a foreign country with a confirmed diagnosis of PTSD ($n = 73$) or exhibiting a clinically relevant score on the PTSD check list, military version (PCL-M; $n = 1$). Dual diagnosis of PTSD-major depressive disorder ($n = 43$) or PTSD/traumatic brain injury ($n = 23$) was permitted as a result of the high comorbidity rates of these psychopathologies. Exclusionary criteria included dual diagnosis with an Axis I disorder from the Diagnostic and Statistical Manual IV other than PTSD or major depressive disorder.

Ninety six individuals met all the above stated criteria and were enrolled as participants in this study. Six (6%) of these individuals dropped out/withdrew from the study following baseline assessment and before participation in the fly-fishing excursion, whereas another 16 (17%) participants from the initially enrolled sample dropped out/withdrew from the study after participating in the fly-fishing excursion and before the follow-up assessment. Independent samples $t$-tests confirmed that the 22 participants who dropped out/withdrew from the study following the baseline assessment or fly-fishing excursion did not differ from the 74 participants who completed the study through the follow-up assessment in terms of age or total baseline score from the PCL-M ($p > 0.3$).

Recruitment for the fly-fishing retreats was through private referral and fliers distributed at recreation therapy offices in Veteran Administration hospitals. All participants signed an informed consent document before participating in this study, which received approval from the Institutional Review Board at the University of Southern Maine. Participants also completed a health and demographics questionnaire designed for the purposes of this study, containing items concerning age, education, ethnicity, marital status, military service, and pharmacologic treatments to date. Sample characteristics are featured in Table I. The sample was predominantly Caucasian (81%), with 23% of the sample reporting no more than a high school education, 63% having an associate's degree, and the remaining 14% of the sample reporting a bachelor's degree or higher. Most of the veterans served in the U.S. Army (68%), with the remaining having served in the Marines (15%), Navy (9%) or U.S. Army National Guard (8%). The median length of military service was 4 years (range = 1–38 years), with 7 veterans still employed by the military at the time of research participation.

Measures and Procedures

This study represents a repeated measures longitudinal assessment of 19 separate 3 night, 2 day fly-fishing excursions offered through the ROR program on the Green River in northern Utah. Each participant served as his/her own control. The fly-fishing excursions took place on Thursdays to Sundays in August and September of 2009 (5 trips) and June to October of 2010 (14 trips). The excursions varied in terms of number of
participants from 2 to 7 veterans ($M = 4$, $SD = 1.6$ veterans). Participants underwent repeated psychosocial assessments of mood, depression, anxiety, and somatic symptoms of stress, across 3 time periods, corresponding to 2 weeks before the fly-fishing excursion (baseline), the last day of the fly-fishing retreat, and a 6-week follow-up assessment. Additional psychosocial assessments of perceptual stress, PTSD symptoms, and sleep quality were administered during the baseline and follow-up periods. All psychosocial assessments were administered online via use of Survey Monkey.

**Intervention**

The fly-fishing excursions involved a small group of veterans sharing lodging accommodations in a 3-bedroom house for 3 nights and spending a total of 16 hours fly-fishing from drift boats on the Green River across 2 days (e.g., arriving on a Thursday evening, fly-fishing on Friday and Saturday, and returning home on Sunday morning). Participants were provided the opportunity to learn the art of fly-fishing by trained specialists, connect with others who have experienced similar life challenges, and enjoy the setting of a pristine natural environment. Transportation to the ROR residential facility was provided by the program. Upon arrival, participants were given time to settle into their lodging before dinner. After dinner, participants were introduced to the ROR staff and fly-fishing guides and discussed the trip activities and fishing schedule. The subsequent 2 days included the following itinerary: breakfast, 4 hours of morning fishing, lunch along the river, 4 hours of afternoon fishing, social hour at the residential facility, dinner, and postdinner games/entertainment. Participants were provided transportation home following breakfast on the morning after the second day of fly-fishing.

**Dependent Variables: Psychosocial Assessments**

The PCL-M was used to assess degree of PTSD symptoms via diagnostic criteria of hyperarousal, re-experiencing, and avoidance behaviors within the past month. Participants rated the 17 PCL-M self-report items on a scale ranging from 1 = not at all to 5 = extremely. This inventory has demonstrated good psychometric properties, with previous research supporting a global cutoff score of “50” or greater to represent clinically relevant PTSD symptomatology. A study of 117 OEF/OIF combat veterans using the PCL-M to index PTSD symptoms reported a high internal consistency ($\alpha = 0.97$).

Psychological distress was measured using the Brief Symptom Inventory-18 (BSI), an 18-item Likert-type scale designed to measure the severity of anxiety, depression, and somatic symptoms of stress in the past week. Possible scores for the total scale range from 0 to 72, with higher values indicative of more severe psychological distress. This inventory has demonstrated adequate internal consistencies (0.71–0.89) and test–retest reliabilities (0.68–0.82).

Mood was assessed with the Positive Affect and Negative Affect Schedule (PANAS), a 60-item Likert-type scale in which participants respond to various emotive adjectives in reference to the past week on a 5-point scale ranging from 1 = very slightly to not at all to 5 = extremely. The PANAS is a widely used inventory with demonstrated convergent validities relative to other standardized mood inventories and adequate internal consistencies across subscales ($\alpha = 0.75–0.93$ amid a sample of 328 adults).
The Perceived Stress Scale (PSS), a 10 item self-report inventory, was used to assess how unpredictable, uncontrollable, and overloaded respondents found their lives in the past month. Participants rated each item on a 5-point scale ranging from 0 = never to 4 = very often. The PSS has demonstrated adequate internal consistencies in across a variety of large samples ($n > 1,000$ each), with $\alpha$ ranging from 0.78 to 0.91.

Participants completed the Pittsburgh Sleep Quality Inventory (PSQI), a 19-item self-report questionnaire designed to measure 7 components of sleep quality in the past month, the sum of which yields one global score. Respondents rated each item from this inventory on a 4-point scale, with “0” = “not in the past month” and “3” = “three or more times a week.” Potential global score values range from 0 to 21, with lower scores indicating better sleep quality. This inventory has been found to display adequate internal consistencies across four clinical samples ($\alpha = 0.80$) with demonstrated convergent and discriminant validities.

Analytic Strategy

All statistical analyses were conducted using the Statistical Package for the Social Sciences, version 19.0, with alpha levels set to 0.05 for delineation of significant effects. To test whether the fly-fishing intervention predicted significant reductions in psychological distress coupled with improvements in mood, three separate multivariate analyses of variance (MANOVA’s) on repeated measures were run on all three time periods, with Bonferroni post hoc procedures to control for Type 1 Error. The first MANOVA evaluated significant differences over time in total scale scores for the BSI, along with the corresponding subscale scores of depression, anxiety, and somatic stress. The second MANOVA evaluated significant differences in PANAS scales of NA, guilt, hostility, fear, and sadness, whereas the third MANOVA evaluated significant changes in PANAS scales of PA, serenity, self-assuredness, attentiveness, and joviality. These three sets of analyses were predicted to reveal that baseline psychosocial assessments would differ significantly from last day and follow-up assessments, revealing significant and sustained reductions in BSI scores and negative mood states, accompanied by improvements in positive mood states. Paired sample $t$-tests were used to assess significant reductions in perceptual stress, PTSD symptoms, and global sleep quality between baseline and follow-up periods.

Pearson product moment correlations tested if reductions in PTSD scores predicted improvements in sleep quality using residualized change scores in accord with recommendations. Residualized change scores for the PTSD and sleep quality variables were created by regressing postfishing trip scores on their respective baseline values, resulting in standardized residual values from these regression equations that represent change over time after controlling for variation because of baseline values. Residualized change in global PCL-M scores was correlated with residualized change in global PSQI scores pertaining to change from baseline to the follow-up period.

Results

Psychosocial Effects

BSI Analyses

A repeated measures MANOVA on the BSI total score and subscales was significant, $F(6, 68) = 32.08$, $p < 0.001$, $\eta_p^2 = 0.79$. All underlying univariate statistics were significant: BSI total, $F(2, 146) = 79.25$, $p < 0.001$, $\eta_p^2 = 0.52$; BSI somatic stress, $F(2, 146) = 25.48$, $p < 0.001$, $\eta_p^2 = 0.35$.
Bonferroni post hoc analyses revealed the fly-fishing excursion to be linked to significant and sustained reductions on all measures, comparing baseline levels to last day and follow-up assessments (p < 0.001).

Positive Affect and Negative Affect Schedule

A second repeated measures MANOVA on the PANAS scales of NA, guilt, hostility, fear, and sadness was significant, F(10, 64) = 17.4, p < 0.001, \( \eta^2 = 0.73 \). The univariate analyses corresponding to these scales were significant: NA, F(2, 146) = 62.84, p < 0.001, \( \eta^2 = 0.46 \); guilt, F(2, 146) = 33.12, p < 0.001, \( \eta^2 = 0.31 \); hostility, F(2, 146) = 71.83, p < 0.001, \( \eta^2 = 0.50 \); fear, F(2, 146) = 32.25, p < 0.001, \( \eta^2 = 0.31 \); and sadness, F(2, 146) = 38.74, p < 0.001, \( \eta^2 = 0.35 \). Bonferroni post hoc analyses revealed significant and sustained reductions on all measures from the last day of the fly-fishing excursion to the follow-up assessment relative to the baseline period (p < 0.001).

The third repeated measures MANOVA on the PANAS scales of PA, serenity, self-assuredness, and joviality was significant, F(10, 64) = 22.21, p < 0.001, \( \eta^2 = 0.78 \), in addition to all underlying univariate statistics: PA, F(2, 146) = 98.84, p < 0.001, \( \eta^2 = 0.58 \); serenity, F(2, 146) = 76.63, p < 0.001, \( \eta^2 = 0.51 \); self-assuredness, F(2, 146) = 44.49, p < 0.001, \( \eta^2 = 0.38 \); attentiveness, F(2, 146) = 38.91, p < 0.001, \( \eta^2 = 0.35 \); and joviality, F(2, 146) = 125.73, p < 0.001, \( \eta^2 = 0.63 \). Bonferroni post hoc analyses indicated significant acute effects for increases on all measures for the last day of the fly-fishing excursion relative to the baseline period (p < 0.001), with the exception of the serenity subscale, which also evidenced sustained increases when comparing the baseline to the follow-up period (p < 0.05). Table II summarizes the findings pertaining to the BSI and PANAS inventories.

PTSD Check List, Military Version, Perceived Stress Scale, and Pittsburgh Sleep Quality Inventory

A paired sample t-test evaluated change in overall PCL-M scores between the baseline and follow-up periods, depicting a significant reduction, t(73) = 6.62, p < 0.001. A set of exploratory paired sample t-tests examined changes in PCL-M subscale scores between baseline and follow-up, indicating significant effects for reductions on all 3 subscales: hyperarousal, t(73) = 6.56, p < 0.001; avoidance, t(73) = 5.88, p < 0.001; and re-experiencing, t(73) = 5.28, p < 0.001. Additional paired sample t-tests evaluated hypothesized reductions in perceptual stress and improvements in sleep quality between baseline and follow-up periods, indicating significant effects for both scales: PSS, t(73) = 5.56, p < 0.001; and PSQI, t(73) = 2.23, p < 0.001. Descriptive statistics pertaining to these analyses are featured in Table II.

Ancillary Psychosocial Analysis

A correlational analysis was performed on residualized change scores for the PCL-M and PSQI total scores to determine whether reductions in PTSD symptoms predicted improvements in overall sleep quality. In support of this exploratory hypothesis, a significant correlation on residualized change from baseline to follow-up was observed between these scales, \( r = 0.657, p < 0.001 \), suggesting that sleep quality may improve (reductions in PSQI score) along with decrements in PTSD symptoms.
Discussion

The purpose of this study was to evaluate the effectiveness of a fly-fishing program in reducing the psychological concomitants of stress among a sample of 74 veterans with PTSD. The results suggest that outdoor recreation is linked to significant improvements in psychosocial well-being. Acute effects indicated significant elevations in attentiveness and positive mood states, accompanied by significant and sustained reductions in symptoms of depression, anxiety, and somatic stress, in addition to negative mood states. Moreover, the psychosocial benefits of the outdoor recreation appear to endure up to the 6-week follow-up assessment. Follow-up analyses revealed increases in sleep quality and significant reductions in perceptual stress and PTSD symptoms. An additional ancillary analysis revealed that reductions in PTSD symptoms served as a driving force that predicted improvements in sleep quality.

The findings regarding outdoor recreation as a medium for improving psychosocial well-being are consistent with other studies investigating the use of leisure coping in response to stressful events. Leisure-coping strategies have been argued to distract individuals from trauma and help them to reconnect with a prior sense of self-established before a traumatic experience. These processes of distraction and reconnection maybe instrumental properties of outdoor recreation that foster improvements in psychosocial wellness. The findings from this study resonate with theoretical orientations that natural environmental settings elicit a restorative impact upon individuals, such as attention restoration theory.

The outdoor recreation of fly-fishing employed in this study involves activities that subtly engage participant attention on a new skill in a pristine natural environment. The acute increases in attentiveness and serenity in this study suggests that participation in the outdoor recreation under investigation may induce a state of calm alertness among the participants. The attentional focus achieved through participation in this program may distract participants from intrusive thoughts of combat-related trauma, one of the key symptoms of PTSD for this population; likewise, the calming environmental setting may serve as a grounding medium that enables participants to reclaim a sense of self unaffected by the combat experience.

The significant reduction in overall PTSD symptoms observed in this study is encouraging. Moreover, exploratory analyses also revealed significant reductions in all three subscales of hyperarousal, avoidance, and repeated thoughts of trauma symptoms from baseline to the follow-up period, findings that parallel the simultaneous reductions in perceptual stress levels amid this sample. Previous research has examined the ability of leisure coping to buffer the effect of stress on mental illness, indicating that social support, generated through therapeutic recreation, moderated the relationship between stress and mental health. Combat-induced trauma is a context specific experience that may distance veterans from their loved ones. A fundamental component of the ROR program is a dynamic social support system emerging in each of the fly-fishing retreats. As such, social support remains an inextricable component of the veteran experience under study and may explain a significant proportion of the favorable changes in psychosocial well-being observed here, including the reductions in PTSD symptoms. In fact, a longitudinal investigation on the benefits of leisure activity among a group of participants from “high stress” occupations of emergency response and law enforcement revealed that although relaxing leisure activities predicted reductions in perceptual stress, “social leisure” and “outdoor recreation” activities were uniquely predictive of improvements in mental health.
Increasing access to group-based outdoor therapeutic recreation interventions maybe effective in reducing symptoms of mental illness. Alongside the significant reduction in PTSD symptoms, results from this study indicate significant reductions in symptoms of depression and anxiety following outdoor recreation, providing data that complement other corelational studies which have revealed an inverse association between depressive symptoms and leisure activities.

In addition to reductions in symptoms of depression and anxiety, this study found a wealth of acute improvements in mood profiles among participants, including significant increases in state measures of attentiveness, serenity, self-assuredness, joviality, and PA. Results also revealed significant decreases in feelings of guilt, hostility, fear, sadness, and NA, reductions that sustained to the follow-up assessment. On the whole, the findings pertaining to improvements in mood profiles are consistent with other reports linking leisure activities to increases in PA, decreases in NA, or both.

The results found throughout this study are consistent with research regarding the beneficial effect of recreation and leisure on various assessment levels of stress and well-being. The significant and sustained reductions in somatic symptoms of stress (e.g., faintness, nausea, chest pain, etc) observed in this study are in line with a variety of cross-sectional evidence linking leisure activity participation to measures of physical wellness. Reductions in perceptual stress and reports of improved sleep quality found among participants in the ROR program were expected in light of research indicating the efficacy of leisure in regards to improvements in health and quality of life. Leisure and recreation has been positively associated with a number of health promoting psychosocial factors, including sleep quality. Participants who engaged in leisure activities with greater frequency were more likely to report higher sleep efficiency and sleep quality. The findings suggest that participation in peer-based outdoor recreation may promote improvements in sleep quality amid a sample of combat veterans with PTSD, a target population known to display poor sleep quality.

Finally, an ancillary exploratory analysis in this study suggests that outdoor recreation-induced reductions in PTSD symptoms may predict improvements in sleep quality over time, preliminary evidence that may merit subsequent examination amid a more substantive study.

The current investigation represents a pilot study program evaluation of an outdoor recreation intervention to reduce the psychological concomitants of stress among a group of veterans with PTSD. As such, the findings from this study should be considered preliminary and interpreted with caution because of numerous limitations, such as the use of a small, self-selected sample without a control group. The current findings merit replication in a larger sample of veterans, perhaps as part of a randomized clinical trial. Future studies should aim to delineate what qualities of the outdoor recreation intervention predict the salubrious changes in psychosocial outcome. For example, an assessment of state social support could be administered as a covariate to determine if the effects of the intervention are significant after controlling for the variance pertaining to social support. Despite the limitations discussed, this study suggests that group-based outdoor recreation interventions may incur psychosocial benefits amid combat veterans with PTSD. The significant improvements in attentiveness and positive mood states, coupled with significant reductions in PTSD symptoms and associated qualities such as stress, depression, anxiety, and negative mood states, have potential implications for PTSD treatment as well as further examination of outdoor recreation as a therapeutic tool.
Adjunctive Atypical Antipsychotic Treatment for Major Depressive Disorder: A Meta-Analysis of Depression, Quality of Life, and Safety Outcomes

PLOS Medicine
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Abstract

Background

Atypical antipsychotic medications are widely prescribed for the adjunctive treatment of depression, yet their total risk–benefit profile is not well understood. We thus conducted a systematic review of the efficacy and safety profiles of atypical antipsychotic medications used for the adjunctive treatment of depression.

Methods and Findings

We included randomized trials comparing adjunctive antipsychotic medication to placebo for treatment-resistant depression in adults. Our literature search (conducted in December 2011 and updated on December 14, 2012) identified 14 short-term trials of aripiprazole, olanzapine/fluoxetine combination (OFC), quetiapine, and risperidone. When possible, we supplemented published literature with data from manufacturers' clinical trial registries and US Food and Drug Administration New Drug Applications. Study duration ranged from 4 to 12 wk. All four drugs had statistically significant effects on remission, as follows: aripiprazole (odds ratio [OR], 2.01; 95% CI, 1.48–2.73), OFC (OR, 1.42; 95% CI, 1.01–2.0), quetiapine (OR, 1.79; 95% CI, 1.33–2.42), and risperidone (OR, 2.37; 95% CI, 1.31–4.30).

The number needed to treat (NNT) was 19 for OFC and nine for each other drug. All drugs with the exception of OFC also had statistically significant effects on response rates, as follows: aripiprazole (OR, 2.07; 95% CI, 1.58–2.72; NNT, 7), OFC (OR, 1.30, 95% CI, 0.87–1.93), quetiapine (OR, 1.53, 95% CI, 1.17–2.0; NNT, 10), and risperidone (OR, 1.83, 95% CI, 1.16–2.88; NNT, 8). All four drugs showed statistically significant effects on clinician-rated depression severity measures (Hedges' g ranged from 0.26 to 0.48; mean difference of 2.69 points on the Montgomery–Asberg Depression Rating Scale across drugs). On measures of functioning and quality of life, these medications produced either no benefit or a very small benefit, except for risperidone, which had a small-to-moderate effect on quality of life (g = 0.49).
Treatment was linked to several adverse events, including akathisia (aripiprazole), sedation (quetiapine, OFC, and aripiprazole), abnormal metabolic laboratory results (quetiapine and OFC), and weight gain (all four drugs, especially OFC). Shortcomings in study design and data reporting, as well as use of post hoc analyses, may have inflated the apparent benefits of treatment and reduced the apparent incidence of adverse events.

Conclusions

Atypical antipsychotic medications for the adjunctive treatment of depression are efficacious in reducing observer-rated depressive symptoms, but clinicians should interpret these findings cautiously in light of (1) the small-to-moderate-sized benefits, (2) the lack of benefit with regards to quality of life or functional impairment, and (3) the abundant evidence of potential treatment-related harm.

Background

Everyone feels miserable occasionally. But for people who are clinically depressed, feelings of sadness and hopelessness and physical symptoms such as sleeping badly can last for months or years and can make them feel life is no longer worth living. Depression affects one in six people at some time during their life. Clinicians diagnose depression by asking their patients a series of questions about their feelings and symptoms. The answer to each question is given a score, and the total score from the questionnaire (“depression rating scale”) indicates the severity of depression. Treatment of depression often involves talking treatments (psychotherapy) such as cognitive behavioral therapy, which helps people change negative ways of thinking and behaving and antidepressant drugs, most commonly “selective serotonin reuptake inhibitors” such as fluoxetine and paroxetine.

Why Was This Study Done?

Atypical antipsychotic medications (for example, aripiprazole, olanzapine/fluoxetine combination [OFC], quetiapine, and risperidone) are also widely prescribed for the treatment of depression. These drugs, which were developed to treat mental illnesses that are characterized by a loss of contact with reality, are used as adjunctive therapy for depression. That is, they are used in addition to antidepressant drugs. Clinicians wrote nearly four million prescriptions for adjunctive treatment of depression with atypical antipsychotic medications in 2007–2008 in the US alone. However, it is not known whether the benefits of using these drugs to treat depression outweigh their side effects, which include weight gain, sedation, and akathisia (a feeling of inner restlessness resulting in an urge to move, which may or may not be accompanied by increased movement). Here, the researchers undertake a systematic review and meta-analysis of the efficacy and safety profiles of atypical antipsychotic medications used for the adjunctive treatment of depression. 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 14 short-term randomized controlled trials (duration 4–12 weeks) that compared adjunctive antipsychotic medications (aripiprazole, OFC, quetiapine, or risperidone) to placebo (dummy drug) in the treatment of depression that had not responded to antidepressant...
medication alone. All four drugs had statistically significant effects (effects unlikely to have happened by chance) on remission, which was most commonly defined as a score of less than eight at the study end point on the Montgomery–Asberg Depression Rating Scale. The researchers calculated the number of patients that would have to be treated for one patient to achieve remission (number needed to treat, or NNT). For OFC, the NNT was 19; for all the other drugs it was nine. All the drugs except OFC also significantly improved response rates (defined as a 50% improvement in depression rating score). However, the medications provided little or no benefit in terms of functioning and quality of life, except for risperidone, which had a small-to-moderate effect on quality of life. Finally, treatment with atypical antipsychotic medications was linked to several adverse effects, including weight gain (all four drugs) and akathisia (aripiprazole).

What Do These Findings Mean?

These results suggest that atypical antipsychotic medications for the adjunctive treatment of depression are efficacious in reducing observer-rated depressive symptoms. However, clinicians should interpret this conclusion cautiously for several reasons. First, adjunctive treatment with atypical antipsychotics provided only small-to-moderate benefits. Moreover, shortcomings in study design and data reporting methods may have inflated the apparent benefits of treatment and reduced the apparent incidence of adverse events. Second, this study provides little evidence that adjunctive treatment with atypical antipsychotics improves patients' quality of life or reduces their functional impairment. Finally, this study highlights abundant evidence of potential treatment-related harm. This evaluation of the safety and efficacy of adjunctive treatments for clinical depression provides critical insights that should help clinicians better understand the risk–benefit profiles of this approach to the treatment of major depressive disorder.

Introduction

Atypical antipsychotic medications are widely used in the treatment of major depressive disorder. In the United States in 2007 and 2008, there were an estimated 3.9 million treatment visits per year in which an antipsychotic medication was prescribed for depression, and nearly all of these (96%) involved prescription of an atypical antipsychotic medication. Although aggregate statistics mask the specific indications for use (i.e., monotherapy versus adjunctive therapy), this represents a substantial increase in antipsychotic treatment of depression over time, as there were just over 2 million such visits annually during 1995 and 1996, of which 405,000 involved prescriptions for atypical antipsychotic medications. These data are also consistent with market reports from industry. Three atypical antipsychotic medications have approval from the US Food and Drug Administration (FDA) as adjunctive therapies in depression for adults, while none are approved for monotherapy. These approvals (and subsequent marketing efforts), along with the volume of prescriptions, suggest that a large number of prescriptions for atypical antipsychotic medications written for the treatment of depression are being used for adjunctive therapy.

The efficacy of adjunctive atypical antipsychotic therapy in reducing depression symptom severity in major depressive disorder is summarized in two previous systematic reviews, but neither comprehensively summarized data on both efficacy and safety. Both reviews analyzed efficacy only in terms of dichotomous response and remission outcomes derived from clinician-rated depression measures and did not assess changes in terms of symptom severity on the underlying continuous rating scales. Safety was only assessed by examining dropout rates due to adverse events; the authors of these meta-analyses and of a relevant narrative review noted that a comprehensive summary of safety data is lacking. A Cochrane
review provided a more thorough assessment of both efficacy and safety outcomes but did not include data on important patient-centered efficacy outcomes such as patient-rated depression, functional impairment, or quality of life. The Cochrane review assessed the frequency of several relevant adverse events, but some critical adverse events of interest, such as elevated cholesterol or triglyceride levels, were not included. Further, and most importantly, effect size estimates presented in these reviews may have been inflated because the authors did not summarize unpublished data, such as those from FDA New Drug Applications (NDAs) or manufacturers' clinical trial registries. Given the importance of functional status, quality of life, and drug-related side effects to the overall assessment of well-being and recovery from depressive mood episodes, we conducted this meta-analysis to provide a comprehensive estimate of the efficacy and safety profiles of atypical antipsychotic medications for the adjunctive treatment of major depressive disorder.

Methods

Ethical Review

Because this was a study-level systematic review and meta-analysis of trials, and did not involve collection and analysis of any individual-level data, ethical approval was not sought for this study.

Search Strategy

This systematic review was reported using PRISMA guidelines; the PRISMA checklist is provided as Text S1. To identify both published and unpublished studies for review, we searched Medline, PsycINFO, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials using the terms depression AND (aripiprazole OR asenapine OR clozapine OR iloperidone OR lurasidone OR olanzapine OR paliperidone OR quetiapine OR risperidone OR ziprasidone). Medline search results were restricted to the following article types: clinical trial, controlled clinical trial, or randomized controlled trial. Our literature search was conducted in December 2011 and updated on December 14, 2012. In addition, we searched the American Psychiatric Association Annual Meeting New Research Abstracts for 2001–2010 using each of the generic drug names as a search term, then winnowed the results down to abstracts that appeared to possibly meet the inclusion criteria. We also examined all references in a previously published meta-analysis as well as those contained in each published study obtained through our literature search.

To obtain additional unpublished data, we searched the drug manufacturers' online clinical trial registries as well as FDA NDAs for the atypical antipsychotic medications that have received an indication for the adjunctive treatment of major depressive disorder (aripiprazole, olanzapine-fluoxetine combination [OFC], and quetiapine). For published studies, we supplemented published data with data available in NDAs or clinical trial registry reports whenever such data were available.

Study Selection
Trials were included if they were acute-phase (i.e., not for relapse prevention or maintenance treatment), placebo-controlled trials in which participants treated with antidepressant medications were randomly assigned to additionally receive an atypical antipsychotic medication or placebo. In order to meet our definition of treatment-resistant depression, participants must have been diagnosed with current major depressive disorder and must have been determined to have had an inadequate response to at least one course of antidepressant medication treatment prior to enrollment in the study. Furthermore, data for at least one outcome measure must have been reported in a manner that allowed calculation of an effect size. No language exclusions were applied.

Data Extraction

Four study authors (G. I. S., A. P., M. I. B., and E. L.) coded study descriptor data. To establish consistency, all coders first coded the articles reporting outcomes from the aripiprazole studies. Then two study authors (G. I. S. and A. P.) jointly coded the OFC and risperidone articles, and two study authors (M. I. B. and E. L.) jointly coded the quetiapine articles. Disagreements were resolved by consensus. Coders were not blind to the results of the coded studies.

Several descriptor variables were coded for each study. (1) Flexible dosing versus fixed dosing regimen. (2) Dosage range. (3) Mean dosing achieved at end point. (4) Number of participants in each group of trial. (5) Duration of acute-phase treatment (weeks). (6) Number of prior failed trials of antidepressant medications, where the number of failed trials prior to study enrollment (historical) and the number of failed trials during the study (prospective) prior to initiation of the study drug for adjunctive treatment were recorded separately. (7) Procedures employed to evaluate for major depressive disorder (structured interview or otherwise). (8) Use of a structured instrument versus open-ended questioning to elicit adverse events (with the latter assumed if no details were reported). (9) Adverse events scale(s) used to systematically assess for any particular adverse event(s), if any. (10) The criterion used to establish a minimum level of occurrence for adverse events reporting in the trial (e.g., if only those adverse events occurring in at least 5% of participants were reported in the associated journal article, the adverse events reporting threshold was coded as 5%). (11) Extent to which the random-sequence generation procedures were adequate versus inadequate or unclear. Adequate sequence generation procedures included use of a computer program, random number table, coin tossing, randomly drawing envelopes, throwing dice, or similar methods. Merely describing the trial as randomized was considered an unclear method of sequence generation. (12) Whether or not the study eliminated placebo responders prior to randomization. (13) Whether or not persons who had a prior nonresponse to the study drug were excluded. (14) Whether or not the placebo was described as identical to the study drug in terms of at least two of the following three criteria: taste, appearance, and smell. (15) Use of blinded raters, coded as affirmative if the following two conditions were met: (a) it was explicitly stated that blinded raters were used, and (b) it was explicitly stated that different personnel were used to rate efficacy measures and adverse events. (16) Funding sponsor.

Efficacy and safety outcome data were independently extracted by two authors (G. I. S. and A. P.) and then checked for agreement. Disagreements were resolved by checking the original data source.

Outcome Measures
Remission was defined variably across studies. We recorded the most stringent definition of remission utilized in each trial while also recognizing that the Montgomery–Asberg Depression Rating Scale (MADRS) was the most commonly used outcome measure in the included trials. One end-point remission measure was selected from each trial according to the following order of priority: MADRS ≤8, then Hamilton Depression Rating Scale (HAM-D) ≤7, then MADRS ≤10. Some trials of OFC defined remission as MADRS ≤8 at two consecutive visits during the study even if these two consecutive visits did not necessarily occur at study end point. The clinical trial registry reports of these trials also provided the number of participants who met remission criteria at an interim time point but then relapsed. For these studies, we calculated the number of participants in remission as the number of participants who achieved interim remission minus the number of patients who subsequently relapsed.

Response was defined across studies as a 50% improvement from baseline to end point on either the MADRS or HAM-D. When studies provided response rates for both measures, we used the MADRS as the response measure, as it was the most commonly reported measure of response.

We recorded data from any continuous measure of depression, quality of life, or functioning but opted not to analyze single rating scale items from larger scales (e.g., individual MADRS items) separately because they were infrequently reported. When data were reported on both the MADRS and HAM-D, we included data from the MADRS, as it was the most commonly used measure of depressive symptoms. The only continuous self-report measure of depression used in these trials was the Inventory of Depressive Symptomatology Self Report. Continuous measures of quality of life included the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and the Short Form 36 Health Survey (SF-36). The only continuous measure of functional impairment employed in these trials was the Sheehan Disability Scale (SDS). As measures of quality of life and functional impairment varied across studies, we pooled such measures together to create an omnibus effect size for each drug, and across all drugs.

We aggregated conceptually similar adverse events into the following categories. (1) Sedation-related: asthenia, fatigue, lethargy, sedation, somnolence, or feeling tired. (2) Akathisia-related (either self-reported or observer-rated): akathisia or restlessness. (3) Extrapyramidal symptoms (EPS), other than akathisia-related (either self-reported or observer-rated): dyskinesia, dystonia, extrapyramidal disorder, EPS, muscle spasms, muscle twitching, parkinsonism, or tremor. (4) Abnormal metabolic laboratory results: elevated fasting or nonfasting total cholesterol, low-density lipoprotein (LDL) cholesterol, or triglycerides; low high-density lipoprotein (HDL) cholesterol; or elevated fasting or nonfasting glucose, glycated hemoglobin; or hyperglycemia. (5) Elevated prolactin. (6) Edema or peripheral edema. (7) Significant weight gain, defined across various trials as weight gain of ≥7%, ≥10%, or >10% from baseline to end point.

We also coded events that were reported in the categories of pain, psychiatric events, nausea, and infection. However, because no sign of elevated risk was gleaned from these data, these analyses are not reported (data available from authors on request).

Statistical Analysis

The quality of data reporting varied across studies. For continuous outcomes, effect sizes were computed from means and standard deviations when possible. When these were not provided, effect sizes were computed based on means and p-values, or p-values only. In some studies,
three or more treatment groups were compared, thereby creating a structural dependency that could affect our estimates. For example, two fixed doses (A and B) of an adjunctive atypical antipsychotic medication might be compared to one group that received adjunctive placebo (C), in which case the estimated efficacy of A and B would be defined relative to the same comparison group. To maintain independence, we pooled these comparisons and utilized their average (e.g., the average of A versus C and B versus C).

Each effect size was weighted by its inverse variance in order to provide a pooled effect size estimate that most accurately approached the true population effect size. We calculated odds ratios (ORs) for categorical measures and used Cohen's d for continuous measures. We converted continuous effect sizes to Hedges'g, which corrects for a small bias in Cohen's d [33]. We reported both efficacy and safety data for each drug individually and across drugs. An OR presents a relative measure of treatment effect; to also provide a measure of absolute benefit/harm, we calculated the number needed to treat (NNT) for treatment benefits and the number needed to harm (NNH) for adverse events. The NNT represents the number of participants who would need to be treated with an adjunctive antipsychotic to gain one additional beneficial response over what would have been obtained had all patients received adjunctive placebo. NNH represents the number of patients who would require treatment to generate one additional adverse event relative to placebo. NNT/NNH values were calculated based on the pooled OR rather than from the risk difference in each study, as the risk difference is associated with more between-study heterogeneity than the OR. Conversions from OR to NNT were performed in Visual Rx software [36]. The baseline risk (required for calculating NNT) was estimated by using the pooled rate of events occurring among placebo-treated patients weighted by each study's total sample size. The baseline risk was calculated separately for each drug, so that placebo participants in one drug's trials were not used to calculate baseline risk for a different drug. As in any meta-analysis, our estimates of NNT and NNH generalize only to situations in which patients receive a similar dosage for a similar treatment duration; further, estimated NNH and NNT apply only when generalizing to patients similar to those in the included trials. Because of various study inclusion and exclusion criteria, patients in the placebo groups in our meta-analysis may not be representative of patients seen in some clinical practice settings.

We performed homogeneity analyses using the Q statistic. Because the Q test of homogeneity often lacks power to detect heterogeneity when the number of trials in a meta-analysis is small, we also calculated the I2 statistic. To pool estimates across studies while incorporating potential heterogeneity, we employed a random effects model in all analyses. Confidence intervals for I2 were calculated using Method III as described in Higgins and Thompson using a spreadsheet. When performing such calculations in pooled analyses based on only two comparisons when Q ≤ k, we added the number 1 to both Q and k in order to avoid the mathematical problem of dividing by zero; this generally resulted in a slight shrinking of the confidence intervals under these conditions. Unless specified otherwise above, all analyses were performed using Comprehensive Meta-Analysis software. We lacked adequate statistical power to perform subgroup analyses.

We examined the potential existence of publication bias by performing trim and fill analysis for pooled continuous depression outcomes. Trim and fill procedures examine potential asymmetry of effect sizes. Based on the assumption that effects are distributed symmetrically, trim and fill analysis imputes the number and likely effect size of missing studies, then recalculates the pooled analysis with imputed data from missing studies.

Results
Study Characteristics

The evidence search flow is described in Figure 1. We obtained one controlled trial of aripiprazole that used low doses (2 or 5 mg); we did not include this trial because the starting dose of 2 mg was administered for 30 d prior to participants switching to the dose of 5 mg that falls within the recommended 5–10 mg range set by the FDA. Characteristics of the 14 included studies are provided in Table 1. The definition of treatment-resistant depression differed somewhat across trials. The process by which diagnoses were made was described clearly in six trials, and the number of prior failed trials varied across studies. Only three studies clearly described their random-sequence generation procedures, and only one trial clearly described using clinical raters who were blind to both treatment assignment and participants’ reports of adverse events. While most trials used rating scales to assess for EPS and akathisia, and a minority of trials used a measure of sexual functioning, no trial reported using a structured instrument for eliciting a broad range of adverse events. All studies were funded by the study drug manufacturer except for one trial that was funded jointly by the study drug manufacturer and the US National Institute of Mental Health.

Efficacy

In terms of remission, adjunctive treatment with each antipsychotic was associated with a statistically significant benefit, with ORs ranging from 1.42 to 2.37 (Table 2). ORs for response were also statistically significant for aripiprazole, quetiapine, and risperidone—but not for OFC (Table 2). The NNT for remission was nine for aripiprazole, quetiapine, and risperidone but was a substantially higher 19 for OFC (Table 2). NNTs for response were seven (aripiprazole), eight (risperidone), and ten (quetiapine). Pooled ORs are displayed visually in Figures 2 and 3. Among participants who achieved remission during treatment, participants assigned to OFC were less likely to remain in remission than participants assigned to placebo. Only two of 56 placebo participants relapsed, compared to 18 relapses among 99 participants on OFC (OR, 0.27; 95% CI, 0.08–0.90).

Pooled effect sizes for continuous outcomes are provided in Table 3. Adjunctive aripiprazole, quetiapine, OFC, and risperidone were all more efficacious than adjunctive placebo based on clinician-rated measures of depression severity (MADRS/HAM-D). Effect sizes were as follows: aripiprazole: $g = 0.35$ (95% CI, 0.23–0.48); OFC: $g = 0.26$ (95% CI, 0.04–0.45); quetiapine: $g = 0.40$ (95% CI, 0.26–0.53); and risperidone: $g = 0.48$ (95% CI, 0.22–0.73). The effects of risperidone may have been exaggerated by the reliance on post hoc analysis rather than a priori analysis in the largest study of the drug, as the effect of the drug was greater at 6 wk ($g = 0.46$) than at the prespecified primary end point of 4 wk ($g = 0.32$) [44]. According to convention, these effect sizes would be considered “small” or “small to moderate” in magnitude [45]. Effect sizes on depression severity measures did not differ significantly between drugs ($QB = 1.93$, $p = 0.59$), though there was limited power to detect such differences. The pooled difference in mean change on the MADRS in the 11 trials that reported such data was 2.69. In these 11 trials, the mean effect size was $g = 0.31$, which differed only slightly from the overall mean effect size when including both the HAM-D and MADRS; thus, the 11 trials reporting MADRS mean change data seem representative of the entire sample of included trials. Only the trials of adjunctive aripiprazole reported self-reported depression symptom severity, yielding a very small effect size of $g = 0.15$. The effects observed on the Clinical Global Impressions–Severity Scale were either small or small-to-moderate, with the exception of risperidone, for which a moderate effect was generated.
With regards to quality of life and functioning, adjunctive quetiapine, aripiprazole, and OFC produced effect sizes that were either not statistically significant or small and clinically negligible in magnitude. Adjunctive risperidone was more efficacious than adjunctive placebo on quality of life/functioning, with a small-to-moderate effect size. The pooled effect across quality of life/functioning measures varied significantly across treatments (QB = 6.88, p = 0.003), with risperidone (g = 0.49) yielding a higher effect than the other three drugs combined (g = 0.11), which did not differ significantly from each other (QB = 4.02, p = 0.13). However, the effect of aripiprazole on quality of life/functioning was small (g = 0.22) and statistically significant (p = 0.001), whereas the effects of OFC (g = 0.04, p = 0.74), and quetiapine (g = 0.05, p = 0.53) were both not statistically significant and of quite small magnitude. The effect of aripiprazole on quality of life/functioning should be interpreted with caution, as the effect for the drug on the SDS was very small and no longer statistically significant when patients who violated study protocol were excluded from analysis (g = 0.12, p = 0.08). Similarly, the effect of risperidone on quality of life/functioning should be interpreted tentatively since it is largely driven by post hoc analyses.

Adverse Events

Atypical antipsychotic medications differed substantially in their reported adverse event profiles. Table 2 reports adverse events that showed increased risk (p≤0.10). A more detailed listing of adverse events and pooled ORs for each event category are provided in Table 4.

Adjunctive aripiprazole was frequently associated with akathisia (NNH, 4; 95% CI, 3–6) and also linked to a statistically significant elevation in the occurrence of sedation (NNH, 14; 95% CI, 8–33) and significant weight gain of ≥7% during trials (NNH, 29; 95% CI, 10–119). Adjunctive OFC was often associated with significant weight gain of >10% or ≥10% (NNH, 9; 95% CI, 5–20), sedation (NNH, 5; 95% CI, 3–12), abnormal metabolic laboratory results (NNH, 10; 95% CI, 5–29), and elevated prolactin (NNH, 6; 95% CI, 4–11). Adjunctive quetiapine had a very high rate of reported sedation (NNH, 3; 95% CI, 2–3) and was also linked to abnormal metabolic laboratory results (NNH, 6; 95% CI, 4–9) and significant weight gain of ≥7% (NNH 37; 95% CI, 12–594). Adjunctive risperidone was not associated with an increased rate of any spontaneously reported adverse events.

All four drugs resulted in statistically significant weight gain (Table 3): mean weight gain in trials of adjunctive aripiprazole, quetiapine, and risperidone was approximately 1 kg, while the average weight gain resulting from adjunctive OFC was 4.20 kg (95% CI, 3.79–4.61). OFC was associated with more weight gain than the other drugs (QB = 58.46, p<0.001), which did not differ significantly from each other (QB = 0.66, p = 0.72).

The thresholds for adverse event reporting in the included publications are shown in Table 1. Adverse events were typically listed in a table and were reported only if a certain proportion of study participants reported that event. For example, if only those adverse events reported by 5% or more of participants in either group were reported in the published journal article, we describe it in Table 1 as “≥5% in any group.” In general, little to no additional information was provided in the study publications regarding adverse events beyond that which was presented in such tables. Meta-analysis of effects on sexual functioning rating scales was not performed because of the often unclear reporting of these measures (see Table 3).
Publication Bias

The trim and fill procedure suggested the existence of three unpublished trials, bringing the overall effect on depression measures to 0.32. A funnel plot showing the results of this analysis can be seen in Figure 4.

Discussion

In this meta-analysis of 14 randomized trials of atypical antipsychotic medications used for the adjunctive treatment of major depressive disorder, we found that all included atypical antipsychotics were more efficacious than adjunctive placebo in terms of their effects on depressive symptom severity and remission. However, the effect sizes were small or small-to-moderate in magnitude, and OFC did not generate a statistically significant benefit on treatment response. All of the studied drugs except risperidone demonstrated substantial risk of several adverse events. Our findings have clinically important implications for comprehensively understanding the risk–benefit profiles of these adjunctive treatments for major depressive disorder.

The overall effect size on depression severity was $g = 0.34$, an effect conventionally deemed as small. In a meta-analysis of antidepressants versus placebo, Kirsch et al. found an effect size of 0.32, which they interpreted as not clinically relevant. This was in line with the recommendations of the National Institute for Health and Clinical Excellence in the United Kingdom, which deemed effect sizes of $g<0.5$ as clinically insignificant, though no evidence was cited for this cutoff [47]. However, Turner et al.'s meta-analysis of antidepressants versus placebo found an effect size of 0.31, which was interpreted as “measurable and significant” [48]. These differing interpretations are understandable given that Cohen noted that his original categorization of effect sizes (0.2 = small, 0.5 = medium, and 0.8 = large) was arbitrary. We interpret the effect of adjunctive antipsychotic treatment on depression measures as of questionable clinical relevance. In addition, sole reliance on depression rating scales to determine treatment benefit is likely inadequate in understanding overall treatment efficacy.

The pooled difference in mean change across 11 trials was 2.69 points on the MADRS. The MADRS consists of ten items, each rated on a 0–6 scale, assessing sadness, inner tension, reduced sleep, loss of appetite, concentration, difficulty with starting daily activities, inability to feel, pessimism, and suicidal thoughts. A small difference favoring an atypical antipsychotic over placebo on the MADRS may thus reflect small differences across several dimensions, or perhaps a sizable difference on one or two dimensions combined with nil differences on other items. For instance, a pooled analysis of the two large quetiapine trials included in our meta-analysis found that quetiapine at 150 mg/d and quetiapine at 300 mg/d were superior to placebo by 2.50 and 2.85 points on the MADRS at study end point, respectively. The treatment advantage in terms of the items “apparent sadness” and “reported sadness” appears to be about a third of that for the “reduced sleep” item (Figure 3b of [49]), suggesting that quetiapine’s sedative effect on sleep may account for a substantial degree of the observed improvement in depression scores. Thus, improvement in overall depression rating scales should be interpreted cautiously.

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Response and remission rates are often used to convey the magnitude of treatment benefit; however, these categorical measures are created arbitrarily from underlying continuous rating scale data. In some circumstances these categorical measures may inflate treatment differences relative to mean change on the continuous scale. While response and remission rates are potentially useful outcome measures, they should be considered only in the context of a wider set of outcome data.

With the exception of risperidone, nearly all of the included trials estimated small or minimal benefits with regards to quality of life and functional impairment. Quetiapine and OFC generated no benefit on such measures, whereas the benefits of aripiprazole were statistically significant yet quite modest. Although risperidone appeared to possess the strongest risk–benefit profile in our analyses, our findings about risperidone were based on the smallest sample size of any of the included drugs. We also have concerns about data reported in the largest risperidone trial. The published version of the study emphasizes outcomes at the end of the 6-wk trial. However, in its discussion section and the trial's associated ClinicalTrials.gov registry entry [52], it is mentioned that the primary study end point was actually 4 wk; this is mentioned neither in the paper's methods section nor in the abstract. The effect size on the HAM-D is 30% smaller at the 4-wk end point relative to the 6-wk end point. Effects on the Q-LES-Q and SDS were reported only at week 6, but it seems likely that these effects would be smaller at the primary study end point. Given that this study included 69% of the total participants in risperidone trials, our pooled estimate of risperidone efficacy is therefore driven by the inclusion of post hoc analyses. Further, a previously published relapse prevention study (not included in our meta-analysis due to its study design) found no benefit for risperidone over placebo, suggesting that risperidone-related gains may be transient.

Taken together, our findings raise significant concerns regarding the impact of these medications in improving overall well-being. Although improvements in quality of life or functional status commonly co-occur with improvements in depression symptom severity, this cannot automatically be assumed. One comprehensive literature review estimated only a moderate degree of correlation between these constructs [55]. It has been argued that changes on quality of life measures may lag changes on depressive symptom measures and that short-term trials may not be an appropriate setting in which to estimate changes on quality of life measures. Contrary to this argument, however, four of five recently published short-term antidepressant medication trials found that benefits of medication over placebo were similar on measures of (1) quality of life or functional impairment (e.g., as measured by the Q-LES-Q and SDS) and (2) depression symptom severity (e.g., as measured by the HAM-D and MADRS). Our findings highlight the fact that reporting data only on symptom response and resolution may provide an incomplete and perhaps overly optimistic summary of a medication's overall effects on well-being. More robust assessments of quality of life and functional impairment should be incorporated into the design of clinical trials of any putative antidepressant.

Without longer-term data on not only depression symptom severity but also quality of life and social functioning, it is difficult to assess the risk–benefit profile of these medications prescribed over the long term. None of the included trials provided data on long-term (i.e., ≥6 mo) outcomes comparing adjunctive antipsychotic medication treatment to adjunctive placebo. Our failure to find long-term outcome data is consistent with that of previous research teams. For example, one systematic review of long-term, two-arm parallel randomized controlled antidepressant trials initially identified 2,693 abstracts, only to ultimately include six trials. This limitation is shared with other treatments; there is very little understanding of how adjunctive treatments for depression influence long-term well-being.
In addition to providing a thorough assessment of efficacy outcomes, our meta-analysis departs from the literature in a second notable way by comprehensively summarizing the available safety information on these medications. Such safety data have not been included in prior quantitative reviews, but our conclusions echo concerns raised in previous meta-analyses and a narrative review regarding potential treatment-related harms associated with use of atypical antipsychotic medication in the adjunctive treatment of depression. Overall, we found that treatment was linked to several adverse events, including akathisia (aripiprazole), sedation (quetiapine, OFC, and aripiprazole), abnormal metabolic laboratory results (quetiapine and OFC), and weight gain (all four drugs, especially OFC). Measures of absolute benefit and harm (NNT and NNH) provide an intuitive metric for understanding treatment-related benefits and harms. However, these measures are dependent on baseline control group risk, which may vary substantially across clinical subgroups [63]. Thus, our findings in terms of NNT and NNH should be interpreted as estimates of effects for each drug relative to control participants who may differ from participants treated in clinical practice.

Our ability to provide an adequate safety profile of these medications was limited in two respects. First, while 11 of 14 included trials used a structured instrument to elicit adverse events, these measures were limited to assessing potential EPS- and akathisia-related events, and, in five studies, sexual functioning. No study reported using a structured checklist to elicit adverse events outside of EPS, akathisia, or sexual functioning, which is a substantial limitation given that adverse events are reported with as much as 20 times greater frequency when elicited through structured checklists versus being recorded in response to patient complaints. The importance of measuring adverse events systematically was demonstrated historically in the case of selective serotonin reuptake inhibitors: in registration trials, sexual dysfunction was neither systematically assessed nor found to be frequently spontaneously reported by patients. Further investigation indicated, however, that sexual side effects on selective serotonin reuptake inhibitors are actually quite common. While the collection of adverse event data via structured checklists is a more sensitive method of collecting adverse event data, it may result in many common (mostly minor) health problems being endorsed even if they are not due to treatment, potentially leading to decreased specificity in differentiating medications from placebo [66]. To bridge the differences between the systematic and open-ended assessment of adverse events in clinical trials, some sort of hybrid method of collecting adverse event data could be performed, such as randomly assigning some participants within both the active treatment and placebo groups to complete a structured checklist while assigning others to complete an open-ended assessment of adverse events.

A second constraint on our ability to adequately summarize the drugs’ safety profiles is that many adverse events were not reported in journal articles and that some of the data were incomplete or reported in a fashion that may have obscured treatment-related harms. We agree with the Cochrane reviewers that “data on side effects were often very poorly described”. Conceptually similar events such as sedation, fatigue, and somnolence were sometimes reported separately, often with no attempt to pool them together. This is in direct contradiction to FDA guidance, which states that events that “represent the same phenomenon (e.g., somnolence, sedation, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect”.

Given the notable side effect profiles of the studied drugs, it is likely that the double-blind was significantly compromised; however, none of the included trials tested the integrity of blinding. For example, patients who rapidly gained weight in an OFC trial, who complained of akathisia in an aripiprazole trial, or who reported sedation in a quetiapine trial would likely cue the awareness of study personnel that they were assigned to the active drug condition. Assuming that proper informed consent was obtained, participants were also likely to accurately guess their treatment
assignment based on side effect cues. This could have led to inflated efficacy ratings by clinical raters and participants. The lack of protocols assessing the integrity of the double-blind in the trials included in our meta-analysis is consistent with the wider clinical trials literature. The potential for unblinding to cause inflated efficacy ratings among clinical raters could be substantially limited if efficacy outcomes were assessed by different personnel than those who assessed adverse events. Yet the use of separate raters to assess efficacy and safety outcomes was reported in only one trial.

The FDA statistical reviewer for aripiprazole wrote regarding Berman et al. [75] that “the medical reviewer is concerned about the considerable number of protocol violations in the study primarily due to usage of opiates/barbiturates” [74]. Regarding the Marcus et al. trial, the FDA reviewer wrote that the difference between groups in the number of participants who used prohibited medications was “huge”, with nine patients in the placebo group doing so compared to 24 in the aripiprazole group. The reviewer thus performed a separate analysis, excluding patients in the two trials who violated the study protocol, the results of which indicated a minimal, non-statistically significant effect of aripiprazole on functional status. In the journal articles, this potentially important issue is not mentioned. The FDA reviewer reported results only from reanalysis of the MADRS and SDS, so it is unknown to what extent these protocol violations may have impacted results on other outcome measures.

Our results differ somewhat from those of Nelson and Papakostas, whose meta-analysis concluded that augmentation with atypical antipsychotics was effective and, further, that “this body of evidence is considerably larger than that for any other augmentation strategy in the treatment of major depressive disorder”. There are seven differences in our analyses that provide reasons why we reached different conclusions. The greatest divergence in our results was regarding OFC, for which we found a lower OR favoring OFC for remission (1.42) than did Nelson and Papakostas (1.83). In this first instance, Nelson and Papakostas utilized whatever definition of remission was provided by the authors of each study, whereas we used a more restrictive definition. Three OFC trials defined remission as achieving a MADRS score of ≤8 at two consecutive visits—even if patients relapsed during the trial. We found that after meeting criteria for remission, OFC-treated participants were more likely to relapse than placebo-treated participants; this contributed to our finding a less favorable result for OFC in terms of remission. Second, we extracted data from all comparison groups that received adjunctive placebo treatment, whereas Nelson and Papakostas excluded one comparison group from each of two OFC trials. Third, Nelson and Papakostas estimated a significant treatment effect for OFC on response, whereas we did not. This difference seems due to a combination of our inclusion of all adjunctive placebo comparison groups and our use of random effects analysis as opposed to their use of a fixed effects model [38]. Our fourth point of difference was that Nelson and Papakostas included data from two conference presentations on quetiapine that showed positive findings; we were unable to obtain data from these authors despite three emailed requests over a span of 4 wk. Additionally, we attempted to contact one author via phone; the attempt did not result in the release of any data. Nonetheless, the pooled ORs generated in our analyses for quetiapine in terms of response (1.53) and remission (1.79) were quite similar to those published in Nelson and Papakostas's meta-analysis (1.60 and 1.89, respectively). Our fifth difference was the use of different definitions of remission in one risperidone trial, and the sixth difference was Nelson and Papakostas's inclusion of data from one small risperidone trial from which we were unable to extract remission data, leading to our finding a slightly lower rate of remission (OR of 2.37 versus 2.63). Lastly, and most importantly, the primary point of difference is that our analysis provides a more comprehensive appraisal of treatment efficacy and safety, which, as discussed above, presents a more accurate assessment of the comparative risks and benefits of treatment.
Our review adds to the Cochrane review on this topic [9] by filling in three important data gaps: (1) unpublished data from the FDA and clinical trial registry reports, (2) data on functioning and quality of life outcomes, and (3) data on metabolic laboratory parameters. Thus, our dataset contained more outcomes and often provided a more comprehensive assessment of included outcomes than the Cochrane review. For instance, the Cochrane review included data from one trial that reported data on clinically significant weight gain for patients on OFC, whereas we included data on both mean weight changes and binary measures of clinically significant weight gain from four such trials. We included laboratory data for several metabolic parameters for both quetiapine and OFC. Despite some differences in methodology, we agree with the Cochrane review that the evidence supporting the use of adjunctive atypical antipsychotics for depression is modest.

Several methodological issues also bear mention. First, while all trials were described as randomized, double-blind trials, only three trials clearly described adequate sequence generation procedures; in the remaining studies, such procedures were unclear. A lack of appropriate randomization or differences in the taste, smell, or appearance of the medication and placebo may allow study personnel and/or participants to guess their treatment assignment. As purportedly double-blind trials with unclear or inadequate randomization are associated with larger effects than trials in which adequate randomization is clearly described, this leads to the possibility that the current set of efficacy ratings were inflated to an unknown extent. Second, the design of some of the included trials may have compromised their validity. In each of the aripiprazole trials, patients were treated with an antidepressant plus adjunctive placebo for 8 wk; at that point, those who showed a treatment response were eliminated from the study, and the remaining patients were assigned to either remain on the same treatment or receive adjunctive aripiprazole in place of adjunctive placebo. Thus, all patients taking placebo during the randomized trial had clearly demonstrated poor response to placebo treatment and were likely predisposed to perform poorly during the randomized portion of the trial, thereby possibly inflating the estimated efficacy of the study drug.

In any systematic review, publication bias is a potentially serious problem. To incorporate as much data as possible, we conducted a thorough literature search and included unpublished data. We did not uncover the existence of any additional unpublished negative trials in our search, but this does not mean that such trials do not exist. Given the small number of trials for each drug in our study, we lacked statistical power to conduct a formal analysis of publication bias for each drug. However, when pooling across drugs, we detected that publication bias may have slightly enhanced the overall effect size on depression measures. Our results likely represent an upper boundary for the efficacy of these compounds (as demonstrated in prior meta-analyses), assuming that relevant unpublished data are more negative than positive in terms of efficacy.

We are aware of no trials that have directly compared adjunctive atypical antipsychotic medication treatment to other adjunctive treatments such as psychotherapy or lithium, or to other treatment strategies such as switching the antidepressant medication initially used for treatment. Further study may answer critical outstanding questions regarding the safety profiles and longer-term outcomes associated with these medications. Taken together, our meta-analysis found evidence of (1) some improvement in clinician-assessed depressive symptoms, (2) little evidence of substantial benefit in overall well-being, and (3) abundant evidence of potential treatment-related harm. Our comprehensive evaluation of safety and both relative and absolute efficacy provides critical insight that may be useful for clinicians attempting to thoroughly understand the risk–benefit profiles of these adjunctive treatments for major depressive disorder.
**ABSTRACT**

Importance  Due to increasing demand for sleep services, there has been growing interest in ambulatory models of care for patients with obstructive sleep apnea. With appropriate training and simplified management tools, primary care physicians are ideally positioned to take on a greater role in diagnosis and treatment.

Objective  To compare the clinical efficacy and within-trial costs of a simplified model of diagnosis and care in primary care relative to that in specialist sleep centers.

Design, Setting, and Patients  A randomized, controlled, noninferiority study involving 155 patients with obstructive sleep apnea that was treated at primary care practices (n=81) in metropolitan Adelaide, 3 rural regions of South Australia or at a university hospital sleep medicine center in Adelaide, Australia (n = 74), between September 2008 and June 2010.

Interventions  Primary care management of obstructive sleep apnea vs usual care in a specialist sleep center; both plans included continuous positive airway pressure, mandibular advancement splints, or conservative measures only.

Main Outcome and Measures  The primary outcome was 6-month change in Epworth Sleepiness Scale (ESS) score, which ranges from 0 (no daytime sleepiness) to 24 points (high level of daytime sleepiness). The noninferiority margin was −2.0. Secondary outcomes included disease-specific and general quality of life measures, obstructive sleep apnea symptoms, adherence to using continuous positive airway pressure, patient satisfaction, and health care costs.

Results  There were significant improvements in ESS scores from baseline to 6 months in both groups. In the primary care group, the mean baseline score of 12.8 decreased to 7.0 at 6 months (P < .001), and in the specialist group, the score decreased from a mean of 12.5 to 7.0 (P <
Primary care management was noninferior to specialist management with a mean change in ESS score of 5.8 vs 5.4 (adjusted difference, −0.13; lower bound of 1-sided 95% CI, −1.5; P = .43). There were no differences in secondary outcome measures between groups. Seventeen patients (21%) withdrew from the study in the primary care group vs 6 patients (8%) in the specialist group.

Conclusions and Relevance Among patients with obstructive sleep apnea, treatment under a primary care model compared with a specialist model did not result in worse sleepiness scores, suggesting that the 2 treatment modes may be comparable.

Obstructive sleep apnea with accompanying daytime sleepiness was estimated during the early 1990s to affect between 2% and 4% of middle-aged adults. With growing awareness of the public health implications of untreated disease and rising obesity rates that have increased the prevalence of obstructive sleep apnea, there has been a steady demand for sleep service provision in specialist centers and growing waiting lists for sleep physician consultation and laboratory-based polysomnography (PSG). As a result, there has been increasing interest in the use of screening questionnaires, home sleep monitoring, and autotitrating continuous positive airway pressure (CPAP), and greater involvement of other health care professionals in providing care.

One-third of primary care patients report symptoms suggestive of obstructive sleep apnea. With appropriate training and simplified management tools, primary care physicians and practice nurses might be ideally positioned to take on a greater role in diagnosis and management. Several randomized controlled studies have shown that ambulatory management of obstructive sleep apnea in specialist sleep centers using home testing and autotitrating CPAP produce comparable patient outcomes with standard laboratory-based sleep study methods. However, whether an ambulatory approach would be noninferior in a primary care setting is unknown. The aim of this study was to compare the clinical efficacy of obstructive sleep apnea management provided by a primary care physician and community-based nurse with currently recommended management in a specialist sleep center.

METHODS
Design Overview

A randomized, controlled, noninferiority study was conducted to compare an ambulatory, primary care–based management strategy vs standard care in a specialist sleep center. The research protocol was approved by institutional research ethics committees at the Repatriation General Hospital and Flinders Medical Centre, South Australia, and the study was registered with the Australian New Zealand Clinical Trials Registry. Patients and primary care physicians provided written informed consent.

Settings and Participants

Patients aged 25 to 70 years attending a primary care consultation for any reason were screened for eligibility by 34 primary care physicians between September 2008 and June 2010. Participants were recruited from 4 geographical locations in South Australia: (1) metropolitan Adelaide
(6 primary care practices, 2 community nurse clinics) and 3 rural regions, (2) South Coast (2 primary care practices, 1 community nurse clinic), (3) Barossa Valley (4 primary care practices and 1 community nurse clinic), and (4) Riverland (4 primary care practices and 1 community nurse clinic). All patients were screened for moderate to severe obstructive sleep apnea using a validated 2-step method\textsuperscript{13} that consisted of a 4-item screening questionnaire which, if positive (ie, score ≥5 out of 10 points), was followed by overnight oximetry (ApneaLink, ReMed). Inclusion criteria were (1) high diagnostic likelihood of moderate to severe obstructive sleep apnea defined as a score of 5 or more on the questionnaire and an overnight 3\% oxygen desaturation index (≥3\% ODI) of at least 16 events per hour and (2) an Epworth Sleepiness Scale (ESS) score of 8 or higher or persistent hypertension despite taking 2 or more antihypertensive agents. The ESS subjectively assesses excessive daytime sleepiness by asking patients to rate their chance of dozing off from 0 (would never doze) to 3 (high chance of dozing) for 8 commonly encountered scenarios, for a total possible score of 24. A cut-off score of 8 or more suggests the presence of at least mild daytime sleepiness. Exclusion criteria were (1) severe morbid obesity (body mass index [BMI], calculated as weight in kilograms divided by height in meters squared, >50); (2) neuromuscular disease; (3) unstable psychiatric disease or cognitive impairment considered likely to interfere with adherence to instructions, completing the study or managing CPAP; (4) hospitalization in the previous 3 months for myocardial infarction, unstable angina, cardiac failure, or cerebrovascular accident or New York Heart Association class III or IV symptoms; or (5) lung disease with awake resting oxygen saturation of less than 92\%.

Demographic and anthropometric data were collected, including sex, age, geographical region, weight, height, BMI, and waist circumference.

Randomization and Interventions

Patients meeting eligibility criteria were randomized into either primary care management or specialist sleep center management. Randomization was conducted by a telephone call to a clinical trials pharmacist independent of the study, using a computer-generated random numbers list.

Primary Care Management. Patients’ treatment was managed by primary care physicians and a community-based nurse who participated in a 6-hour education program on obstructive sleep apnea and its management. The education program was developed and presented by sleep physicians and a specialist nurse from the university hospital sleep medicine center and accredited by the Royal Australasian College of General Practitioners. Patients were reviewed in-person by 1 of 4 nurses who held clinics at 5 community locations (2 nurse clinics in metropolitan Adelaide and 1 in each of the 3 rural regions) to review progress and were given advice on managing CPAP-related adverse effects, encouraged to maintain adherence to therapy, advised to discuss alternative treatment options with primary care physicians if necessary, educated about lifestyle changes to improve obstructive sleep apnea, and asked to complete relevant research questionnaires. One nurse had 15 years of experience in a tertiary care sleep medicine service and at the 2 metropolitan-based clinics and at the South Coast clinic. The other 3 nurses were newly trained in obstructive sleep apnea management but had worked as rural-based practice nurses prior to their involvement (1 nurse cared for patients at the Barossa Valley clinic and the other 2 nurses cared for patients at the Riverland clinic). In addition to the 6-hour education program that they attended with the primary care physicians, the sleep training provided to the community-based nurses also involved 5 days of in-service training with specialist nurses at the tertiary sleep center. Home autotitrating CPAP (REMstar Auto, Respironics or S8 AutoSet Spirit, ResMed) was used over 3 consecutive nights to determine a fixed treatment pressure based on the 90th (REMstar Auto) or 95th (S8 AutoSet Spirit) percentile pressure. Continuous positive airway pressure devices were converted to a fixed pressure mode for the remainder of the study. Patients were followed up by their nurse with a telephone call within 2 weeks of commencing therapy and in person at months 1, 3, and 6. Primary care
physician appointments were set for months 3 and 6. Adherence to CPAP was objectively recorded by each device. Data information cards were downloaded at 1-, 3-, and 6-month reviews. Although CPAP was considered the primary treatment, physicians could initially prescribe, or at a subsequent review, switch their patients to alternative therapies if deemed appropriate, including lifestyle measures, a mandibular advancement splint (MAS), or upper airway surgery. Physicians were provided with contact details of a dentist expert in the fashioning of MAS (SomnoDent MAS, SomnoMed Ltd). Continuous positive airway pressure and MAS were available at no charge to participants. Physicians were advised that a sleep physician could be contacted for advice or to request a formal consultation.

Specialist Sleep Centre Management. Patients were referred to 1 of 9 sleep specialists for ongoing management. Sleep specialists had completed their Fellowship of the Royal Australasian College of Physicians, having undertaken at least 3 years of respiratory medicine training including 1 year of full-time sleep-medicine training. Sleep specialists were provided with the patient’s overnight oximetry trace. Further investigations, including full or split-night laboratory PSG, and treatment recommendations were left to the discretion of the treating physician. Continuous positive airway pressure titration, if recommended, was conducted manually during laboratory PSG or by home autotitration. Experienced nurses at the specialist center provided support for CPAP setup and education. The same models of CPAP machines were used as those in the primary care group. In-person follow-up visits occurred at the same time points as the primary care group.

Outcomes and Follow-Up

The primary outcome measure was the change in ESS score from baseline to 6 months. Secondary outcome measures were the Functional Outcomes of Sleep Questionnaire (FOSQ), Sleep Apnea Symptoms Questionnaire (SASQ), Short-Form 36 Health Survey (SF-36) vitality and mental health components, CPAP adherence, blood pressure, and weight, which were measured at baseline and 6 months. Vitality and mental health components of the SF-36 have been most responsive in previous CPAP studies; therefore, only changes in these 2 scores are reported. A Visit-Specific Satisfaction Questionnaire (VSQ-9) was also completed at 6 months. The eMethods includes a detailed description of the questionnaires.

Statistical Analysis

Statistical analyses were performed using STATA/IC 11.2 for Windows (StataCorp LP). Missing values for the main outcome measures were replaced by multiple imputation with multivariate normal regression using demographic and baseline outcome data and with the creation of 10 complete data sets. Comparisons between groups for the mean change in ESS, FOSQ, SASQ, and SF-36 scores; weight; and blood pressure after 6 months were conducted in an intention-to-treat manner including all patients randomized using analysis of covariance with adjustment for baseline scores and region. Results for data analyzed by carrying forward baseline observations for missing values and by inclusion of patients with complete data have also been conducted as a sensitivity analysis. A t test was used to evaluate for group differences in CPAP use and VSQ-9 scores. The difference in the mean change in ESS scores after 6 months was evaluated for noninferiority of the primary care group using an a priori determined noninferiority margin of −2.0 based on past studies of minimal clinically important differences for health-related quality of life instruments, clinical studies that have assessed natural variations in ESS scores and ESS responses to placebo CPAP in patients with obstructive

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sleep apnea, and consensus among sleep physicians in a previously published study. For the noninferiority analysis, significance testing using a 1-sided P value of .05 was used to determine the probability of rejecting the null hypothesis of inferiority. Statistical significance for secondary outcomes was determined using a 2-sided α of .05.

Sample Size

The study was powered to assess for noninferiority of the primary care group relative to the specialist group in the mean change in ESS score after 6 months. A sample size of 138 patients (69 patients in each group) was required for a study with 90% power and a type I error of 5%, assuming a noninferiority margin of −2.0 and a standard deviation of 4.0 for the change in ESS score. A total of 155 patients were recruited to allow for potential withdrawals and loss to follow-up.

Within-Trial Costs

Within-trial sleep diagnostic and treatment costs were collected and compared during the 6-month follow-up for nurse consultations, primary care physicians, and sleep physician consultations and for travel, sleep study, and treatment-related costs. Within-trial costs were also calculated for the US context and reported in US dollars. The eAppendix describes how costs were calculated.

RESULTS

A flow diagram outlining the recruitment and randomization pathway is shown in the Figure. In all, 402 patients were referred by primary care physicians after initial screening to community-based nurses for review of eligibility criteria and oximetry monitoring. Of those, 301 patients agreed to participate and were eligible for overnight oximetry. One hundred fifty-five patients were eligible and were randomized into the study.

Figure. Flow Diagram of Participant Recruitment and Randomization

ODI indicates oxygen desaturation index; CPAP, continuous positive airway pressure. aThe total number of patients initially screened by primary care physicians for eligibility is unknown. bPrimary analysis was conducted in an intention-to-treat manner and missing values were replaced by multiple imputation.

Baseline Characteristics

Eighty-one patients (27 from Adelaide; 3, South Coast; 24, Barossa Valley; and 27, Riverland) were randomized to the primary care group and 74 patients (18 from Adelaide; 1, South Coast; 26, Barossa Valley; and 29, Riverland) to the specialist group. Both groups were comparable and consisted of predominantly middle-aged, obese men from rural regions with at least mild daytime sleepiness.
Treatment

The principal treatments recommended to patients at baseline and used at 6 months are outlined in Table 2. At baseline, 90% of patients in the primary care group initiated CPAP, whereas 70% in the specialist group initiated CPAP with a higher proportion of patients being managed with conservative measures only. In the specialist group, 73 of 74 patients had a laboratory-based PSG: 38 for a full night and 35 for a split night. Three patients (4%) in the primary care group were referred for sleep specialist consultation during the study, 1 of whom had a laboratory full-night diagnostic PSG.

After 6 months’ follow-up, the proportions of patients using CPAP were similar in both cohorts (63% in the primary care group; 61% in the specialist group). More patients withdrew from the study in the primary care group. Baseline demographic, anthropomorphic, and obstructive sleep apnea severity indices were similar in patients who withdrew and those who completed the study in each study group.

Outcomes

Daytime Sleepiness: ESS score. The mean ESS for the entire study population was 12.6 (95% CI, 12.0-13.3). The mean ESS scores in the primary care group improved from 12.8 at baseline to 7.0 at 6 months, for an adjusted mean difference of 5.8 (95% CI, 4.4-7.2; P < .001) and in the specialist group from a baseline mean of 12.5 to 7.0 at 6 months, for an adjusted mean difference of 5.4 (95% CI, 4.2-6.6; P < .001). After controlling for baseline ESS score and region, the adjusted difference in the mean change in the ESS score was −0.13 (lower bound of 1-sided 95% CI, −1.5; P = .43). Sensitivity analyses using baseline observations carried forward for missing values and using data only from patients who completed the study produced similar outcomes. For the analysis using baseline observations carried forward for missing data, the adjusted difference in mean change in the ESS score was −0.63 (lower bound of 1-sided, 95% CI, −1.80; P = .19). When including only the 64 patients in the primary care group and the 68 in the specialist group who completed the study, the adjusted difference in the mean change in the ESS score was −0.14 (lower bound of 1-sided 95% CI, −1.28; P = .42). These results support noninferiority of primary care management because the lower bounds of the 1-sided 95% CI for all analyses were greater than the prespecified noninferiority margin of −2.0.

Secondary Outcomes. After 6 months, there were significant improvements in the mean FOSQ, SASQ, or SF-36 scores in both primary care and specialist groups compared with baseline (P < .001 for all measures), but no difference was evident between groups.

Adherence to CPAP use among those using it at 6 months was no different between the 2 groups, with mean (SD) usage of 4.8 (2.1) hours per night of the 51 patients in the primary care group and 5.4 (0.3) hours per night among the 44 patients in the specialist group (P = .11). No differences in systolic or diastolic blood pressure or weight were evident in either primary care or specialist groups after 6 months, and there was no difference in the mean change between groups. There were small, but statistically significant, differences in 5 out of 9 items in the VSQ-9 patient satisfaction survey in favor of the primary care group, although no difference in overall satisfaction was evident. Furthermore, effect sizes for the 9 items were small (range, 0.14-0.41) and may not therefore be clinically significant.
Within-Trial Costs

Comparison of within-trial sleep diagnostic and treatment costs revealed a total average cost per randomized patient of $1606.48 in the primary care group and $2576.47 in the specialist group. When considered in the US context, the equivalent total average costs per patient were estimated at $1819.44 in the primary care group and $3067.86 in the specialist group. Sleep study costs, sleep physician consultations, and travel costs appeared to be the main contributors to the increased within-trial costs in the specialist group.

COMMENT

In this study, patients identified by a 2-step screening process as having a high likelihood of moderate to severe obstructive sleep apnea and who were at least mildly sleepy were randomized to either primary care or specialist care management. Clinically significant improvements in the primary outcome measure, daytime sleepiness, were observed following treatment in both settings and outcomes for patients managed in primary care were not inferior to those treated in a specialist center. No differences between groups were found in secondary outcomes, including change in obstructive sleep apnea symptoms, quality of life, CPAP adherence, and overall patient satisfaction.

These results extend the findings of previously published studies of ambulatory models of care for obstructive sleep apnea deployed in specialist sleep centers. Mulgrew et al used a strategy of portable monitoring and autotitrating CPAP and found no differences in major outcomes, including change in ESS scores and quality of life compared with laboratory-based care. Furthermore, CPAP adherence was higher in the ambulatory care group. Berry et al conducted a similar study in a veteran population in which patients with obstructive sleep apnea were randomized to either portable monitoring and autotitrating CPAP or to laboratory PSG and CPAP titration. After 6 weeks, no differences were observed in CPAP adherence, change in ESS or FOSQ scores, patient satisfaction with CPAP or residual AHl. Kuna et al found that functional outcomes and CPAP adherence were not inferior to laboratory-based care when using an ambulatory strategy for obstructive sleep apnea. None of these studies assessed the relative costs of the simplified management strategies.

More recent studies evaluating ambulatory strategies have examined within-study costs. Andreu et al randomized patients to either home sleep monitoring and follow-up, hospital PSG and follow-up, or home monitoring and hospital follow-up. They found no differences in CPAP adherence or in ESS, FOSQ, or symptom scores after 6 months. They also reported significant mean (SD) cost savings for home diagnosis and follow-up ([euro]590 ([euro]43)) and home diagnosis with hospital follow-up ([euro]644([euro]93)) compared with laboratory PSG and hospital follow-up ([euro]849 ([euro]11)). Rosen et al showed that home diagnosis and autotitrating CPAP was associated with higher adherence, similar to the study by Mulgrew et al, with no difference in the change in ESS scores or functional outcomes after 3 months compared with laboratory-based management. Within-trial costs were 25% less expensive for the home-treatment group.

We previously conducted a randomized controlled trial to evaluate a simplified model of care for obstructive sleep apnea led by sleep-trained nurses in a tertiary care setting. The primary outcome, mean change in ESS scores at 3 months, for patients assigned to the nurse-led
approach was not inferior to the specialist-led group and had within-study cost savings of A $1111 per patient. These results led us to consider the potential role of primary care physicians and nurses in the diagnosis and management of obstructive sleep apnea.

The present study, which recruited patients from metropolitan and rural communities, had a longer follow-up than previous studies (ie, 6 months vs 1-3 months). We believe that important elements in the success of the study were the training given to primary care physicians and nurses and access to specialist support. Thus, although primary care physicians and community nurses were encouraged to take primary responsibility for patient management, this simplified strategy was designed as a hub-and-spoke–like model of care, with a central specialist sleep center overseeing and supporting a number of primary care–based obstructive sleep apnea clinics. Of note however is that primary care physicians cross-referred only 3 of 81 patients (4%) to sleep specialists for a second opinion. This could be because two-thirds of the study population were recruited in rural regions located 90 to 240 km from the city-based specialist sleep service. However, only 1 out of 21 metropolitan-based patients (5%) enrolled in the primary care group were cross-referred suggesting perhaps that, at least in the context of the research study, primary care physicians and nurses were reasonably confident in their management decisions.

At baseline, CPAP was recommended more frequently in the primary care group. However, by 6 months a considerable number of patients in the primary care group had stopped using CPAP, and the proportion of patients using CPAP was similar to that in the specialist group. Average daily CPAP use at 6 months was no different between groups. These observations could suggest that specialists, who have additional information from laboratory PSG and are more experienced at obstructive sleep apnea management, may be better at predicting which patients will adhere to CPAP in the long term. Alternatively, attendance at a specialist or nurse review, or both in a tertiary sleep center may itself have had an influence on long-term adherence. There could also be an effect of experience such that with time, the primary care physicians may become more confident with managing sleep apnea and thus promote greater CPAP adherence or recommend alternative therapies such as a MAS or conservative measures earlier in the course of treatment for patients who are reluctant to use or are intolerant of CPAP. However, in spite of the different approaches to management, patient outcomes were ultimately similar in both groups.

Analysis of within-trial sleep-related diagnostic and treatment costs revealed that primary care management of obstructive sleep apnea was approximately 40% cheaper than specialist care in both the Australian and US contexts. However, our study reports within-trial sleep management-related costs only and not indirect costs nor does it assess the longer-term economic implications of an ambulatory strategy in primary care. Recent debate has resulted from a study by Pietzsch et al that showed full-night PSG to be more cost-effective than unattended home monitoring in the management of obstructive sleep apnea because of its superior diagnostic accuracy. It was pointed out in an accompanying editorial, however, that several assumptions used in their modeling could have magnified the effects of false-positive and false-negative results and elevated the costs of portable monitoring. More detailed cost-effectiveness analyses that account for increased access and reduced waiting lists, the impact of false-positive and false-negative tests, potential adverse health consequences of untreated disease and benefits of therapy, and indirect costs of ambulatory, primary care–based management strategies for obstructive sleep apnea are needed.

Several limitations of our study are acknowledged. We excluded patients with a BMI higher than 50, significant respiratory or cardiac disease, and serious psychiatric illness or cognitive impairment. Thus, the results of this study cannot be generalized to these populations. It is possible that...
patients with predominantly central sleep apnea, including Cheynes Stokes respiration, may have been misdiagnosed in the primary care group, because only oximetry was used to identify patients with disease. However, we excluded patients with disorders prone to central sleep apnea (e.g., heart failure) plus residual AHI was monitored on CPAP devices and, at 6 months, only 1 patient in the primary care group had a residual AHI exceeding 15/h.

One of the community-based nurses assigned to the primary care group who predominantly managed patients in the metropolitan region had 15 years of experience in a tertiary care sleep medicine service, whereas the other 3 rural-based community nurses were newly trained in obstructive sleep apnea management. The more experienced nurse was included in the primary care group to assist in the training and to mentor the newly recruited nurses. We would anticipate that if such a model of care were to be translated into real practice, some nurses employed to care for patients with obstructive sleep apnea in a community-based clinic would likely have some prior experience in obstructive sleep apnea management, particularly in the metropolitan region where there is a larger pool of experienced, CPAP-trained nursing staff. The more experienced nurse cared for a total of 30 patients (37%) in the primary care group based in the metropolitan and rural South Coast regions, while the 3 less experienced nurses cared for the other 51 patients (63%) patients located in the rural Barossa Valley and Riverland regions.

We have attempted to account for the difference in nurse experience by adjusting for geographical region in addition to baseline ESS score in our analyses. Furthermore, withdrawal rates, change in ESS scores from baseline to 6 months, 6-month CPAP adherence, and auto-CPAP titration results were not significantly different between the experienced vs newly trained nurses. Therefore, we do not believe that inclusion of an experienced nurse in the primary care group significantly biased our results.

For reasons that are not entirely clear, more patients withdrew from the primary care group. It is possible that patients were more inclined to remain in the study if they were receiving specialist consultations. Alternatively, participants may have had less faith in the advice of the primary care team and the greater number of withdrawals may be because physicians were less skilled in educating patients about obstructive sleep apnea and treatment options. Although overall patient satisfaction was no different between groups, the opinions of patients who withdrew were not sampled. Interestingly, one-half of patients who withdrew from the primary care group did so because of CPAP intolerance; whereas this was not cited as a reason in the specialist group. The higher number of withdrawals in the primary care group may have biased study results by excluding data from patients with worse outcomes. However, we believe our findings are robust because in both the primary analysis using multiple imputation for missing values and in 2 sensitivity analyses, patient outcomes in the primary care group remained clinically noninferior.

In conclusion, in this randomized controlled study, a simplified management strategy for obstructive sleep apnea based in primary care was not clinically inferior to standard care in a specialist sleep center. It possibly could be delivered at a lower cost. Thus, with adequate training of primary care physicians and practice nurses and with appropriate funding models to support an ambulatory strategy, primary care management of obstructive sleep apnea has the potential to improve patient access to sleep services. This would be particularly beneficial for rural and remote regions, as well as developing nations, where access to specialist services can be limited. However, some caution needs to be exercised in extrapolating these findings to actual practice in which primary care physicians may not be as skilled and motivated as those who participated in

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this randomized controlled trial and in which patient outcomes may not be as good as those observed in this study. Our comparison of within-trial costs cannot be considered a cost-effectiveness analysis, and further investigation is needed in this regard.

**Substance Abuse**

**Improving Opioid Prescribing**

The Journal of the American Medical Association

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On January 10, 2013, New York City Mayor Michael Bloomberg announced new guidelines for the prescribing of opioid analgesics to patients being discharged from the city's emergency departments. The guidelines were developed by a panel of emergency physicians and are intended to reduce opioid addiction and overdose deaths while preserving access to opioids for patients in whom the benefits are expected to exceed the harms. Because most opioids are prescribed by primary care physicians, the introduction of these guidelines alone is unlikely to effect a large decrease in opioid-related harm. Nevertheless, it is worth considering why such guidelines are necessary and what complementary actions physicians, patients, and health authorities should take to address the increasing problem of opioid-related harm.

The 9 New York recommendations are modeled after similar initiatives in Washington State and elsewhere. Emergency physicians are encouraged to use low doses of short-acting opioids for a few days at most, rather than long-acting or extended-release products. The guidelines also suggest that physicians exercise caution when prescribing opioids to patients taking benzodiazepines, that they inform patients about the risks of opioid dependence and overdose, and that they consult the state's prescription drug monitoring program to ascertain details of previous prescriptions. The latter will soon become a statewide requirement for prescription durations of 5 days or longer.

However, the guidelines are optional and do not restrict physicians from providing the care they consider to be in a patient's best interest. That such guidelines are even necessary is a testament to the magnitude of the problem. From 2004 to 2009, the number of emergency department visits in New York City related to the misuse and abuse of opioid analgesics more than doubled (from 4456 to 9254), and nonmedical use of opioids (ie, use without a prescription or use with a prescription but in a manner other than prescribed) increased by roughly 40%. Approximately 4% of the city's population 12 years or older—estimated at more than a quarter of a million New Yorkers—have reported opioid misuse. Although emergency departments are generally not where these problems originate, they often are key to perpetuating misuse.

The problem of opioid-related harm is neither limited to emergency departments nor unique to New York City. It is estimated that more than 200 million opioid prescriptions are issued nationwide each year, and approximately 16 000 people die annually from prescription opioid overdose. For
every opioid-related death, many more individuals experience opioid addiction. This morbidity and mortality evolved over 2 decades from the complex interplay of several factors, including well-meaning physicians with few other drug therapies for patients with pain and a uniquely successful but often misleading (and sometimes illegal) promotional effort centering on assessing pain and prescribing opioids for analgesia—an effort that heightened expectations of patients and physicians while minimizing concerns about opioid use. The key factor, however, has been the pleasurable effects imparted by prescription opioids, many of which are chemically similar to heroin.

Underlying the recommendations outlined in the guidelines are several underappreciated facts. First, despite the widely held perception that opioids are the most potent medications available for the treatment of pain, for most conditions there is little evidence that opioids are more effective than other therapies. Most of the available prescription opioid products have gained regulatory approval largely on the basis of studies in which they were compared with placebo—a treatment no clinician would contemplate for pain. Second, the risks of opioid dependence and addiction are far greater than generally appreciated—up to one-third of patients receiving chronic opioid therapy meet criteria for an opioid use disorder. Third, physicians often issue prescriptions for a larger supply of opioids than necessary and sometimes initiate therapy with extended-release formulations in situations in which short-acting preparations would be preferred (eg, for acute pain). Although this may reflect a desire for compassionate care, it is worth emphasizing that every individual who spirals into addiction or dies from an overdose of prescription opioids has an initial exposure and that this initial exposure typically involves opioids obtained via prescription rather than theft from a manufacturer, distributor, or pharmacy.

Some may argue that the New York City guidelines will lead to undertreatment of pain. Moreover, physicians may resent what they perceive to be bureaucratic meddling or interference with their professional judgment, although the voluntary nature of the guidelines should dispel this concern. Like most clinical practice guidelines, excessively rigid application may have unintended consequences. For example, patients who rely on emergency departments for primary care could be adversely affected if the guidelines are misinterpreted as policy.

There also may be repercussions involving patient satisfaction. Two decades of marketing and advocacy have led some patients to perceive that they have an entitlement to pain control with opioid analgesics. In fact, they have an entitlement to good care; these are not synonymous. Dissatisfaction with the type or duration of analgesics prescribed in an emergency department may undermine the response to treatment, spur complaints against physicians, or have financial implications if satisfaction measures are a determinant of physician income. This could be mitigated by the development of more robust patient experience metrics and by recognizing that a discussion about the causes of pain and the risks of available treatment options may result in an informed decision not to treat with opioids.

Another concern is that the guidelines alone will be insufficient. Evidence from other areas of medicine suggests that the passive dissemination of guidelines, or even the use of more intensive techniques such as “audit and feedback,” have only a modest effect on practice. For this reason, some jurisdictions and payers have tied the introduction of guidelines to regulations that mandate certain practices. For example, physicians in Washington State who care for patients with chronic pain are required to use treatment agreements when prescribing opioids to patients with a history of substance abuse or psychiatric illness and to seek specialist consultation when prescribing doses greater than 120 mg of morphine (or equivalent) daily. In Ontario, Canada, the Workplace Safety Insurance Board will only pay for short-acting opioids for the first 12 weeks following

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an injury. A few health systems have also launched large-scale initiatives to improve the safety and effectiveness of opioid prescribing—for example, Group Health in Washington State has implemented a multifaceted strategy including individualized treatment plans, urine drug screens, and decision support using electronic health records.

Many physicians and patients have had unreasonable expectations of opioids and have seriously underestimated their risks. It is time to collectively lower expectations and prescribe these drugs less readily, to fewer patients, at lower doses, and for shorter periods. The New York City guidelines align with this view and are simple, sensible, and easy to follow. The next steps should be to monitor for intended and unintended consequences and to develop similar guidelines for other specialties, understanding that such measures may encounter resistance. As with impaired driving, meaningful change in the prescribing of opioids may require legislative action. Any such measures must ensure that patients with chronic pain or opioid addiction are not abandoned.

Emergency department prescribing of opioid medications is not the cause of the opioid epidemic, but these guidelines and others are important first steps toward addressing this public health problem. Other specialties should follow this lead. Only by changing how opioids are prescribed can the toll of addiction and death from these drugs be reduced.

Chronic Back Pain With Possible Prescription Opioid Misuse

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ABSTRACT

Importance  Data on the effectiveness and safety of long-term opioid therapy for chronic pain are limited. Opioid adherence monitoring includes urine drug testing. Determining whether a patient's opioid prescription should be discontinued after an unexpected urine test result can be clinically complex.

Objective  To review safe opioid prescribing practices and appropriate interpretation and management of unexpected urine drug test results.

Evidence Review  Systematic reviews of the effectiveness and safety of long-term opioid therapy for chronic noncancer pain. Clinical management recommendations are derived from clinical guidelines generated by several professional medical organizations including the American Pain Society, the American Academy of Pain Medicine, and the Federation of State Medical Boards.
Findings  Informed consent and patient-prescriber agreements are important strategies to ensure that patients understand treatment goals and potential opioid risks. Monitoring for benefit and opioid misuse is accomplished by having frequent face-to-face assessments, performing urine drug tests, monitoring pill counts, and reviewing prescription drug monitoring program data, when available.

Conclusions and Relevance  The underlying causes for worrisome behaviors such as urine drug test results that are negative for the prescribed opioid should be fully investigated. Subsequent opioid prescriptions should be based on the revised risk and benefit assessment.

DR LIBMAN: Mr O is a 71-year-old man who had been treated for chronic low back pain since 1981 when he underwent surgery for a herniated lumbar disk. He continued to have pain, which was unsuccessfully managed with acetaminophen and tricyclic antidepressants. Nonsteroidal anti-inflammatory drugs were not used because of a history of gastritis and Barrett esophagus. Steroid injections offered temporary relief. For more than a decade he achieved reasonable pain control by taking oxycodone-acetaminophen 3 times a day as needed (84 tablets every month). He signed a controlled substance agreement. However, urine drug testing (UDT) found no oxycodone on 2 occasions. He explained that he occasionally drinks alcohol and does not take his oxycodone-acetaminophen when doing so. His oxycodone-acetaminophen was discontinued for this violation of his agreement. Since then, he reports that his pain is inadequately controlled and his function has decreased.

His medical history is notable for hypertension, hyperlipidemia, chronic obstructive pulmonary disease, dyspepsia, Barrett esophagus, anxiety, and depression. He is under psychiatric care.

His medications include atorvastatin, hydrochlorothiazide, bupropion, alprazolam, venlafaxine, esomeprazole, gabapentin, and fluticasone, albuterol, and ipratropium inhalers.

Mr O is divorced and lives alone. He receives long-term disability due to chronic back pain. He drinks beer occasionally (remote history of heavy drinking) and smokes 2 to 3 packs of cigarettes a day. There is no history of illicit substance use.

MR O: HIS VIEW

I had a ruptured disk in 1981. Since then I have had back injections and pain medication. One doctor said I had sciatic nerve root damage and ever since I have been suffering. I started on Percocet and it was doing its job. I would still get pain and it was still tough walking, but the Percocet helped the pain. I still get injections, which help for 2 weeks only.

The Percocet was stopped when I took a blood test, and they did not see it in my system. There was no Percocet in my system because I had just gone to the city club and had a few drinks. When I have a few drinks I don't take the Percocet. I guess they assumed that I was selling it.

I needed the Percocet. I don't think they ever should have taken me off it. I lay down most of the time and don't go anywhere because I cannot walk far. When I started on the narcotics, they gave me a form to sign where I wasn't going to overdo it. I never raised the dosage.
I believe that there are people that do sell Percocet. I have seen a lot out there, but I am not going to sell what I need, so I don't think that applies to me. I am 71 years old. I don't know what addiction really is. Addiction to me is when you take something you cannot get off and it is bad for you. I was so mad I wanted to see a different doctor but I ended up not.

SCOPE OF THE PROBLEM

DR ALFORD: Approximately 100 million Americans have chronic pain. The safe and effective use of opioids for the management of chronic pain is complex. Clinicians must balance the goals of relieving pain and suffering while not harming the patient (eg, addiction or overdoses). Because of the lack of pain medicine specialists, even the most complex patients with chronic pain are primarily managed in primary care. This is compounded by the lack of pain management curricula in medical training. This results in some clinicians overprescribing and others underprescribing. In a survey of community clinicians, the 2 most common opioid prescribing concerns were patients becoming addicted or diverting (eg, selling) the opioid. Unrealistic expectations regarding the potential benefits of opioids and an underappreciation for the potential harms also complicate opioid prescribing. As opposed to acute pain, not all chronic pain improves while taking opioid therapy. For those patients who do not respond, uncontrolled dose escalation often ensues, all in a desperate, yet futile, attempt to obtain pain relief.

Since the 1980s when the medical literature began to support opioid therapy for chronic noncancer pain, there has been a 4-fold increase in opioid prescribing. During the same period, unintentional opioid overdose deaths has increased 4-fold and substance abuse treatment admissions for prescription opioid addiction has increased 5-fold. In the United States, nonmedical use of prescription opioids is the second most prevalent type of illicit drug use after marijuana.

OPIOID EFFECTIVENESS AND SAFETY

Opioids are powerful analgesics that act peripherally by inhibiting activation of nociceptors and act centrally by turning on descending inhibitory pain pathways and by preventing ascending transmission of pain signals. Patients’ response to and ability to tolerate different opioids is influenced by genetic variations in μ-opioid receptor binding and opioid metabolism. Therefore, a trial of several opioids may be needed to find an acceptable balance between analgesia and tolerability.

Data on the effectiveness of long-term opioids are limited. Most of the published studies are uncontrolled case series. The randomized clinical trials are of short duration, less than 8 months. Studies find statistically better analgesia with opioids than controls, but the pain relief is modest. Whether function and quality of life improves is inconclusive. In a systematic review of opioid treatment for chronic back pain, the study quality was considered weak and there was no significant benefit of opioid therapy. Because of the poor quality of evidence, it remains unclear whether long-term opioid therapy is effective. However, it is not uncommon in clinical practice to have patients like Mr O with apparent benefit from long-term opioids.
Allergies to opioids are extremely rare, but adverse effects such as nausea, sedation, and constipation are common. Patients will develop tolerance to most adverse effects over time; however, constipation can be a persistent problem. Respiratory depression is a concern because opioids have also been linked to both central and obstructive sleep apnea. Unlike other analgesics—nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen—organ toxicity to opioids is rare. Opioids can suppress the hypothalamic-pituitary-gonadal axis resulting in opioid-induced hypogonadism leading to sexual dysfunction, fatigue, and poor bone health. A study found that higher-dose opioids (>50 mg of morphine equivalent dose) are associated with a 2-fold increase in fracture risk. Another concern is the development of a paradoxical increase in pain sensitivity due to opioid-induced hyperalgesia. The mechanism for this hyperalgesia is unclear.

Opioid addiction and opioid induced overdoses are 2 major concerns. The true rate of opioid addiction in patients prescribed opioids for chronic pain is unclear but is reported from 0% up to 50%. This uncertain incidence results from different populations studied and different definitions of addiction used. Annually, patients taking opioids long term have a 1.8% risk of overdosing. Recent observational studies have shown a correlation between opioid dose and risk of fatal overdoses and adverse events with a 9-fold increase in fatal overdoses for morphine equivalent doses of more than 100 mg/d and a 2-fold increase in substance-related health services utilization for morphine equivalent doses of more than 120 mg/d. Because Mr O was prescribed a low dose of oxycodone, he was at a lower risk of experiencing these opioid-related complications.

TERMINOLOGY

The use of opioids to treat chronic pain is complicated by misunderstood terminology. Physical dependence is a predictable physiological response to chronic opioid exposure resulting in a withdrawal syndrome with abrupt cessation or rapid dose reduction. Most patients who are receiving long-term daily opioid therapy will become physically dependent. Mr O was not physically dependent because he did not complain of withdrawal symptoms when not taking his opioids for days. Physical dependence does not indicate maladaptive behaviors and does not meet the diagnostic criteria of opioid dependence, without, for example, loss of control or continued use despite negative consequences. Criteria for opioid addiction were developed to better address the need to identify problems in patients with chronic pain. Addiction is characterized by behaviors that include one or more of the 4Cs: impaired Control over drug use, Compulsive use, Continued use despite harm, and Craving. Although the term pseudoaddiction is based on a single case report, it describes behavior suggestive of addiction that is triggered by unrelieved pain. Patients seeking pain relief should be focused on pain relief and be willing to try nonopioid therapies while the addicted patient is solely focused on obtaining more opioid. Prescription drug misuse refers to drug use in a way different from that prescribed or for reasons other than for which it was prescribed. Diversion is when opioids are shared or sold. Federal surveillance programs have shown an increase in prescription opioid diversion due to their significant street value. Aberrant medication-taking behavior describes a spectrum of behaviors that may reflect drug misuse. Although Mr O’s behavior was not suggestive of opioid addiction, that his urine drug tests results were negative for his prescribed opioid raises concern for diversion.

Before Prescribing an Opioid

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Prior to starting opioids for chronic pain, it is important to review what the patient's experience has been with nonopioid and nonpharmacotherapies. Because all patients taking opioids long term have potential for prescription opioid misuse, “Universal Precautions for Pain Medicine” are now recommended. That is, all patients should be assessed for risk before starting opioids and monitored for harm and benefit while taking opioids. Although this recommendation is not evidence based, it is increasingly used. Specific risk factors for prescription opioid misuse include younger age (16-45 years), mental illness, personal or family history of substance abuse, or legal history of substance abuse.

Numerous risk assessment tools have been developed to risk stratify patients including the Screener and Opioid Assessment for Patients with Pain (SOAPP) and the Opioid Risk Tool (ORT). The ORT is a brief 5-item self-report that classifies patients as low, moderate, and high risk. The risk level can help determine the intensity of monitoring that will be required of the patient. Some patients with a history of prescription opioid addiction may not be suitable candidates for prescription opioids and ideally should be referred to specialty care (ie, pain medicine, addiction medicine).

Patient education regarding realistic treatment goals and opioid risks is critical. Patients must understand that the initial and subsequent opioid prescriptions are a test and not necessarily a commitment to long-term opioids. This discussion is often aided by using a risk-benefit framework. This framework, not dissimilar to what clinicians use with other treatments for chronic diseases, focuses attention on judging the treatment (ie, opioid therapy), not the patient. This serves to clarify the clinician's role as a caregiver and not as a police officer or a judge.

Patient education is enhanced by the use of a standardized patient-prescriber agreement. The agreement articulates the rationale for and risk of long-term opioid therapy and the monitoring strategies (eg, UDT, pill counts) and consequence of aberrant medication taking behavior (eg, unsanctioned dose escalation). When a patient, such as Mr O, exhibit behavior for opioid misuse (eg, UDT negative for the prescribed opioid), the clinician should first confirm that the urine result is accurate. If confirmed, the clinician should interview the patient considering the full differential diagnoses for the behavior of concern. Once the etiology has been determined, a change in treatment plan (eg, medication change, increased monitoring, or both) should occur. Although the efficacy of agreements in decreasing opioid misuse has not been well established, they are increasingly being used. Mr O's so-called violation of his agreement was the basis of discontinuation of his opioids. Because of the inherent risks of opioids, clinicians should obtain informed consent from patients. This should include a description of the patient's responsibilities (eg, safe storage and disposal and not diverting) and potential opioid risks including adverse effects (short- and long-term), physical dependence, risk of drug (eg, sedatives) interactions resulting in central nervous system and respiratory depression, addiction, and overdose. It is particularly important to warn the patient about the elevated risk of driving and overdose when the opioid is started and titrated. The risk for overdose seems greatest shortly after the initial opioid prescription or after a refill. Despite Mr O's being on a low-dose opioid, his concurrent benzodiazepine use puts him at higher risk of adverse outcomes (eg, central nervous system depression).

Selecting an Opioid

Opioid therapy should be individualized based on its onset and duration of action as well as the patient's prior experience. Although there are efforts to develop abuse-resistant opioids, currently all opioids and opioid formulations are potentially abusable. Clinical guidelines recommend
long-acting (extended-release) opioids for treating chronic persistent pain and short-acting (immediate-release) opioids for intermittent or incidental pain. However, there is insufficient evidence in the literature to determine whether long-acting opioids are more effective or safer than short-acting opioids in treating chronic pain. It is prudent to start with less potent opioids (eg, codeine) before prescribing higher potency opioids (eg, morphine). A trial of several opioids may be necessary before an acceptable balance between efficacy and adverse effects is achieved. If an opioid loses efficacy or has intolerable adverse effects, switching from one opioid to another (ie, opioid rotation) may improve clinical outcomes at lower opioid doses. When switching from one opioid to another, equianalgesic tables should be used cautiously because they do not take into consideration individual variability in metabolism, receptor polymorphisms, and drug-drug interactions. To improve clinical outcomes and to decrease the total amount of opioid required, multimodal analgesia (ie, NSAIDs, tricyclic antidepressants, gabapentin) should be considered.

To eliminate the need for weekend refills and to ensure that the patient taking opioids daily will be due for a refill on the same day of the week every month, clinicians can give a 28-day rather than 30-day opioid prescription.

Monitoring for Benefit and Harm

Much of what is recommended for monitoring is based on expert opinion rather than on research. When starting opioids, frequent face-to-face visits (eg, weekly to every 2 weeks) are prudent. In managing chronic pain all measures of benefit and harm are subjective. Despite this limitation, clinicians must evaluate the efficacy and safety of the opioid therapy they have started or are continuing. All patients prescribed opioids should be agreeable to having their opioid use closely monitored for benefit and harm.

Monitoring for benefit includes measuring improvement in pain, function and quality of life. Most of the validated instruments to measure benefit (eg, Brief Pain Inventory) are too cumbersome for primary care settings. A validated 3-question pain, enjoyment, general activity (PEG) scale now makes this assessment practical in primary care.

Monitoring for harm includes detecting opioid misuse including addiction and diversion. It includes UDT, pill counts, use of state prescription drug monitoring programs (PDMPs), and identifying and documenting instances of aberrant medication-taking behaviors. As mentioned earlier, this monitoring should be implemented for all patients.

Urine drug testing confirms therapeutic adherence (ie, the medication prescribed is detected in the urine) and detects use of illicit or nonprescribed drugs. Urine drug testing is increasingly used in clinical practice because self-reported illicit drug use is unreliable, because observing patients for aberrant medication-taking behavior detects only some problems, and because it may improve treatment adherence (eg, decreased illicit drug use). Although UDT is recommended, a major barrier is the lack of skill clinicians have interpreting the results. Although UDT detects use of illicit drugs or nonuse of prescribed opioids, it does not diagnose prescription opioid abuse, addiction, or diversion. To accurately interpret UDT results, clinicians must order the correct assay (eg, immunoassay, gas chromatography/mass spectrometry), understand the major and minor opioid metabolic pathways, and know expected drug detection times and potential causes of false-positive and false-negative results. Before sending a UDT, it should be documented when the patient last took the medication being tested for. If the patient has not taken the opioid in 72 hours, it will

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not be detected. It does not appear that Mr O was asked when he last took his oxycodone-acetaminophen prior to his test. The level of concern and next steps would be different if Mr O disclosed that he had not taken his opioid prior to his test rather than in response to the unexpected test results. The rationale of requiring a UDT should always be discussed openly with patients. It is less about catching patients doing something wrong and more about assessing increased prescription opioid misuse risk. Mr O seemed unaware of the UDT based on his statement: "I took a blood test, and they did not see it in my system." Because of the complexity of UDT interpretation, clinicians need access to a laboratory toxicologist to help with both UDT ordering and assessment.

Pill counts can be used to monitor patients for medication adherence and to detect possible diversion. If a patient “forgets” to bring in the remaining pills, it is useful to have the patient return later that week for a pill count. Conducting pill counts would have been helpful in determining how Mr O was taking or not taking his opioids prior to the unexpected UDT result.

Prescription-Drug Monitoring Programs are statewide electronic databases that serve to help clinicians identify patients obtaining controlled substances from multiple prescribers (ie, “doctor shopping”). Currently 42 states have an operational program.

TO CONTINUE OR DISCONTINUE OPIOIDS

Decisions to continue or discontinue opioids should be based on the risk:benefit ratio. Does the opioid therapy benefit more than harm Mr O? If there is benefit in the absence of harm, then opioid therapy can be continued. If there is a small benefit in the absence of harm, then a dose increase may be warranted. Although opioids do not appear to have an analgesic ceiling effect, it is now known that higher opioid doses are associated with increased risk. Therefore, clinicians should ensure that patients take the lowest effective opioid dose possible.

If there is no benefit and no harm, then the clinician should consider trying a different opioid (ie, opioid rotation). If there remains no benefit and the patient is not meeting treatment goals, then the treatment benefit cannot outweigh risks and the clinician should stop or taper (should the patient be physically dependent) the opioid therapy. When there is a lack of benefit, the clinician should reiterate his/her belief that the patient’s pain is real and express frustration at the lack of benefit from opioid therapy. The clinician should show commitment to continue caring for the patient. The clinician is not abandoning the patient but rather abandoning an ineffective treatment.

If the patient is engaging in aberrant medication-taking behavior, the clinician should consider the complete differential diagnoses for that behavior; eg, is the patient treatment seeking for unrelieved symptoms, drug seeking due to addiction, or a combination of both. If the behavior is because of addiction (ie, loss of control, compulsive use, continued use despite harm), the clinician should give specific and timely feedback to the patient for why the behaviors raise concern for possible addiction. In cases of suspected addiction, the benefits can no longer outweigh risks and the patient should be referred to addiction treatment.

RECOMMENDATIONS FOR MR O

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It is unclear how Mr O is taking his opioid. With negative UDT results, he has not taken his oxycodone-acetaminophen for at least 48 to 72 hours on multiple occasions despite being prescribed enough medication to be taken 3 times a day. Lack of physical withdrawal also suggests that Mr O does not take his opioid daily. I would perform pill counts to better assess his opioid use.

The differential diagnosis for his unexpected UDTs (ie, medication not detected) is broad. It includes that he does not take his opioid daily as prescribed. Does he only skip doses when he is drinking as he states? If so, then it appears that he is drinking for extended periods of time (48-72 hours) and thus is at risk for the negative health consequences of unhealthy alcohol use. If he is not taking his opioids daily, which may be clinically appropriate, what is he doing with his extra medication? Is he hoarding them or diverting them? Alternatively, is he taking more than prescribed on certain days and running out of medication early? Is the UDT assay insufficiently sensitive to detect the medication at the concentration present, that is, there is oxycodone present but it is below the laboratory set cutoff (50 ng/mL)? Has he adulterated or substituted the sample to avoid detection of illicit drug use? A laboratory error is always possible in clinical laboratories that don't use chain of custody procedures, but this is less likely in this case because it was confirmed negative in 2 separate specimens. I would express my concern about his unexpected test results and ask him in a nonjudgmental way to explain the results.

If he were benefiting but taking less than prescribed, I would inquire about the status and safe storage of his extra medication. I would decrease his dose and schedule close follow-up with random pill counts and UDTs. Prior to sending each urine sample to the laboratory, I would document when he took his last opioid dose.

If there was too much risk (eg, misuse such as diversion) despite benefit, I would discontinue his opioid therapy as was done in this case. There would be no need for an opioid taper in the absence of physical dependence.

QUESTIONS AND COMMENT

QUESTION: How do pill counts work when the patient comes back on the 28th day so by definition they have run out?

DR ALFORD: Follow-up visits with me are not necessarily at the same time that refills are due. Although inconvenient for some patients it's the best way to ensure medication adherence. Refills are processed in between physician visits with the help of our nursing staff.

QUESTION: How do you respond to patients who say, “It's not working because you are not giving me enough?”

DR ALFORD: I remind them that not all chronic pain responds to opioids. Initially, if there is inadequate response, I might increase the dose once or twice. Keep in mind that some patients may not report benefit because of fears that the dose will be decreased or stopped or the workup for the cause of their pain will stop. Remind the patient that your goal is not necessarily to stop the medication if it is helping. Another level of complexity is determining how much benefit—pain relief and functional improvement—is enough to justify continued opioid therapy for any given patient.
There are times when I believe there is insufficient benefit but the patient disagrees. These uncomfortable conversations go much smoother when I am able to be specific about why I believe there is insufficient benefit based on what the patient has been telling me.

**QUESTION:** What tips can you offer for treating the patient with addiction and pain?

**DR ALFORD:** For the patient addicted to nonopioids such as cocaine or marijuana, I discuss how treating them with opioids is too risky because studies show that they are at higher risk of opioid misuse. I recommend that they seek addiction treatment. Although addiction treatment may be hard to access, mutual help groups such as Narcotics Anonymous are effective, widely available, and free. I emphasize that I will only prescribe opioids if the patient is abstinent from illicit drugs. For patients with active opioid addiction, it is too risky to prescribe opioids, so I recommend managing them with nonopioids only. One other option is to refer the patient to a physician qualified to treat opioid addiction (and pain) with buprenorphine.

**QUESTION:** So even when opioids are given appropriately, the magnitude of improvement is not that big. How do you introduce that to the patient?

**DR ALFORD:** Setting realistic goals is extremely important before starting (or continuing) opioids and must be readressed during therapy. Unrealistic expectations foster repeated requests for limitless dose escalations. Although opioids do not have an analgesic ceiling effect, there seems to be a point of diminishing return at higher doses and the risks such as overdose seems to increase. Unfortunately, patients hold out hope that if the current dose is not helping, they just need more. Educating patients about the limitations of opioids and the risks including opioid-induced hyperalgesia is a difficult yet critical conversation that needs to be reinforced.

**Suicide**

**Connecting inflammation with glutamate agonism in suicidality**

Neuropsychopharmacology
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Abstract
The NMDA-receptor antagonist ketamine has proven efficient in reducing symptoms of suicidality, although the mechanisms explaining this effect have not been detailed in psychiatric patients. Recent evidence points towards a low-grade inflammation in brains of suicide victims. Inflammation leads to production of quinolinic acid (QUIN) and kynurenic acid (KYNA), an agonist and antagonist of the glutamatergic N-methyl-D-aspartate (NMDA) receptor, respectively. We here measured QUIN and KYNA in the cerebrospinal fluid (CSF) of 64 medication-free suicide attempters and 36 controls, using gas chromatography mass spectrometry and high-performance liquid chromatography. We assessed the patients clinically using the Suicide Intent Scale and the Montgomery–Asberg Depression Rating Scale (MADRS). We found that QUIN, but not KYNA, was significantly elevated in the CSF of suicide attempters (P<0.001). As predicted, the increase in QUIN was associated with higher levels of CSF interleukin-6. Moreover, QUIN levels correlated with the total scores on Suicide Intent Scale. There was a significant decrease of QUIN in patients who came for follow-up lumbar punctures within 6 months after the suicide attempt. In summary, we here present clinical evidence of increased QUIN in the CSF of suicide attempters. An increased QUIN/KYNA quotient speaks in favor of an overall NMDA-receptor stimulation. The correlation between QUIN and the Suicide Intent Scale indicates that changes in glutamatergic neurotransmission could be specifically linked to suicidality. Our findings have important implications for the detection and specific treatment of suicidal patients, and might explain the observed remedial effects of ketamine.

Introduction

Attempted suicide is associated with significant patient suffering, vast societal costs and an increased risk for completed suicide (Bruffaerts et al, 2011; Hawton and van Heeringen, 2009). Despite increased treatment of suicidal individuals over the past decade, the incidence rates of suicidal behavior have remained largely unaltered (Nock et al, 2008). Although many patients contact a physician shortly before the attempt, health care is frequently unable to prevent both attempted and completed suicides. Consequently, improved methods for detection of suicide risk and specific treatments for suicidal patients are both highly warranted (Da Cruz et al, 2011).

The neurobiology of suicidality is poorly understood. Biological factors that have previously been associated with suicidality include serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) as well as growth factors, such as brain-derived neurotrophic factor (Sher, 2011). Certain studies have shown an association between low levels of CSF 5-HIAA and suicidal behavior independent of depression (Asberg and Traskman, 1981). Reduced serotonergic neurotransmission and suicidal behavior might thus be linked, but after more than 30 years of research, the association remains unspecific (Ernst et al, 2009).

Interestingly, production of serotonin might be compromised during states of inflammation due to a consumption of tryptophan, the substrate for serotonin production (Oxenkrug, 2010). Recent studies provide accumulating evidence that brain immune activation may be involved in the pathogenesis of suicidality. A post-mortem study shows brain microglia activation in suicide victims (Steiner et al, 2008), and the cytokine IL-6 is increased in the cerebrospinal fluid (CSF) of suicide attempters (Lindqvist et al, 2009). In addition, some studies indicate that inflammation is more pronounced in suicidal patients than in non-suicidal depressed patients (Janelidze et al, 2011; Steiner et al, 2008). In support of a causal relationship between inflammation and psychiatric symptoms, several studies show that immunotherapy with cytokines in patients induces
depressive symptoms approximately 1 month after the beginning of the medication (Raison et al, 2009; Wichers et al, 2005). Several case reports also describe suicidal ideation in previously psychiatrically healthy individuals after treatment with interferon-β (Fragoso et al, 2010).

Inflammatory stimuli, such as central nervous system (CNS) infections, induce the kynurenine pathway of tryptophan degradation (Figure 1) and greatly increase CSF levels of kynurenine and its metabolites (Heyes et al, 1992). Pro-inflammatory cytokines, especially interferon-γ, are considered the major inducers of indoleamine-2,3-dioxygenase (IDO-1), one of the enzymes regulating the first step of the kynurenine pathway (Guillemin, 2012). Metabolism further along this pathway produces several neuroactive compounds, including quinolinic acid (QUIN) and kynurenic acid (KYNA), both of which affect glutamatergic neurotransmission. A potential pathogenetic mechanism underlying suicidal behavior could thus be via activation of the kynurenine pathway and through increased synthesis of QUIN and/or KYNA. Blood kynurenine levels were recently found to be elevated in suicide attempters, as compared not only with healthy controls but also with patients with depression who never attempted suicide (Sublette et al, 2011).

QUIN is an N-methyl-D-aspartate (NMDA)-receptor agonist, activating receptors containing the NR1+NR2A and the NR1+NR2B subunits (de Carvalho et al, 1996; Stone, 1993). By contrast, KYNA, besides blocking the cholinergic α7 nicotinic receptor, antagonizes the glycine site of the NMDA-receptor (Hilmas et al, 2001; Stone, 1993). Interestingly, the NMDA-receptor antagonist ketamine was recently shown to reduce suicidality in four small-scale clinical studies (DiazGranados et al, 2010b; Larkin and Beautrais, 2011; Price et al, 2009; Zarate et al, 2012). This finding may principally suggest enhanced NMDA-receptor signaling as part of the pathophysiology of suicidal behavior, although ketamine also has other effects in the central nervous system (Duman and Aghajanian, 2012).

We hypothesize that QUIN, and the QUIN/KYNA quotient, is elevated in suicide attempters due to a low-grade CNS inflammation. This might lead to excessive NMDA-receptor signaling, tentatively explaining the observed remedial effects of ketamine on suicidality. Here, CSF levels of QUIN and KYNA are measured in suicide attempters and healthy controls. Furthermore, we assess whether the QUIN levels are related to the depressive symptoms, and to suicidal intent using the Suicide Intent Scale (Beck, 1974). We also analyze whether QUIN and KYNA correlate with CSF levels of the cytokine IL-6, which we have previously reported elevated in the suicide attempters (Lindqvist et al, 2009). A subset of the patients returned to the clinic at a follow-up occasion within 6 months of the suicide attempt and provided a new CSF sample. This enables us to determine whether QUIN and KYNA levels change longitudinally in the same patients, at a time-point when the patients were not suicidal.

Materials and Methods

Participants, QUIN CSF study

We enrolled 64 patients (30 male and 34 female individuals), between 1988 and 2001, following admission to Lund University Hospital after a suicide attempt. Psychiatric diagnoses of the patients are displayed in Table 1. Mean age of the patients was 37 years (range 19–72). The patients underwent a washout period when they did not receive any antipsychotic or anti-depressive medication (14.6±9 days, mean±s.d.). Anxiolytic and hypnotic medications, as well as somatic medications, were allowed during the wash-out. All medications taken are specified in Supplementary
Table 1. At the end of the washout, lumbar punctures and psychiatric evaluations were carried out as below (section 2.2). Thirty-six (29 male and 7 female individuals) healthy controls were recruited via the Psychiatric Clinics at the University Hospitals in Lund and Linköping, Sweden, between 2003 and 2009. Mean age of the controls was 30 years (range 18–66). They did not suffer from any previous or ongoing psychiatric condition or substance abuse, and were somatically healthy. They were thoroughly checked for psychiatric morbidity using the Structured Clinical Interviews for DSM Disorders (SCID I and II). All controls were free of medication. Our study was carried out in accordance with ‘The code of ethics of the world medical association (Declaration of Helsinki)’ for experiments including humans: http://www.wma.net/e/policy/b3.htm. The Regional Ethical Review Boards in Lund, Linköping and Malmö approved the study. After complete description of the study to the subjects, written informed consent was obtained.

Physical examination and lumbar punctures

All patients and controls underwent a general physical examination. The BMI for patients and controls were 23.7±3.5 (mean±s.d.) and 24.2±3.9, respectively. In all, 31% of the patients used nicotine vs 19.4% of the controls. In order to identify subjects with potential infections at the time of the lumbar punctures, we analyzed blood samples for white blood cell count, erythrocyte sedimentation rate or C-reactive protein, and the subjects were checked for fever. No evidence of ongoing clinical infection was found, as defined by the normal reference intervals of these parameters. A complete medical history was taken. Somatic diagnoses of the patients are shown in Table 1. We performed lumbar punctures in the morning between 0800 and 0900 hours, after a night of fasting and bed rest. CSF was collected from the L4–L5 interspace using a standardized protocol, and immediately stored at −80 °C.

Psychiatric diagnostics and rating scales

Briefly after the suicide attempt, a psychiatrist diagnosed the patients according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IIIIR Axis I and II Disorders (American Psychiatric Association, 1987). The diagnoses were set after a ~2-hour long structured interview using the Comprehensive Psychiatric Rating Scale and the Structured Clinical Interview for DSM Disorders (SCID I and II). The patients were also evaluated by means of the Suicide Intent Scale, measuring the determination to commit suicide (Beck, 1974). The scale is subdivided in two parts, dealing with objective (active preparation) and subjective circumstances related to the attempt. Some, but not all studies also find an association between high scores on the scale and future completed suicide (Freedenthal, 2008; Stefansson et al, 2012). In all, 53 out of 64 patients completed the Suicide Intent Scale. Moreover, we evaluated depressive symptoms using the Montgomery–Asberg Depression Rating Scale (MADRS), which is a 10-item scale with a maximum score of 60 (Montgomery and Asberg, 1979). In all, 60 out of 64 patients completed the MADRS rating.

Definition of suicide attempts

A suicide attempt was defined as ‘situations in which a person has performed an actually or seemingly life-threatening behavior with the intent of jeopardizing his/her life or to give the appearance of such intent, but which has not resulted in death’ (Beck et al, 1973). The intent to commit suicide was explicit upon interview. Patients who did not state a clear intent were not enrolled. Suicide attempts were classified into violent and nonviolent acts as defined (Traskman et al, 1981). Drug overdoses by ingestion, single wrist-cuts or a combination are considered nonviolent suicide attempts, whereas all other methods (for example, hanging, drowning, gas poisoning, several deep cuts) are classified as violent.
Participants, follow-up study

A subset of the patients that were originally enrolled in the study at the suicide attempt participated in a follow-up study. The patients returned to the clinic and contributed with CSF samples at repeated occasions after the suicide attempt. Paired samples from eight patients, three male and five female individuals, were available from the index (the suicide attempts) and a time-point within 6 months after the attempt. Mean age of these patients was 38 years, range 22–51 years. Five of the patients received antidepressant medication at the follow-up occasion and one patient received disulfiram.

Biological assays
Analysis of QUIN

QUIN was analyzed by gas chromatography mass spectrometry as previously described (Smythe et al, 2002). The internal standard, [2H3]QUIN (99%) was purchased from Le Research Inc. (St Paul, MN, USA). Trifluoroacetic anhydride and 1,1,1,3,3,3-hexafluoro-2-propanol of GC derivatization grade, QUIN and other organic solvents of analytical-grade were all obtained from Sigma-Aldrich (St Louis, MO, USA). We injected 1 μl of sample into an Agilent 6890 gas chromatograph, interfaced to an Agilent 5973 mass selective detector via an auto-sampler Agilent Technologies 7683 operating in negative ionization mode, and controlled using Agilent ChemStation software (Agilent, Santa Clara, CA, USA). Inter- and intra-assay precision is consistently 5–8%.

Analysis of KYNA

KYNA was analyzed as previously described (Olsson et al, 2010) utilizing an isocratic reversed-phase high-performance liquid chromatography system, including a dual piston, high liquid delivery pump (Bischoff, Leonberg, Germany), a ReproSil-Pur C18 column (silica pore size, 3μm (4 × 100 mm, Dr Maisch GmbH, Ammerbuch, Germany) and a fluorescence detector (Jasco Ltd, Hachioji City, Japan) with an excitation wavelength of 344 nm and an emission wavelength of 398 nm (18 nm bandwidth). A mobile phase of 50 mM sodium acetate (pH 6.2, adjusted with acetic acid) and 7.0% acetonitrile was pumped through the reversed-phase column at a flow rate of 0.5 ml/min. 50 μl samples were manually injected (ECOM, Prague, Czech Republic). 0.5 M zinc acetate (not pH adjusted) was delivered post-column by a peristaltic pump (P-500, Pharmacia, Uppsala, Sweden) at a flow rate of 0.10 ml/min. The signals from the fluorescence detector were transferred to a computer for analysis with Datalys Azur (Grenoble, France). Retention time of KYNA was 7–8 min. Standard concentrations were used to relate the height of the peaks in the chromatogram to the correct concentration of KYNA in the samples. Inter- and intra-assay precision is consistently 3–8%. For KYNA analysis, CSF was available from 60 patients and 37 controls.

Analysis of IL-6

We analyzed IL-6 in CSF using high-sensitivity electrochemiluminescence (MesoScale Discovery, Gaithersburg, Maryland, USA) as per the manufacturer’s protocol. CSF samples were analyzed in duplicates on a SECTOR 6000 instrument (www.mesoscale.com). The detection limit was...
0.1 pg/ml. The absolute IL-6 measures have been published elsewhere (Lindqvist et al, 2009). Here, the correlation with QUIN was analyzed. For the correlation analyses, IL-6 measures from 63 patients and 24 controls were available.

Statistical analysis and potential confounders

The Statistical Package for the Social Sciences (SPSS) program version 18.00 for Windows was used (IBM Corporation, New York, NY, USA). CSF levels of IL-6 and QUIN displayed skewness >2, and the values were transformed into normal distribution using the natural logarithms for statistical analysis. The potential impacts of age, gender, weight, BMI, smoking and length of wash-out period on QUIN and KYNA levels were investigated with Student’s t-tests and Pearson correlations. To correct for age, linear regression models were used with QUIN as dependent variable and age as independent variable. Student’s t-tests were used for comparisons of KYNA and age-corrected QUIN between independent groups. As KYNA and QUIN have opposing effects on the NMDA receptor, the ratio between CSF QUIN (age-corrected) and CSF KYNA (CSF QUIN/CSF KYNA) was calculated and the ratio was compared between suicide attempters and controls with Student’s t-tests. In addition, linear regression analyses were conducted to determine the effect of sample storage time: QUIN or KYNA were entered as dependent variable, whereas group (patients vs controls), age and sample storage time as independent variables. Age-corrected QUIN was compared between healthy controls, suicide attempters with a diagnosis of a primary mood disorder (major depressive disorder and depression NOS) and suicide attempters with other diagnoses using one-way ANOVA followed by Bonferroni–Dunn’s post-hoc test. Age-corrected QUIN was also compared between the control group and five main diagnostic groups (Major Depressive Disorder, Dysthymia, Adjustment Disorder, Substance Abuse, Depression NOS) using one-way ANOVA. Finally, the impact of personality disorder, type of suicide attempt and wash-out on age-corrected QUIN were determined using one-way ANOVAs. Spearman’s ρ was used for correlation analysis of age-corrected QUIN and scores on the Suicide Intent Scale, as well as MADRS. Paired t-tests were used for QUIN, KYNA and MADRS measures within the same individuals in the follow-up study. α-level of significance was set at P=0.05.

As KYNA and QUIN have opposing effects on the NMDA receptor, we investigated the CSF QUIN/CSF KYNA ratio. We found that this ratio was significantly larger in the suicidal patients than in the healthy controls (Student’s t-test, t=−3.72, df=74.41, P<0.001) (Figure 2c). There was also a significant positive correlation between the cytokine IL-6 in CSF and QUIN (n=87, Pearson’s R=0.23, P=0.033) (Figure 3a).

Demographics and potential confounders

We investigated the potential impact of age, gender, weight, BMI, smoking, storage-time and length of wash-out period on QUIN and KYNA levels. QUIN showed a slight but significant increase with age of the subjects (n=100, Pearson’s R=0.21, P=0.038) (Figure 3b). We therefore used age-corrected variables for all statistical analyses except the within-subject analysis in the follow-up study (section 3.4). Age of the subjects did not correlate with KYNA (n=97, Pearson’s R=0.043, P=0.68) (Figure 3c). There was no impact of gender, smoking, weight, BMI or wash-out length on QUIN nor KYNA (t-tests and Pearson correlations, P>0.1 for all variables).

As the patient samples had been stored for a long time in our biobank, we also conducted a linear regression analyses to see if storage time had affected the levels of QUIN and KYNA. The model was still highly significant; β=0.81, P=0.001 for suicidality (patients vs controls). There was a
trend for a storage dependent decline of CSF QUIN; $\beta=-0.41$, $P=0.075$ for storage-time (Figure 3d). Thus, the QUIN levels in the samples from the suicide attempters in the biobank were potentially even higher initially. There was no effect of storage-time on CSF-KYNA (linear regression, $P>0.1$).

Both patients who were unmedicated at the suicide attempt ($n=6$) and those who went through the wash-out ($n=58$) had significantly elevated QUIN levels compared with the controls (one-way ANOVA ($F(2,97)=11.15$, $P<0.001$; followed by Bonferroni–Dunn’s post-hoc tests, $P=0.003$ for unmedicated vs controls; $P<0.001$ for washed-out vs controls; NS for washed-out vs unmedicated) (Table 2).

QUIN, suicidality and depressive symptoms

The mean score on the SIS was $18.3\pm0.8$ (±s.e.m.). We found that QUIN measures in CSF correlated positively with the total score on the Suicide Intent Scale ($n=53$, Spearman $\rho=0.30$, $P=0.028$) (Figure 3e). The most robust correlation was between QUIN and the subscale concerning objective circumstances in conjunction with the suicide attempt ($n=53$, Spearman $\rho=0.34$, $P=0.012$) (Figure 3f). The definition of the objective circumstances can be found in section 2.3.

CSF samples from suicide attempters were furthermore divided with regards to the use of violent ($n=16$) or nonviolent ($n=48$) methods for the attempts, as defined in the ‘Materials and Methods’ section. QUIN levels differed significantly between control subject, violent suicide attempters and nonviolent suicide attempters (one-way ANOVA ($F(2,97)=13.16$, $P<0.001$). There was a trend for higher levels of CSF QUIN in patients who had made violent suicide attempts than the patients who had made nonviolent suicide attempts (Bonferroni–Dunn’s post-hoc test, $P=0.059$) (Figure 2d and Table 2). Both violent and nonviolent attempter groups showed higher QUIN compared with the control group (Bonferroni–Dunn’s post-hoc test, $P<0.001$ for violent attempters vs controls and $P=0.002$ for nonviolent attempters vs controls).

The mean score on the MADRS was $16.3\pm1.4$ (±s.e.m.). We found no significant correlation between QUIN and the MADRS scores ($n=60$, Spearman $\rho=0.006$, $P=0.97$). There was no correlation between QUIN and MADRS suicidality item ($n=60$, Spearman $\rho=0.072$, $P=0.59$).

QUIN in diagnostic subgroups

We compared the QUIN levels in suicide attempters with a diagnosis of a primary mood disorder (Major Depressive Disorder and Depression NOS) ($n=31$) with suicide attempters with other diagnoses ($n=33$) and controls. A one-way ANOVA showed significant differences between the groups ($F(2,97)=9.81$, $P<0.001$). Post-hoc testing showed that there was no significant difference in mean QUIN levels between suicide attempters with and without a mood disorder (NS), whereas both groups differed significantly vs the healthy controls ($P=0.001$ for primary mood disorder vs controls; $P<0.001$ other diagnoses vs controls; Bonferroni–Dunn’s post-hoc tests) (Figure 2e and Table 2).

We also found significant differences in QUIN levels when comparing control group and the five main diagnostic groups of suicide attempters including Major Depressive Disorder, $n=22$; Adjustment Disorder, $n=11$; Depression NOS, $n=9$; Substance Abuse, $n=6$ and Dysthymia, $n=4$ (one-way ANOVA, ($F(5,82)=4.64$, $P=0.001$). Post-hoc testing showed that QUIN levels were not different between the five main diagnostic groups (Bonferroni–Dunn’s post-hoc test, $p>0.1$ for all comparisons).

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QUIN levels did not differ between suicide attempters with (n=38) and without (n=22) personality disorder, but was higher in both groups compared with controls (one-way ANOVA (F(2,93)=11.42, P<0.001; followed by Bonferroni–Dunn’s post-hoc test, P>0.1 for personality disorder vs no personality disorder; P<0.001 for personality disorder vs controls and P<0.001 for no personality disorder vs controls) (Table 2).

QUIN levels 6 months after the suicide attempt (follow-up)

The CSF QUIN levels decreased significantly from the time of the suicide attempt to the follow-up occasion, from 41.6±12.4 nM to 16.2±4.5 nM (mean±s.e.m.) (paired samples t-test, t=2.39, df=7, P<0.05) (Figure 2f). Thus, CSF QUIN in the patients at follow-up had normalized to that of controls. There was no significant change in CSF KYNA, which decreased from 1.3±0.3 nM to 1.2±0.3 nM (mean±s.e.m.) (paired samples t-test, t=0.37, df=7, P=0.72). There was a trend for a decrease in MADRS scores, from 16.8±2.0 (mean±s.e.m.) at the suicide attempt to 10.0±4.3 (mean±s.e.m.) at the follow-up occasion, in these eight patients (paired samples t-test, t=2.0, df=7, P=0.09).

Discussion

We found significantly increased levels of the NMDA-receptor agonist QUIN in the CSF of suicide attempters. In line with previous studies showing that inflammation can trigger generation of QUIN (Achim et al, 1993; Heyes et al, 1995), there was a significant correlation between CSF levels of QUIN and the pro-inflammatory cytokine IL-6. In contrast, levels of the NMDA-receptor antagonist KYNA were not elevated. This suggests that an overall agonistic effect on the NMDA-receptors is present in suicide attempters. Moreover, this finding provides a neurobiological rationale for the recent reports describing that ketamine, by blocking NMDA-receptor transmission, can alleviate symptoms of suicidality (DiazGranados et al, 2010b; Larkin and Beautrais, 2011; Price et al, 2009; Zarate et al, 2012). In our patients, the raised QUIN levels were also significantly associated with the degree of suicidal intent, further strengthening the association between QUIN and suicidality.

KYNA, which is mainly synthesized in astrocytes, blocks NMDA receptors and has neuroprotective and anticonvulsive properties (Erhardt et al, 2009; Schwarcz et al, 2012). In contrast, QUIN, which is produced by activated microglia, is a potent excitotoxin with neurotoxic, gliotoxic and pro-inflammatory properties (Guillemin, 2012; Schwarcz et al, 2012). Increased levels of QUIN might therefore potentially contribute to the neuronal loss and to the reduced hippocampal volume observed in patients with major depression (Bremner et al, 2000; McKinnon et al, 2009). Moreover, increased extracellular levels of QUIN, as reflected by increased CSF concentrations in suicide attempters, are likely to facilitate glutamate neurotransmission prior to causing apoptosis. In addition to being a direct NMDA receptor agonist, QUIN increases neuronal glutamate release as well as decreases glutamate uptake and recycling by astrocytes (Guillemin, 2012). Effects on the glutamate system have been suggested to contribute to the pathogenesis in patients with severe mood disorders (Hashimoto, 2009; Sanacora et al, 2008; Schwarcz et al, 2012). There has been no evidence of increased CSF QUIN in patients with primary depressive disorders or suicidality until now. In line with our findings, Steiner et al, (2011) recently observed increased QUIN-immunoreactivity in microglia in the anterior cingulate gyrus post-mortem of suicide victims that suffered from severe depression. Interestingly, the increase in CSF QUIN observed in our current study was not related to the severity of depressive symptoms. In agreement with this, QUIN levels were increased in all suicide attempters, regardless if they had a diagnosis of a mood disorder or not. Therefore, our study may suggest that elevated QUIN is specifically linked to suicidality rather than to the severity of depression.
However, no non-suicide attempters with depressive symptoms were included in our study. Therefore, inflammation and subsequent stimulation of glutamate neurotransmission could potentially be prevalent in so-called treatment-resistant or severe depression; diagnostic groups where suicides, attempts and suicidal ideation all are common (Brent et al, 2009; Price et al, 2009; Steiner et al, 2011). There are several studies showing an effect of ketamine on patients with treatment-resistant depression, where suicidality has not specifically been an outcome measure (Diazgranados et al, 2010a; Ibrahim et al, 2012; Murrough et al, 2012). Further studies evaluating CSF QUIN in diagnostic subgroups should be undertaken in order to develop tailor-made treatments in the future.

It should be pointed out that we did not study any causal relation between biological factors and symptoms. This study analyzes associations and significant changes in primary psychiatric patients and controls. Important studies showing a causal relation between inflammatory factors and depressive symptoms have previously been performed in patients with hepatitis C, and demonstrated that peripheral injection with interferon-α increased CSF levels of QUIN, KYNA and pro-inflammatory cytokines along with depressive symptoms (Raison et al, 2010; Raison et al, 2009).

In addition to the elevation in QUIN at the suicide attempt, we here also found a decrease of CSF QUIN in the eight patients who returned for a follow-up lumbar puncture within 6 months of the attempt. At this time-point, there was also a trend towards decreased depressive symptoms. However, the follow-up study sample was small, and the patients had initiated different types of medications. It is thus not possible to draw any conclusions about what caused the decrease in QUIN at the follow-up occasion, or whether this was related to a decrease in depressive symptoms and/or suicidality. Analysis of long-term variation of symptoms and biological factors in large numbers of psychiatric patients is highly warranted in the future.

Our study supports the hypothesis that a low-grade CNS inflammation induces production of QUIN, which has effects on glutamate neurotransmission and might lead to symptoms of suicidality. The positive correlation between the cytokine IL-6 and QUIN in suicide attempters is in line with findings in patients suffering from CNS infections, where both CSF IL-6 and QUIN are elevated (Heyes et al, 1995). Studies showing immunohistochemical evidence of microgliosis and an increased density of QUIN-immunoreactive microglial cells in suicide victims further support that brain inflammation, increased QUIN levels and suicide are linked (Steiner et al, 2008; Steiner et al, 2011). As an additional mechanism, reduced activity of the enzyme downstream of QUIN production, quinolinate phosphoribosyltransferase, could potentially lead to an accumulation of QUIN. The enzyme degrades QUIN into nicotinic acid ribonucleotide and causes subsequent NAD+ formation (Figure 1). It is also possible that peripheral inflammation may contribute to the synthesis of brain QUIN and KYNA. Plasma levels of kynurenine (precursor of QUIN and KYNA) are elevated in patients with major depressive disorder and a history of suicide attempts (Sublette et al, 2011). Kynurenine can pass the blood brain barrier and subsequently be metabolized into QUIN and KYNA by microglia and astrocytes. However, QUIN and KYNA themselves do not pass the blood-brain barrier and therefore CSF samples are needed to study the levels of these neuroactive metabolites in the CNS compartment (Schwarcz et al, 2012). An intriguing question is why QUIN is accumulating in excess over KYNA in suicide attempters, as both metabolites are generated in states of inflammation. In this respect, the regulation of enzymes in the kynurenine pathway deserves further investigation and could potentially depend on genetic variants (Claes et al, 2011). An imbalance in the activity of enzymes along the kynurenine pathway might explain why QUIN accumulates, or is produced in preference over KYNA in suicidal patients.
Considering that inflammation and dysregulation of glutamate neurotransmission might contribute to the pathophysiology of suicidal behavior, we propose that novel treatments of suicidality should be directed against these systems. Clinical trials using cyclo-oxygenase-2 inhibitors as add-on therapy in patients with treatment-resistant depression are promising (Akhondzadeh et al, 2009; Muller et al, 2006). Novel therapeutic strategies include inhibition of the enzyme IDO-1 or microglial activation (in order to reduce synthesis of QUIN), specific cytokine blockers or direct blockade of the NMDA-receptor (Haroon et al, 2012). These treatments could be tested in future trials enrolling patients based on suicidality. As mentioned above, the NMDA receptor antagonist ketamine was effective in initial trials treating suicidal symptoms. Moreover, the primary trigger of the elevated immune parameters in suicidality is currently unknown and once unraveled, it might constitute another drug target. In this context, it is of importance to keep in mind that suicidality is likely to be a complex phenomenon, not depending on a single cause. So-called distal risk factors include genetic loading, trait impulsivity and early traumatic life events, whereas proximal risk factors include psychological crisis or acute stress (Mann and Currier 2010); Gradus et al, 2010; Hawton and van Heeringen, 2009). It has been demonstrated that pro-inflammatory cytokines IL-6 and IL-1β increase after acute stress (Steptoe et al, 2007). Psychological factors could thus potentially trigger a cascade of reactions ultimately leading to increased QUIN production. Another factor that recently has been associated with suicidality is the neurotrophic parasite T. gondii (Pedersen et al, 2012; Zhang et al, 2012). The parasite has been suggested to increase dopamine production as well as induce low-grade inflammation. These examples show that in order to achieve optimal symptom relief for suicidal patients, it would most likely be vital to identify and treat triggers of inflammation, as well as acute symptoms.

In summary, this is to our knowledge the first report of elevated QUIN, an endogenous NMDA agonist of microglial origin, in the CSF of suicide attempters. CSF QUIN was associated with the degree of suicidal intent and when a subgroup of patients came back for a follow-up visit, CSF QUIN levels had returned to normal. These findings suggest that increased CSF QUIN is specifically related to the pathophysiology of suicidality. As QUIN is an NMDA receptor agonist, our findings may provide a scientific rationale for the reduced suicidal ideation by the NMDA-receptor antagonist ketamine. Given that suicidal behavior is a major public health problem worldwide, with a poorly understood pathophysiology, our findings may lead to the development of novel tools to diagnose, follow and treat this source of morbidity and mortality across diagnostic boundaries.
Objectives: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) peptide, a product of the proteolytic degradation of AMPA receptors in healthy nonathletes and athletes with concussions, is assessed. The detection of AMPAR peptide in conjunction with neuropsychological testing and neuroimaging is undertaken. Subjects: Persons (n = 124, 19–23 years) are enrolled in the pilot-blinded study according to approved Institutional Review Board protocols at Kennesaw State University and DeKalb Medical. Methods: AMPAR peptide plasma assay was performed using magnetic particles-enzyme-linked immunosorbent assay. All participants had neurocognitive tests (ImPACT); selected subjects with concussions were followed-up with magnetic resonance imaging and neurologic consultations. Results: Athletes (n = 33) with clinically defined single or multiple concussions were compared to 91 age and gender matched controls without a history of concussion. AMPAR peptide values of 0.05–0.40 ng/mL for controls and 1.0–8.5 ng/mL for concussions are found. The biomarker sensitivity of 91% and a specificity of 92% (0.4 ng/mL cut off) to assess concussions are calculated. Poorer ImPACT scores correlated with abnormal levels of the biomarker. In athletes with multiple concussions, increased AMPAR peptide values (2.0–12.0 ng/mL) were associated with minor findings on magnetic resonance imaging. Conclusion: AMPAR peptide assay combined with ImPACT and neuroimaging is a promising tool for assessment of concussions. Additional clinical validation studies are required.

INTRODUCTION

Mild traumatic brain injury (TBI) is the most prevalent form of injury in military and civilian settings. Brain injuries caused by explosions have become some of the most common combat wounds suffered in the field. Sports and recreational activities contribute up to 21% of all cases of mild TBI including concussions.

Assessment of concussion regardless of origin is complicated. Many primary concussions go unrecognized or are not reported, particularly when there is no loss of consciousness. Additionally, without sufficient reports of prior incidents, soldiers and competitive athletes are often subjected to multiple concussions. Advanced neuroimaging techniques (diffusion tensor imaging, functional magnetic resonance imaging, and positron emission tomography) that can register minor structural and functional changes are primarily used for research. These modalities are not available in emergent situations or for routine clinical evaluations and have a limited application in persons with metal implants or claustrophobia.

Currently, there is an unmet diagnostic need for a rapid and affordable assay to detect brain-specific biomarkers in the bloodstream following a concussion. A novel biomarker should be able to differentiate subtle brain injury associated with concussions from non-central nervous system-injured individuals. In addition, it could speed up assessment of concussions on the field in competitive contact sports or during combat to assist in determining when an injured athlete should return to play or a soldier may return to duty.

It is well known a family of location-specific glutamate receptors is involved in more than 80% of cortical and subcortical neuronal communications underlying superior mental functions. However, the practical application of glutamatergic mapping in human brain injuries is limited. Recently, it was shown that an ionotropic type of glutamate receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [AMPAR]) represents a biomarker of neurotoxicity cascade underlying subtle brain injury.
AMPARs are primarily distributed in the forebrain and subcortical pathways including the hippocampus, amygdala, thalamus, hypothalamus, and brain stem. This architecture supports the noncortical nature of subtle brain injury. These regions of the brain are predictable sources of biomarkers given the functional spatial–temporal coherence, developmental pathways, and cerebral plasticity subjected to coup–countercoup mild brain injury.

During the acute phase of mild TBI or following axonal injury, a massive release of glutamate, which up-regulates excitotoxic AMPARs has been detected. The GluR1-subunit, of N-terminal AMPAR fragments is rapidly cleaved by extracellular proteases and released into the bloodstream through the compromised blood–brain barrier. This degradation product can be detected directly as AMPAR peptide fragments (molecular weight 5–7 kD) by use of a specific immunoglobulin raised against AMPAR peptide.11

The AMPAR peptide has not previously been assessed as a biomarker in subjects with concussions. In this study we examine the diagnostic potential of the AMPAR peptide assay in conjunction with neuropsychological testing and neuroimaging to differentiate those with concussions from healthy controls.

METHODS

This article summarizes data from a and T1 prospective, blinded study performed from September 2011 to March 2012 at two clinical sites. The local Institutional Review Boards for each site approved the study, and written informed consent was obtained from each enrolled subject. Participants with semiacute (1–2 weeks) concussion and healthy controls were recruited at Kennesaw State University (KSU). All participants completed a standard questionnaire detailing medical history, medication use, and history of any prior concussion, in addition to informed consent.

Subjects

A total of 84 club sport athletes (56 male, 28 female; ages 20.8 ± 1.8 years) and 40 nonathletes without a history of concussion (21 male, 19 female; ages 22.0 ± 4.1 years) were included in the pre-season (baseline) study (n=124). The majority of participating athletes represented the KSU Sports & Recreation Department, where rugby (23%), soccer (23%), lacrosse (16%), and cheerleading (14%) occupy about 76% of the athletic curricula.

Among the athletes, 33 had clinically confirmed single (n = 20) or multiple (n = 13) concussions registered by a certified athletic trainer on the field and confirmed by an experienced neurologist within 1–2 weeks of the event. The 40 non-athletes and 51 athletes without a history of recent concussions (eg, within the previous year) formed the control group (n = 91). Data from all participants were included in the final study analysis.

Neurocognitive Testing
All study participants had baseline neurocognitive testing (ImPACT, version 2.1). In addition, the postconcussion scale embedded in ImPACT testing was offered to all participants at baseline to determine the presence of 1 to 22 commonly reported symptoms after concussions.

Clinical and Radiological Procedures

Selected athletes (n = 3) underwent a standard neurological and general medical evaluation by an experienced neurologist.

Standard MRI included: axial fluid attenuation recovery and T1-sagittal, T2-weighted axial that shows areas of permanent axonal damage and the total number of lesions, respectively. MRI images were obtained on a clinical MRI scanner (Siemens 1.5 Tesla). General Electric (GE) Centricity software was used for image analysis.

Sample Collection and Storage

At the time of enrollment, each study subject had a single blood draw. Selected subjects had two additional blood samples drawn during a follow-up visit (within 6 months of the first sample withdrawal). Blood samples (5 mL) were drawn by venipuncture into vacuum tubes (Becton Dickinson) containing sodium ethylenediaminetetraacetic acid, placed on ice. Plasma drawn from each participant was separated by centrifugation at 3,000 rpm for 5 minutes at 4°C. Sample processing was completed within 30 minutes of blood collection to protect the AMPAR peptide from depletion by endogenous proteases. Hemolyzed plasma was not accepted for the study because of cross-reaction with hemoglobin.

Processed samples were stored as multiple 0.5-mL aliquots (n = 6) at −80°C at KSU Lab.

AMPAR Peptide Detection in Plasma

Aliquots from each batch of samples were analyzed for AMPAR peptide (GRACE Labs, LLC, Decatur, GA) by a blinded investigator. Once an aliquot was thawed for testing and used, remaining amounts were discarded.

Briefly, 20 μL plasma samples, five calibrators, negative/positive controls in duplicates, and 80 μL of working mixture consisting of magnetic particles with covalently attached specific antibodies against AMPAR peptide were added to the microtiter plate. The mixture was incubated for 2 minutes at 37°C; AMPAR antibodies labeled with horseradish peroxidase solution were then added for 20 minutes at 37°C. After the bound magnetic particles were washed with a buffer using a magnetic separator, the reaction was revealed by pipetting 100 μL ready-to-use tetramethyl benzidine substrate into each well of the microtiter plate. The color reaction was developed for 8 minutes. At 25°C, the reaction was stopped with acid solution (100 μL), and monitored at 490/630 nm on a microplate reader (Bio Tek ELx800, BioTek Instruments).
AMPAR peptide concentrations in plasma were determined by plotting absorbance values on a calibration curve constructed from the absorbance units of each calibrator and their known concentrations. The intra-assay coefficient of variation was 5.1%–6.2%, and the interassay coefficient of variation was 5.7%–9.5%.

Statistical Analysis

Differences between groups were assessed using descriptive statistics and standard tests of significance. Univariate statistical analyses with 95% confidence interval (CI) were calculated. Analyses were performed on the study subjects using R Statistical Package (http://www.r-project.org/). Continuous independent variables were compared by the use of the one-way analysis of variance followed by post-hoc test.

A receiver operator characteristic (ROC) curve was used to calculate the cutoff value for optimal sensitivity and specificity. ROC curves (sensitivity vs. 1-specificity) for concussion vs. controls by varying the cutoff value were built. The gold standard used for constructing the ROC curve was based on the diagnoses. We used the partial area under the ROC curve for the region with specificity between 0.75 and 0.95, as a global measure of the diagnostic effectiveness of the AMPAR peptide assay. To test the global null hypothesis that the AMPAR peptide does not have adequate accuracy to differentiate concussions from controls, we evaluated whether the area under curve was at least 0.8.

RESULTS

The athletes with concussion(s) had significantly lower visual memory scores (p = 0.02, independent samples t-test, Welch test, 95% CI) and cognitive efficiency index (p = 0.007, independent samples t-test, Welch test, 95% CI). Baseline assessment of the postconcussion scale embedded in ImPACT showed that athletes, independently of number of concussions and the time since last injury, complained about poor memory and trouble concentrating, problems with falling asleep and drowsiness, persistent fatigue, and headaches.

Samples from apparently healthy males (n = 66) and apparently healthy females (n = 25), in the clinically relevant age range of 19–23 years, were evaluated with the AMPAR peptide assay. The distributions of enrolled control population (n = 91) according to AMPAR peptide levels.

The reference interval calculated from the samples (96%) was found to be 0.05–0.40 ng/mL for both genders. In control group, 4.3% persons had AMPAR peptide levels of >0.40 ng/mL.

Distribution of plasma AMPAR peptide concentrations in A: (1) nonathletes (n = 40); (2) athletes with no history of recent concussions (n = 51); and (3) concussions (n = 34). ROC curve for plasma AMPAR peptide (B). AUC is 0.95 calculated for the biomarker potential to distinguish concussions vs. controls.

There were no adverse events from performing the AMPAR peptide assay. Thirty athletes with concussions had an increased AMPAR peptide level with a median concentration of 2.15 ng/mL (0.96–8.49 ng/mL). Three subjects with concussions had low AMPAR peptide concentrations.
Nonathletes (n = 40) had a median value of 0.19 ng/mL (0.043–0.40 ng/mL). A group of athletes with no history of recent concussions (n = 44) had a median value of 0.21 ng/mL (0.003–1.10 ng/mL), whereas seven individuals from the same group showed increased AMPAR peptide values (0.44–1.10 ng/mL). Group comparison of median values of the AMPAR peptide concentration showed significant differences (p < 0.0001, independent samples t-test, Welch test, 95% CI) for the concussion group compared with all controls. AMPAR peptide values within controls belong to the same distribution (p < 0.001, one-way analysis of variance, Levene's test for equality of variances).

There was a moderate correlation between high AMPAR peptide levels in concussion group. The predictive values and likelihood ratios at specific cutoff points were chosen to approximate a sensitivity of 82%, 91%, 98%, and specificities of 83%, 92%, 98%, respectively. A sensitivity of 91% and a specificity of 92% with a positive predictive value of 82% for the AMPAR peptide assay to diagnose concussions are achieved at optimal cutoff value of 0.4 ng/mL. Considering a pretest probability of concussions of 0.37, positive and negative posttest probabilities resulted in 96% (95% CI, 88%–98%) and 4% (95% CI, 2%–8%), respectively.

The trade-offs between true-positive and false-positive rates are shown by presenting the data as a traditional ROC curve. The proportional areas under curve comparing concussions vs. controls yielded a close-up value of 0.95.

Based on poor ImPACT scores and abnormally high AMPAR peptide values, 3 athletes with multiple concussions were recommended for neurological consultation and MRI. There were no abnormal signals in the typical locations for axonal shearing damage in 1.5T images for all three subjects. No significant motor, sensory, or cognitive deficits on their neurological exams were noted. These athletes had a history of multiple concussions with persistent headache and mild cognitive dysfunction. The symptoms appeared to be resolved within 3 weeks for two athletes, with corresponding reduction of AMPAR peptide values. The individual who maintained high AMPAR peptide values for 6 months after injury (5.2 ng/mL) showed minor changes on MRI with slightly increased number of enlarged high-convexity white matter Virchow–Robin spaces (VRS).

Basic 1.5T MRI of individual with concussions performed within 1 month after concussion. Arrows in Axial Flair and T2-weighted images (TE/TR = 103/4790 ms; FOV 424 × 23 mm; slice thickness = 5 mm, flip angle = 150°, matrix 0/512/224/0) depicted areas of micro bleeding and slightly increased number of enlarged high-convexity white matter VRS.

DISCUSSION

Biomarkers of excitatory neurotransmitter receptors may assist in the assessment of subtle, or asymptomatic, dendritic or axonal injuries. It has been proposed that biomarkers of neurotoxicity and abnormal spiking activity may be useful in the assessment of concussions. It is known that AMPA excitatory receptors are located on dendrites and axons of neurons, and regulate glutamatergic neurotransmission.

This study focused on the diagnostic potential of the AMPAR peptide assay to differentiate subjects with concussions from controls. The analysis of AMPAR peptide value variance in subjects with concussions and all controls yielded statistically significant (p < 0.0001) increases in AMPAR peptide values in those with concussions.
Data analyses provided a preliminary cutoff value of 0.4 ng/mL. Several athletes (7 of 91) with no history of recent concussions showed an increase AMPAR peptide of 0.44–1.10 ng/mL, perhaps due to a prior unreported concussion. Even with this false-positive levels, a statistically significant increase in AMPAR peptide in concussions compared with controls (p < 0.0001) has been observed. An association between AMPAR peptide values and decrease in visual memory scores or reduced cognitive efficiency index for athletes with concussions was found. It could be hypothesized that the glutamate synaptic transmission dysfunction may contribute to the development of cognitive deficits and alteration of plasticity in visual system at the subcortical level.

In three subjects who presented with concussions, the AMPAR peptide concentrations were below the 0.4 ng/mL threshold. We treated these results as false negative. Measurement of the AMPAR peptide with a preliminary threshold of 0.4 ng/mL for persons with concussions because of sporting activities, car accidents, or blasts may have a potential clinical indications; ie, to assist in the emergent diagnosis of mild TBI vs. non-TBI before other diagnostic procedures. This premise is supported by the predictive value of the test for recognizing individuals with concussions (91% at 0.4 ng/mL cutoff; likelihood ratio, 11.9) and preliminary assessment of correlating biomarker with ImPACT scores. Conversely, the test could be used for ruling out individuals without concussions. If the test is negative at a preliminary cutoff point of 0.4 ng/mL, the posttest probability of concussions would be low (about 4%).

In this pilot study, the biomarker was measured in a single blood draw taken on enrollment from all participants. However, three 3 athletes with persistent symptoms had additional AMPAR peptide assays within 6 months after the initial enrollment. One of these three had an increased number of dilated white matter VRS depicted on Axial T1 and T2-weighed MRI scans, perhaps due to shear–strain injury. Further investigations of the biomarker in acute concussions applying advanced 3T MRI modalities (functional magnetic resonance imaging, diffusion tensor imaging, and diffusion weighted image) may clarify the nature of AMPAR peptide changes in diffuse axonal injury.

These results suggest that the AMPAR peptide could serve as a brain-specific biomarker to differentiate concussed athletes from nonconcussed individuals. Combined with neuropsychological testing and advanced neuroimaging, the biomarker has a diagnostic potential to assess concussions. Further studies of the AMPAR peptide assay should be devoted to evaluating this clinical indication for subjects with acute mild TBI.

STUDY LIMITATIONS

The pilot study examined the diagnostic potential of the AMPAR peptide assay in conjunction with neuropsychological testing and neuroimaging to differentiate those with concussions from healthy controls. In this study, the pre-season, or baseline assessment of AMPAR peptide values in club sport athletes relatively nonathletes control has been undertaken. Future investigations analyzing the in-season (or after season) AMPAR peptide concentration in these athletes and comparing them with preseason values will help estimate the potential of false-positive AMPAR peptide assays.
An additional study with increased sample size is needed performance characteristics. According to a guideline for the minimum number of cases to include in such a study, the smallest proportions of negative or positive cases in each group with proportion of positive cases in the population about 0.30 (30%) should be >67.

A body of advanced MRI-based analyses of micro-lesion size should be performed simultaneously with biomarker detection to estimate the preliminary correlation between damaged area and AMPAR peptide levels. There may be a significant time lag between blood draw and MRI (24–72 hour), which could confound findings. A study of a subpopulation of subjects who presented early after concussion (within 3 hours) and who had rapid advanced imaging to gain a first glimpse into the relation between dynamic changes in brain tissue and its effect on biomarker levels would be needed.

**Summary of evidence-based guideline update: Evaluation and management of concussion in sports**

Neurology
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**ABSTRACT**

Objective:

To update the 1997 American Academy of Neurology (AAN) practice parameter regarding sports concussion, focusing on 4 questions: 1) What factors increase/decrease concussion risk? 2) What diagnostic tools identify those with concussion and those at increased risk for severe/prolonged early impairments, neurologic catastrophe, or chronic neurobehavioral impairment? 3) What clinical factors identify those at increased risk for severe/prolonged early postconcussion impairments, neurologic catastrophe, recurrent concussions, or chronic neurobehavioral impairment? 4) What interventions enhance recovery, reduce recurrent concussion risk, or diminish long-term sequelae? The complete guideline on which this summary is based is available as an online supplement to this article.

Methods:
We systematically reviewed the literature from 1955 to June 2012 for pertinent evidence. We assessed evidence for quality and synthesized into conclusions using a modified Grading of Recommendations Assessment, Development and Evaluation process. We used a modified Delphi process to develop recommendations.

Results:

Specific risk factors can increase or decrease concussion risk. Diagnostic tools to help identify individuals with concussion include graded symptom checklists, the Standardized Assessment of Concussion, neuropsychological assessments, and the Balance Error Scoring System. Ongoing clinical symptoms, concussion history, and younger age identify those at risk for postconcussion impairments. Risk factors for recurrent concussion include history of multiple concussions, particularly within 10 days after initial concussion. Risk factors for chronic neurobehavioral impairment include concussion exposure and

Concussion is recognized as a clinical syndrome of biomechanically induced alteration of brain function, typically affecting memory and orientation, which may involve loss of consciousness (LOC). Estimates of sports-related mild traumatic brain injury (mTBI) range from 1.6 to 3.8 million affected individuals annually in the United States, many of whom do not obtain immediate medical attention.

The table summarizes the currently available data for the overall concussion rate (CR) and the CRs for 5 commonly played high school and collegiate sports in males and females. Variability in care provider experience and training, coupled with an explosion of published reports related to sports concussion and mTBI, has led to some uncertainty and inconsistency in the management of these injuries. This evidence-based guideline replaces the 1997 American Academy of Neurology (AAN) practice parameter on the management of sports concussion.

It reviews the evidence published since 1955 regarding the evaluation and management of sports concussion in children, adolescents, and adults. This document summarizes extensive information provided in the complete guideline, available as a data supplement on the Neurology

This guideline addresses the following clinical questions:

1. For athletes, what factors increase or decrease concussion risk?

2a. For athletes suspected of having sustained concussion, what diagnostic tools are useful in identifying those with concussion?

2b. For athletes suspected of having sustained concussion, what diagnostic tools are useful in identifying those at increased risk for severe or prolonged early impairments, neurologic catastrophe, or chronic neurobehavioral impairment?

3. For athletes with concussion, what clinical factors are useful in identifying those at increased risk for severe or prolonged early postconcussion impairments, neurologic catastrophe, recurrent concussions, or chronic neurobehavioral impairment?
4. For athletes with concussion, what interventions enhance recovery, reduce the risk of recurrent concussion, or diminish long-term sequelae?

DESCRIPTION OF THE ANALYTIC PROCESS

This guideline was developed according to the processes described in the 2004 and 2011 AAN guideline development process manuals.

After review of conflict of interest statements, the AAN selected a multidisciplinary panel of experts. A medical research librarian assisted the panel in performing a comprehensive literature search. Articles were selected for inclusion and rated for quality independently by 2 authors. Evidence was synthesized using a modified form of the Grading of Recommendations Assessment, Development and Evaluation process.

The panel formulated recommendations on the basis of the evidence systematically reviewed, from stipulated axiomatic principles of care, and, when evidence directly related to sports concussion was unavailable, from strong evidence derived from non-sports-related mTBI. The clinician level of obligation of recommendations was assigned using a modified Delphi process.

ANALYSIS OF EVIDENCE

The definitions for concussion/mTBI used in the identified studies were not identical but were judged by the panel to be sufficiently similar to allow for review.

For athletes, what factors increase or decrease concussion risk?

Some athletes may be at greater risk of sport-related concussion (SRC) associated with different factors (e.g., age, sex, sport played, level of sport played, equipment used) there is insufficient evidence to determine whether age or level of competition affects concussion risk overall, as findings are not consistent across all studies or in all sports examined.

Sex.

Because of the greater number of male participants in sports studied, the total number of concussions is greater for males than females for all sports combined. However, the relationship of concussion risk and sex varies among sports. Based on Class I and Class II studies, it is highly probable that concussion risk is greater for female athletes participating in soccer or basketball.

Type of sport.
It is highly likely that there is a greater concussion risk with American football and Australian rugby than with other sports. It is highly likely that the risk is lowest for baseball, softball, volleyball, and gymnastics. For female athletes, it is highly likely that soccer is the sport with the greatest concussion risk (multiple Class I studies).

Equipment.

It is highly probable that headgear use has a protective effect on concussion incidence in rugby (2 Class I studies). There is no compelling evidence that mouth guards protect athletes from concussion (3 Class I studies).

Data are insufficient to support or refute the efficacy of protective soccer headgear. Data are insufficient to support or refute the superiority of one type of football helmet in preventing concussions.

Position.

Data are insufficient to characterize concussion risk by position in most major team sports. In collegiate football, concussion risk is probably greater among linebackers, offensive linemen, and defensive backs as compared with receivers (Class I and Class II studies).

Body checking in ice hockey.

Body checking is likely to increase the risk of SRC in ice hockey (1 Class I study).

Athlete-related factors.

Athlete-specific characteristics such as body mass index greater than 27 kg/m and training time less than 3 hours weekly likely increase the risk of concussion (1 Class I study).

For athletes suspected of having sustained concussion, what diagnostic tools are useful in identifying those with concussion?

The reference standard by which these tools were compared was a clinician-diagnosed concussion (by physician or certified athletic trainer). None of these tools is intended to “rule out” concussion or to be a substitute for more thorough medical, neurologic, or neuropsychological evaluations.

Post-Concussion Symptom Scale or Graded Symptom Checklist.

The Post-Concussion Symptom Scale (PCSS) and Graded Symptom Checklist (GSC) consist of simple checklists of symptoms. They may be administered by trained personnel, psychologists, nurses, or physicians, or be self-reported. Evidence indicates it is likely that a GSC or PCSS will
accurately identify concussion in athletes involved in an event during which biomechanical forces were imparted to the head (sensitivity 64%–89%, specificity 91%–100%) (multiple Class III studies).

Standardized Assessment of Concussion.

The Standardized Assessment of Concussion (SAC) is an instrument designed for 6-minute administration to assess 4 neurocognitive domains—orientation, immediate memory, concentration, and delayed recall—for use by nonphysicians on the sidelines of an athletic event. The SAC is likely to identify the presence of concussion in the early stages postinjury (sensitivity 80%–94%, specificity 76%–91%) (multiple Class III studies).

Neuropsychological testing. Instruments for neuropsychological testing are divided into 2 types on the basis of their method of administration: paper-and-pencil and computer. Both types generally require a neuropsychologist for accurate interpretation, although they may be administered by a non neuropsychologist. It is likely that neuropsychological testing of memory performance, reaction time, and speed of cognitive processing, regardless of whether administered by paper-and-pencil or computerized method, is useful in identifying the presence of concussion (sensitivity 71%–88% of athletes with concussion) (1 Class II study, multiple Class III studies). There is insufficient evidence to support conclusions about the use of neuropsychological testing in identifying concussion in preadolescent age groups.

Balance Error Scoring System.

The Balance Error Scoring System (BESS) is a clinical balance assessment for assessing postural stability that can be completed in about 5 minutes. The BESS assessment tool is likely to identify concussion with low to moderate diagnostic accuracy (sensitivity 34%–64%, specificity 91%)

Sensory Organization Test.

The Sensory Organization Test (SOT) uses a force plate to measure a subject’s ability to maintain equilibrium while it systematically alters orientation information available to the somatosensory or visual inputs (or both). The SOT assessment tool is likely to identify concussion with low to moderate diagnostic accuracy (sensitivity 48%–61%, specificity 85%–90%) (multiple Class III studies).

Diagnostic measures used in combination. A combination of diagnostic tests as compared with individual tests is likely to improve diagnostic accuracy of concussion (multiple Class III studies 25,26,30,31). Currently, however, there is insufficient evidence to determine the best combination of specific measures to improve identification of concussion.

For athletes suspected of having sustained concussion, what diagnostic tools are useful in identifying those at increased risk for severe or prolonged early impairments, neurologic catastrophe, or chronic neurobehavioral impairment?
In addition to use for confirmation of the presence of concussion, diagnostic tools may potentially be used to identify athletes with concussion-related early impairments, sports-related neurologic catastrophes (e.g., subdural hematoma), or chronic neurobehavioral impairments.

No studies were found relevant to prediction of sports-related neurologic catastrophe or chronic neurobehavioral impairment.

Studies relevant to the prediction of early postconcussion impairments provided moderate to strong evidence that elevated postconcussive symptoms, lower SAC scores, neuropsychological testing score reductions, and deficits on BESS and SOT are likely to be associated with more severe or prolonged early postconcussive cognitive impairments. It is possible that gait stability dual-tasking testing identifies athletes with early postconcussion impairments.

For athletes with concussion, what clinical factors are useful in identifying those at increased risk for severe or prolonged early postconcussion impairments, neurologic catastrophe, recurrent concussions, or chronic neurobehavioral impairment?

Predictors of severe or prolonged early post-concussion impairments. It is highly probable that ongoing clinical symptoms are associated with persistent neurocognitive impairments demonstrated on objective testing. There is also a high likelihood that history of concussion is associated with more severe/longer duration of symptoms and cognitive deficits. Probable risk factors for persistent neurocognitive problems or prolonged return to play (RTP) include early posttraumatic headache; fatigue/fogginess; and early amnesia, alteration in mental status, or disorientation.

It is also probable that younger age/level of play is a risk factor for prolonged recovery. In peewee hockey, body checking is likely to be a risk factor for more severe concussions as measured by prolonged RTP. Possible risk factors for persistent neurocognitive problems include prior history of headaches.

Possible risk factors for more prolonged RTP include having symptoms of dizziness, playing the quarterback position in football, and wearing a half-face shield in hockey (relative to wearing full-face shields, 1 Class III study e26). In football, playing on artificial turf is possibly a risk factor for more severe concussions (1 Class I study, but small numbers of repeat concussions). There is conflicting evidence as to whether female or male sex is a risk factor for more postconcussive symptoms, so no conclusion could be drawn.

Predictors of neurologic catastrophe.

Data are insufficient to identify specific risk factors for catastrophic outcome after SRCs.

Predictors of recurrent concussions.

A history of concussion is a highly probable risk factor for recurrent concussion study. It is also highly likely that there is an increased risk for repeat concussion in the first 10 days after an initial concussion, an observation supported by pathophysiologic studies.
Probable risk factors for recurrent concussion include longer length of participation and quarterback position played in football. Predictors of chronic neurobehavioral impairment. Prior concussion exposure is highly likely to be a risk factor for chronic neurobehavioral impairment across a broad range of professional sports, and there appears to be a relationship with increasing exposure in football, soccer, boxing, and horse racing.

One Class II study in soccer found no such relationship. Evidence is insufficient to determine whether there is a relationship between chronic cognitive impairment and heading in professional soccer. Data are insufficient to determine whether prior concussion exposure is associated with chronic cognitive impairment in amateur athletes. Likewise, data are insufficient to determine whether the number of heading incidents is associated with neurobehavioral impairments in amateur soccer.

APOE genotype is likely to be associated with chronic cognitive impairment after concussion exposure, and preexisting learning disability may be a risk factor. Data are insufficient to conclude whether sex and age are risk factors for chronic postconcussive problems. For athletes with concussion, what interventions enhance recovery, reduce the risk of recurrent concussion, or diminish long-term sequelae?

Each of several studies addressed a different aspect of postconcussion intervention, providing evidence that was graded as very low to low.

On the basis of the available evidence, no conclusions can be drawn regarding the effect of postconcussive activity level on the recovery from SRC or the likelihood of developing chronic postconcussion complications.

PRACTICE RECOMMENDATIONS

For this guideline, recommendations have each been categorized as 1 of 3 types: 1) preparticipation counseling recommendations; 2) recommendations related to assessment, diagnosis, and management of suspected concussion; and 3) recommendations for management of diagnosed concussion (including acute management, RTP, and retirement). In this section, the term experienced licensed health care provider (LHCP) refers to an individual who has acquired knowledge and skills relevant to evaluation and management of sports concussions and is practicing within the scope of his or her training and experience. The role of the LHCP can generally be characterized in 1 of 2 ways: sideline (at the sporting event) or clinical (at an out-patient clinic or emergency room).

Preparticipation counseling.

1. School-based professionals should be educated by experienced LHCPs designated by their organization/institution to understand the risks of experiencing a concussion so that they may provide accurate information to parents and athletes (Level B).
2. To foster informed decision-making, LHCPs should inform athletes (and where appropriate, the athletes’ families) of evidence concerning the concussion risk factors. Accurate information regarding concussion risks also should be disseminated to school systems and sports authorities (Level B).

Suspected concussion.

Use of checklists and screening tools.

1. Inexperienced LHCPs should be instructed in the proper administration of standardized validated sideline assessment tools. This instruction should emphasize that these tools are only an adjunct to the evaluation of the athlete with suspected concussion and cannot be used alone to diagnose concussion (Level B). These providers should be instructed by experienced individuals (LHCPs) who themselves are licensed, knowledgeable about sports concussion, and practicing within the scope of their training and experience, designated by their organization/institution in the proper administration of the standardized validated sideline assessment tools (Level B).

2. In individuals with suspected concussion, these tools should be utilized by sideline LHCPs and the results made available to clinical LHCPs who will be evaluating the injured athlete (Level B).

3. LHCPs caring for athletes might utilize individual baseline scores on concussion assessment tools, especially in younger athletes, those with prior concussions, or those with preexisting learning disabilities/attention-deficit/hyperactivity disorder, as doing so fosters better interpretation of postinjury scores (Level C).

4. Team personnel (e.g., coaching, athletic training staff, sideline LHCPs) should immediately remove from play any athlete suspected of having sustained a concussion, in order to minimize the risk of further injury (Level B).

5. Team personnel should not permit the athlete to return to play until the athlete has been assessed by an experienced LHCP with training both in the diagnosis and management of concussion and in the recognition of more severe traumatic brain injury (TBI) (Level B).

Neuroimaging.

CT imaging should not be used to diagnose SRC but might be obtained to rule out more serious TBI such as an intracranial hemorrhage in athletes with a suspected concussion who have LOC, posttraumatic amnesia, persistently altered mental status (Glasgow Coma Scale,15), focal neurologic deficit, evidence of skull fracture on examination, or signs of clinical deterioration (Level C).

Management of diagnosed concussion.
RTP: Risk of recurrent concussion.

1. In order to diminish the risk of recurrent injury, individuals supervising athletes should prohibit an athlete with concussion from returning to play/practice (contact-risk activity) until an LHCP has judged that the concussion has resolved (Level B).

2. In order to diminish the risk of recurrent injury, individuals supervising athletes should prohibit an athlete with concussion from returning to play/practice (contact-risk activity) until the athlete is asymptomatic off medication (Level B).

RTP: Age effects.

1. Individuals supervising athletes of high school age or younger with diagnosed concussion should manage them more conservatively regarding RTP than they manage older athletes (Level B).

2. Individuals using concussion assessment tools for the evaluation of athletes of preteen age or younger should ensure that these tools demonstrate appropriate psychometric properties of reliability and validity (Level B).

RTP: Concussion resolution.

Clinical LHCPs might use supplemental information, such as neurocognitive testing or other tools, to assist in determining concussion resolution. This may include but is not limited to resolution of symptoms as determined by standardized checklists and return to age-matched normative values or an individual’s preinjury baseline performance on validated neurocognitive testing (Level C).

RTP: Graded physical activity.

LHCPs might develop individualized graded plans for return to physical and cognitive activity, guided by a carefully monitored, clinically based approach to minimize exacerbation of early postconcussive impairments (Level C).

Cognitive restructuring.

Cognitive restructuring is a form of brief psychological counseling that consists of education, reassurance, and reattribution of symptoms.

Whereas there are no specific studies using cognitive re-structuring specifically in sports concussions, multiple studies using this intervention for mTBI have shown benefit in decreasing the proportion of individuals who develop chronic postconcussion syndrome.
Therefore, LHCPs might provide cognitive restructuring counseling to all athletes with concussion to shorten the duration of subjective symptoms and diminish the likelihood of development of chronic postconcussion syndrome (Level C). Retirement from play after multiple concussions:

Assessment.

1. LHCPs might refer professional athletes with a history of multiple concussions and subjective persistent neurobehavioral impairments for neurologic and neuropsychological assessment (Level C).

2. LHCPs caring for amateur athletes with a history of multiple concussions and subjective persistent neurobehavioral impairments might use formal neurologic/cognitive assessment to help guide retirement-from-play decisions (Level C).

Retirement from play: Counseling.

1. LHCPs should counsel athletes with a history of multiple concussions and subjective persistent neurobehavioral impairment about the risk factors for developing permanent or lasting neurobehavioral or cognitive impairments (Level B).

2. LHCPs caring for professional contact sport athletes who show objective evidence for chronic/persistent neurologic/cognitive deficits (such as seen on formal neuropsychological testing) should recommend retirement from the contact sport to minimize risk for and severity of chronic neurobehavioral impairments (Level B).

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DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. Formal practice recommendations are not intended to replace clinical judgment

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Development of a Measure to Inform Return-to-Duty Decision Making After Mild Traumatic Brain Injury

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Abstract

Mild traumatic brain injury (mTBI), a principal injury of the wars in Iraq and Afghanistan, can result in significant morbidity. To make accurate return-to-duty decisions for soldiers with mTBI, military medical personnel require sensitive, objective, and duty-relevant data to characterize subtle cognitive and sensorimotor injury sequelae. A military-civilian research team reviewed existing literature and obtained input from stakeholders, end users, and experts to specify the concept and develop a preliminary assessment protocol to address this need. Results of the literature review suggested the potential utility of a test based on dual-task and multitask assessment methods. Thirty-three individuals representing a variety of military and civilian stakeholders/experts participated in interviews. Interview data suggested that reliability/validity, clinical feasibility, usability across treatment facilities, military face validity, and capacity to challenge mission-critical mTBI vulnerabilities were important to ultimate adoption. The research team developed the Assessment of Military Multitasking Performance, a tool composed of eight dual and multitasking test-tasks. A concept test session with 10 subjects indicated preliminary face validity and informed modifications to scoring and design. Further validation is needed. The Assessment of Military Multitasking Performance may fill a gap identified by stakeholders for complex cognitive/motor testing to assist return-to-duty decisions for service members with mTBI.

Introduction

From 2000 through the third quarter of 2011, 229,106 individuals in the Armed Services have been diagnosed with a traumatic brain injury, with over 75% of these injuries classified as “mild.” Service members (SMs) with mild traumatic brain injury (mTBI), also referred to as concussion, may present with an array of multisystem, overlapping symptoms that affect ability to perform military duties. These often include headache, dizziness, imbalance, nausea and vomiting, sleep disturbances, sensitivity to noise and light, slowed thinking and reaction time, memory problems, difficulty concentrating, executive dysfunction, and visual changes. SMs who sustain mTBI may also experience visual-vestibular symptoms (e.g., vertigo, gaze instability, and motion intolerance) and emotional reactions.
Symptom identification and monitoring after mTBI are important to both medical management and decision making regarding readiness to resume normal activities. SMs with suspected mTBI must be removed from combat or physically demanding duty until they are symptom-free for many reasons. First, cognitive and sensorimotor consequences of mTBI may threaten Warfighter proficiency and thereby the safety and effectiveness of the unit and their mission. Second, SMs with mTBI who incur a second concussion during acute recovery from a first injury may be at risk for prolonged cognitive recovery. Furthermore, symptom identification and monitoring guide referrals to higher levels of medical and/or rehabilitative care. In addition to treating mTBI-related symptoms, medical professionals are often asked to conduct exertional testing and determine when the SM demonstrates adequate symptom resolution to permit safe return to duty. It is important to note, however, that symptom resolution and clinical recovery may not reflect true neurophysiological recovery; SM with mTBI may still be in a period of neurological vulnerability.

Given the above, current theater policy was established to standardize the evaluation and management of clinical concussion so that all SMs involved in a potentially concussive event are screened, temporarily removed from the battlefield to facilitate recovery, and provided a mandatory medical evaluation. At lower echelons, the algorithms provide clear guidance to Combat Medics, Corpsmen, and primary care providers on acute concussion evaluation. Medical care standards specify command and medically directed rest, early identification of red flags that signify need for evacuation, patient education, and initial symptom management. Centers devoted to concussion care in Afghanistan have established return-to-duty protocols that are largely modeled after those for return-to-play after sports-related concussion. However, these protocols lack objective, evidence-based, return-to-duty criteria. A given SM’s readiness for duty in deployed environment is a clinical decision informed by the following: his or her report of symptom resolution; neurological and physical examination findings; whether or not symptoms can be elicited following exertional testing; and results of balance testing, a functional assessment, and/or a postinjury neurocognitive assessment (if available).

Methods and measures currently used to specify symptom resolution and readiness for return to duty are problematic for many reasons, including their reliance on self-reports. This is of particular concern as many SMs with mTBI minimize or do not report symptoms at the time of injury, possibly because they desire to stay with their unit and remain in combat. At present, clinical biomarkers that could potentially specify neurometabolic recovery involve experimental neuroimaging approaches that are still under investigation and lack clinical feasibility. In addition, there is no consensus regarding the use of neuropsychological assessment in understanding mTBI-related impairment. It is also unclear which neuropsychological tests, if any, strongly predict real-world functioning after mTBI. Neuropsychological tests generally assess isolated cognitive skills and abilities, which match neither the multisystem nature of mTBI symptomatology nor the complex cognitive and sensorimotor demands of duty. Traditional standardized rehabilitation assessments are also inadequate and have not been validated on this population. Most functional assessments used in physical and occupational therapy were designed for patients with stroke and moderate to severe TBI, have ceiling effects, and who lack sensitivity to mTBI-related vulnerabilities. Finally, existing return-to-duty assessment protocols (as described above) have not been empirically evaluated or validated.

To improve return-to-duty decisions for SMs with mTBI, medical personnel require sensitive, objective, and duty-relevant data. Military leaders have called for standardization of return-to-duty decision making in theater and stateside settings through use of objective, functional assessment that challenges multisystem mTBI symptoms.6 Widely used but poorly specified, the term “functional assessment” generally refers to the systematic attempt to objectively measure the level at which a person is functioning in various aspects of life (e.g., health, roles, activity). At present, no such assessment exists for mTBI, much less for SMs with mTBI, and innovative alternatives are needed.
With funding from the U.S. Army Medical Research Materiel Command (USAMRMC), a military-civilian rehabilitation research team has begun to address the need for an mTBI-specific functional assessment to provide guidance regarding duty readiness. This article summarizes a 1-year project, in which the team developed a preliminary protocol for the Assessment of Military Multitasking Performance (AMMP), a functional assessment designed to challenge the vulnerabilities commonly seen after combat-related mTBI and help inform return-to-duty decision making. The project had two central goals: (1) to specify the assessment concept and (2) to develop a protocol comprising military-related test-tasks that are sensitive to multisystem mTBI symptoms and produce objective scores.

Methods

The team used an iterative development process to ensure strong clinical feasibility, psychometric properties, and face validity for stakeholders (leaders and policy makers with interest and influence in matters related to return to duty) and end users (clinicians who currently make or contribute to return-to-duty decisions). The first two steps involved analysis of existing literature and collection and analysis of stakeholder, end user, and researcher input.

Analysis of Existing Literature

The team conducted an extensive literature review to identify existing assessment methods for detecting impairments following mTBI that involve combined motor and cognitive skills with emphasis on dual-task and performance-based assessment methods.

Dual-Task Assessment Methods

Dual-task assessment methods require that an individual perform a primary motor task (such as walking) while simultaneously performing a secondary cognitive task (such as remembering or mental arithmetic). Reduced performance of one task when performed with the secondary task reflects the “cost” of performing tasks simultaneously. This is often measured as the added number of errors or added time required for the two tasks versus the primary motor task. Deficiency in dual-task performance is associated with safety problems, which may not be evident if motor or cognitive tasks are assessed singly and not in combination.

Dual-task costs are significantly greater in people with concussion than those observed in age-matched control subjects. Dual-task costs have been documented in walking speed, variability, and stability; the ability to perceive and avoid obstacles is also impaired. In laboratory studies following sports concussion, cognitive dual-task costs manifest as slower reaction and response times and increased task error. Dual-task costs are particularly evident when combining visuospatial tasks with balance tasks. Dual-task deficiencies following mTBI are not confined to postural control tasks. Dual-task deficits have also been observed following mTBI during concurrent upper extremity and math tasks. After mTBI, some people have problems allocating attention to accomplish two tasks simultaneously (evidence of executive dysfunction), which may explain decrements in dual-task performance.
The literature suggests that existing dual-task measures are problematic in terms of practicality and military relevance. Most studies of dual-task methods employ laboratory methods with precise measurement equipment during basic postural control functions, such as standing or walking. The sophisticated instrumentation needed to discern subtle variations in movement is not readily available in the typical clinical environment, much less in the deployed setting. Furthermore, the motor demands of SM's activities (e.g., running while carrying a load over uneven terrain in a complex environment) are vastly different from simple standing or walking tasks. However, although existing measures have limitations, the literature suggests that dual-task methods may be important in the development of a functional assessment for return-to-duty decision making after mTBI.

Performance-Based Assessment Methods: Multitasking

Performance-based assessment requires the patient to perform a task (or tasks) that simulate an everyday activity, "...under the observation of the examiner, who utilizes behaviorally-based measures to quantify different aspects of functional capacity." Many disciplines and fields (e.g., occupational therapy, educational psychology, neuropsychology) use this assessment approach to characterize activity performance under standardized, directed conditions. Performance-based assessments vary widely in their structure and complexity, ranging from simple activities of daily living to assessments involving complex multitasking. Performance-based multitask assessments approximate how the person will perform a complex activity that requires many cognitive and motor processes necessary in a real-world environment, often described as an "ecologically-valid" approach. Multitasking assessments include several common features: many tasks are required; tasks are dovetailed; only 1 task is performed at a time; interruptions occur unexpectedly; and one must remember to do a task at some point in the future during the assessment. There is growing evidence that performance-based assessments that involve multitasking discriminate between healthy controls and individuals with executive dysfunction.

Several performance-based multitask assessments focus on executive dysfunction and frontal lobe damage associated with stroke and TBI. Some assessments use tasks that are overly simple and lack face validity in a military context. For example, the Naturalistic Action Test was developed for adults with stroke and TBI and examines performance of learned sequences of movement involved in making toast and coffee and wrapping a gift. Others are more complex but still lack military face validity. The Complex Task Performance Assessment requires patients to complete a library inventory control sheet while periodically answering the telephone and taking messages and managing prospective memory tasks. The Multiple Errands Test is the most studied of the performance-based multitask assessments. It requires the patient to organize and perform a series of unstructured errands in either a shopping mall or hospital while adhering to task rules and remembering prospective memory tasks. With all of these tests, the evaluator observes performance, characterizes errors of action (e.g., omission, rule breaks, sequencing, accuracy), and records performance time. Although this test concept holds promise for sensitivity to mTBI symptoms, no existing performance-based multitask assessments could be directly adopted for inclusion in the AMMP because they are either irrelevant to typical military duty, lengthy, or lack clinical feasibility.

Stakeholder, End User, and Researcher Input
Interviews with stakeholders, end users, and researchers were conducted early in the project to clarify military issues and rehabilitation practices in return-to-duty decision making, including current assessment methods and mTBI symptoms driving duty-readiness decisions. Referral sampling was used to identify 53 potential interviewees from military medical leaders, line commanders, occupational and physical therapists who provide services to SMs with mTBI, physicians who make return-to-duty decisions as part of medical boards, and test development experts in dual-task and multitasking paradigms (Table I). Thirty-five of these individuals agreed to participate in telephone interviews, with 33 ultimately giving written informed consent and participating in a private semistructured interview (Allina Institutional Review Board Number 2685-1X; USAMRMC Human Research Protection Office Log Number A-15671).

Seven 30 to 45 minute interview scripts/questions were developed and tailored to capture pertinent input from the varied participant groups. Interviewers followed the script and posed follow-up questions as needed to gain more depth or specific information. Interviews were audio-recorded, transcribed by a commercial provider, and checked for errors in transcription or interpretation by the principal investigator before analysis. Transcripts were assigned identification codes to maintain confidentiality and to blind reviewers.

Transcripts went through multiple phases of analysis. During the first phase, two members of research team read each transcript and identified central categories and themes, which were subsequently discussed by the entire team. In the next phase, two members of the research team reviewed and extracted contents of each interview transcript and entered interview data into the analysis template based on five key areas of input (Table II). Next, aggregate analyses were performed in which frequency of codes within categories were assigned, reviewed, and consolidated based on overarching themes. The results were reviewed, revised, and ultimately approved by the entire research team as accurately reflecting the process and findings of the stakeholder interviews. Interview findings relative to the five key areas of input are summarized in Table II.

Throughout the project, consultants with expertise in dual-task and multitask assessment informed the development and refinement of the test-tasks that ultimately comprised the AMMP assessment protocol. This included periodic teleconference calls with consultants and a daylong consultation with one expert who has studied both dual and multitask assessment approaches in TBI.

Results

Analysis of stakeholders’ requirements and needs, findings from the literature review, and expert consultation informed the specification of AMMP concept and development of multiple prototype test-tasks, which ultimately comprised the AMMP Version 1.0.

Concept Specification

The above processes supported a functional assessment concept with the following attributes: employs dual-task and multitasking assessment methods; sensitive to mTBI-related vulnerabilities; comprises test-tasks based on military scenarios that simultaneously challenge cognitive and sensorimotor systems in ways that approximate the demands of military occupational tasks. Recognizing that clinical test-tasks and environments
can never simulate real-world military demands, the team adopted a verisimilitude approach to ecological validity. In this approach, although the characteristics of the test protocol may differ from the real-world tasks, the stimuli and cognitive-sensorimotor demands of the test protocol resemble that of the real-world task or environment.

AMMP Version 1.0

An array of test-tasks were developed to assess SM's proficiency in performing complex, military-relevant tasks that collectively challenge cognitive functions (attention, memory, executive function, visual and auditory information processing, and reaction time), sensory functions (visual tracking and eye gaze stability, and vestibular function), and motor functions (bending/lifting, balance, exertion, and motor speed). Table III lists the five complex/multitask test-task scenarios and three dual tasks that comprise the AMMP Version 1.0.

As indicated earlier, none of the existing dual-task or multitasking assessments was suitable for direct inclusion in the AMMP. However, the team worked with experts in dual-task and multitask assessment to use existing measures with established sensitivity to mTBI-related vulnerabilities as prototypes to develop an array of novel dual-task and multitasking test-tasks based on military scenarios. For example, the “Duty Roster” multitasking test-task uses the structure of the Complex Task Performance Assessment but requires completion of a multiple week military duty roster while listening to a military briefing for key information as directed by the examiner. Similarly, the “Load a Magazine” test-task (quickly loading a magazine while listening for specific content within radio chatter) is modeled after the upper extremity dual task discussed earlier. In a similar fashion, the team modeled AMMP test-task scoring metrics after existing dual-task measures (dual-task cost) and performance-based multitasking assessments (task completion time and accuracy and frequency and categories of observed errors related to sequencing, rule breaks, subtask omissions etc.). In designing test-tasks, the research team also studied skills considered to be essential to all military personnel, as described in the Soldier's Manual of Common Tasks. Additional complex test-tasks were created that specifically challenge the ability to integrate physical exertion with cognitive and sensorimotor function. For example, the “Run-Roll-Aim” task requires rapid head position changes in a 3-to 5-second rush and combat rolls, thus requiring at least minimum stamina and challenging for individuals with vestibular impairment. The “SALTE” task requires that SM view and remember a simulated video scenario while performing an exercise step test, simulating the visual oscillations that would occur on foot-patrol with exertion. At the end of the test, the SM must provide an accurate “SALTE” report (size, activity, location, time, and equipment). Each test-task was subject to multiple revisions based on team discussion and problem solving, expert consultation, stakeholder input, and the results of preliminary testing.

Near the end of the project, a Summit Meeting was convened at the National Intrepid Center of Excellence in Psychological Health and TBI (Bethesda, MD) involving 15 participants (stakeholders, end users, and subject matter experts) and the research team. Summit participants reviewed the findings of the process, endorsed the AMMP concept, gave input regarding the functionality and military relevance of preliminary test-tasks developed by the research team, and supported the AMMP's potential utility in informing return-to-duty decision making in deployed and stateside settings.
After formal completion of the 1-year project, the research team conducted a weeklong concept validation exercise at the U.S. Army Research Institute of Environmental Medicine (Natick, MA) in which ten healthy soldiers performed the AMMP Version 1.0 test-tasks (total administration time ranging from 2.0–2.5 hours). Performance observation and formal feedback from participants in the validation exercise provided preliminary evidence to support face validity and objective scoring of test-tasks. This input also informed protocol modifications, refinement of scoring procedures, and preliminary test sequence optimization with the ultimate goal of reducing administration time closer to the 30-to 60-minute time frame preferred by end users. The Institutional Review Board overseeing the work stipulated that data from the validation exercise be used exclusively for refinement of assessment methods; therefore, data from the exercise is not included in this report.

Discussion

In a 1-year project, an interdisciplinary research team launched preliminary work to respond to the Army's need for an objective, relevant, functional assessment to help standardize and inform return-to-duty decision making after mTBI. The team used stakeholder and expert input and existing research literature to develop the resulting AMMP protocol. This approach is consistent with methods designed to drive dissemination of new information by trying to understand the needs and constraints of the practitioners who may benefit from the protocol in future clinical practice. Throughout this process, investigators were particularly sensitive to factors deemed critical to long-range adoption including potential test-task reliability and validity, clinical utility, face validity, and the capacity to challenge mission-critical mTBI vulnerabilities.

Assessment development in any area of medicine or rehabilitation is a lengthy and complex process, and developing a functional assessment to inform return to duty after mTBI faces some specific challenges. First, controversy remains regarding the precise symptoms of mTBI and their duration. In addition, the civilian literature offers limited existing options for functional assessment after mTBI: most dual-task measures that are sensitive to high-level postural control disturbances require expensive instrumentation and performance-based multitasking assessment is in its relative infancy. Experts in sports-concussion are also trying to identify new tools and methods to specify symptom resolution after concussion. Finally, the research team appreciated that SMs (with or without mTBI) are unlike typical “healthy controls” or rehabilitation clients. SMs' baseline levels of fitness and agility and the demands of their daily activities make traditional rehabilitation evaluation measures irrelevant. These realities and the critical nature of return-to-duty decisions necessitated the innovation-oriented approach to concept specification and protocol development.

There were limitations to the AMMP development process. Experts, consultants, and Summit participants may have been biased in their recommendations or offered opinions, not widely shared among most military leaders, practitioners, or researchers. Although repeated analyses were performed of stakeholder interview data to optimize objectivity of findings and impressions, researchers may have been vulnerable to hearing and reading information that conformed to their own opinions and preferences. Furthermore, protocols for existing standardized military tasks (such as those described in the Soldier's Manual of Common Tasks) did not easily lend themselves to modification with dual or multitask overlays. Therefore, researchers developed military test-task scenarios modeled after existing measures and metrics.
A follow-on 2-year study was recently funded. The goals of this effort are to establish reliability and preliminary validity and to further refine the test battery based on logistic requirements (e.g., administration time, cost, storage space required) and psychometric properties of test-tasks. This study will also examine whether or not the test differentiates between SM with mTBI and those who are healthy, and the extent to which SM task performance correlates with performance on known neuropsychological, sensorimotor, and physical measures. Future validation will determine whether or not AMMP test-tasks present equal challenge to SM with mTBI from various military occupational specialties as well as addressing internal validity threats related to the test, testers, and the population being examined. The potential practice effects of test components are an important factor that will be considered in the funded study. Administration of dual tasks will include preliminary practice repetitions to account for learning effects. The need for parallel forms of the multitask assessments will be necessary if the AMMP is to be used for repeated tests, as these scenarios represent a novel "problem to be solved" that will likely benefit from an effort to derive a solution. Practice effects of novel dual-task scenarios will also be quantified so that change in performance of two test administrations can be interpreted based on indices of responsiveness.

The extent to which the AMMP may differentiate individuals with mTBI from those who are healthy may be affected by examiner bias, if history of injury is known. Given the complexity of issues that could cause difficulty with military duty, there is the potential for other factors to contribute to performance problems (e.g., musculoskeletal pain, ongoing stress reactions, social factors, incentives or disincentives to return to duty). Therefore, the test administrator will be blinded to comorbidities and health history when administering the tasks. Data on these potential covariates will be collected for analysis in the funded project.

The AMMP is not intended as a diagnostic test of mTBI, rather a method to reflect areas of performance that could cause problems with return to duty. Future study will specify typical performance standards on the AMMP that will allow decrements to be identified regardless of reasons and provide military decision makers with additional information upon which to base important return-to-duty judgments.

Conclusions

mTBI remains a significant threat to Warfighters, although its effects can be challenging to detect within deployed and clinical environments. Military medical and rehabilitation practitioners consider many factors in making return-to-duty decisions but at present, lack valid and reliable performance data regarding how an SM with mTBI performs tasks that place simultaneous demands on cognitive and sensorimotor systems. Functional assessment protocols such as the AMMP may provide additional information to assure the soundness and standardization of return-to-duty decision making so that after mTBI, SMs are able to function safely and advance mission objectives.
Abstract

Background: Penetrating head injuries (PHIs) are common in combat operations and most have visible wound paths on computed tomography (CT). Objective: We assess agreement between an automated trajectory analysis-based assessment of brain injury and manual tracings of encephalomalacia on CT. Methods: We analyzed 80 head CTs with ballistic PHI from the Institutional Review Board approved Vietnam head injury registry. Anatomic reports were generated from spatial coordinates of projectile entrance and terminal fragment location. These were compared to manual tracings of the regions of encephalomalacia. Dice's similarity coefficients, kappa, sensitivities, and specificities were calculated to assess agreement. Times required for case analysis were also compared. Results: Results show high specificity of anatomic regions identified on CT with semiautomated anatomical estimates and manual tracings of tissue damage. Radiologist's and medical students' anatomic region reports were similar (Kappa 0.8, t-test p < 0.001). Region of probable injury modeling of involved brain structures was sensitive (0.7) and specific (0.9) compared with manually traced structures. Semiautomated analysis was 9-fold faster than manual tracings. Conclusion: Our region of probable injury spatial model approximates anatomical regions of encephalomalacia from ballistic PHI with time-saving over manual methods. Results show potential for automated anatomical reporting as an adjunct to current practice of radiologist/neurosurgical review of brain injury by penetrating projectiles.

Introduction

Traumatic brain injury (TBI) is the signature injury of recent military conflicts in Iraq and Afghanistan and is a leading public health burden in the United States. Recent research on combat casualties in Iraq reveals that trajectories are consistently identified by radiologists and that a majority of intracranial injuries are easily identified. However, in combat hospitals, there are occasionally computed tomography (CT) scanners in the absence of radiologist or neurosurgeon expertise. CT triage is an important tool in combat. Although immediate decisions on salvageability are paramount, decisions are often made by primary care providers without subspecialty expertise. For example, some physicians without subspecialty training may predict that a bihemispheric high-velocity perforating head injury is uniformly fatal or would result in need for permanent life support and significant caretaker burden. Our population and recent combat experience with dramatic craniectomies demonstrates this is not true at all.

There is, therefore, the need for increased decision support, automation, and quantification of penetrating TBI. Wound path identification on CT has proven paramount in effectively diagnosing critical organ damage. Steenburg et al verified that trajectories can be determined, and that trajectory analysis positively affects treatment decisions and optimizes patient care.
Computer-aided diagnostic programs such as our pilot studies have been successful in automating detection of traumatic findings on CT imaging. These developments, along with decision support tools, may greatly enhance care in deployed combat hospitals with limited expertise.

We created and applied semiautomated anatomic trajectory reporting software that we call Semi-automated Modeling & Anatomic Reporting of Trajectories (SMART). SMART utilizes image-processing techniques (e.g., registration to a template brain) common to the neuroimaging research community.

By identifying entry and terminal fragment location, and calculating fragment trajectory, we have semiautomated estimation of penetrating head injury (PHI) damage in a time-efficient manner without the use of in-field expertise. To demonstrate that subspecialty expertise is not required for use and to demonstrate the potential of a fully automated process, we determined the degree of agreement between a trauma-experienced radiologist and two medical students utilizing SMART to analyze ballistic PHIs.

Methods

Data Analyzed

The data reviewed were from the Vietnam Head Injury Study registry of soldiers who survived TBIs sustained in Vietnam between 1967 and 1970. Preinjury characteristics of the participants were available from military and Veterans Affairs records. All participants gave written informed consent, and the study was approved by the Institutional Review Board of the National Institutes of Health.

All living subjects who participated in phase 2 (1981–1985) were invited to participate in Phase 3. Those who agreed and were consented for Phase 3 underwent contiguously acquired axial noncontrast-enhanced head CT studies between 2003 and 2006 at the Vietnam Head Injury Study at Bethesda Naval Hospital on a LightSpeed Plus CT scanner (General Electric Medical Systems, Milwaukee, Wisconsin). Images were reconstructed with an in-plane voxel size of 0.4 mm × 0.4 mm, overlapping slice thickness of 2.5 mm, and a slice interval of 1 mm.

A total of 199 CTs were available; however, only 179 patients demonstrated penetration of the skull. The excluded cases demonstrated only superficial or facial penetration. Of the 179 penetrating head injured veterans, 80 demonstrated a visible fragment and deep (>2 cm) fragments (or exit wounds in perforating injuries) and were therefore included. Entry wounds involving the face were excluded since wound paths were indiscernible. Therefore, cases with lack of deep fragment, extensive surgery, no visible entrance, evidence of likely fragment migration (e.g., in ventricles), and large postoperative metallic plates with extensive beam hardening were excluded.

Software Used
We developed SMART to allow a user to calculate a region of probable injury (RPI, or the volume of estimated area of damaged tissue) as a result of a PHI. This RPI was modeled by selection of fragment entrance and terminal locations, allowing for multiple fragments as well as ricocheted fragments. The following steps highlight the user interface with the program we developed for this analysis.

Steps

Figure 1 demonstrates the software (SMART) we created that prompts for cursor placement for the entrance site. There are similar prompts for cursor location and clicking for terminal fragment location and/or ricochet point. This screenshot shows three orthogonal planes to assist in the analysis. In cases with more than one fragment, the steps were repeated for each fragment. Visualization of the RPI in color on the CT scan of the injured brain is presented to the user for visual assessment of accuracy. Figure 2 describes how entrance wounds and fragments are identified and analyzed. More information is available in the appendix.

Analysis

One radiologist (LF) with 20 years experience (8 years in trauma, including combat trauma in Iraq) and two of the authors, both third-year medical students (TF and JD), without previous experience in trauma or radiology, independently located entrance and terminal fragment locations on the 80 cases that met inclusion criteria. Before conducting analysis independently, the medical students were trained with the radiologist on 5 cases and then split the cases analyzed. Cases used to train TF were used in analysis by JD and cases used to train JD were used in analysis by TF. Training cases included two ricochet injuries and two with multiple fragments. Ricochet was easily identified by the wound path leading to the inner skull with an intuitive path after bounce leading to the fragment. In cases with multiple fragments, each was analyzed independently starting superiorly and ending with the most inferior fragment.

A three-dimensional (3D) trajectory vector estimation was then determined based on the landmarks of fragment entrance and terminus locations; for ricochets, the single vector became two vectors that connected at the selected ricochet point. Figure 2C is a flowchart of the steps taken to analyze each case. The 3D vector is parameterized as shown in Equation 1.

\[
(x, y, z) = (x_1, y_1, z_1) + t[(x_2 - x_1)i + (y_2 - y_1)j + (z_2 - z_1)k]
\]

where t has a range of 0 to 1 and represents intervals determined by how many voxels extend along the 3D vector; (x1, y1, z1) represents the coordinate in 3D-space of the fragment entrance point, (x2, y2, z2) represents the coordinate of the fragment terminus, and (xt, yt, zt) represents the current location based on the value of t, and i, j, and k represent unit vectors in the x, y, and z directions.

As t increments, we followed the 3D vector from the entrance to the terminus 1 voxel at a time. At each voxel, a sphere was created with the radius equal to the radius of the fragment as seen in Equation 2.

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This allowed for modeling of damage from the fragment(s) as it went through the brain. Once this was done for each voxel along the 3D vector, regions that extended beyond the entrance or terminus points were removed from our model as we suppose they were not affected by the fragment. This was accomplished by determining planes perpendicular to our 3D vector and discarding regions outside of the two planes, as described by Joy K.

This method involves computing the dot product of the vector with the normal at the entrance and terminus points. If the dot product was greater than 0, then the point was included; otherwise, it was excluded.

On initial review of the CT images, we immediately observed that the wound paths had conical shapes (wider near entrance and narrow at the terminal fragment). To model a conical path, an angle was determined between the diameter of the entrance wound and the diameter of the fragment at the terminus point. For each voxel along the 3D vector, the radius of the sphere is modified according to Equation 3.

\[
\text{radius} = \tan(\alpha) \times \text{dist} \times (1 - t)
\]

where \(\alpha\) is the angle between the entrance diameter and the fragment diameter at the terminus point and \(\text{dist}\) is the distance between the entrance and terminus (or ricochet point). As \(t\) increases (following the vector from entrance to terminus), the radius of the sphere decreases linearly.

Our trajectory analysis software incorporates a modified version of the ABLe (component of MEDx 3.44, Medical Numerics, Germantown, Maryland) brain lesion analysis software. The modification of ABLe allows for fully automated reporting of brain structures intersected by the fragment’s trajectory.

SMART spatially normalizes a patient’s CT data to a CT template image, which is in Montreal Neurological Institute space using a 12 parameter affine transformation. To optimize this process, SMART first removes all nonbrain tissue (e.g., skull, scalp) from the CT scan. The spatial transformation matrix saved from the affine transformation is applied to an image representing the cone model of the fragment’s 3D trajectory, and this normalized image is automatically overlaid on the Automated Anatomical Labeling (AAL) digital brain atlas, containing 116 anatomic structures. Intersections of the RPI model with the brain structures defined in the AAL atlas are automatically reported as percentage of brain structure loss.

Statistical Analysis

The degree of agreement between the radiologist and medical students was determined.
We compared the RPIs determined by the radiologist and medical student with the manual tracings completed by one of the authors (VR), a neuropsychiatrist with 17 years of clinical and research imaging experience. The manual tracings were made by noting the visible outline of each lesion in addition to any encephalomalacia on each consecutive scan slice. This was marked using a cursor to outline the entire lesion area and confirmed by one of the authors (JG) (in consensus, when appropriate), cognitive neuroscience researcher with 30 years of experience studying penetrating brain injuries (adhering to local structural anatomy).

The Dice similarity coefficient (DSC) was used to measure agreement between the spatial location and volume of RPIs determined by the radiologist, the medical students, and the manually traced areas (consensually agreed upon by VR and JG) of encephalomalacia. As seen in Equation 4 below, DSC is computed by calculating twice the number of voxels that are within both RPI and manual tracings (intersection) divided by the total number of voxels in both regions (union). The range of DSC is [0–1].

$$DSC = \frac{2 \times (\text{RPI} \cap \text{Manual})}{|\text{RPI}| + |\text{Manual}|} \quad (4)$$

Kappa analysis, sensitivity, and specificity were also used to assess the agreement of SMART with manual tracings. Here, the agreement was based on the common anatomic structures reported by the ABLe software when using both RPI and manual tracings as input. Sensitivity and specificity are calculated as in Equations 5 and 6.

$$\text{Sensitivity} = \frac{\#\text{Structures}_{\text{RPI} \cap \text{Manual}}}{\#\text{Structures}_{\text{Manual}}} \quad (5)$$

$$\text{Specificity} = \frac{\#\text{Structures}_{\text{Outside RPI} \cap \text{Outside Manual}}}{\#\text{Structures}_{\text{Outside Manual}}} \quad (6)$$

Times to analyze cases manually and using our SMART program were obtained and compared.

Results

Of the 199 Vietnam Veteran CT studies available, 80 met our inclusion criteria and were analyzed using conical zones of probable injury. The excluded cases were those without skull penetration (no intracranial fragments or fracture), those that were superficial injuries (no wound path), those with facial entrances without clear paths, and those with extensive surgery and beam hardening artifact.

For a typical size RPI, the brain structures reported by SMART were a small subset of the total number of brain structures in the AAL atlas. Therefore, the specificity or agreement between SMART and manual tracings on unreported brain structures was guaranteed to be high. Therefore, we included a kappa analysis to account for agreement by chance alone. Equation 7 shows how kappa was computed.
kappa = \frac{Pr(a) - Pr(e)}{1 - Pr(e)} \quad (7)

where Pr(a) is the probability of agreement and is the fraction of AAL brain structures that both methods agree are within the injured brain and outside the site of injury, and Pr(e) represents the hypothetical probability of chance agreement. The values of kappa range from 1 to +1, with a value of 0 meaning agreement is by chance alone and 1 is perfect agreement.

Figure 3 demonstrates an overlay of the manual tracing results, SMART conical RPI overlying the injury zone demonstrating overlap and underlap that result in the differences.

The medical students had minimal training on the method and SMART (less than 2 hours); however, they were able to analyze cases as fast as a radiologist, at 10 minutes per case. This is significantly reduced from the 90 minutes per case required by the manual method, taking into account initial training and time to reach a consensus decision between VR and JG.

The students had good agreement (kappa = 0.64) with manual tracings by VR/JG as did the trauma-experienced radiologist (kappa = 0.69). Table I summarizes rater comparisons with each other and against manual tracings. Agreement of radiologist compared to medical students was close, kappa = 0.8, two-tailed t-test p < 0.001.

Figure 4 demonstrates an example analysis of a case with multiple fragments. Of note, the percentage of ricochet was 23 (19 out of 80), midline crossing was 25 (20 out of 80), and a majority (73%, 59 out of 80) had multiple fragments in our select deep PHI data (n = 80).

Discussion

We created and validated trajectory imaging analysis software for PHIs that estimates expected tissue damage volume of anatomic structures. In one of the author’s experiences in a combat hospital, trajectory imaging analysis of PHI provides rapidly needed clinical information that can establish early prognostic indicators. Wound path vectors appear very similar to acute penetrating trajectories with straight paths between analyzed points. Future work can include comparisons in longitudinal studies including clinical correlation.

Our pilot study demonstrates semiautomated analysis can be accomplished without subspecialty expertise and substantially faster than manual tracings. Correlation of radiologist's and medical students' anatomic region reports suggests that fully automated anatomical report may be possible with advancing automated techniques.
Our methods agree well with manually traced areas of brain damage in this population of PHI. This method may thus assist with decision analysis and data comparisons in both military and civilian trauma centers, especially those without available neuroradiologists or neurosurgeons. We believe our method is translatable to acute care setting because of recent experiences in combat and PHI in civilian trauma centers.

From a scene investigation perspective, trajectory analysis has the potential to expedite analysis at the scene providing key evidence in forensic investigations. This was recently demonstrated in ballistic CT phantoms that were shot in controlled field conditions where radiologists could determine angle shot within 5 degrees.

Correlating clinical information with anatomic estimates based on trajectory analysis of damage in identified populations such as ours may improve subsequent morbidity and mortality determinations. The automated report and comparison with known similar cases may help determine prognosis or priority of patient in an emergent medical environment. Use of the SMART may also be helpful in imaging triage in combat or mass casualty situations. When coupled with clinical correlation studies, modeling in our database may predict long-term outcomes such as rehabilitation success, cognitive progression, and caretaker burden.

Long-term consistent and automated recording of information will be paramount to effective data mining, including analysis of the Joint Theater Trauma Registry that includes all injured soldiers in recent conflicts in Iraq and Afghanistan. This database consists of all combat casualties (over 20,000; including fatally injured) from recent conflicts, many with CT images that have been read by radiologists but have not been analyzed quantitatively for injury/severity correlations or body armor optimization.

Automated anatomic labeling with trajectory analysis may optimize CT triage in mass casualty incidents or in hospitals with CT that may see a gunshot wound (GSW) to the head without an available neurosurgeon to guide immediate therapeutic options. Long-term prognosis may be possible by comparison of outside incidents (both military and civilian) with existing cases where we have detailed clinical information.

MRI Finds Possible Vascular Injury After Mild Head Injury

Medscape
Megan Brooks
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Using MRI, researchers have detected linear hemorrhagic brain lesions suggestive of primary injury to the vasculature early after mild traumatic brain injury (mTBI), a finding that could have implications for acute treatment.
These "discrete linear-shaped lesions we think may represent vascular injury," study investigator Gunjan Parikh, MD, from the National Institute of Neurological Disorders and Stroke and the University of Maryland R Adams Cowley Shock Trauma Center in Baltimore, noted in an interview with Medscape Medical News.

If confirmed, they could potentially be used as "an imaging-based biomarker to select out [mTBI] patients who may benefit from medications that target the endothelium or the vasculature in general. That's one down-the-road clinical implication that I can see," he added.

The findings, from the Traumatic Head Injury Neuroimaging Classification (THINC) study, were released March 12, ahead of their presentation at the American Academy of Neurology (AAN) 65th Annual Meeting, to be held from March 16 to 23 in San Diego, California.

THINC Study

The study involved 256 adults who were admitted to the emergency department during a 2-year period after mild head injuries, most due to falls or road accidents.

The median time between injury and imaging was 17 hours. "Hyperacute imaging in the first 24 hours after TBI is not standard of care," Dr. Parikh said. "Traditionally acute imaging using MRI after TBI could be considered in a time frame as far out as 1 week; here the average time from injury to MRI was 17 hours, so I think we are capturing injury that wasn't captured before in a sense," he added.

A total of 104 patients (41%) had evidence of cerebral hemorrhage on MRI; 67% had experienced a loss of consciousness and 65% had amnesia. Their scores on the Glasgow Coma Scale on arrival were 13 to 15 in 91% of cases.

Twenty-one (20%) of the patients with cerebral hemorrhage had microbleeds (punctate), whereas 34 (33%) had linear lesions (tube-shaped, branching, multiple axial slices).

Microbleeds were distributed throughout the brain, whereas linear lesions were found primarily in the anterior corona radiata (82%) and traversing the white matter, gray matter, and sulcus (59%).

"We think the small hemorrhagic lesions are tracking into the deep white matter from the meninges," Dr. Parikh said. "This type of injury was routinely seen in more severe patients on postmortem histopathology, so it's interesting to see that we have imaging findings in patients who are considered mild that mimic those findings that we see in more severe patients," he commented.

Dr. Parikh noted that this was an observational study, "and the next step is to confirm our suspicion based on this evidence" that these are in fact vascular lesions.

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Our objective is to determine the prevalence of recurrent headaches in military-dependent children and to study the changes in headache frequency, severity, and duration during a parental deployment. Recurrent headaches are common in children and are often intensified by stressful life events. Military-dependent children are subjected to unique stressors, most significantly parental wartime deployment. No studies have evaluated the effect of deployment on somatic complaints, to include headaches. We conducted a parental, cross-sectional questionnaire-based study in patients aged 5 to 17 years who were seen in the pediatric or adolescent clinics at a regional military medical center. The overall prevalence of recurrent headaches in the preceding 12 months was 30%. Almost half reported headache worsening in frequency, severity, or duration over the previous 12 months, whether a parent was deployed or not. For children who had experienced parental deployment, younger children and females were affected more often. Younger females had the highest rates of headache worsening. This trend may indicate a more detrimental effect of parental deployment on childhood headache in certain populations.

INTRODUCTION

Headaches occur commonly in children and adolescents. A recent systematic review calculated the estimated prevalence of headaches in children and adolescents over periods between 1 month and lifetime to be 58.4%.1 Recurrent headaches can impact a child's life by negatively affecting psychosocial functioning,2 school attendance and performance, and overall quality of life. Comparatively, recurrent migraine headaches can negatively impact a child's quality of life to an extent similar to children with other chronic illnesses, such as arthritis and cancer.

Headaches and other somatic complaints are often associated in adolescents with stressful life events, such as serious injury in the family, changing schools, and an increased absence of a parent from the home. Unique life stressors are placed upon military-dependent children and adolescents. The specific stressors are related to parental military duties and can include frequent moves and separation from extended families, but are most significant for parental wartime deployment.8 Parental military deployment has been shown to be associated with higher levels of stress and an increase in behavioral and emotional difficulties in dependent children. An increasing awareness of these effects has resulted in recognition of the importance of this issue by the American Academy of Pediatrics with a resultant expansion of resources for military families.
There is no published data, however, describing the effect of parental military deployment on somatic complaints, to include headaches, in dependent children. We conducted a cross-sectional, parental questionnaire-based study to determine the prevalence of recurrent headaches among military-dependent children and adolescents at a tertiary care military treatment facility and to study the changes in headache characteristics during parental deployment.

METHODS

The study protocol was approved by the institutional review board, 59th Clinical Research Division, 59th Medical Wing, Wilford Hall Medical Center, Lackland Air Force Base, Texas. Questionnaires were handed out to parents of patients aged 5 to 17 years arriving for routine or acute visits within the general pediatric and adolescent clinics at both Wilford Hall Medical Center and Brooke Army Medical Center over a period of 5 months (April–August 2010). A letter accompanied the questionnaire, providing parents with information regarding the purpose of the study, general content of questions, and the voluntary nature of participation. Completion of the questionnaire designated consent to participate in the study.

The questionnaire asked demographic information, including age, sex, and ethnicity of the patient, as well as questions regarding the history of headaches. Only children and adolescents between the ages of 5 to 17 years were included. When multiple ethnicities were reported, the category of “other” was designated. Questionnaires that were either turned in and not filled out or not filled out completely were excluded. The initial question asked whether the patient had experienced recurrent headaches over the preceding 12 months. A positive response to this question self-defined the criteria of “recurrent headaches” as inclusion in the study. With a positive response, questions followed to provide information regarding the frequency, average severity, and duration of headaches as well as the average frequency of missed school days because of headache. Headache severity was self-defined as mild, moderate, or severe, rather than using formal validated scales to facilitate maximal participation through the wide age ranges included in this study. The questionnaire then asked whether a parent had been deployed during the preceding 12 months and the length of deployment, with questions following regarding the frequency, severity, and duration of headaches and missed school days while the parent was deployed. Patients with a negative parental history of deployment were also asked if there had been any change in the frequency, severity, or duration of headaches over the preceding 12 months.

Questionnaires were distributed and collected by clinic staff not involved with the study. Results were recorded on a password-protected Microsoft Excel spreadsheet. Data were analyzed using Pearson's chi-square test.

RESULTS

A total of 13,111 military-dependent children and adolescent patients between the ages of 5 to 17 years were seen in the Wilford Hall Medical Center and Brooke Army Medical Center pediatric and adolescent clinics between April 1 and August 31, 2010. A total of 1,795 questionnaires were completed.
Recurrent headaches were reported more often in females (33%) than in males (28%) (p < 0.027). Older adolescents (38%, 14 to 17 years old) were more likely to report recurrent headaches than younger children (34%, 10 to 13 years old; 23%, 5 to 9 years old) (p < 0.001). Blacks (35%) and Hispanics (30%) were more likely to report recurrent headaches than Caucasians (27%) or Asians (26%).
The majority of children and adolescents with recurrent headaches had at least one headache a month (71%). Headache severity was mostly described as moderate (54%), as lasting 1 to 2 hours (45%), but rarely or never resulting in lost school days (77%).

Of those patients with recurrent headaches, 24% had a parent deploy in the preceding year. Almost half (47%, 95% confidence interval [CI] 42.7%–51.2%) of all children with recurrent headaches at baseline reported headache worsening in either frequency, severity, or duration over the previous 12 months independent of whether a parent was deployed (49%) or not (46%). There were no statistically significant differences in baseline headache characteristics between these two groups. For those children with baseline recurrent headaches and “with” a recent parental deployment, younger children (5 to 9 years old) had the highest rates of headache worsening (60%, p < 0.072) during parental deployment compared with older children (10 to 13 years old, 48%; 14 to 17 years old, 34%). Females as a whole were affected more than males (55% vs. 44%, p < 0.225). Overall, younger females (5 to 9 years old) had the highest rates of headache worsening during parental deployments (65%, p < 0.205). For those children with baseline headaches but “without” a recent parental deployment, the trend of a higher incidence of headache worsening with decreasing age was not observed (5 to 9 years old, 39%; 10 to 13 years old, 48%; 14 to 17 years old, 52%; females, 53%; males, 47%).

DISCUSSION

Our study sought to describe the prevalence of recurrent headaches in U.S. military-dependent children and the changes in prevalence during parental military deployment. To our knowledge, this is the first study analyzing the changes in rates of somatic complaints, such as headaches, during military parental deployment.

We found recurrent headaches in our military-dependent population over the previous 12 months to be commonly reported with a prevalence of 30%. In comparison, 66% of children will report having had any headache over the previous 12 months, with 20% to 25% being described as severe, as defined by stopping normal activity. More recent population studies of children and adolescents in the United States have estimated the prevalence of “frequent or severe headaches” (FSHs) over the previous 12 months as 6.7% through the National Health Interview Survey (NHIS), whereas the National Health and Nutrition Examination Survey (NHANES) estimated a higher prevalence of FSHs at 17.1%. Our study asked about “recurrent headaches” and then expanded to examine the frequency and severity of headaches, as opposed to the NHIS and NHANES studies in which patients were asked the screening question of “during the past 12 months, has [child's name] had frequent or severe headaches, including migraines”. In our study, the prevalence of headaches occurring at least once a month was 22% (391/1,795). The prevalence of severe headaches in our study was 3% (54/1,795), lower than the NHIS and NHANES, although this could be explained by the limitation to severe headaches only and not FSHs, and also by difference in patient self-reporting.

Within our study, we found a higher prevalence of recurrent headaches with increasing age and a higher overall prevalence in females. This trend is similar to previously reported trends. Our study also found a higher prevalence in Blacks or Hispanics, as opposed to Caucasians or Asians. The NHIS found that Hispanics had lower reported rates of headaches, but Blacks reported the highest prevalence of headaches. The NHANES
found both Blacks and Hispanics (non-Mexican) to have the highest reported rates of headaches. The reasons for the differences among these studies are not known, but could be due, in part, to population differences.

Our study also sought to evaluate how deployment affected the characteristics of recurrent headaches. During parental deployments, of those children and adolescents who had recurrent headaches at baseline, 49% reported worsening in headache frequency, severity, or duration. Similarly, of those patients “without” a parental deployment over the last 12 months, 46% reported worsening in frequency, severity, or duration over the previous 12 months. In comparison, headache worsening over a 12-month period has been reported to occur in 21% of children and adolescents aged 8 to 15 years.

However, evaluation of our data within age groupings and by gender demonstrated that among patients with baseline recurrent headaches, higher rates of headache worsening was reported with decreasing age during parental deployments. Females in the youngest age group (5 to 9 years) demonstrated the highest incidence of headache worsening (65%) during parental deployments. Although not statistically significant, this trend may indicate a more influential effect of parental deployment on childhood headache in certain populations, such as younger females. We did not observe this trend among those children and adolescents with recurrent headaches but without a deployed parent.

Our study population is a special and unique population—the dependent children of service members of the U.S. military. It is known that stressful life events in children and adolescents are associated with somatic complaints, to include headaches. The unique stressors of our population may help explain, in part, some of the trends seen in our data—in particular the high rates of reported headaches worsening in all patients, regardless of parental deployment status. These unique stressors noted within military families include regular parental absence for training in other parts of the country, frequent uprooting for moves to new duty stations, and the constant threat of war with its resultant deployments. It is also important to consider our current active conflict and the length of our involvement in Iraq and Afghanistan. Even without a current deployed family member, military families tend to perceive high levels of stress. Recent interest in the effects of the military-unique and specific stressors of war and parental deployment on dependent children has provided some insight into the behavioral and emotional effects on children. Children of deployed parents have higher rates of emotional difficulties and behavioral difficulties with resultant increased utilization of mental health services. Although our study found that younger females, as a trend, had higher rates of headache worsening during parental deployment, this trend was not seen in prior studies looking at behavioral and emotional symptoms during parental deployment. Jensen et al reported more emotional difficulties in males and younger children, whereas Chandra et al found more emotional difficulties in older youth and females during parental deployments. The reasons for these differences are uncertain.

Thus, in support of our military families and children, health care providers should start by developing an awareness of the unique culture of military children and adolescents. Resources are increasingly available as a result of an increasing awareness and recognition of the importance of this issue by the American Academy of Pediatrics. Although behavioral and emotional difficulties in children are known effects of parental wartime deployments, increased somatic symptoms such as headaches may also be manifested in certain susceptible populations.
There are several limitations to our study. First, our data are cross-sectional, thus causality cannot be directly inferred between the variables studied. Although questionnaires were made available to patients coming in for clinic visits, bias can be introduced because of the voluntary nature of the study. This is further accentuated by our low rate of response (14%). Questionnaires asking about symptoms over the previous 12 months are subject to recall bias, but the alternative of prospective diaries over a 12-month period is very difficult to accomplish. Our data consist of self-reported symptoms rather than clinical evaluation. International Classification of Headache Disorders was not used to distinguish among types of headaches (i.e., migraine, tension) but rather a broad term of "headaches." Further exploration to differentiate primary from secondary headaches was also not pursued, although it is known that children with chronic headaches and normal examinations rarely have significant neuroimaging findings.

Our questionnaires were distributed to parents for completion instead of the patient because of the broad age distribution included in this study, to include younger children who require parental assistance. However, parents were able to interact with their children to complete the questionnaire. Previous studies have shown that parents tend to underestimate their child's responses on questionnaire studies of pain symptoms. Although we sought to study changes in headache characteristics during parental deployment, specific questions regarding locations of the deployment, to include the level of risk of harm, and the support structure of the family at home were not explored. Parental stress, which has been associated with child psychosocial functioning during wartime deployment, is another variable potentially affecting parental reporting that was not explored. Furthermore, other factors not explored include school stressors—which have been related to increased headaches in children, recent moves—which are an inherent part of life for military families, and family dynamics. Finally, this study is based out of a tertiary care military treatment facility that tends to have in its population a higher number of patients with complex medical histories.

Despite these limitations, as an initial study seeking to understand the prevalence of headache within the military-dependent population and the changes in prevalence of a specific somatic symptom such as recurrent headaches during deployment, we feel that these parental responses provide us with useful data regarding general trends that should be followed up with further studies.

CONCLUSIONS

Recurrent headaches are common in military-dependent children and adolescents. There is a high incidence of reported headache worsening over the previous 12 months, independent of whether a parent is deployed or not. However, during military parental deployments, younger children report a higher incidence of worsening headaches. Although not statistically significant, this trend may indicate a more influential effect of parental deployment on childhood headache in certain populations. Health care providers caring for military children and adolescents should be aware of the high incidence of reported headache worsening and seek to understand the effects of parental deployments to improve the quality of life of patients and families by facilitating proper diagnosis, support, and treatment. Furthermore, this study brings to attention an area in need of further study, with prospective data, and the utilization of validated headache scales.
Adverse health consequences of the Iraq War

Lancet
Prof Barry S Levy MD, Prof Victor W Sidel MD
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Summary

The adverse health consequences of the Iraq War (2003—11) were profound. We conclude that at least 116 903 Iraqi non-combatants and more than 4800 coalition military personnel died over the 8-year course. Many Iraqi civilians were injured or became ill because of damage to the health-supporting infrastructure of the country, and about 5 million were displaced. More than 31 000 US military personnel were injured and a substantial percentage of those deployed suffered post-traumatic stress disorder, traumatic brain injury, and other neuropsychological disorders and their concomitant psychosocial problems. Many family members of military personnel had psychological problems. Further review of the adverse health consequences of this war could help to minimise the adverse health consequences of, and help to prevent, future wars.

Introduction

The USA and its coalition partners initiated the Iraq War in March, 2003, because of unfounded perceptions that the Saddam Hussein regime was capable of developing nuclear, biological, and chemical weapons, and that it had ties with Al Qaeda terrorists. The war began with intensive aerial bombing, intended to create so-called shock and awe that would lead to a quick surrender by the regime. Instead, the war, which spawned an insurgency campaign, continued for 8 years. Although the USA withdrew its troops in 2011, sporadic incidents of extreme violence in Iraq have continued.

War-related mortality

Iraqi non-combatants

The number of war-related deaths among Iraqi non-combatants is uncertain, but we conclude from our review of studies that it was at least 116 903. However, studies by research groups using different methodologies arrived at widely different estimates. In a systematic review published in 2008, Tapp and colleagues identified 13 primary research studies that estimated Iraqi deaths during the period from March 20, 2003, to January, 2008. Three of these studies were population-based, reported in peer-reviewed journals, and had estimated both the excess number of deaths attributable to all causes since the start of the war and the number of deaths caused by violence. In these studies, the estimated number of excess Iraqi deaths as a consequence of the war ranged from 98 000 during the first 18 months of the war to about 655 000 in the first 40 months.
Key messages

- *The Iraq War caused much mortality, mainly among non-combatant Iraqi civilians*

- *The war also caused much morbidity, including many cases of mental health disorders, among coalition military personnel and their family members*

- *The war also led to substantial environmental damage, displacement of millions of Iraqis, many violations of human rights, and diversion of substantial human and financial resources—all of which adversely affected health*

- *If the issues that provoked the war had been resolved non-violently, all its adverse health consequences could have been prevented*

In the discussion section of their systematic review, Tapp and colleagues stated that among the population-based studies that they had reviewed, reports by Roberts and coworkers and Burnham and colleagues provided “the most rigorous methodology as their primary outcome was mortality.” The study by Burnham and colleagues, which had by far the highest estimate of Iraqi deaths attributed to the war, was criticised for the small number of clusters studied, lack of randomness of household sampling within clusters, possible over-reporting of mortality, and other alleged inadequacies; however, the authors responded to these criticisms, and others supported their methods and stated that “indirect deaths, from loss of public health infrastructure” add to the death toll among Iraqis. Subsequently, this study was criticised for its methodology and ethical and data-integrity problems.

The Iraq Body Count, administered by Conflict Casualties Monitor, maintains and updates a database of war-related violent non-combatant civilian deaths in Iraq, with media reports of deaths being crosschecked to at least one other source (eg, hospital or morgue information) before being added to the database. It documented, by March 5, 2013, at least 116 903 deaths of civilian non-combatants. A study based on this database which examined 92 614 Iraqi civilian deaths attributed to armed violence during the first 5 years of the war showed that unknown perpetrators caused 68 396 (74%) of these deaths, coalition forces 11 516 (12%), and anti-coalition forces 9954 (11%). Analysis of a subset of 60 481 civilian deaths attributed to 14 196 lethally violent short-duration events showed that a third were attributable to extrajudicial executions by unknown perpetrators. Of the events in which civilians died, the largest average number of civilians killed were in suicide bombings by unknown perpetrators that targeted civilians (19 per lethal event) and in coalition aerial bombings (17 per lethal event). The most indiscriminate effects on women and children, as measured using a so-called Dirty War Index, were from unknown perpetrators using mortar fire and non-suicide vehicle bombs, and from coalition air attacks.

The US National Counterterrorism Center also reported that many Iraqi deaths occurred because of terrorist attacks by (anti-coalition) insurgents. During 2005 and 2006, 21 602 terrorist incidents occurred, accounting for 10 098 deaths. Another report of 60 481 Iraqi civilian deaths during the first 5 years of the war showed that 19 706 (33%) were caused by extra-judicial executions, 11 877 (20%) by small-arms gunfire, 8708 (14%) by suicide bombs, 5360 (9%) by vehicle bombs, 2854 (5%) by roadside bombs, 2079 (3%) by mortar fire, and 3050 (5%) by air attacks.

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One study documented 1003 suicide-bomb events in Iraq between 2003 and 2010, which caused 12 284 (11%) civilian deaths and injured 30 644 (26%) civilians. Suicide bombers on foot caused 43% of deaths and those who used cars caused 40% of injuries. A higher proportion of demographically identifiable deaths in children were caused by suicide bombings (14%) than were caused by general armed violence (9%). For each lethal suicide-bomb event, on average more Iraqi civilians were killed (12) than coalition soldiers (three).

Coalition military personnel

As of Jan 14, 2013, the US Department of Defense reported that 4409 US military personnel died in Iraq and nearby areas between March, 2003, and January, 2013 —3480 killed in action and 929 deaths attributed to non-hostile causes, such as diseases and self-inflicted wounds. 4804 coalition military fatalities occurred, including 179 among UK military personnel.

War-related morbidity

Iraqi civilians

The numbers of cases of war-related illnesses and non-fatal war-related injuries among Iraqis has not been established, although many resulted from extensive damage to the health-supporting infrastructure, including medical care and public health services, food production and supply systems, water treatment and supply systems, and sewage treatment and sanitation facilities. Medical care facilities—which were challenged to serve the many people who were injured or became ill because of violence—urgently needed generators, drugs, and laboratories. As a result of widespread looting at the start of the war, public health offices, clinics, and laboratories were damaged; equipment was stolen; and records were ruined. Core public health services—such as vaccination programmes, control of vector-borne disease, and tuberculosis treatment—were disrupted. In 2008, 401 Iraqi refugee doctors who were interviewed in Jordan stated that there was a progressive decline in health services in Iraq from 2003 to 2006. However, a national survey of 1256 Iraqi households in May, 2010, recorded widespread satisfaction with primary health-care services.

Many health workers were displaced within Iraq or left the country. A study of 1243 physician specialists who were based at 12 tertiary hospitals located in Baghdad, Basrah, Erbil, and Mosul on Jan 1, 2004, reported that, by late 2007, the total number of physician specialists decreased by 76 (6%) in Iraq, and by 193 (22%) in Baghdad. Of the latter group, many fled from Baghdad, but remained within Iraq.

Many injuries to Iraqis, such as injuries from electric shock, unintentional explosions, unintentional gunshot wounds, and falls, resulted from breakdown of the infrastructure in Iraq, as was shown by a 2009 survey that established the injury rate to be 54.9 per 1000 person-years. Only 8.4% of these injuries were from intentional causes and only 4% were due to intentional explosions. Injury incidence was highest in men, displaced individuals, and illiterate people.

Coalition military personnel
For the remainder of this Review, the terms “service members,” “military personnel,” and “veterans” represent participants in studies of US service members in the wars in both Iraq and Afghanistan, unless otherwise specified. With regard to non-fatal injuries, as of Jan 14, 2013, the US Department of Defense reported that 31 926 US military personnel had been wounded in action in the Iraq War. Explosions have caused a greater percentage of injuries in the wars in Iraq (and Afghanistan) than in other large-scale conflicts. Between March, 2004, and December, 2007, 4623 combat explosion episodes occurred in Iraq, causing an average of 3·8 injuries or disorders per episode; the most frequent were mild traumatic brain injury (TBI, 10·8%), open leg wounds (8·8%), and open face wounds (8·2%, including tympanic membrane rupture). Body parts most often injured were arms and legs (41·3%), and head and neck (37·4%).

As of 2010, more than 950 military personnel had a combat-related amputation. Military personnel with major traumatic limb loss had significantly worse quality of life when they had a combat-associated head injury, had a combat-associated injury to the non-amputated limb, or required assistance in activities of daily living.

War-related mental health disorders are highly prevalent among veterans. According to data obtained from routine postdeployment health assessments, of 222 620 military personnel who returned from Iraq between May, 2003, and April, 2004, 42 506 (19%) reported mental health problems and 68 923 (31%) used mental health services during the first year after returning home. A study reported that 151 (17%) of 882 US Army personnel and 127 (16%) of 813 US Marines met screening criteria for major depression, generalised anxiety, or post-traumatic stress disorder (PTSD). Among 9990 UK Iraq and Afghanistan veterans, prevalence of probable PTSD was 4·0% and prevalence of symptoms of common mental disorders was 19·7%. Among 552 UK Reservists who had been deployed to Iraq in 2003, deployment was associated, 16 months after their return, with common mental disorders, PTSD, and poor general health.

Risk factors for PTSD after combat deployment include: (1) combat exposures, especially the threat of death, serious injury, and witnessing injury or death; (2) killing or being responsible for killing; (3) previous assault; (4) low mental or physical health status before combat; and (5) adverse childhood experiences, such as physical neglect. Military sexual trauma, defined as exposure to sexual assault or sexual harassment during service, was reported by 15·1% of 17 580 women and 0·7% of 108 149 men surveyed; it was associated with having a mental health disorder, including PTSD, other anxiety disorders, depression, and substance use disorders.

Mild TBI, defined as “an injury with loss of consciousness or altered mental status (eg, dazed or confused),” is common among soldiers returning from Iraq. A study of 327 388 veterans using US Veterans Health Administration services in 2009 showed that 6·7% were diagnosed with TBI; much comorbidity existed, with 89% of those with TBI having had a diagnosed mental health disorder during fiscal year 2009, most commonly PTSD. A survey of 2525 US Army infantry soldiers 3—4 months after returning from a 1-year deployment in Iraq showed that 124 (4·9%) reported injuries with loss of consciousness (43·9% of whom met criteria for PTSD) and 260 (10·3%) reported injuries with altered mental status (27·3% of whom met criteria for PTSD). In a study of 760 US Army soldiers assessed before and after deployment to Iraq, 9% reported TBI (predominantly mild TBI), 17·6% of whom screened positive for PTSD and 31·3% of whom screened positive for depression. Among 2235 military personnel surveyed after deployment, 12% reported a history consistent with mild TBI and 11% screened positive for PTSD; mild TBI was common among
veterans injured by bullets or shrapnel, blasts, motor vehicle crashes, air or water transport incidents, and falls. Among 781 men injured during military combat between September, 2004, and February, 2005, 15·8% met criteria for TBI. A study based on data from the Combat Trauma Registry of the US Navy-Marine Corps who had served in Iraq identified 115 who had received about 200 TBI-related diagnoses; compared with individuals not injured in battle, those injured in battle were more likely to have had two or more TBI diagnoses and more severe TBI, and to have been medically evacuated. Among 4620 UK military personnel returning from deployment in Iraq and Afghanistan, the prevalence of mild TBI was 4·4%, but among those who had had a combat role it was 9·5%. Psychological distress and alcohol misuse before deployment were also associated with subsequent mild TBI.

Symptoms of PTSD are common among service members with TBI. So-called re-experiencing symptoms of PTSD, such as flashbacks and nightmares, have been strongly associated with blast-related mild TBI. Post-concussive symptoms (headache, dizziness, balance problems, irritability, and memory problems) have been associated with mild TBI alone and PTSD alone, and strongly associated with the combined presence of mild TBI and PTSD.

A reduction in cognitive function occurs frequently among service members with TBI. A study of 502 service members showed that 31% of those reporting TBI had a decline in cognitive performance over time, as measured by a battery of neuropsychological tests.

Some evidence suggests that some military personnel with mild TBI have axonal injury to the brain, even without intracranial injury detectable on CT. A study of 63 US military personnel with mild TBI who did not have detectable intracranial injury on CT, who were studied with diffusion tensor imaging (a form of MRI sensitive to axonal injury), showed that 18 (29%) had brain abnormalities that were consistent with multifocal traumatic axonal injury.

TBI has been associated with self-reported hearing and self-reported visual impairment. Among 12 521 Iraq and Afghanistan veterans, 34·6% self-reported dual sensory impairment, 31·3% auditory impairment only, and 9·9% visual impairment only. Veterans with both TBI and a history of blast exposure had the highest rate of dual sensory impairment. Studies have documented not only noise-induced hearing loss, but also tinnitus, eardrum perforation, and dizziness among military personnel sustaining blast injuries.

Many veterans with TBI have had infectious complications. These infections have been associated with blast injuries and burns; retained bullet or shrapnel fragments; and lung injury, intubation, or tracheostomy; and include hospital-acquired infections and infections from implanted prosthetic devices.

Sex differences have been identified in the prevalence of psychiatric diagnoses and neurobehavioral symptoms. Among 12 605 veterans with TBI, PTSD was more common among men than women, but women were twice as likely to be diagnosed with depression. Women reported more severe symptoms than men in several neurobehavioural domains.
Alcohol and drug abuse occur frequently among military personnel returning from Iraq. Among 12 092 Veterans Administration outpatients, 22% of male veterans returning from Iraq (and Afghanistan) screened positive for alcohol misuse, compared with 11% of veterans who did not serve in either country. Among 6527 US Army soldiers surveyed 3–4 months after returning from Iraq, 27% screened positive for alcohol misuse, which was frequently associated with serious alcohol-related behaviours, such as drinking and driving, being convicted of driving under the influence, using illicit drugs, and riding with a driver who had been drinking. These findings are much the same as from another study of 1120 veterans 3–4 months after their return from Iraq, of whom 25% screened positive for alcohol misuse and 12% exhibited alcohol-related behaviour problems; alcohol misuse was associated with exposure to threat of injury or death; alcohol-related behaviour problems were associated with exposure to atrocities. Among 48 481 Reserve and National Guard personnel, new-onset heavy weekly alcohol consumption was significantly associated with combat exposure. Among 1382 service members, 941 of whom were followed up after 3 years, increased alcohol consumption was especially great among those who thought they might be killed and those who experienced hostility from civilians during deployment.

Many veterans have had both mental health disorders and substance abuse disorders. A study of more than 1 million veterans showed that, among those with a diagnosed mental health disorder, 21% had a comorbid substance abuse diagnosis; especially high rates of comorbid substance use disorder occurred among those with bipolar disorder or schizophrenia. Among 287 veterans studied, those who screened positive for PTSD or depression were twice as likely to report alcohol misuse compared with others. Among 678 382 veterans, increased diagnoses of major depression and substance use disorders were associated with deployment. Among 456 502 veterans, 11% had received a diagnosis of substance abuse disorder; use of alcohol, drugs, or both was between 3·08 and 4·68 times more likely in veterans with either PTSD or depression.

The total number of deaths by suicide among military personnel who served in Iraq is not known. However, a report stated that there were, in fiscal year 2008, 96 deaths by suicide among US veterans of the Iraq and Afghanistan wars; and that having a diagnosed mental health disorder was associated with an increased risk of suicide. Suicidal ideation has been frequently described among service members returning from Iraq. Among 2854 US soldiers returning from deployment there, 67 (2.3%) reported suicidal thinking, 16 (0.6%) reported a desire for self-harm, and four (0.14%) reported both; significant predictors for self-harm after deployment were a previous suicide attempt and PTSD after deployment. Among 1740 veterans, 113 (6.5%) reported suicidal ideation at time of interview; major risk factors were female sex, a previous suicide attempt, and a diagnosis of a depressive disorder.

On return from deployment, service members have had problems in social functioning and mental health, affecting reintegration. A study of 754 veterans estimated that 25—56% of combat veterans who use Veterans Administration health services report some degree of difficulty in social functioning, productivity, community involvement, or self-care. National Guard troops studied after deployment frequently had readjustment problems (45% reported financial or family problems); those who reported the most readjustment stressors were 5-5 times more likely to have suicidal ideation. Among 4991 UK veterans studied after deployment to Iraq (or Afghanistan), reservists, as compared with regular personnel, were more likely to feel unsupported by the military and to have difficulties with social functioning.
A study of infections complicating the care of trauma patients in Iraq (and Afghanistan) showed that among 16 742 patients in the Joint Theater Trauma Registry, 921 patients (5·5%) had codes indicating one or more infections with only 16 recorded deaths attributable to infections. Most common were skin or wound infections (286, 26·7%) and lung infections (156, 14·6%).

With regard to respiratory disorders, a prospective study of 46 077 military personnel deployed to Iraq and Afghanistan between 2001 and 2006 showed increased rates of newly reported respiratory symptoms among those who were deployed, but rates of chronic bronchitis, emphysema, and asthma were not associated with deployment. Open-air exposure to burning of rubbish and other waste in so-called burn pits had been thought a possible cause of respiratory symptoms among military personnel, but a study of 22 844 military personnel did not find an association between exposure to burn pits and respiratory outcomes. A study of 1·2 million military personnel deployed as of the end of 2005 showed that rates of respiratory symptoms and medical encounters for obstructive pulmonary disease increased after deployment. Another study showed no significant associations between exposure to particulate matter less than 2·5 μm and cardiorespiratory outcomes in deployed military personnel, who were young and relatively healthy. A study of military personnel exposed to a sulphur plant fire in 2003 showed that they had increased symptoms of, but no increase in, clinical encounters for chronic respiratory disorders.

Family members of coalition military personnel

Mental health and related problems have been frequently reported among spouses and partners of military personnel deployed to Iraq. Among 250 626 wives of active-duty US Army soldiers who received outpatient care between 2003 and 2006, those whose husbands had been deployed for 1—11 months received more diagnoses of depressive disorders (2·7% excess), sleep disorders (1·2% excess), anxiety (1·6% excess), and acute stress reaction and adjustment disorders (1·2% excess) than did wives of non-deployed military personnel. Deployment of husbands for more than 11 months was associated with even greater excesses: depressive disorders (3·9%), sleep disorders (2·4%), anxiety (1·9%), and acute stress reaction and adjustment disorders (1·6%). A study of 940 spouses of military personnel deployed in Iraq or Afghanistan showed that spouses had much the same rates of mental health problems as did soldiers, but they were more likely to seek care for their mental health problems and were less concerned with the stigma of mental health care than were soldiers. Among 5928 married male enlisted soldiers deployed to Iraq or Afghanistan, marital quality decreased and reports of past-year infidelity and separation or intent to divorce increased; however, the rate of marital dissolution did not increase.

Mental health disorders and related problems have also been reported among children of deployed military personnel. A study of 307 520 children between the ages of 5 and 17 years who had at least one parent in active duty in the US Army in Iraq (or Afghanistan) showed that these children had an excess of 6579 mental health diagnoses during a 4-year period compared with children whose parents had not been deployed; there was an association between length of parental deployment and increased mental health diagnoses in these children. A review of nine US-based studies of the effect on children of parental deployment identified an increase in emotional and behavioural problems in children when a parent was deployed; psychopathology among parents was most consistently identified as a risk factor for childhood emotional and behavioural disorders.
Mothers of military personnel have also been affected. Mothers of sons serving in the US Marines reported significantly higher levels of emotional distress and more health risk behaviours compared with mothers of sons not deployed.

Caring for injured or ill veterans places a major burden on family members. A study of families caring for US service members with TBI and multiple traumatic injuries established that 25% of the caregivers were providing more than 40 h a week of care; many of them might need additional resources to meet the long-term needs of their family members.

Beyond statistics

This Review has provided many statistics concerning morbidity and mortality of non-combatants and military personnel and their families. However, as we have noted before, statistics are people with the tears washed off. Many personalised accounts of suffering due to the Iraq War have been published.

Population health status

In the two decades before the Iraq War, the health of the population of Iraq had been adversely affected by the Iran—Iraq War (1980—88), the Persian Gulf War (1990—91), and economic sanctions (1990—2003). Analysis of data from two parallel studies done by UNICEF showed that, as a result of the Persian Gulf War and economic sanctions, between 1991 and 1998 an estimated 400 000—500 000 excess deaths occurred in children in Iraq.

During the war, the rate of childhood malnutrition was high, but not as high as it had been during much of the 1990s, when it increased mainly because of economic sanctions. Data from the World Bank suggest that the prevalence of malnutrition (low weight-for-age among children younger than 5 years) increased from 10·4% to 12·9% between 1991 and 2000, but then decreased to 10·1% in 2003, 8·0% in 2004, and 7·1% in 2006. Other sources of data often showed higher rates of malnutrition. For example, a survey in 2004, done by the Iraq Ministry of Planning and Development Cooperation in partnership with the UNDP, showed that among Iraqi children between 6 months and 5 years of age, 23% had chronic malnutrition (low height-for-age), 12% had general malnutrition (low weight-for-age), and 8% had acute malnutrition (low weight-for-height). In 2006, another survey showed that about 25% of Iraqi children were chronically malnourished and many more were underweight.99 Another report from UNICEF stated that, between 2003 and 2009, an estimated 6% of children younger than 5 years were moderately or severely underweight, and 26% had moderate or severe stunting.

The war, a general economic slowdown in Iraq, and economic sanctions adversely affected Iraq's food security, although the situation has improved in recent years—mainly due to improved availability of food and reduction in violence. A 2007 World Food Programme survey estimated that 933 000 people (3·1% of households sampled) were food insecure, compared with 4 million (15·4%) 2 years before. During the same period, the proportion of people dependent on a monthly food ration decreased from 31·8% (8·3 million) to 9·4% (2·8 million). The table shows recent health status data for Iraq, now with a population of about 33 million.
Environmental health

As far as we are aware, there has been no systematic analysis of environmental health problems related to the Iraq war. Available data are scarce and are neither comprehensive nor necessarily representative.

Data from the World Bank provide an overview of sanitation and of access to safe drinking water. Between 1991 and 2010, a progressive increase occurred, from 67% to 73%, in the proportion of the population with access to improved sanitation facilities. Between 1990 and 2010, there was a progressive increase, from 44% to 56%, in the proportion of the rural population with access to an adequate amount of water from improved water sources; however, among the urban population, this proportion progressively decreased from 97% in 1990, to 91% in 2010. By contrast, UN agencies have reported that more than 7-6 million Iraqis did not have access to safe drinking water at some point during the war, and that, at the start of the war, millions of tons of raw sewage were dumped into rivers in Iraq.

In 2005, the UNEP published a report on so-called environmental hot spots in Iraq, which had been selected by the Iraq Ministry of Environment. These sites included: a metal plating facility, which had been bombed, looted, and demolished, that had hazardous wastes, including several tons of cyanide compounds, scattered over a publicly accessible site; a pesticides warehouse, which had been looted; a petrochemicals warehouse, which had been looted and partially burnt down; a large sulphur mining complex, which had been damaged by fire; and a military scrapyard site.

At and around US military bases, contamination with depleted uranium has occurred, in addition to oil spillages, contaminated ash, and unexploded ordnance. Depleted uranium, which has been used in antitank munitions, is both chemically toxic and radioactive, although its health effects are unclear. In people, the most sensitive target organ after ingestion or inhalation of soluble uranium is the kidney; another important target organ is the lung after inhalation of small particles of insoluble uranium. The surveillance programme for long-term health consequences attributable to exposure to depleted uranium and retained embedded fragments of depleted uranium in US veterans of the 1991 Persian Gulf War or the Iraq War has, thus far, not identified clinically significant health effects related to depleted uranium, but it has shown that fragments of depleted uranium embedded in muscle continuously release soluble uranium. Because of its long half-life (4·5 billion years for 238uranium, 700 million years for 235uranium) depleted uranium potentially represents a long-lasting hazard to those exposed. However, no adequate studies have documented adverse health effects of depleted uranium on human populations.

Forced migration

In the first 4-5 years after the onset of the Iraq War, an estimated 2·2 million refugees fled the country. An estimated 2·7 million people were internally displaced, many of whom have faced greater health risks, because of problems such as inadequate shelter and lack of security, than refugees who left Iraq. Prior to the Iraq War, almost 1 million Iraqis became internally displaced because of repression, draining of marshland, and human-rights abuses under the Saddam Hussein regime.
During the first 2 years of the Iraq War (2003—05), more than 400 000 people were displaced. Most Iraqi refugees fled to Jordan and Syria. For these refugees, food insecurity was a major problem. Among 1200 households of Iraqi refugees in Jordan surveyed in 2008, 18% had received food aid and 10% cash assistance. A similar survey of 813 households of Iraqi refugees in Syria a year later reported that 90% had received food aid and 25% cash assistance.

A study of adult Iraqi refugees showed that their prevalence of chronic diseases, mainly hypertension and musculoskeletal disorders, was 51·5% among 2342 in Syria and 41·0% among 3414 in Jordan, with 7·1% of those in Syria and 3·4% in Jordan identified as disabled, mainly because of conflict. Among 7642 Iraqi refugees and asylum-seekers in Jordan, 17% of those who sought health assistance had conditions classified as neurological disorders, mainly back pain, headache, and epilepsy.

As of January, 2013, UNHCR: the UN Refugee Agency estimated that there were 1·4 million refugees who had left Iraq (with an estimated 480 000 living in Syria and 450 500 in Jordan) and 1·3 million internally displaced people within Iraq. Even though an estimated 67 089 Iraqi refugees had returned to Iraq and an estimated 193 610 internally displaced people had returned to their homes, many of these people face continuing challenges, such as inadequate security, unemployment (including getting back their former jobs), inadequate basic services, and scarcity of personal documentation

Violations of human rights and their health consequences

We have summarised the health consequences of the violations of human rights that occurred before and during the Iraq (and Afghanistan) wars previously, although the full effects of these violations have not been adequately documented.

Briefly, before the war, human rights were violated by the Saddam Hussein regime; during the war, both insurgents and coalition forces violated the rights of Iraqi civilians. The US administration of George W Bush reportedly authorised so-called enhanced interrogation—deemed by many experts to be torture under international law—of prisoners of war whom it suspected were aiding or abetting terrorism. Health workers helped to design enhanced interrogation techniques, and participated in such interrogations. These methods occasionally led to death and frequently led to health problems among detainees, including mental health problems. Human rights of more than 1000 detainees deemed by the US Government to be enemy combatants and held at the US military base at Guantanamo Bay, Cuba, have likewise been violated. Further interrogations in countries with poor human-rights records, such as Syria, were carried out on prisoners detained by the USA and transferred by rendition. Other human rights abuses in the Iraq War included the use of cluster munitions and weapons containing depleted uranium by coalition forces.

Division of human and financial resources

As of Jan 15, 2013, the Iraq War had cost the USA about US$810 billion (not including interest on debt). The ultimate cost of the war to the USA could be $3 trillion. Clearly, this money could have been spent instead on domestic and global programmes to improve health. The diversion of human resources was also substantial, in Iraq, the USA, and other coalition countries.
Conclusion

The Iraq War caused a huge amount of morbidity and mortality among non-combatants and military personnel and their families. What are the main lessons from reviewing the adverse health consequences of this war? First, the health consequences of a specific war are likely to be much more extensive than envisioned before the war began. Second, government and military leaders should resort to war only as a last resort when all other measures to resolve conflict have failed—and then only if the goals of war are clear, the use of military force is proportionate to the threat, and non-combatants and the health-supporting infrastructure of society are protected. And third, the only way to prevent morbidity and mortality of non-combatants and military personnel during war is to prevent war itself. If the issues that provoked the Iraq War had been resolved non-violently, all the adverse health consequences described in this Review could have been prevented.