



# Army Medicine Peer-Reviewed Publications

April 2013

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## **Executive Summary**

April 2013 – Journal coverage for April is light in relation to topics relevant to Army Medicine with little original research, but varieties of data analysis or case study research.

From malaria vaccines and public health strategies, to cost-cutting measures aimed at improving hospital efficiencies and the introduction of low cost, lightweight tools, topics related to disease and medical protocol comprised the majority of peer review journal articles.

High-profile research, or information that is frequently of interest to media, includes the relationship between military sexual trauma (MST) and post-traumatic stress disorder (PTSD), along with information related to stellate ganglion blockers (SGBs) as a PTSD treatment. Research on SGBs in PTSD treatment continued from previous reporting periods, with a compilation of case studies detailing Soldiers' experiences with the treatment.

## **Medical Journal Coverage**

### ***Disease***

#### **Lancet Neurology: Changing the research criteria for the diagnosis of Parkinson's disease: obstacles and opportunities**

In a summary of research, Lancet Neurology argues that new criteria need to be developed for the analysis of Parkinson's disease, much like recent updates to Alzheimer's disease. Parkinson's disease does, however, offer significant complexities in biochemical markers, genetic phenotype and molecular mechanisms that may inhibit further development of these criteria. Updates to diagnostic criteria can influence medical procedures of Army Medicine.

#### **PLOS Neglected Tropical Diseases: A Success Story: Togo Is Moving toward Becoming the First Sub-Saharan African Nation to Eliminate Lymphatic Filariasis through Mass Drug Administration and Countrywide Morbidity Alleviation**

Through a detailed approach to disease eradication, the Togolese Ministry of Health employed the Rapid Assessment of Geographic Distribution of Filariasis (RAGFIL) to determine the rate of lymphatic filariasis infection. Following the RAGFIL and mapping the affected areas, mass drug administration (MDA) took place through the use of a unique pyramid healthcare system, where a community health worker (CHW) is largely responsible for a set population. Education and awareness campaigns drove public understanding of available treatments resulting in an effective

national strategy to eliminate the disease. Coverage of region-specific illnesses and public health campaigns to eradicate the disease(s) provides awareness to Army Medicine prior to engaging with global public health campaigns.

### **Lancet Infectious Diseases: US Department of Defense contributions to malaria surveillance**

The article from Lancet Infectious Diseases highlights the decades of Department of Defense leadership in research on malaria drug-resistance. Starting in Cambodia and moving through several African countries, the article notes the DoD malaria surveillance network's reach. Authors call for more surveillance across Africa and more clinical trial evidence. Given the particular media interest in anti-malarial drugs such as Lariam and Mefloquine, Army Medicine can highlight past involvement with DoD efforts to expand malaria surveillance and further discuss recent research on anti-malarial clinical trials.

### **Lancet Infectious Diseases: Efficacy of RTS,S malaria vaccines: individual-participant pooled analysis of phase 2 data**

Research aimed at determining the best practices of malaria vaccines produces results that are relevant to Army Medicine. Recent media coverage of anti-malarial drugs, such as Lariam, offer the potential for Army Medicine to promote new, advanced, low-risk alternatives to these treatments.

### **Lancet: ACT II: treatment of anal cancer comes full circle**

Beginning in 1974, the research notes potential breakthroughs in the treatment of anal cancer through use of radiation therapy with concurrent fluorouracil or mytomycin. Focusing on very advanced local disease, the treatment did not produce a "groundbreaking improvement" in patient outcome. As Army Medicine serves as an industry leader in cancer research, especially in breast cancer research, the ongoing study of and awareness of best practices in cancer treatment offers the command more in-depth knowledge on anal cancers.

### ***Medical Protocol and Training***

### **Military Medicine: Usability Study of a Novel, Self-Lighted, Disposable Speculum: Military Applications**

Research on the OfficeSPEC speculum, a better value tool for use in the field highlights the lack of barriers, formerly present, surrounding gynecological care in an austere environment. The research is relevant to Army Medicine due to both the cost effectiveness of the tool and the improvement on combat gynecological care.

## **JAMA: Relationship Between Occurrence of Surgical Complications and Hospital Finances**

Research on the potential for financial risk associated with providing healthcare allows Army Medicine a brief glimpse into money-saving data analysis for private hospital systems. The research provides Army Medicine the opportunity to learn how civilian hospitals avoid financial risk, specifically regarding the potential economic consequences for decreasing postsurgical complications. With ongoing discussions of military budget cuts, the ability of Army Medicine to respond quickly to financial concerns.

## **Military Medicine: Operational Cost Analysis of Dental Emergencies for Deployed U.S. Army Personnel During Operation Iraqi Freedom**

Looking at the financial and indirect costs of dental emergency (DE) care in combat, the authors note that DEs range from 26 to 260 per 1000 military personnel per year. With the added risk of being vulnerable to enemy fire during transport, the authors assert that a force in need of dental emergencies, i.e. a less dentally fit force, indirectly affects combat readiness and effectiveness. Awareness of the effects of Soldiers' dental health on combat readiness allows Army Medicine to promote dental health in Soldiers.

## **JAMA: “Nightmare” Bacteria on the Rise in US Hospitals, Long-term Care Facilities**

With a specific focus on the prevalence of carbapenem-resistant Enterobacteriaceae (CRE) in long-term care facilities, research indicates an increase in the presence of these bacteria and in resistance to even last-resort antibiotics. The Northeast United States is more likely to see the bacteria presence, along with elderly patients facing a higher rate of resistant bacteria. The authors suggest a potential move from long-term care facilities into the greater community, classifying CRE as an “urgent threat.” The authors then lay out a multipronged approach to the potential outbreak, which includes a coordinated response that includes an increased focus on hygiene. Army Medicine can utilize its structure to disseminate information on Soldier hygiene to prevent any possible infections.

## **PLOS one: New System for Digital to Analog Transformation and Reconstruction of 12-Lead ECGs**

The article focuses on a digital-to-analog conversion (DAC) system for electrocardiographs (ECGs), where researchers compared 12-lead ECGs in 10 patient cases. The analysis quantitatively and qualitatively compares results of a DAC system, and the results indicate that original analog signals can be reconstructed effectively through the use of digital data files. The resulting information provides Army Medicine with further knowledge on the use of ECGs.

### ***Obesity***

## **Military Medicine: Compliance With Regulations on Weight Gain 6 Months After Delivery in Active Duty Military Women**

Discussion of female military personnel's ability to return to pre-pregnancy weight standards focuses on Navy personnel within 6 months post-childbirth. At the beginning of the study, 68% had body weight within Navy regulation and 52% had a normal body mass index with only 48% and 32% exhibiting those same numbers after six months following birth, respectively. The only resulting information linked to post-childbirth return to weight standards is prepregnancy BMI and the possibility for a non-cesarean delivery. Army Medicine can utilize the Navy data to promote fitness during pregnancy in an effort to maintain a healthy BMI, while also noting the benefits of natural non-cesarean delivery.

## **Lancet Respiratory Medicine: Food production and obesity linked to climate change**

With a recent media focus on various high-profile accidents related to food consumption, coverage features comments from experts on the global effects on food from climate change. From the potential for domestic animals overrunning humans in terms of ecological space to the effect of human food production on climate change, Timothy Lang coins the term “food miles” to designate the amount of carbon agriculture is responsible for – 14%. Lang then focuses on government policy related to food, with Leonard Bielory noting a predicted increase in allergenic airway disease. With a concern for Soldier nutrition, Army Medicine can utilize its vast database of patient information to analyze and come to conclusions about trends in high-impact topics, such as climate change.

### ***PTSD***

## **Public Library of Science: Symptoms and Subjective Quality of Life in Post-Traumatic Stress Disorder: A Longitudinal Study**

Research discovers how a reduction in war related PTSD symptoms raised the subjective quality of life (SQOL), resulting in reduced hyperarousal symptoms. The study advises those treating war related PTSD that hyperarousal symptoms should a primary topic addressed in improving SQOL and how evidence suggests selective serotonin reuptake inhibitors, mood stabilizers and atypical anti-psychotics may be effective in reducing hyper arousal symptoms. Research on the intersection of PTSD symptoms and hyperarousal symptoms permits Army Medicine to orient and discuss PTSD treatment programs with a particular sensitivity.

## **Public Library of Science: A Systematic Review of PTSD Prevalence and Trajectories in DSM-5 Defined Trauma Exposed Populations: Intentional and Non-Intentional Traumatic Events**

Research aims to discover the differences in PTSD recovery time between individuals who have experienced intentional traumatic events and those who have experienced non-intentional traumatic events. Results showed how the prevalence of PTSD over time increased for those with intentional traumatic events and decreased for those with non-intentional traumatic events. Research of this topic helps Army Medicine understand how traumatic events can cause a large burden on public healthcare.

## **Military Medicine: Efficacy of Stellate Ganglion Block in the Treatment of Anxiety Symptoms From Combat-Related Post-Traumatic Stress Disorder: A Case Series**

In continued research on stellate ganglion block as a treatment for PTSD anxiety, four case studies from Tripler Army Medical Center provide examples of Soldiers' reactions to the treatment. The study of the four Soldiers saw "markedly" reduced PTSD Checklist (PCL) scores after the minimally invasive procedure, thus pointing to sustained relief in the personnel without using psychotropic intervention. The use of SGBs on PTSD symptoms can be integrated into Army Medicine discussions on PTSD and ongoing treatments that show promise for the disorder.

### ***Sexual Assault***

## **Military Medicine: Military Sexual Trauma Increases Risk of Post-Traumatic Stress Disorder and Depression Thereby Amplifying the Possibility of Suicidal Ideation and Cardiovascular Disease**

The article links women with MST to having depression, suicidal tendencies, physical health complications and behavioral health problems. It argues that female veterans require gender-sensitive, extensive care from the VA. This includes treatment and assessments on the effectiveness of the treatment provided to victims of MST. With reporting on MST in the media, the prevalence of PTSD in victims remains a common storyline.

### ***Sleep***

## **The Lancet Neurology: Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study**

Research on idiopathic rapid-eye-movement sleep behavior disorder (IRBD) provides Army Medicine the opportunity to discover how to slow or stop neurodegenerative processes, such as Parkinson's disease. *Idiopathic REM sleep behavior disorder in the development of Parkinson's disease* discusses similar research.

## **PLOS One: Neuroendocrine Regulation and Metabolism of Glucose and Lipids in Primary Chronic Insomnia: A Prospective Case-Control Study**

With a particular focus on the impact of certain foods and behaviors on sleep, research notes a trend in consumption and activity that could lead to a curtailment of sleep. Researchers set out to determine the impact of glucose and lipid metabolism when compared to age, sex, and BMI. Results indicated an association between the dysregulation of the HPA-axis, resulting in chronic primary insomnia. No specific relationship was discovered between glucose or lipids' impact on diabetes.

### ***Stress***

## **Lancet: Proposals for mental disorders specifically associated with stress in the International Classification of Diseases-11**

The discussion of mental disorders' inclusion in the International Classification of Diseases criticizes various bodies for overdiagnosis of PTSD. The concern over the frequency of diagnoses relates to the cause of the trauma: man-made or natural. Researchers also contemplate introducing Complex PTSD into the tome. Army Medicine can make use of distinctions of PTSD and Complex PTSD and has the potential to rebut any claims that war, as a man-made event, would not allow diagnosing of Soldiers, seeing as they are actively pursuing the traumatic event.

### ***Substance Abuse***

## **JAMA: Global Alcohol Use**

Canadian researchers turned to expansive amounts of data to analyze the frequency and patterns of alcohol abuse in various countries. Data on alcohol consumption aids Army Medicine in developing an international strategy to both understand potential background differences, but also to tailor effective strategies to certain demographics.

## **Military Medicine: Internet Versus In-Person Counseling for Patients Taking Varenicline for Smoking Cessation**

With TRICARE's recent decision to provide smoking cessation tools to servicemembers, research on the effectiveness of internet-based tobacco counseling could provide the military health system with a new tool to reduce smoking in the military.

## **New England Journal of Medicine: Conflicts and Compromises in Not Hiring Smokers**

Research argues that employers need to take a stronger stance on cessation of smoking by terminating employees who use tobacco. Due to recent media coverage of TRICARE's provision of tobacco cessation tools, the research is relevant to Army Medicine.

## **TBI**

### **JAMA: Guideline: Tailor Appraisal of Concussion During Sports**

Research posits that the evaluation of possible sport-related concussions should be revised in favor of individual care including follow-up assessments. Given the relationship between the Army and major sports leagues, such as the initiative with the NFL on concussive injury, Army Medicine can utilize the research and focus on patient-centered care in coverage of concussive injury.

## **Other**

### **Public Library of Science: Alterations in Spontaneous Brain Oscillations during Stroke Recovery**

The article briefly mentions TBI as researchers seek to determine various differences in stroke recovery. Looking at alterations in rolandic oscillations, the potential for recovery prediction, and how ALFMA is associated with stroke recovery, researchers determine whether future studies of temporo-parietal oscillations can accurately predict recovery potential. Army Medicine can utilize future information on stroke recovery in order to integrate effective rehabilitation and recovery programs.

### **Lancet: Mapping the mind—smart thinking for brain health?**

The BRAIN Initiative research has the potential to help Army Medicine better understand ways to treat, prevent and cure brain disorders, such as TBI. However, there is controversy over if the funds used for the BRAIN Initiative could be better applied to research that is more likely to have a more immediate clinical impact.

### **Military Medicine: Dependent Adolescent Pregnancy Rates and Risk Factors for Pregnancy in the Military Health Care System**

Research aimed at discovering the pregnancy rate in military dependents enrolled in TRICARE shows how female dependents have a much lower likelihood of adolescent pregnancies compared to the national and state rates. Army Medicine has the potential to positively highlight low adolescent pregnancy rates in the Army in the event of a national or local interest in the topic.

### **Military Medicine: Cypriot and Greek Army Military Boot Cushioning: Ground Reaction Forces and Subjective Responses**

Research on the effect of Soldiers using commercial insoles in their military boots is relevant to Army Medicine because of the injuries caused to lower limbs while training. The study advises that comfortable military boot design does not necessarily lead to injury prevention.

## **Medical Journal Clips**

### ***Disease***

### **Changing the research criteria for the diagnosis of Parkinson's disease: obstacles and opportunities**

Lancet Neurology

Prof Daniela Berg MD, Prof Anthony E Lang MD, Ronald B Postuma MD, Walter Maetzler MD, Prof Guenther Deuschl MD, Prof Thomas Gasser MD, Andrew Siderowf MD, Prof Anthony H Schapira MD, Prof Wolfgang Oertel MD, Prof José A Obeso MD, Prof C Warren Olanow MD, Prof Werner Poewe MD, Prof Matthew Stern MD

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#### Summary

Recent findings question our present understanding of Parkinson's disease and suggest that new research criteria for the diagnosis of Parkinson's disease are needed, similar to those recently defined in Alzheimer's disease. However, our ability to redefine Parkinson's disease is hampered by its complexity and heterogeneity in genetics, phenotypes, and underlying molecular mechanisms; the absence of biochemical markers or ability to image Parkinson's disease-specific histopathological changes; the long prodromal period during which non-motor manifestations might precede classic motor manifestations; and uncertainty about the status of disorders diagnosed clinically as Parkinson's disease but without Lewy pathology. Although it is too early to confidently redefine Parkinson's disease, the time has come to establish a research framework that could lead to new diagnostic criteria. We propose the establishment of three tiers encompassing clinical features, pathological findings, and genetics or molecular mechanisms. Specific advances in each tier, bridged by neuroimaging and biochemical data, will eventually lead to a redefinition of Parkinson's disease.

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# A Success Story: Togo Is Moving toward Becoming the First Sub-Saharan African Nation to Eliminate Lymphatic Filariasis through Mass Drug Administration and Countrywide Morbidity Alleviation

PLOS Neglected Tropical Diseases

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## Introduction

Lymphatic filariasis (LF) is a debilitating vector-borne disease predominantly caused by the helminths *Wuchereria bancrofti* and *Brugia malayi* [1], [2]. Endemic in 72 countries, LF is responsible for 5.9 million DALYs lost and is implicated as the second leading cause of disability worldwide by the World Health Organization (WHO) [3]–[5]. Although 70% of those infected do not exhibit symptoms, almost all persons infected have subclinical damage to the lymphatic vessels [6], [7]. An estimated 40 million people are symptomatic with the predominant morbidities associated with LF: lymphedema and/or hydrocele [8].

In recognition of the worldwide burden of LF, in 1997, the World Health Assembly passed the resolution WHA 50.29 calling for collaborative efforts by member states to eliminate the disease as a public health problem [9]. In 2000, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) was formed in response to the WHA resolution and aimed to eliminate the disease by 2020. The program adopted a two-pronged strategy: (1) to interrupt transmission of the causal parasite and (2) to alleviate morbidities associated with the disease [10]. The two pillars of the GPELF's strategy form the basic framework for any successful LF program.

Togo is one of the 34 African countries endemic for lymphatic filariasis and is surrounded by the endemic countries of Benin, Ghana, and Burkina Faso [11]. The National Program to Eliminate Lymphatic Filariasis (NPELF) was founded in 2000 and is one of the few LF programs that address the dual goals of the global elimination program on a national scale. Togo is the first sub-Saharan country to achieve probable interruption of transmission and to move to the post-MDA surveillance phase as defined by the WHO [12]. Here we describe the elements that proved successful in the national strategy to address LF in Togo.

## Assessing the Burden

### Infection

The Togolese Ministry of Health (MoH) used the Rapid Assessment of Geographical Distribution of Filariasis (RAGFIL) methodology, developed by the Special Programme for Research and Training in Tropical Diseases (TDR), to assess countrywide infection [11], [13]. National mapping was performed in two stages [11]. Thirty-seven villages representing 17 of Togo's 35 health districts (with 5 in Lomé, the capital city) participated in the initial mapping in 1998. In 2000, an additional 24 villages were selected using the WHO's Health Mapper software version 3.0 to ensure that the whole country was covered [11]. The distance between two mapped villages in the final map was never more than 50 km; each selected village represents the state of the transmission in a radius of 25 km. The tests for both stages entailed collection of 100 µl of capillary blood from a person's fingertip and subsequent testing using rapid immunochromatographic tests (ICT) (AMRAD, Townsville, Queensland, Australia). The ICT used is specific for *W. bancrofti* and detects the presence of circulating filarial antigen (CFA) [14]. From the 2009 samples collected in 61 villages, 89 persons (1.8%) were ICT positive. Seven districts were classified as endemic because the prevalence of ICT positivity exceeded the 1% threshold [15], [16] (Figure 1). Several districts along the Togo–Benin border in the south were unexpectedly classified as nonendemic although they were endemic in the past and currently have a high prevalence of LF morbidity [17]. Possibly, LF transmission was interrupted by intensive vector-control methods implemented in the area by the malaria program in the 1970s.

#### Morbidity

As accurate estimates of the national burden of LF morbidity are difficult to obtain, Mathieu and others described different methods to obtain LF morbidity prevalence in Togo [18]. Prevalence estimates for lymphedema and hydrocele were calculated based on information collected during LF mapping and from sentinel sites. Morbidity questions were also added onto three 30-cluster drug coverage surveys that were conducted in six of Togo's endemic districts and onto a nationwide malaria bed net coverage survey.

Sentinel site data, cluster survey data, and the malaria bed net coverage survey data detected a hydrocele prevalence of 0.61% (95% CI 0.00–1.41), 0.63% (95% CI 0.20–1.06), and 2.6% (95% CI 1.8–3.4), respectively [19]. These same sources revealed a lymphedema prevalence of 0.80% (95% CI 0.00–1.98), 0.17% (95% CI 0.00–0.34), and 0.6% (95% CI 0.3–0.9).

#### Program Implementation

##### Mass Drug Administration

Shortly after the mapping, mass drug administration (MDA) campaigns were launched. All of Togo's LF districts are coendemic for onchocerciasis, and the communities with less than 2,000 inhabitants have been undergoing an annual or biannual MDA with ivermectin since the late 1980s [20], [21]. The NPELF modified the distribution system established by the onchocerciasis program through the coadministration of albendazole with ivermectin. The timings of the campaigns were synchronized since LF elimination distributions are required to be organized at the same time in all endemic areas. The geographic coverage in the districts was also expanded to treat villages that were not endemic for onchocerciasis or that had a population above 2,000 inhabitants.

The processes of drug distribution and reporting were facilitated by utilizing Togo's decentralized pyramidal health structure. A single community health worker (CHW) was selected to represent every 300 people in the endemic districts. As the first step toward calculating drug needs, the

CHWs visited their respective households prior to each MDA in order to count all inhabitants. The results of the CHWs' annual census were used by the national coordinator to calculate drug needs. The NPELF requested ivermectin (Merck & Co., Inc., White House Station, New Jersey, United States) and albendazole (GlaxoSmithKline, Brentford, United Kingdom) from the Mectizan Donation Program (MDP). Drug distribution followed the reverse chain of reporting and ended with house-to-house distribution by the CHWs. As children under the age of five are ineligible to receive the treatment, the CHWs used a measuring stick to aid in age estimation and excluded all children with heights below 90 cm [22]. Seriously ill individuals and pregnant women were also excluded from the treatment. The number of people who ingested the drugs was recorded by the CHWs. This data was sent through the appropriate channels back to the NPELF and reported coverage rates calculated.

The first LF MDA was held in the district of Binah in 2000, and within three years, distributions scaled up to all seven endemic districts. Since 2004, reported drug coverage in each district has exceeded 80% of the total population (Table 1). Coverage levels submitted by the CHWs were verified by a coverage survey performed in 2004 (described below). Scaling down started in 2008 and in 2009 when the final MDAs were organized in the districts of Tone and Doufelgou.

#### Lymphedema Management

In collaboration with the CDC and funded by IMA World Health-USAID, the Togo MoH engaged in an innovative approach to implement WHO-recommended lymphedema management techniques on a national scale (including the nonendemic districts). The lymphedema management program began in 2007 by training at least one staff member in each of the 570 health facilities in lymphedema education and care. This was followed by an awareness campaign to inform the population that care for "swollen legs" was available. Patients were trained in self-care by using WHO education materials that were locally adapted, and support structures for patients were created. The program sought to ensure sustainability beyond external funding by being low in cost and by including lymphedema treatment in standard medical training programs.

Over the course of one year, the lymphedema management program scaled up to achieve national coverage. A total of 1,083 patients were enrolled into the program; approximately 30% of whom lived in nonendemic districts. An evaluation of the program, which was conducted three years after the launch, showed that 62% of the persons with a swollen leg, regardless of the cause or severity (reversible swelling was included), were still enrolled in the program.

#### Hydrocele Surgeries

Another key element to success was participation in the multicountry West African LF Morbidity Project. Multiple workshops on the current WHO-recommended surgical techniques for hydrocele were held for district-level surgeons on an annual basis from 2005 to 2007 and then again in 2009. Following each workshop, surgical campaigns were conducted [23], along with a series of national campaigns to increase the availability of hydrocelectomies to the affected population.

Since the program's inception, 24 district surgeons have participated in the surgical trainings. During the three campaigns that ran from 2005 to 2006, 257 hydrocelectomies were performed. In 2007 and 2008, 215 hydrocelectomies were performed with additional financial assistance from Health & Development International (HDI).

#### Monitoring and Evaluation

The success of the NPELF was partially due to the rigorous monitoring and evaluation system.

#### MDA Coverage

Following each annual drug distribution, reported drug coverage was collected using the participation tally submitted by the CHWs. The denominator used was the total population (annual census), which was calculated by the CHWs prior to each MDA. In each, the WHO's goal of 70% drug coverage was achieved, and since 2004, all districts' reported drug coverage has exceeded 80% (see Table 1). In 2004, coverage surveys were conducted with technical assistance from the CDC using the probability proportional to estimated size (PPES) 30-cluster design, and the reported coverage was validated [16].

#### Impact of MDA

A system of sentinel and spot-check sites was set up in the endemic districts in order to evaluate the impact of the MDA campaigns on microfilaremia. Seven sentinel sites were initially selected; due to budget constraints, the number of sites was later trimmed to three sites. Each of these three sites represented a cluster of districts. After the baseline collection in 2000, subsequent sentinel-site activities were conducted before the third and fifth year of MDA in each district. Blood samples were collected from 500 people in each sentinel site between the hours of 22:00 and 02:00. In adherence with WHO guidelines [16], spot-check sites were also selected from the endemic districts as an additional monitoring mechanism prior to the fifth round of MDA using a similar testing methodology to the sentinel sites. Between 2005 and 2009, 13 spot-check sites were conducted from urban sites, cross-border areas, and other locations that were suspected to carry an elevated risk for ongoing transmission.

The baseline results from the sentinel sites indicated a microfilaremia prevalence between 1% and 36%. Since 2004, microfilaria samples from the sentinel sites (see Figure 2) and spot checks have all been below 1%. Five of the seven districts have consistently registered prevalence levels of 0% in all sentinel and spot-check sites. MDAs were halted in 2008 following six to seven MDAs. Additional MDA campaigns were conducted in 2009 in two districts: i) in Tone, after seven MDAs, where a prevalence of 2% was detected at the spot-check site of Woriwouri, a village in close proximity to endemic areas in Burkina Faso and Ghana and ii) in Doufelgou, where an additional MDA was organized because, although prevalence level was reported at 0% in the sentinel site after the third MDA, this sentinel village was not assessed after the fifth MDA. No detection of bancroftian filaria was found after the subsequent MDAs. The results from the sentinel and spot-check sites indicate that nine years of MDA campaigns have succeeded in reducing levels of microfilaria in Togo to 0%, thus most likely achieving interruption of transmission.

#### Ongoing Surveillance

Togo is the first country to implement a nationwide LF surveillance system. Implemented in 2006, Togo put in place a system to identify and track cases with active infection. Forty laboratories were selected throughout the country for inclusion in surveillance activities. This system utilized nocturnal thick blood smears for malaria diagnosis, as they can concurrently be used to make LF diagnoses [24]. Participation in the surveillance system required laboratory technicians to send all slides with identified *W. bancrofti*, in addition to ten randomly selected slides per month, to the reference laboratory in Lomé.

Within the first four years of the surveillance system, 8,050 slides were accrued by the reference laboratory and two LF-positive slides were identified. Both cases were followed up according to a predetermined algorithm of action, and no further positive cases followed. An evaluation of the system showed that some border areas were not as well covered. It was decided to increase the coverage of the surveillance system by implementation of centralized ELISA-based testing for antigenemia using filter-paper blood spots collected in dispensaries (Figure 3). No active transmission focus has been detected so far by the system.

#### Operational Research

Added components that contributed to the success of the NPELF were several operational research projects that further addressed the pillars of the GPELF and expanded program outreach.

#### Lymphedema Management Program

As mentioned, operational research implemented with the CDC's assistance resulted in the formation of Togo's national lymphedema program. One of the evaluation tools was a cohort survey (2004–2010) of 188 LF patients to assess impact. The survey addressed indicators such as current and previous treatment practices, quality of life, economic factors, and overall program impact among patients with lymphedema [25]. Between the preprogram assessment in 2007 and the assessment at the end of the funding in 2010, the proportion of patients ( $n = 107$ ) who did not seek treatment or sought traditional methods decreased from 30.8% to 2.8%. An increase of positive treatment practices was also observed: the practice of cleaning the limb increased from 10.3% to 92.5% and exercising increased from 3.7% to 78.5%, ( $p < 0.0001$ ) (unpublished data).  
Transmission Assessment and Post-treatment Surveillance

As the macrofilaremia in the sentinel sites and spot-check sites were  $< 1\%$ , the NPELF conducted a 30-cluster survey to establish interruption of disease transmission among children two and six years of age. In May 2008, the cluster survey was carried out with support from the Emory University LF Support Center, Atlanta following the WHO 2005 guidelines [16]. ICT card and blood spots for Og4C3 ELISA were performed. The ELISA testing conducted by the CDC indicated that all but one child was negative.

In 2006, the NPELF collaborated with the MDP and the CDC to develop an innovative ongoing national surveillance system. Several sampling modalities, such as using military recruits and blood banks, were considered, but it was decided to base the system on nocturnal thick smears collected to diagnose malaria as described above [24]. This surveillance system was eventually taken over by the MoH as part of the ongoing LF activities. With the financial support of RTI/USAID, the NPELF and the CDC evaluated this system in 2010 and validated also the initial mapping.

In 2012, the first post-MDA transmission assessment surveys (TAS) using the WHO's new guidelines [12] were conducted in the seven districts grouped into four evaluation units (EU). The results suggested that all EUs passed as the number of ICT-positive cases was below the cut-off value of 18. The positive cases included: eight cases in Tone-Kpendjal EU, one case in Binah-Doufelgou EU, four cases in Amouh-Haho EU, and no cases in Kozah EU.

In order to confirm the absence of recrudescence and prepare the country for certification, the post-MDA surveillance activities will continue until 2015. These activities include ongoing surveillance and the implementation of the second and final WHO-recommended TAS scheduled for 2015.

Other Research

In 2005, the NPELF also contributed to guide the global integrated NTD program by launching a three-year program supported by the CDC. The national NTD program coordinators developed an integrated NTD program during a one-year preparation phase to elaborate integrated tools and guidelines for an integrated NTD program. The integrated areas covered were mapping, baseline data, MDA, health education, and monitoring and evaluation. Thanks to a praziquantel donation from the Schistosomiasis Control Initiative (SCI), the integrated approach was twice piloted in the district of Binah and achieved good results. The coverage rates were high, program managers adhered to the concepts, and chances for sustainability were believed to be strengthened by linking unfunded NTD programs (STH, schistosomiasis) with well-funded programs. Based on this success, the MoH was able to secure funding for a national scale-up.

Furthermore, the NPELF program conducted operational research to validate drug coverage surveys with assistance from the MDP and the CDC. The accuracy of the results of such surveys was tested one, six, and 12 months after an MDA in Togo in which three drugs (albendazole, ivermectin, and praziquantel) were distributed. Survey results indicated that the respondents were able to accurately recall if they took the drugs.

Advocacy and Fundraising

The main key to success in Togo was the mixture of an opportunistic approach from the NPELF combined with strategic and generous partners. Since the 1990s, Togo has been an underfunded country due to the political climate and subsequent digression from democracy [26], [27]. However, the NPELF was initiated and carried out thanks to financial and technical support from Health & Development International (HDI), a Norwegian NGO which provided support during the first nine years of the program [28]. HDI also made the program visible and attractive to new external partners such as LF program support centers in Atlanta and Liverpool and the CDC. This enabled the NPELF to capitalize on the strength of partnerships and networking and allowed them to implement all the activities required for the elimination of LF. In addition to HDI funding, in 2000, the program was awarded a portion of the DFID grant through the WHO. The collaboration with the onchocerciasis control program facilitated the reduction of the costs of drug distribution and sustained high MDA coverage. The collaboration with the national malaria program resulted in submitting an innovative joint malaria/LF proposal to the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) that secured five years of implementation funding for MDA and impact assessments.

Discussion

This paper describes not only the first sub-Saharan LF program that probably interrupted transmission, but demonstrates that it is possible and essential for morbidity programs to be codeveloped along with the MDA campaigns in order to fully address the burden of the disease in endemic territories.

The ability to implement an LF national program was not evident due to a variety of embargoes that were placed on Togo in the late 1990s. These embargoes kept the country in a state of severe economic stress. Although in this political climate LF was not perceived as a health priority, the dedication and endorsement of the concept of LF elimination by the MoH has, and continues to be, a critical factor in setting up a successful program. For example, during some years, the program was unable to provide the small MDA incentive of \$3 to \$6 USD per CHW volunteer. Regardless, the CHWs distributed the medications, motivated by the spirit of the collaborative environment created by the NPELF. Highly motivated CHWs also facilitated high compliance in the communities where LF was either largely unknown or not perceived as a health problem.

A factor contributing to success was the fact that the MoH used existing structures. Indeed, the MDAs for LF elimination were initiated using the preexisting structure of the community-directed ivermectin treatment (CDTI) established by the national onchocerciasis control program [21]. The surveillance and M&E activities in the Togo program required the MoH to engage the decentralized clinical laboratory network to conduct cost-effective impact assessments. It also allowed the MoH to establish robust relationships with research institutions. The NPELF also identified resources within Togo's existing health structure to implement lymphedema and hydrocele management. It was found that the decentralized health system could be used to disseminate lymphedema management training through multiple layers of health staff and community workers.

Additionally, the NPELF demonstrated the ability to recognize and capture each funding opportunity to implement all components of the program. To date, the NPELF remains the only LF program in Africa that has been awarded financial aid from the GFATM. The collaboration with the CDC on several operational research projects enabled the program to implement some crucial aspects of the elimination program such as morbidity management and surveillance. It has also increased the visibility of the program and provided access to even more resources.

It is also important to point out that the impact of this successful program is not limited to only alleviating the filariasis burden in Togo. The program was the base for RTI/USAID funding for an integrated NTD program resulting in finalizing national mapping [29] and implementing national schistosomiasis and STH MDAs. The results of the operational research projects and the lessons learned by the NPELF are widely discussed at international meetings and shared with peers. The NPELF is also assisting other countries in replicating the lymphedema management pilot program through the creation of a national morbidity training manual that describes program components and contains useful information for implementing a national morbidity management program in low-resource settings [30]. This manual is widely shared and is used by other partners such as Handicap International and the CDC Foundation to implement programs in other countries (e.g., Benin and Mali). Based on the Togo experience, surveillance systems will be set up in two additional African countries and the program coordination is providing technical assistance to countries in the region.

The success of the NPELF in Togo shows that lymphatic filariasis can be effectively addressed in countries with limited funds when cooperative efforts combine with motivation and innovation. Ministries of health play a critical role in embracing the scaling up of program activities, and new

avenues for partnerships and funding must be vigorously pursued. The main lesson learned is that when developing a national disease elimination strategy, a key component must be putting forth the time and effort to build strong collaborations among appropriate partners. This networking with program collaborators when combined with persistent advocacy and fundraising was the crucial component that permitted the NPELF to address LF in Togo.

In conclusion, as summarized in Table 2, the success of the National Program to Eliminate Lymphatic Filariasis in Togo was facilitated by charismatic, innovative, and trustworthy program managers able to i) timely identify issues and solutions, ii) ensure visibility at the highest levels of the MoH, iii) adopt an opportunistic approach using existing health interventions and a decentralized health system to integrate LF activities, and most importantly, iv) develop a variety of partnerships and pioneering approaches to mobilize resources for a synchronized implementation of the twin-pillar strategies as recommended by the GPELF. The adoption of these approaches could aid other countries that are not on target to reach the 2020 LF elimination goal in sub-Saharan Africa.

#### Way Forward

In agreement with the new guidelines of the WHO [12], in 2010, the NPELF of Togo entered into a five-years post-MDA surveillance phase that will take the country to the WHO's independent verification of absence of the transmission in 2015. During this surveillance phase, the lab-based surveillance will continue throughout the country with an emphasis on areas bordering endemic districts of the three neighboring countries where the MDAs are still ongoing. In addition, the final TAS will be implemented in 2015 in the seven previously identified endemic districts. The current challenge is to maintain momentum for adequate human and financial resources allocation in order to support the implementation of the critical endgame activities. The program coordination is closely working with the national malaria control program in order to reach/maintain universal insecticide-treated net coverage. Most importantly, it is the desire to increase the net compliance rate that was demonstrated to be a problem in the Togolese communities [31]. The morbidity control activities are expected to be fully integrated within the health system and are deemed to continue providing care to patients even beyond the verification target.

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## **US Department of Defense contributions to malaria surveillance**

The Lancet Infectious Diseases

David Saunders, Christopher Duplessis, Andres Lescano, Ben Andagalu, Alaina Thomas, Mark Fukuda, James Cummings  
April 2013

In response to an Article<sup>1</sup> and a Personal View<sup>2</sup> on the spread of artemisinin resistance in the November 2012, issue of The Lancet Infectious Diseases, we would like to present several examples of previous and continuing malaria resistance work sponsored by the US Department of Defense (DoD).

The US DoD has been actively involved in the study of malaria drug-resistance for several decades, and has supported many antimalarial resistance studies worldwide. The US DoD has played an active part in artemisinin-resistance surveillance in southeast Asia after the recommendation of artemisinin combination therapies (ACT) as first-line antimalarial treatments by WHO in 2006. The US DoD Global Emerging Infections Surveillance and Response System (GEIS) has supported malaria surveillance and drug-resistance studies in southeast Asia through network laboratories such as the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok, Thailand, and the Naval Medical Research Unit 2 (NAMRU-2) in Cambodia.

AFRIMS was the first institution to report clinical cases of artemisinin resistance in western Cambodia.<sup>3</sup> NAMRU-2 characterised ACT failures in southern Cambodia,<sup>5</sup> a region previously overlooked in the quest to characterise artemisinin resistance along the Thailand—Cambodia border. The investigation by Chanaki Amaratunga and colleagues<sup>1</sup> is one of several studies showing the existence of artemisinin-resistant *Plasmodium falciparum* parasites in Cambodian provinces. Beyond its initial focus in southeast Asia, the US DoD has increased efforts to characterise artemisinin resistance worldwide. A major effort involves the coordinated execution of harmonised trials of artesunate—mefloquine efficacy in four DoD laboratories in Peru, Ghana, Kenya, and Thailand. These trials will take a standardised multicentre approach to characterise and compare parasite clearance rates for 72 h after artesunate dosing with published methods.<sup>6—8</sup> Clinical and laboratory methods, such as microscopy and in-vitro drug-sensitivity testing will be standardised across all four sites and samples will be contributed to existing genome-wide association studies to identify markers of artemisinin resistance. To our knowledge, this marks the first effort to expand artemisinin-resistance surveillance into the Americas with this approach.

With sites in two countries in Africa, these trials exemplify how the US DoD is helping to establish and support malaria surveillance networks to include the African continent. Ambrose Talisuna and colleagues<sup>2</sup> called for the reinstatement of pan-African malaria-surveillance networks, citing the need for additional antimalarial-resistance surveillance, and calling for the rapid sharing of baseline parasite clearance-rate data derived from clinical trials. We agree with these sentiments and designed the GEIS harmonised artesunate—mefloquine clinical trials with those needs in mind.

All authors were equally involved in the drafting and reviewing of this manuscript. Authors are the designated representatives from their respective institutions. The GEIS has a scientific coordination role in the preparation and execution of the clinical trials at the four Department of Defence network laboratories. DS, CD, AL, and BA are investigators involved in these harmonised trials at each of the four sites, and represent laboratory staff that have contributed substantially and equally to the development of the harmonised trial protocols and other study documents. All representatives have contributed to this manuscript and have consented to its submission to *The Lancet Infectious Diseases*. The Armed Forces Health Surveillance Center (AFHSC) sponsors the harmonised malaria drug-resistance trials mentioned in this paper. Authors were not funded specifically to write or edit this article.

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**[Efficacy of RTS,S malaria vaccines: individual-participant pooled analysis of phase 2 data](#)**

## The Lancet Infectious Diseases

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### Summary

#### Background

The efficacy of RTS,S/AS01 as a vaccine for malaria is being tested in a phase 3 clinical trial. Early results show significant, albeit partial, protection against clinical malaria and severe malaria. To ascertain variations in vaccine efficacy according to covariates such as transmission intensity, choice of adjuvant, age at vaccination, and bednet use, we did an individual-participant pooled analysis of phase 2 clinical data.

#### Methods

We analysed data from 11 different sites in Africa, including 4453 participants. We measured heterogeneity in vaccine efficacy by estimating the interactions between covariates and vaccination in pooled multivariable Cox regression and Poisson regression analyses. Endpoints for measurement of vaccine efficacy were infection, clinical malaria, severe malaria, and death. We defined transmission intensity levels according to the estimated local parasite prevalence in children aged 2–10 years (PrP2–10), ranging from 5% to 80%. Choice of adjuvant was either AS01 or AS02.

#### Findings

Vaccine efficacy against all episodes of clinical malaria varied by transmission intensity ( $p=0.001$ ). At low transmission (PrP2–10 10%) vaccine efficacy was 60% (95% CI 54 to 67), at moderate transmission (PrP2–10 20%) it was 41% (21 to 57), and at high transmission (PrP2–10 70%) the efficacy was 4% (–10 to 22). Vaccine efficacy also varied by adjuvant choice ( $p<0.0001$ )—eg, at low transmission (PrP2–10 10%), efficacy varied from 60% (95% CI 54 to 67) for AS01 to 47% (14 to 75) for AS02. Variations in efficacy by age at vaccination were of borderline significance ( $p=0.038$ ), and bednet use and sex were not significant covariates. Vaccine efficacy (pooled across adjuvant choice and transmission intensity) varied significantly ( $p<0.0001$ ) according to time since vaccination, from 36% efficacy (95% CI 24 to 45) at time of vaccination to 0% (–38 to 38) after 3 years.

#### Interpretation

Vaccine efficacy against clinical disease was of limited duration and was not detectable 3 years after vaccination. Furthermore, efficacy fell with increasing transmission intensity. Outcomes after vaccination cannot be gauged accurately on the basis of one pooled efficacy figure. However, predictions of public-health outcomes of vaccination will need to take account of variations in efficacy by transmission intensity and by time since vaccination.

#### Funding

Medical Research Council (UK); Bill & Melinda Gates Foundation Vaccine Modelling Initiative; Wellcome Trust.

## Introduction

The increasing application of interventions for malaria control over the past 10 years has been linked to reductions in morbidity and mortality associated with malaria infection. A vaccine for malaria could have an important role in further reduction of the burden of disease. The candidate malaria vaccine RTS,S/AS01 is now in phase 3 clinical trials, for which preliminary data for the first 12 months of follow-up are available. Efficacy against clinical malaria was 55•8% (97•5% CI 50•6—60•4) among children age 5—17 months. Combined efficacy against severe malaria for children aged 5—17 months and 6—12 weeks was 34•8% (95% CI 16•2—49•2).

RTS,S protects at pre-erythrocytic stages of the parasite's lifecycle. It is partly effective and has been described as a leaky vaccine—ie, no individual is protected consistently against every episode of exposure, but the risk of acquiring infection after any single episode of exposure is reduced. In field trials, RTS,S has been given with either of two different adjuvant systems: AS01 or AS02. Although RTS,S/AS01 seems to be more immunogenic than RTS,S/AS02, efficacy trials of RTS,S/AS01 and RTS,S/AS02 have not resulted in definitively powered comparisons. Furthermore, the variation in vaccine efficacy over time remains unknown, with conflicting evidence from individual trials.

Vaccine efficacies are usually summarised with point estimates. However, if vaccine efficacy is heterogeneous by subgroups within the population, this efficacy figure will be a mean of the vaccine efficacy in the various subgroups, weighted according to the proportion of the population. For instance, if vaccine efficacy is higher in older children then the overall efficacy in a particular trial will depend on the proportion of older children to younger children that are vaccinated.

Analysis of phase 2b data to date shows variations in measured efficacy between trials. These differences might be attributable to the vaccine formulation, intensity of transmission, length of follow-up, or age-range of participants. To ascertain which covariates are associated with variations in vaccine efficacy, we did a pooled analysis of data from phase 2b trials.

## Methods

### Data collection

We identified phase 2b trials of RTS,S from the GlaxoSmithKline Biologicals registry of trials (data on file), and raw data were provided by GSK Biologicals to three academic investigators (PB, MTW, and ACG). One of us (PB) checked data for completeness by comparing data summaries with the primary publications; all investigators analysed the data. Characteristics of the trials, done at 11 sites in total (from six countries), are summarised in table 1.

In the identified trials, healthy adults or children were recruited after clinical and laboratory screening to exclude participants with clinically significant disease. Five trials of children or adults used active case detection for *Plasmodium falciparum* infection (ACDi),<sup>6,8–11</sup> one used active case detection for clinical malaria (ACDc),<sup>12</sup> and two used passive case detection (PCD) for clinical malaria<sup>10, 13</sup> (one trial used both ACDi and PCD). Trials using ACDi and ACDc included assessment of participants who presented with acute illness between scheduled visits, which is usually referred to as PCD in protocols. For simplicity, in our analysis here we use ACDi to refer to the combination of ACDi and PCD, ACDc to refer to combined ACDc and PCD, and PCD to refer to exclusive use of PCD. ACDi was done after antimalarial treatment during the vaccination course and was then monitored with regular finger-prick blood smears. Deaths and severe malaria episodes were monitored in all five trials in which children were enrolled.

## Procedures

We used four primary endpoints in our analysis: infection, clinical malaria, severe malaria, and death. In the trials we identified, infection was defined as any detectable *P falciparum* parasitaemia, with or without a measured fever. We defined clinical malaria as the presence of 2500 or more *P falciparum* parasites per  $\mu\text{L}$  of blood in association with reported or measured fever ( $\geq 37.5^\circ\text{C}$ ).<sup>17, 18</sup> We deemed clinical malaria episodes occurring within 28 days of a previous episode to be part of the same episode. We did not censor time of monitoring according to antimalarial drug use or reported absences from the study area.

We analysed episodes of infection identified by ACDi as one dataset. We combined clinical malaria episodes identified by ACDc and PCD and analysed these as a second dataset. ACDc and PCD were included in the initial study protocols, except for one trial,<sup>13</sup> in which the efficacy assessment was included after a protocol amendment as an exploratory objective, for which some data were extracted retrospectively.

We identified episodes of severe malaria from safety data reporting. Criteria for severe malaria were derived from the WHO definition<sup>19</sup> and were applied by the clinical investigators at every site, comprising asexual *P falciparum* parasitaemia, no alternative (or more probable) cause of illness, and either severe malaria anaemia (haemoglobin  $< 50$  g/L), cerebral malaria (Blantyre coma score  $< 2$ ), or another symptom (multiple generalised convulsions in 24 h, prostration, hypoglycaemia [ $< 2.2$  mmol/L], acidosis, or shock).

Our primary analysis was vaccine efficacy, which was assessed per-protocol. Hence, cohorts monitored for infection or clinical malaria included all participants who had received three doses of vaccine, from 2 weeks after the third dose. We did not judge adults at risk of severe disease or death from malaria. Analysis of severe malaria or death was based on intention to treat and included all children who received at least one dose of vaccine, from the time of the first vaccination.

In Mozambique, one cohort (cohort 2) first underwent ACDi in a double-blind phase then subsequently underwent PCD for clinical malaria in a single-blind phase. We included data from the double-blind phase in the ACDi dataset and those from the single-blind phase in the clinical malaria dataset, taking the start of the single-blind phase as the initial time of monitoring for clinical malaria.

We recorded the following covariates across the seven trials: sex, age at the time of vaccination, country, bednet use, adjuvant used (ie, AS01 vs AS02), and clinical disease surveillance method at the site level (ie, ACDc vs PCD only). To ascertain transmission intensity, we used estimates from the Malaria Atlas Project (MAP) for prevalence of asymptomatic parasitaemia in children aged 2—10 years in 2007 (PrP2—10),<sup>20</sup> identified with the ge positioning coordinates of the trial sites. We refer to this measure here as the local parasite prevalence.

### Statistical analysis

We summarised unadjusted vaccine efficacy for the four endpoints of infection, clinical malaria, severe malaria, and death with Kaplan-Meier curves and efficacy estimates with unadjusted Cox proportional-hazard models for first or only event. To analyse ACDi and combined ACDc and PCD, we assessed the effect of covariates with adjusted Cox proportional-hazard models. We analysed multiple episodes of clinical malaria with Poisson regression, adjusting for the time of follow-up as an offset variable, implemented as one observation per participant.

Rather than present subgroup analyses according to strata (which would be necessarily narrow and be typically confounded by other important covariates), we pooled individual participant data and estimated the linear and non-linear effect of covariates in the data and the interactions of these covariates with vaccine efficacy. We used these empirically observed functions to estimate efficacy in subgroups by multiplying the fixed effect of vaccination (ie, the estimate of the effect of vaccination among those with the baseline value of the covariate) by the interaction term (ie, the estimate of how vaccine efficacy varies for each different level of the covariate). We added variances and the covariance matrix to calculate SEs. All covariates were included in an initial model, and we excluded covariates or interaction terms with  $p$  greater than 0.05 to produce a final model. To examine the possibility that analyses of clinical malaria risk were biased by unequal durations of follow-up in some subgroups, we did an additional analysis restricted to 1 year of follow-up.

We calculated vaccine efficacy as either 1 minus the hazard ratio or 1 minus the incidence rate ratio. We modelled the non-linear effects of age at vaccination and local parasite prevalence as multiple fractional polynomials, according to the method of Royston and colleagues. We fitted changes in vaccine efficacy over time as an interaction between time and vaccination status in Cox regression models, using the Anderson Gill modification, with clustering by individual to include multiple episodes.

We examined parametric survival models to fit a  $\gamma$  distribution to the unmeasured heterogeneity in exposure. We used a Gompertz survival distribution for parametric models, since this method fitted the data better than the alternatives (exponential, log normal, or Weibull) and gave hazard ratios for vaccination that were nearly identical to those estimated using Cox proportional-hazards.

### Role of the funding source

We did this pooled analysis after a call for proposals initiated and facilitated by GlaxoSmithKline Biologicals. Employees of GSK Biologicals were investigators on the original phase 2 studies and were authors on the primary reports. Employees of GSK Biologicals reviewed the analysis plan

and commented on early drafts of the pooled analysis, but were not required to give final approval of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

We analysed pooled data for 4453 participants in seven trials (table 1). 1376 participants received all three vaccinations, were given curative antimalarial treatment, and underwent ACDi. 3184 participants received all three vaccinations and were monitored for episodes of clinical malaria, either by ACDc or PCD. 465 adults received one or more vaccination; these data were excluded from the analysis for severe malaria or death. 3988 children (ie, younger than 6 years at vaccination) received one or more vaccination and were included in intention-to-treat analyses for severe malaria or death.

The survival functions for the four endpoints are shown in figure 1. Unadjusted efficacy by ACDi was 33% (95% CI 23—42;  $p < 0.0001$ ). Vaccine efficacy by ACDi did not vary significantly with respect to the covariates tested (table 2). Unadjusted efficacy against clinical malaria by ACDc and PCD was 25% (95% CI 16—33;  $p < 0.0001$ ) for first episodes and 19% (12—25;  $p < 0.0001$ ) for all episodes. However, significant interactions were noted between vaccine efficacy and other covariates (table 2).

On Cox regression, vaccine efficacy against first episodes of clinical malaria was 37% (95% CI 23 to 48) with a local parasite prevalence of 20% (moderate transmission; table 2). However, estimated efficacies were 48% (41 to 50) at a local parasite prevalence of 10% (low transmission) and 7% (-55 to 44) at a local parasite prevalence of 70% (high transmission; figure 2). Vaccine efficacy against all episodes of clinical malaria on Poisson regression, allowing for the non-linear effects shown in figure 3, was 41% (95% CI 21 to 57) at a local parasite prevalence of 20% (table 2). Estimated vaccine efficacies were 60% (54 to 67) at a local parasite prevalence of 10% and 4% (-10 to 22) at a local parasite prevalence of 70% (figure 2). Vaccine efficacy also varied by adjuvant choice—eg, at low transmission (PrP2—10 10%) efficacy varied from 60% (95% CI 54 to 67) for AS01 versus 47% (14 to 75) for AS02; however, efficacy did not differ by bednet use or by gender. Vaccine efficacy varied significantly by age for all episodes of clinical malaria ( $p = 0.038$ ), but not for first episodes of clinical malaria ( $p = 0.62$ ; table 2).

Repeating the analysis but restricting follow-up to the first year after vaccination resulted in a similar pattern of results to those reported in table 2, albeit with wider CIs and more marginal significance. For the interaction with adjuvant, the hazard ratio was 1.46 (95% CI 1.00—2.12,  $p = 0.049$ ) and the incidence rate ratio was 2.22 (1.35—3.64). For the interaction with local parasite prevalence, the hazard ratio was 1.51 (0.61—3.72,  $p = 0.38$ ) and the incidence rate ratio was 1.89 (0.93—3.8,  $p = 0.078$ ).

Unadjusted efficacy against severe malaria was 37% (95% CI 6 to 58,  $p = 0.023$ ); data were from 39 children with severe malaria from a total of 2080 RTS,S vaccinated people, versus 58 children with severe malaria from a total of 1908 controls. Efficacy against death was 48% (-8 to 75,  $p = 0.081$ ); 11 deaths occurred in the 2080 people receiving vaccine and 19 deaths happened among the 1908 controls. We judged the frequency of severe malaria and death to be too low to justify further multivariable analysis.

The survival plot of time to infection during ACDi by vaccination status shows convergence after the initial divergence (figure 1A), and the plot of time to clinical malaria by ACDc and PCD shows a gradual slowing in the rate of divergence (figure 1B). An interaction between efficacy and time gave similar goodness of fit (judged by Akaike's information criterion) for various powers of time (2, -1, -2, 0.5, 0.25) and linear and log functions. We therefore selected a linear fit for simplicity and to make interpretation of the interaction terms more intuitive (figure 4).

In unadjusted analysis of ACDi, efficacy seems to wane rapidly (figure 4A), but after adjustment for local parasite prevalence and for a  $\gamma$ -distributed shared frailty ( $\theta=0.96$ ,  $p<0.0001$ , indicating that significant evidence exists for pronounced heterogeneity of risk), the effect of vaccination did not vary by much over time (figure 4B, table 3). In unadjusted and adjusted analyses of ACDc and PCD, including single and multiple clinical episodes, the estimated vaccine efficacy fell over time, from 36% efficacy (95% CI 24 to 45) at time of vaccination to 0% (95% CI -38 to 38) at 3 years (figures 4C—E).

We tested for heterogeneity in the rate of declining vaccine efficacy against clinical malaria by estimating the three-way interactions between time (in years), vaccination, and every covariate in turn. None of these three-way interaction terms were significant at the 5% level (AS02 vs AS01, hazard ratio 0.94, 95% CI 0.82—1.09,  $p=0.46$ ; local parasite prevalence hazard ratio 1.35, 0.74—2.46,  $p=0.33$ ; age in years hazard ratio 0.97, 0.93—1.01,  $p=0.15$ ).

## Discussion

The findings of our pooled analysis show that the RTS,S malaria vaccine is protective against infection and disease. However, unadjusted efficacy against clinical malaria was lower than previous estimates in children age 5—17 months and substantial heterogeneity was noted in efficacy between population subgroups and over time. Vaccine efficacy against clinical malaria was lowest at high (70%) transmission intensity, and it was reduced for the AS02 adjuvant compared with AS01. Weak variation in efficacy was noted according to age on Poisson regression, which was not significant on Cox regression. Vaccine efficacy did not vary by gender or bednet use. Results for efficacy from Cox regression for first episodes and Poisson regression for all episodes were similar, although CIs suggested greater precision when all episodes were included.

A higher vaccine efficacy with PCD versus ACDc might indicate bias resulting from a prophylactic effect of antimalarial drugs administered for episodes of malaria that do not meet the case definition. These malaria episodes are likely to be more common in unvaccinated children and hence could result in an underestimate of vaccine efficacy on ACDc. However, no sites used PCD and ACDc alongside each other, hence there is confounding by site and the difference might reflect other variations between sites that were not measured by the available covariates. To examine whether additional unmeasured factors that segregate by site might lead to varying efficacy, we fitted a post-hoc interaction term between vaccination and stratification by site, in addition to the previous model (table 2). These additional interactions significantly improved model fit ( $p<0.0001$ , by likelihood-ratio test), indicating that other unmeasured factors cause vaccine efficacy to vary between sites.

Transmission intensity (as measured by local parasite prevalence in children age 2—10 years) had a non-linear effect on clinical malaria incidence. The incidence of clinical malaria reached a peak in areas with a local parasite prevalence of 40%. This finding could be accounted for

by children who acquire greater immunity with increasing exposure, which offsets the rises in incidence of clinical malaria that otherwise might be seen at a higher local parasite prevalence.

RTS,S can be regarded as a leaky barrier to infection, because it protects against some infectious bites but not against others. The probability of protecting a participant exposed to two infective bites during the course of a night against a subsequent episode of clinical malaria is half the probability of protecting a participant exposed to one bite. This statistic suggests that vaccine efficacy will be lower at high transmission intensity, which accords with our observations.

We used MAP estimates of age-adjusted prevalence of asymptomatic malaria (PrP2—10) to gauge transmission intensity. These approximations were based on several thousand surveys in the countries where trial sites were located. We chose these standardised independent measures rather than within-trial factors, such as incidence of malaria among controls, because monitoring was not the same between trials. MAP estimates do not account for changes over time, but transmission intensity at our sites is likely to be stable enough over a few years for these data to be a reasonable approximation. Variations in seasonal transmission have a modest effect on the relation between entomological inoculation rate and asymptomatic parasitaemia, but in view of the limitations of using data from 11 sites, we did not feel that more complex characterisations of transmission intensity were warranted.

Our finding that vaccine efficacy is not affected by use of insecticide-treated bednets but is diminished at higher levels of transmission intensity might seem contradictory, since bednet use might be expected to reduce exposure and, hence, enhance vaccine efficacy. However, individual use of insecticide-treated bednets might be only modestly protective (compared with greater mass effects at reducing transmission when whole communities use bednets). Furthermore use of insecticide-treated bednets was not distributed evenly by site, varying from 4•5% to 100% of children. Tests for variation in vaccine efficacy by bednet use are, therefore, vulnerable to ecological confounding by site.

We identified significant interactions between time and vaccine efficacy. We can confidently reject the null hypothesis that vaccine efficacy is constant over time ( $p < 0\cdot0001$ ), but we cannot be confident about the shape of the plotted decline, which is reflected in the wide CIs surrounding estimates of efficacy at later timepoints (figure 4). We chose a linear interaction for simplicity of presentation, although power functions of time fit the data slightly better. Therefore, we cannot extrapolate beyond the data to longer durations of follow-up, since the shape of the line is determined by statistical convenience rather than biological understanding.

A fall in vaccine efficacy over time might be attributable to systematic bias in estimates obtained using survival analysis because of heterogeneous exposure from a partly effective vaccine, as previously described. Comparison of figure 4A with figure 4B suggests that systematic bias resulting from heterogeneous exposure can account for the apparent waning of efficacy in the ACDi dataset, rather than a genuine biological waning of efficacy taking place. However, similarity between figures 4C—E suggests that no clear systematic bias exists in estimates of efficacy over time when using data from ACDc or PCD for clinical malaria. The difference could be because ACDi was monitored during one transmission season, with only 60% of participants having an episode during this period. A few unexposed individuals can lead to a biased estimate of rapidly declining efficacy. However, data for clinical malaria included 4 years of monitoring during many transmission seasons. Furthermore, individual exposure could vary from year to year. Hence, a discrete unexposed population is less likely to exist with ACDc or PCD compared with ACDi.

Heterogeneous exposure, therefore, seems to be a sufficient explanation for the observation that efficacy wanes more rapidly in the ACDi dataset than it does in the ACDc and PCD dataset.

We report here all phase 2 data for RTS,S malaria vaccines (panel), including efficacy outcomes for clinical malaria (ACDc and PCD) and for malaria infection (ACDi). Some phase 2 trials also included cross-sectional surveys for asymptomatic parasitaemia. In the Mozambique trial, substantial protection against asymptomatic parasitaemia was noted 45 months after vaccination in cohort 1, which is longer than would have been predicted by our analysis. On the other hand, protection against asymptomatic parasitaemia was not noted in Mozambique cohort 2 at 21 months after vaccination. This finding could be explained by differential acquisition of blood-stage immunity between these two cohorts. Our data do not allow us to distinguish waning vaccine-induced immunity from delayed acquisition of blood-stage immunity, but analysis of the effect of the booster vaccination—planned as part of the phase 3 trial—is likely to be highly informative. A booster dose can restore vaccine-induced immunity but will not have an immediate effect on immunity to blood-stage parasites. Furthermore, the larger sample size in the phase 3 trial will provide more accurate point estimates for efficacy in the age-groups assessed (ie, 6—12 weeks and 5—17 months) than is possible in a meta-analysis of phase 2b data.

#### Systematic review

We searched PubMed with the MeSH terms “RTS,S-AS02D vaccine [Substance Name]” OR “RTS,S-AS01E vaccine [Substance Name]” OR “RTS,S-AS01B vaccine [Substance Name]” OR “RTS,S-AS02A vaccine [Substance Name]” OR “PfCSP DNA vaccine [Substance Name]” AND “Malaria, falciparum/prevention and control”. All phase 2 trials identified are included in our analysis and no previous meta-analyses have been done. Two publications describe preliminary data from phase 3 trials, for which follow-up is ongoing. These preliminary reports have not reported subgroup analyses, and data were not available for inclusion in our analysis.

#### Interpretation

Vaccine efficacy varied by transmission intensity, adjuvant, and time since vaccination. Age at first vaccination was of borderline significance, but bednet use or sex had no effect on efficacy. Vaccine efficacy against clinical disease was of limited duration and fell with increasing transmission intensity. Outcomes after vaccination cannot be predicted accurately on the basis of one pooled efficacy figure. When predicting public health outcomes of vaccination, variations in efficacy—by transmission intensity and by time since vaccination—will need to be accounted for.

In summary, we noted significant variation in estimated vaccine efficacy by population subgroups and a significant decline in protection against clinical malaria over time. One might argue that the unadjusted pooled estimates of efficacy nevertheless reflect what was actually seen in the population tested. However, the unadjusted pooled efficacy is merely a weighted mean of efficacies seen in the component subgroups of the population and, therefore, cannot be generalised to other populations. For instance, if the vaccine is more effective at lower transmission intensity, the pooled vaccine efficacy will depend on the proportion of children recruited in sites at low transmission intensity. Predictions of public health outcomes of vaccination will need to take account of these variations in efficacy by transmission intensity and by time since vaccination.

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## ACT II: treatment of anal cancer comes full circle

The Lancet

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In 1974, Nigro and colleagues<sup>1</sup> reported the results of treatment of three patients with anal cancer with preoperative pelvic radiation therapy (30 Gy in 15 fractions) with one cycle of fluorouracil (25 mg/kg per 24 h) infused continuously over 5 days and bolus mitomycin (0.5 mg/kg) infused on day 1, then abdominoperineal resection roughly 6 weeks later. Two patients had no residual cancer in the resection specimen and the third patient had a complete clinical response, declined surgery, and was doing well without recurrence 13 months later. For a cancer that had been historically managed by extirpative surgery often with unsatisfactory outcomes and devastating sequelae, these findings pointed to a potential breakthrough in treatment, aiming for cure, sphincter preservation, and enhanced quality of life.

Since Nigro's report, clinical trials<sup>2</sup> have established radiation therapy with concurrent fluorouracil and mitomycin as the definitive treatment of anal cancer, with surgery reserved for salvage. These studies have also reported poor results for patients with locally advanced tumours and significant rates of acute and late treatment-related toxic effects. Many advances have also been made in our understanding of the biology of this disease and the crucial role of human papillomavirus in its development. These findings have led to innovative screening and prevention strategies for patients at high risk of developing anal cancer.<sup>3</sup>

Randomised trials from Europe<sup>4, 5</sup> and the USA<sup>6—9</sup> have explored changes to the standard template of radiation treatment with concurrent fluorouracil and mitomycin to improve outcomes in patients with locally advanced anal cancer and reduce treatment-related toxic effects. Modifications have included induction or maintenance chemotherapy, radiation dose escalation, and planned treatment interruptions or substitution of mitomycin with cisplatin.

In the Lancet Oncology, Roger James and colleagues<sup>4</sup> report the results of a randomised 2x2 factorial trial of radiation therapy and chemotherapy with or without maintenance chemotherapy for squamous-cell carcinoma of the anus. The trial is the largest phase 3 trial for anal cancer. 940 patients with T1—T4 squamous-cell carcinoma of the anal canal and anal verge were randomly assigned to receive mitomycin (12 mg/m<sup>2</sup> on day 1; n=472) or cisplatin (60 mg/m<sup>2</sup> on days 1 and 29; n=468) with fluorouracil (1000 mg/m<sup>2</sup> on days 1—4 and 29—32) and radiation therapy (50.4 Gy in 28 daily fractions). They were also randomly assigned to either two courses of maintenance chemotherapy (fluorouracil and cisplatin 5 and 8 weeks after chemoradiation; n=448) or no maintenance (n=446). This trial design provided sufficient statistical power to address two comparisons: a direct comparison of mitomycin versus cisplatin in patients receiving chemoradiation, with the endpoints of complete response at 26 weeks and acute toxic effects; and the value of maintenance chemotherapy versus no maintenance as assessed by 3-year progression-free survival. Median follow-up was 5.1 years.

Complete response at 26 weeks after chemoradiation was 90•5% (391 of 432 patients) in the mitomycin group versus 89•6% (386 of 431 patients) in the cisplatin group (difference -0•9%, 95% CI -4•9 to 3•1; p=0•64). The proportion of patients who had acute toxic effects (grade 3 or 4) was similar in each group: 71% (334/472) versus 72% (337/468). Non-haematological grade 3 or 4 toxic effects occurred in 294 of 472 (62%) patients versus 316 of 468 (68%) patients and any haematological grade 3 or 4 toxic effects occurred in 124 of 472 (26%) patients versus 73 of 468 (16%). 3-year progression-free survival was 74% in the maintenance group and 73% in the no maintenance group (hazard ratio 0•95, 95% CI 0•75—1•21; p=0•70). The investigators concluded that chemoradiation with fluorouracil and cisplatin had similar complete response and overall toxic effects as fluorouracil and mitomycin, but less haematological toxic effects. Maintenance chemotherapy did not improve progression-free survival. Thus, they advocate fluorouracil plus mitomycin and 50•4 Gy in 28 fractions as standard practice and ascribe their outcomes to an efficient radiobiological schedule.

Two other contemporary trials have investigated treatment of anal cancer—RTOG 98-11 and the ACCORD 3 trial (table).<sup>5—9</sup> In RTOG 98-11, 682 patients were randomly assigned to receive treatment with induction fluorouracil and cisplatin, followed by concurrent fluorouracil and cisplatin with radiation therapy versus concurrent fluorouracil and mitomycin and radiation therapy without induction.<sup>6—9</sup> In the ACCORD 3 trial,<sup>5</sup> all treatment groups (induction and initial combined modality treatment) received cisplatin, not mitomycin chemotherapy. Patients were assigned to receive a total radiation dose of either 60 Gy or 65—70 Gy after a 3 week rest period following combined modality treatment. A 2x2 factorial design provided sufficient statistical power to address two questions (the role of induction cisplatin and fluorouracil, and total radiation dose) but not the individual results of the four treatment groups.

The data in these three trials can be summarised by the endpoints of colostomy-free survival, overall survival, and grade 3 or 4 acute and late toxic effects.<sup>4—9</sup> First, the results of these three studies show that additional chemotherapy provides no benefit to colostomy-free survival or overall survival (as induction or maintenance).

Second, the results of ACT II show that cisplatin compared with mitomycin does not improve of complete response rates or overall toxic effects with radiation therapy and fluorouracil. Likewise, 3-year colostomy-free survival and overall survival did not differ significantly between cisplatin and mitomycin groups. The long-term results<sup>9</sup> of RTOG 98-11 show that disease-free and overall survival was significantly lower for patients receiving induction and concurrent cisplatin compared with concurrent mitomycin.

Third, acute toxic effects are common in treatment of anal cancer, with haematological grade 3 or 4 toxic effects in up to 61% of patients and non-haematological grade 3 or 4 toxic effects in up to 74% of patients, irrespective of treatment approach. Finally, little progress has been made in improving the outcomes of patients with advanced primary tumours.<sup>4, 5, 7</sup> In the ACT II trial,<sup>4</sup> patients with tumours larger than 5 cm had unacceptably high failure rates, with 3 year progression-free survival of 62—67% versus 80—84% for patients with tumours 5 cm or smaller.

Ultimately, the results of these trials do not suggest a groundbreaking improvement in outcome for these patients, especially those with very advanced local disease. At present, radiation therapy with fluorouracil and mitomycin remains the standard of care. Acute toxic effects can be mitigated by innovations in radiation delivery—eg, intensity-modulated radiation therapy techniques—which are being rapidly adopted into clinical

practice.<sup>10</sup> Clinical trials are underway to assess EGFR inhibitors with radiation therapy and chemotherapy. Further understanding of the biology of human papillomavirus in anal cancer and translation of this knowledge to screening, prevention, and treatment resistance are also needed to advance the care of these patients.

We declare that we have no conflicts of interest.

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### ***Medical Protocol and Training***

## **Usability Study of a Novel, Self-Lighted, Disposable Speculum: Military Applications**

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### **ABSTRACT**

Study design: Data collected from a postutilization questionnaire were used to evaluate the usability of the OfficeSPEC disposable vaginal speculum, specifically the effectiveness, efficiency, and acceptability, in clinical, hospital, and austere environments. Results: Usability data analysis showed the OfficeSPEC speculum had an effectiveness rating of 4.6/5, efficiency rating of 4.5/5, and acceptability rating of 4.6/5; overall usability in deployed environments was favorable. The overall rankings were 3.4 for plastic, 4.2 for metal ( $p < 0.001$ ), and 4.5 for OfficeSPEC ( $p < 0.001$ ). Cost analysis of the OfficeSPEC placed the disposable speculum as a reasonable alternative with yearly cost of \$129,200, compared to traditional metal (\$209,100) and plastic (\$319,175). Conclusion: By evaluating the OfficeSPEC speculum within a usability framework, it proved to be practical, viable alternative in all environments, particularly in the forward deployed environment.

### **INTRODUCTION**

The vaginal speculum is the basic tool of any health care provider who performs gynecological examinations. Speculums come in many sizes, are made with a variety of materials, and can have optional features such as light attachments and suction ports. Selection of a specific speculum is largely based on provider preference, but this decision may also be dictated by availability or institutional policy.

Although military physicians perform gynecological examinations no differently than their civilian counterparts, the environment in which these examinations take place can vary and present frequent challenges. Gynecological examinations may take place in a makeshift clinic or room, and electricity for lightning sources was often generator dependent. Thus, in an austere environment, such as a military deployment or humanitarian mission, equipment is often dictated by availability.

The objective of this study was to assess the OfficeSPEC speculum's (OBP Medical, Lawrence, Massachusetts) potential for military applications (Fig. 1).

Specifically, we aim to determine the usability of the OfficeSPEC vaginal speculum using 3 parameters—effectiveness, efficiency, and acceptability—in military treatment facilities and forward deployed locations. The Walter Reed Army Medical Center (WRAMC) Institutional Review Board approved the study.

## METHODS AND MATERIALS

We developed a prospective observational pilot study to assess the usability and military application of the OfficeSPEC disposable, self-lighted speculum. The OfficeSPEC is a Food and Drug Administration-approved, commercially available, single-use, disposable vaginal speculum (<http://www.obpmedical.com/>). Approximately, 150 speculums were donated to WRAMC Department of OB/GYN by OBP Medical for the purpose of this study. The speculums were distributed between providers (OB/GYN nurse practitioners, residents, and staff) at WRAMC and deployed WRAMC staff physicians. Deployed physicians received two boxes of speculums; postage was paid in full by OBP Medical, and the speculums were used at the discretion of the provider. Deployed physicians performed gynecological examinations in combat theaters. Patient encounters were completed within battalion aid stations and Level 2 and 3 echelon medical care facilities.

Providers at WRAMC had speculums available for use in the clinic, inpatient floor consults, or emergency room. Providers who performed routine vaginal examination had the choice of traditional metal speculums, traditional plastic speculums, or the OfficeSPEC speculum. The choice of speculum was left up to each provider. The standard of care for gynecological pelvic examinations was not affected.

Providers completed an anonymous postutilization questionnaire with 12 questions (Table I). Participants were asked to mark their responses from 0 to 5, along a continuous scale, from Strongly Agree to Strongly Disagree. Providers also indicated the environment in which the examination took place: the clinic, hospital ward, emergency room, a simulated pelvic model, or in a deployed setting. Deployed providers completed the same questionnaire. The data collected were divided into the three categories (as seen in Table I): Effectiveness, Efficiency, and Acceptability.

Additional information was gathered regarding the average number of speculums conducted a day at WRAMC Gynecology department and the cost of equipment and supplies. A cost analysis was performed using the adjusted unit cost, represented by the cost of a speculum per use, and expenses incurred with the operation of the device, specifically lights, cables, and sterilizations supplies. Data collected for cost analysis were obtained using clinic invoices.

A sample size calculation was done and was based on a continuous response variable from matched pairs of study subjects. If the true difference in the mean response of matched pairs is 0.4, we would need to study 51 pairs of subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The type I error probability associated with this test of this null hypothesis is 0.05.

Metal speculums analyzed using an amortization over the life of the metal speculum projected to be 5 years (and 2.5 years for the light cable used with the plastic speculums). Statistical analysis was performed using SPSS for Windows, Version 16.0 (SPSS, Chicago, Illinois; 2007).

## RESULTS

A total of 78 questionnaires were returned. Surveyed providers included staff physicians, residents, and nurse practitioners. The authors did not participate in this study. The OfficeSPEC speculum was made available to providers at WRAMC, and 31 encounters were evaluated in an austere deployed environment.

Table II shows the demographic breakdown of all 78 surveys; 40% were in a deployed environment and 60% in the hospital/clinic. 62% were staff level and 38% were residents. 45% had prior experience working in austere (deployed) environments, whereas 55% did not.

Figure 2 represents the Effectiveness data. Responses were scored from 0 to 5 on a continuous scale; 5 indicating a response of Strongly Agree and 0 Strongly Disagree. The red line indicated a favorable response and was arbitrarily set at 4 (80%). The respective mean scores from each question were Q2 = 4.5 ( $\pm 0.7$ ), Q3 = 4.3 ( $\pm 1.1$ ), Q5 = 5.0 ( $\pm 1.5$ ), and Q7 = 4.7 ( $\pm 0.8$ ).

Figure 3 reflects the average Efficiency rating of the OfficeSPEC speculum. Overall, the OfficeSPEC speculum has a favorable efficiency rating. The respective mean scores from each question were Q1 = 4.6 ( $\pm 0.5$ ), Q4 = 4.6 ( $\pm 0.6$ ), and Q6 = 4.2 ( $\pm 1.0$ ).

The final aspect of usability, the Acceptability of the OfficeSPEC speculum, is depicted in Figure 4. Once again, the rating is favorable. The respective mean scores from each question were Q8 = 4.8 ( $\pm 0.8$ ), Q9 = 4.6 ( $\pm 1.3$ ), Q10 = 4.6 ( $\pm 1.3$ ), Q11 = 4.5 ( $\pm 0.6$ ), and Q12 = 4.6 ( $\pm 0.7$ ).

The participant's preferential ranking of the plastic, metal, and OfficeSPEC speculums, results of which are found in Figure 5, assessed overall product satisfaction. The respective mean scores from each question were plastic = 3.4 ( $\pm 1.4$ ), metal = 4.2 ( $\pm 0.9$ ), and OfficeSPEC = 4.5 ( $\pm 0.7$ ). The comparison identified a statistically significant difference using plastic as the reference, comparing metal ( $p < 0.001$ ) and OfficeSPEC ( $p < 0.001$ ).

## Cost Analysis

The military health care program does not operate on a revenue-generating model like the civilian sector; however, costs are still incurred and must be constantly scrutinized. A cost analysis was performed within the confines of the military health care system (Table III). The unit cost of

each speculum, the average number of metal speculums used per day at Walter Reed GYN clinic and the required supplies such as light sources, disposable plastic sleeves, and light bulbs were amortized across a presumed life span of 5 years for a metal speculum. In large tertiary hospitals such as Walter Reed, it is difficult to assess the cost of sterilization of just speculums; therefore, we used published data from the United Kingdom for sterilization costs. Once again, the cost of equipment is amortized over 5 years.

The adjusted unit cost represents the cost of the speculum per use plus expenses incurred with the operation of the device, amortization over the life of the metal speculum, projected to be 5 years (and 2.5 years for the light cable used with the plastic speculums). The adjusted cost of the metal speculum is \$4.92, the plastic speculum is \$7.51, and the OfficeSPEC is \$3.04. The daily sterilization cost of metal speculums is \$27.20, a cost not incurred with plastic or OfficeSPEC. Overall, the cost analysis is favorable for the OfficeSPEC.

## DISCUSSION

Performing gynecological examinations in an austere environment, such as a military deployment or humanitarian medical mission, or even a natural disaster, can present unique challenges. Obstacles to overcome as cited by providers can include lack of adequate lighting, lack of sterilization equipment or supplies, or even basic requirements such as reliable electricity. Deployed physicians cite cramped examination rooms and lack of proper lighting as factors most often contributing to inadequate gynecological examinations.

When utilizing the OfficeSPEC speculum in an austere environment, many of the limiting factors confounding adequate gynecological examinations were eliminated. The light source is self-contained in the handle of the light, therefore eliminating the need for external lighting. Sterilization equipment and supplies are not needed, as the speculum is single use and can be disposed with other medical waste. Faulty generators or unreliable electricity sources do not affect or limit the quality of lighting.

By evaluating the OfficeSPEC within a usability framework, we were able to determine the single-use, disposable speculum that met all criteria (effectiveness, efficiency, and acceptability) for being a valid alternative to the traditional metal and plastic speculums. Analysis of staff versus resident responses was not significant, and neither was comparing responses from providers who have experience in an austere environment from those who do not.

The cost analysis revealed the single-use disposable nature of the OfficeSPEC speculum provides a reasonable replacement for the traditional metal speculum and plastic counterpart when taking into consideration the cost of lighting, sterilization, supplies, and cost of replacing metal speculums.

Disposal costs and environmental concerns arise whenever medical waste is created. Regardless of the type of speculum selected by providers, medical waste can be expected. Whether it is in the form of chemicals for disinfection and excess secondary packaging for the metal speculum or single-use plastic disposal, all speculums must be properly disposed of. None of the speculums studied are without associated disposal costs and environmental concerns.

The OfficeSPEC speculum appears to be a practical, viable alternative in all environments. Providers performing gynecological examinations in austere environments may benefit by opting for the OfficeSPEC speculum versus the traditional metal or plastic speculums. Also, when considering the cost of this system versus the entire cost of traditional speculums, the OfficeSPEC is competitive. The OfficeSPEC speculum is shown to be effective, efficient, and acceptable.

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## Relationship Between Occurrence of Surgical Complications and Hospital Finances

The Journal of the American Medical Association

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### ABSTRACT

**Importance** The effect of surgical complications on hospital finances is unclear.

**Objective** To determine the relationship between major surgical complications and per-encounter hospital costs and revenues by payer type.

**Design, Setting, and Participants** Retrospective analysis of administrative data for all inpatient surgical discharges during 2010 from a nonprofit 12-hospital system in the southern United States. Discharges were categorized by principal procedure and occurrence of 1 or more postsurgical complications, using International Classification of Diseases, Ninth Revision, diagnosis and procedure codes. Nine common surgical procedures and 10 major complications across 4 payer types were analyzed. Hospital costs and revenue at discharge were obtained from hospital accounting systems and classified by payer type.

**Main Outcomes and Measures** Hospital costs, revenues, and contribution margin (defined as revenue minus variable expenses) were compared for patients with and without surgical complications according to payer type.

**Results** Of 34 256 surgical discharges, 1820 patients (5.3%; 95% CI, 4.4%-6.4%) experienced 1 or more postsurgical complications. Compared with absence of complications, complications were associated with a \$39 017 (95% CI, \$20 069-\$50 394;  $P < .001$ ) higher contribution margin per patient with private insurance (\$55 953 vs \$16 936) and a \$1749 (95% CI, \$976-\$3287;  $P < .001$ ) higher contribution margin per patient with Medicare (\$3629 vs \$1880). For this hospital system in which private insurers covered 40% of patients (13 544), Medicare covered 45% (15 406), Medicaid covered 4% (1336), and self-payment covered 6% (2202), occurrence of complications was associated with an \$8084 (95% CI, \$4903-

\$9740;  $P < .001$ ) higher contribution margin per patient (\$15 726 vs \$7642) and with a \$7435 lower per-patient total margin (95% CI, \$5103-\$10 507;  $P < .001$ ) (\$1013 vs -\$6422).

**Conclusions and Relevance** In this hospital system, the occurrence of postsurgical complications was associated with a higher per-encounter hospital contribution margin for patients covered by Medicare and private insurance but a lower one for patients covered by Medicaid and who self-paid. Depending on payer mix, many hospitals have the potential for adverse near-term financial consequences for decreasing postsurgical complications.

National health expenditures for surgical procedures are estimated to cost \$400 billion annually and are expected to outpace economic growth during the next 10 years. The rate of inpatient surgical complications is significant, with estimates ranging from 3% to 17.4%, depending on type of procedure, type of complications, length of follow-up, and data analyzed. In addition to patient harm, major complications add substantial costs, previously estimated at \$11 500 per patient.

Effective methods for reducing surgical complications have been identified. However, hospitals have been slow to implement them. Resource constraints may be a factor. Quality improvement efforts often require expenditures for staff time and technologies, and financial benefits are uncertain. Improvements can reduce revenues under per diem reimbursement schemes and even diagnosis related group–based reimbursement because complications can result in severity adjustments or diagnosis related group changes that increase revenues. For example, a colectomy patient's diagnosis could change from code 148 (major bowel procedure with complications) to 483 (tracheostomy with mechanical ventilation >96 hours), triggering a 5-fold increase in Medicare reimbursement. On the other hand, some complications—such as certain “never event” complications—are no longer reimbursed by many payers. Previous estimates suggest that reducing surgical complications could harm hospital financial results but have been limited by use of small data sets or simplified surrogates such as patient length of stay.

We therefore conducted a study to measure the financial implications associated with postsurgical complications, using internal claims-administration and cost-accounting data of a nonprofit southern US hospital system with both higher- and lower-volume facilities located in urban and suburban/rural areas that included academic and nonacademic surgical departments. The goal was to evaluate the fixed and variable hospital costs and revenues associated with the occurrence of 1 or more major postsurgical complications for 4 primary payer types—private insurance, Medicare, Medicaid, and self-payment.

## METHODS

### Study Population and Procedures

Harvard School of Public Health and the nonprofit hospital system provided institutional research approval. The study population was generated from the administrative data of 12 hospitals in 1 southern hospital system for inpatient surgical patients who were discharged during the 2010

calendar year. Both elective and emergency procedures were included. Certified professional coders coded all data, following the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

For each patient encounter, age, sex, admission status (emergency or elective/scheduled), length of stay, discharge status, insurance payer, and all ICD-9 procedure, diagnosis, and present-on-admission codes were collected. The first listed diagnosis and procedure code were identified as the principal diagnosis and principal procedure, respectively.

Patients were entered into the study if they had inpatient status, a charge for the minimum unit of 60 minutes of operating room time, validated charges of more than \$0.10, at least 1 coded diagnosis and 1 coded procedure, a date of discharge in calendar year 2010, and no principal procedure code for cesarean delivery (ICD-9-CM procedure codes 74.00, 74.10, 74.40, and 74.99).

Nine common procedure groups were identified with Clinical Classifications Software—defined grouping of procedure codes craniotomy, colorectal resection, total or partial hip replacement, knee arthroplasty, coronary artery bypass graft, spinal surgery (laminectomy, excision of intervertebral disk, or spinal fusion), hysterectomy (abdominal or vaginal), appendectomy, and cholecystectomy and common bile duct exploration. The specific clinical classification software—defined groups are listed in eTable 1. Patient encounters were included in a procedure group according to their principal procedure code.

#### Complications and Comorbidities

A subset of 10 potentially preventable, severe surgical complications was identified in our data set. This subset is referred to as “complications” in this article, does not capture all possible complications, and includes surgical site infection, wound disruption, sepsis/severe inflammatory response syndrome/septic shock, pulmonary embolism or deep vein thrombosis, stroke, myocardial infarction, cardiac arrest, pneumonia, ventilator use of 96 hours or longer, and infections (other than surgical site). Each complication was identified by a predefined set of ICD-9-CM codes and confirmed to be absent on admission according to ICD-9 codes for present on admission. In addition, for the postsurgical complication of mechanical ventilation for 96 hours or longer, additional exclusion ICD-9 diagnosis codes were also applied. In-hospital mortality for patients who had inpatient surgery was captured separately from postsurgical complications, using discharge status.

Patient comorbidities were assessed with modified Charlson comorbidity scores, which were incorporated into propensity score models.

#### Financial Information

For each inpatient surgical discharge, financial information (net revenue, total cost, fixed cost, and variable cost) was extracted from the hospital system's EPSI cost accounting system (Allscripts Inc). EPSI uses actual payroll and general ledger expenses and categorizes them as either fixed or variable costs. Fixed costs are defined as those that do not vary with patient volume, whereas variable costs are those that do. Examples of fixed costs include the cost of constructing parking or purchasing a computed tomography scanner. In this hospital system's implementation of

EPSI, fixed costs are allocated to each revenue department that treats patients. A patient discharge is allocated a portion of the fixed costs from revenue departments whose services were accessed by that patient, according to the specific charges incurred. Variable costs are those incurred during treatment of patients; examples include knee implant hardware and nursing labor. For each discharge, total hospital costs were calculated according to expenses accrued from both fixed and variable costs. Net revenue was based on actual reimbursement from the payer. (Gross revenue is sometimes defined as hospital charges; we do not use this terminology and revenue is always used to correspond to net revenue.) Physician professional fee or salary data were not collected.

We calculated and report both contribution margin and total margin but focus on the former. Hospital managers seeking to improve financial performance work to maximize contribution margin. As long as it is positive and hospital and operating room capacity exists, a hospital is financially motivated to provide care, even if total margin is negative.

#### Box. Definitions of Costs and Margins

Variable costs: Costs that vary with patient volume (ie, supplies and nurse staffing).

Fixed costs: Costs that do not vary with patient volume (ie, costs for the hospital building, utilities, and maintenance).

Total margin: Revenue minus variable costs and fixed costs.

Contribution margin: Revenue minus variable costs. These are revenues available to offset fixed costs.

However, hospitals with negative total margins will ultimately go bankrupt. To calculate total margin, hospital managers must allocate a portion of fixed costs to each patient. As activities in a hospital increase, the total fixed costs remain the same but the proportion of fixed costs attributed to each activity decreases. We report total margin because eventually it reflects the comprehensive financial outlook of a hospital. We focus on contribution margin analysis because it drives hospital decision making in the near term.

#### Statistical Analysis

We calculated results with means, totals, medians, and proportions, with 95% CIs for each. Because the continuous outcome variables (eg, revenue, costs, margin) were right skewed, 95% CIs for unadjusted and adjusted totals, means, medians, and differences were calculated with a nonparametric bootstrap percentile method, which does not assume normality, with resampling to account for clustering at the facility level. For testing whether a continuous outcome variable had the same underlying probability distribution for patients with and without complications, the nonparametric Wilcoxon rank sum test adjusting for clustering at the facility level was used. For dichotomous outcomes (eg, mortality, complications), 95% CIs were calculated with a modified Wilson CI for clustered binary data.

Our main analysis concerns differences in costs by complication occurrence and payer. Propensity-score weighting was used to adjust for case-mix differences between patients with and without complications within payer group. By estimating the propensity for being in the groups of interest, propensity score methods provide better control for observed confounding factors than regression models alone. Propensity methods improve the ability to compare groups in observational studies. The propensity for being in the 2 complication groups was calculated with logistic regression models, with all demographic covariates available as predictors: patient age (age and age squared), sex, Charlson score (0, 1-2,  $\geq 3$ ), and risk of death according to clinical classification software–defined procedure group (scored as low, medium, or high).<sup>35</sup> We ran logistic regression models for each of the 4 payers, with noncomplications as the reference group and main effects for the covariates. The clinical classification software–defined covariate was obtained with group-level mortality rate data from the Nationwide Inpatient Sample and divided into tertiles. In the propensity-weighted approach, each patient's information was weighted by the inverse propensity of being in the given payer/complication group, with the goal of balancing characteristics across the complication groups. The Hosmer-Lemeshow goodness-of-fit statistic was used to assess the fit of the logistic regression propensity score models.

To determine the sensitivity of the results, we performed sensitivity analyses, including linear mixed-model regression adjustment, as well as other propensity-score model adjustments.

All tests and 95% CIs were 2-sided.  $P < .05$  was considered statistically significant. All analysis was completed with SAS/STAT version 9.2.

## RESULTS

There were 35 394 unique surgical inpatients discharged during calendar year 2010. We analyzed the 34 256 surgical inpatients who did not have cesarean delivery (eFigure). A total of 1820 procedures (5.3%; 95% CI, 4.4%-6.4%) were identified as having at least 1 complication (Table 1). We identified 428 postsurgical inpatient deaths, for a 1.25% inpatient mortality rate (95% CI, 0.90%-1.75%). The inpatient mortality rate was 0.6% (95% CI, 0.49%-0.82%) for patients without an identified complication and 12.3% (95% CI, 9.31%-15.96%) for patients with a defined complication. The median length of stay (Table 2) was more than 4 times higher for surgical patients who developed 1 or more complications (3 vs 14 days; 95% CI for the difference, 8.5-12.0;  $P < .001$ ). Table 2 displays the total hospital revenue, variable costs, total costs, and resulting contribution margin and total margin for patients with and without 1 or more complications. The occurrence of 1 or more complications was associated with a \$22 398 higher per-patient variable cost (95% CI for the difference, \$18 097-\$25 682;  $P < .001$ ) and with a \$37 917 higher per-patient total cost (95% CI, \$31 017-\$43 801;  $P < .001$ ). The occurrence of 1 or more surgical complications was associated with an \$8084 higher per-patient contribution margin (95% CI, \$4903-\$9740;  $P < .001$ ) and with a \$7435 lower per-patient total margin (95% CI, \$5103-\$10 507;  $P < .001$ ).

For this particular hospital system, private insurers covered 40% of patients (13 544); Medicare, 45% (15 406); Medicaid, 4% (1336); and self-payment, 6% (2202). Other types of insurance (eg, worker's compensation) constituted 5% of coverage (1768).

The results in Table 4 are propensity adjusted; the Hosmer-Lemeshow goodness-of-fit statistic indicated that the logistic regression models for the propensity of being in the 2 complication groups were excellent fits to the data ( $P > .36$  for observed being different than expected for all of the 4 payers). Thus, the observed confounding factors are important to control for when comparing cost and revenue across patients with and without complications. Finally, the sensitivity analyses for Table 4 (regression adjustments and other propensity-score model adjustments) yielded similar results in terms of estimated revenue to contribution margin and total margin and their 95% CIs and thus affirm that the results presented in this article are robust and not sensitive to the approach that we used.

## COMMENT

We found that under private insurance and Medicare, which cover the majority of US patients, the occurrence of surgical complications was associated with higher hospital contribution margins. Depending on payer mix, efforts to reduce surgical complications may result in worsened near-term financial performance.

The financial effects of surgical complications varied considerably by payer type. Complications were associated with more than \$30 000 greater contribution margin per privately insured patient (\$16 936 vs \$55 953) compared with less than \$2000 per Medicare patient (\$1880 vs \$3629). In contrast, for Medicaid and self-pay procedures, those with complications were associated with significantly lower contribution margins than those without complications. As a result, the payer mix will determine the overall economics of surgical complications for a given hospital. The studied hospital system's inpatient surgical payer mix (Medicare, 45%; private, 40%; Medicaid, 4%; and self-pay, 6%) was comparable to that of an average US hospital in 2010 (Medicare, 40%; private, 41%; Medicaid, 9%; and self-pay, 5%) (Marc Capuano, BS/BA, The Advisory Board Company, Washington, DC, October 2012).

Most US hospitals treat patient populations primarily covered by Medicare or private payers, and programs to reduce complications may worsen their near-term financial performance. Some US hospitals, often referred to as safety net hospitals, treat populations primarily covered by Medicaid or selfpayment, and complication reduction efforts might improve their financial performance.

Contribution margin, defined as revenue minus variable costs, describes the financial resources generated by hospital activities that are available to pay for a hospital's fixed costs. Hospital managers seeking to improve financial performance typically prioritize contribution margin when evaluating hospital activities. For hospitals with substantial unused capacity, which comprises the majority of US hospitals, any activity with a positive contribution margin is financially beneficial, regardless of total margin.

We also examined the relationship between occurrence of surgical complications and hospital financial performance on a total margin basis, which provides an understanding of the long-term sustainability of hospital operations. For inpatient procedures covered by private payers, the occurrence of complications was associated with a more than \$25 000 greater total margin. In contrast, Medicare, Medicaid, or self-pay encounters all had negative total margins whether a complication occurred or not, and the total margin was worse with a complication. As a result, some hospitals could financially benefit in the long run by reducing complications if they could accept substantial near-term losses.

We did not estimate the effect of 3 potential factors that could affect the hospital economics of surgical complications. First, the shorter lengths of stay of procedures without complications could benefit the small percentage of hospitals operating at full capacity because they might be able to admit additional patients with favorable insurance who were “crowded out.”

Second, reduced complications could improve hospital reputation, thereby increasing market share. This effect is unclear, given the absence of public reporting of surgical complication rates.

Third, reducing surgical complications is likely to reduce readmission rates, which may help hospitals subject to reimbursement penalties, but our current study was not structured to study the consequences of this effect.

In contrast to previous financial studies that focused on smaller surgical patient pools or fewer procedures, the data set used here comprises a large number of surgical inpatient encounters with a typical mix of surgical procedures. Our identification of postsurgical complications in administrative data built on previously existing methods, added new codes, and used present-on-admission codes to improve the clinical relevance of the administrative data, as recommended elsewhere. Our study also avoided the use of surrogates for cost data.

Our study has several potential limitations. A number of studies suggest that administrative data may underestimate surgical complication rates. Furthermore, we did not seek to capture all complications (and in fact recorded postoperative deaths in which there was no complication captured). However, the overall rate of surgical complications we report of 5.3% was within the range of that of other studies. Rates of specific complications that we included in our overall complication index were also within the range of that of other studies. The consequence of underestimating the number of surgical complications is that we would also have underestimated the financial influence of complications.

Although we report hospital revenues from Medicare, Medicaid, and private payers, we were not able to account for regional or local variation in reimbursement rates. Variations in Medicare rates (eg, because of adjustments for local wage index) would need to be corrected for in applying our results to individual hospitals. Private payer rates and contracting structures vary widely across the country and even in the same region or city. For example, private payer reimbursement rates range from 100% to 250% of Medicare rates, depending on local market factors.<sup>52</sup> Our results thus must be interpreted in light of these factors. It is possible that with certain combinations of insurances and procedures, findings will differ from our conclusions. However, we believe the hospital system studied reflects a fairly typical set of procedures and payer contracting rules.

All payers benefit financially when surgical complications are avoided because they are associated with higher average payments to hospitals. The present study suggests that strategies such as payers bundling the average costs of complications into the base diagnosis related group payment for a surgical procedure or limiting the hospital's ability to recode retrospectively into a higher-paying diagnosis related group may give hospitals a stronger financial incentive to avoid complications.

## CONCLUSIONS

In this hospital system, the occurrence of postsurgical complications was associated with higher per-encounter hospital contribution margin for patients covered by Medicare and private insurance but lower contribution margin for patients covered by Medicaid and self-payment. Depending on payer mix, some hospitals have the potential for adverse near-term financial consequences for decreasing postsurgical complications.

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## **Operational Cost Analysis of Dental Emergencies for Deployed U.S. Army Personnel During Operation Iraqi Freedom**

Military Medicine

MAJ Paul M. Colthirst, DC USA; Rosann G. Berg, BSc; COL Philip DeNicolo, DC USA; John W. Simecek, DDS, MPH

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Abstract

The documentation of dental emergency (DE) rates in past global conflicts has been well established; however, little is known about wartime DE costs on the battlefield. Using DEs as an example for decreased combat effectiveness, this article analyzes the cost of treating DEs in theater, both in terms of fixed and variable costs, and also highlighted the difficulties that military units experience when faced with degradation of combat manpower because of DEs. The study found that Dental-Disease and Non-Battle Injury cost the U.S. Army a total of \$21.4M between July 1, 2009 and June 30, 2010, and \$21.9M between July 1, 2010 and June 30, 2011. The results also revealed that approximately 32% of DE required follow-up treatment over the 2-year period, which increased the costs associated with a DE over time. Understanding the etiology and cost of DE cases, military dental practitioners will be better equipped to provide oral health instructions and preventive measures before worldwide deployments.

Introduction

War has always been a costly venture. Dental emergency (DE) rates in past conflicts have been well documented.<sup>1,2</sup> DE rates during combat range from 26 to 260 per 1000 personnel per year.<sup>3</sup> However, little is known about wartime costs for DEs on the battlefield. Adding the cost of decreased combat effectiveness, it can be shown that the cost of DEs has far-reaching implications beyond the actual treatment costs of the emergency. DEs can result in loss of life, both from the actual dental disease or from the potential of engagement with the enemy during transport of the patient to a treatment facility. Additionally, a unit that has decreased manpower will undoubtedly struggle to accomplish its mission, which results in a degradation of combat effectiveness. Chaffin and Moss<sup>4</sup> concluded that a less dentally fit force would see a higher number of DEs, which can diminish the combat effectiveness of a unit, albeit indirectly.

This article analyzes the cost of treating DEs in theater, both in terms of fixed and variable costs, and also highlights the difficulties that military units experience when faced with the degradation of combat manpower because of DEs.

## Methods

### Dental Emergencies

DE care is designed to relieve oral pain, eliminate acute infection, control life-threatening oral conditions (hemorrhage, cellulitis, or respiratory difficulty); and treat trauma to teeth, jaws, and associated facial structures. It is considered the most austere form of dental care provided to deployed soldiers engaged in tactical operations.<sup>5</sup>

Dental officers document each DE visit by completing a questionnaire contained in the Dental Emergency Encounter Module of the Corporate Dental Application. The module enables the provider to categorize the DE into one or more of the 47 choices of DE etiology. The 47 categories were divided by the authors into three subsets: severe, moderately severe, and pain/loss of function (see Table I). The severe category was defined as DEs causing debilitation because of infection or loss of function and/or might, if left untreated, result in a life-threatening condition. The moderately severe category consists of DEs causing moderate to severe pain and/or infection, and the pain/loss of function category includes DEs that result in discomfort and/or loss of function that can be tolerated by patients until dental support is available.

All U.S. Army DE encounters and unique DE cases during the periods of July 1, 2009 to June 30, 2010 and July 1, 2010 to July 1, 2011 were included for this study.

### Operational Costs (Total Dollar Cost)

DE Operational Costs, also called Total Dollar Cost (TDC), is defined as all measureable dollar costs, both fixed and variable, that are associated with the treatment of DEs on the battlefield. The DE cost includes (1) transportation to and from the dental treatment facility (DTF), (2) time away from the soldier's unit, and (3) treatment costs.

### Fixed Costs

Fixed costs are expenses that are not subject to high degrees of variations<sup>6</sup> in utilization of dental services, such as the cost of treatment and the pay associated with the soldiers, dental officers, and dental assistants. Treatment is calculated after categorizing the type of DE and assigning the American Dental Association Current Dental Terminology<sup>7</sup> (CDT) treatment codes associated with treating the problem (Table I). The CDT codes correlate with fiscal year (FY) 2009 to 2010 and FY 2010 to 2011 Department of Defense (DOD) Dental Weighted Value<sup>8</sup> (DWV) costs, which have dollar costs associated with treatment. The DWVs are based on the 95% level of the National Average American Dental Association fee survey and other regional fee schedules. One DWV represents approximately \$100 in cost for dental treatment. The authors determined the CDT

codes most likely to reflect the treatment provided for each DE category. Our treatment cost analysis is calculated by taking the mean of the estimated definitive treatment costs associated with the specific DE.

Variations in transportation (i.e., how the soldier arrives at the DTF) is a key criterion in calculating total cost. If the soldier arrives by helicopter (medical evacuation or in-theater service transport flights) or ground vehicle, two different types of costs can be associated with the trip. Special-cause variations, such as transportation costs, are considered nonquantifiable, unpredictable, and unusual conditions that appear within a process.<sup>9</sup> Even though there are costs associated with transporting DE patients to the nearest DTF, and in many cases, the expenses are considerable, this analysis did not incorporate those special-cause variation costs because of the uncertainty of the method by which soldiers arrived at the DTF. We therefore consider our estimates to be conservative at best.

#### Variable Costs

Variable costs are defined as expenses that change over time and are dependent upon the level of activity<sup>10</sup> or utilization of dental services. The variable cost associated with a DE is time lost from a unit. Because there are no data that describe time lost for military personnel because of DE, former deployed dental commanders, operational medical planners, and clinic noncommissioned officers who deployed to Iraq were contacted and asked to estimate the average time lost for a soldier seeking treatment. These experts were asked to determine the average travel time to their DTF, the average wait time before being seen, the average length of treatment, and how soon after treatment the soldiers could return to their respective units. The averages of these times were used as the basis of our calculations.

Information provided by the FY 2009 to 2010 Department of Defense (DOD) Military Personnel Composite Standard Pay and Reimbursement Rates<sup>6</sup> was used to calculate the average hourly rate of a typical deployed soldier (enlisted service member with a pay grade of E-5). The FY 2009 to 2010 and FY 2010 to 2011 DOD Military Personnel Composite Standard Pay and Reimbursement Rates provided by the Office of the Under Secretary of Defense were referenced to obtain the average annual rate of a typical deployed soldier (enlisted service member with a pay grade of E-5). The annual rates indicated were \$76,878 and \$78,666, respectively. Per the guidelines, hourly rates were calculated by multiplying the annual rate by the ratio factor of 0.00055.<sup>11,12</sup> Accordingly, the FY 2009 to 2010 and FY 2010 to 2011 hourly rates of a typical deployed soldier were \$42.28 and \$43.26, respectively.

The following formula was used to calculate TDC of DEs for this study:  $TDC = \text{Fixed Dollar Cost (Treatment)} + \text{Variable Dollar Cost (Time)}$ .

#### Results

We determined that 11,642 soldiers were seen for DEs between July 1, 2009 and June 30, 2010. Of the 11,642 soldiers, there were 14,547 DE encounters (1.2 encounters [treatment visits] per patient). Additionally between July 1, 2010 and June 30, 2011, a total of 10,810 soldiers were seen for DEs, with 13,428 DE encounters (1.2 encounters per patient). The aforementioned group of experts determined that the average time lost by a unit was 3 days with an 8-hour work schedule for a total of 24 hours. This translated into a variable cost (time) of \$14.7M between July 1,

2009 and June 30, 2010, and \$13.9M between July 1, 2010 and June 30, 2011 (Table II). Additionally, the total fixed cost (treatment) for the severe, moderately severe, and pain/loss of function categories was \$6.7M between July 1, 2009 and June 30, 2010, and \$8.0M between July 1, 2010 and June 30, 2011, respectively (Table III). The total combined cost to the U.S. Army totaled \$21.4M between July 1, 2009 and June 30, 2010, and \$21.9M between July 1, 2010 and June 30, 2011 (Table IV). Table IV suggests that the vast majority of DE operational costs may be attributed to variable cost, i.e., calculated dollar cost because of time lost from unit.

Comparison of FY 2009 to -2010 and FY 2010 to 2011 shows that >50% of all DEs were treated and returned to duty, whereas the remainder required follow-up evaluation, treatment, or advanced specialty care, which may have resulted in increased numbers of hours away from their units (Table V).

## Discussion

In analyzing the cost of DE in theater, we estimate a TDC of \$44M over a 24-month period or \$1.8M per month. Although the amount is large, as previously stated, it is most likely an underestimate because of our inability to quantify and include the cost to transport 22,452 soldiers from their unit to the DTF.

The greatest expense was because of time away from a soldier's unit. This result is significant with respect to combat effectiveness of a unit and overall dental fitness of our soldiers. Although some DEs cannot be avoided, others can be mitigated. Using the DOD Dental Fitness Classification (DFC) system, teeth with problems are assigned a classification of 2 or 3 based on their probability of causing a DE over a 12-month period. For example, a tooth identified as a DFC 2 indicates the probability of a soldier developing a DE within 12 months is low. Although the DFC system has been validated,<sup>13,14</sup> dental providers should take additional steps to ensure their examinations and diagnoses are indeed accurate and justifiable, especially for deploying soldiers. Simecek<sup>15</sup> reported that 51% of restorative DE and 47% of endodontic DE were not predicted on previous annual oral examinations. If a tooth was identified as a DFC 2 but has a DE experience within 365 days then perhaps that tooth should have been categorized as a DFC 3 (the likelihood of having a DE within 12 months is high). Future DE epidemiological studies should be designed to track previous oral examination to time of first initial DE experience. Failure to accurately classify a deploying soldier's dental readiness puts the soldier at a greater risk of becoming a DE casualty in theater.

Another cost not routinely documented for DE is risk avoidance. According to U.S. Army Field Manual 100-14, risk management (avoidance) is the utilization of risk management techniques to help units protect combat power through identifying and controlling hazards to conserve combat power and resources.<sup>16</sup> The absence of one soldier because of a DE can obviously be calculated in dollars; however, the true value of that one soldier to the unit is not quantifiable. The unit, minus one or more soldiers, means that the combat power and effectiveness of the cohesive unit is degraded. The fact that another soldier must "cover down" to replace the missing soldier for an average of 3 days can suggest decreased morale, adjustments of time-off schedules, work schedules, tower guard schedules, and perimeter guard duties. It is evident the second- and third-order effects of DE go far beyond treatment cost and undoubtedly affect the entire unit's combat readiness and morale.

The overall cost seen in theater justifies the case for predeployment dental screenings and treatment. The majority of DEs seen in a dentally fit force can be definitively managed in theater. It is believed that if predeployment treatments were not conducted, the DE rates and associated costs would far exceed what is currently observed in theater. This underscores the need for having adequate dental services within the theater of operations to support the overall war effort. For example, the data showed that 43% of all DEs from July 1, 2009 through June 30, 2010 and 32% of all DEs from July 1, 2010 through June 30, 2011 required some type of follow-up or specialty care. This suggests that a unit lost a soldier for a longer period of time or the soldier returned at a later date for treatment that had not been initially resolved. In 2000, Mahoney and Coombs<sup>17</sup> reported that a well-prepared dentally ready volunteered force would experience an annual DE rate of approximately 150 to 200 per 1000 soldier case. In contrast, Mahoney also wrote that a less dentally ready force would see an annual DE rate of 750 per 1000 soldier case. We can therefore conclude that if the U.S. Army was not a dentally fit force, the cost to treat these soldiers on the battlefield would be three times the amount that it currently costs. Dela Cruz and Colthirst<sup>18</sup> concluded "Oral diseases can cause impaired duty performance, work loss, restricted activity, poor diet, difficulty pronouncing words, inability to sleep, and excruciating pain. If they are not prevented or treated early, oral diseases can cause severe, life-threatening illness and may even require medical evacuation from theater."

Chaffin and Moss<sup>4</sup> suggested researchers should develop a predictive model of DEs that considers known risk factors, such as tobacco usage, access to fluoride during deployment, and stress management. Chaffin argued that understanding external environmental factors and implementing behavioral modification programs are essential in preventing DE. If indeed such a model were to be developed, it would no doubt be revolutionary. However, knowing the types of DE and the associated costs (i.e., treatment and combat power lost) is a first step in developing such a model.

#### Conclusion

Although the majority of DEs are preventable, the result of the study estimates the overall DE operating costs within theater to be over \$1.8M per month. The authors recommended that dental providers reference the type of DEs seen in past military conflicts and meticulously assess the status of predeployment oral health. With a better understanding of the etiology and cost of DE cases, dental practitioners will be better equipped to provide oral health instructions and preventive measures before deployment.

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## **"Nightmare" Bacteria on the Rise in US Hospitals, Long-term Care Facilities**

Journal of the American Medical Association

Bridget M. Kuehn, MSJ

17 April 2013

Carbapenem-resistant Enterobacteriaceae (CRE) are gaining a foothold in US health care facilities, particularly long-term care facilities, according to the latest data from the US Centers for Disease Control and Prevention (CDC).

In 2012, only a decade after the CDC first identified a case of carbapenem-resistant *Klebsiella pneumoniae* in a North Carolina long-term care facility, nearly 5% of acute care hospitals and nearly 18% of long-term care facilities reported at least 1 carbapenem-resistant infection associated with health care, according to a CDC report (MMWR. 2013;62[09]:165-170). These infections are difficult or impossible to treat because the organisms are resistant to even the last-resort antibiotics. As a result, about half of these patients die, according to the CDC.

The spread of these bacteria, which may house drug-resistance genes in a plasmid that can easily be transferred to other bacteria, poses an additional risk of spreading genes for antibiotic resistance to other common bacteria, such as *Escherichia coli*, warned CDC Director Thomas Frieden, MD, MPH, during a press briefing in March. Frieden described CRE as “nightmare bacteria.”

“We only have limited opportunity to stop these bacteria from spreading to the community,” he said.

#### An Urgent Threat

Another analysis suggests that CRE make up a growing proportion of Enterobacteriaceae and that the Northeast has been particularly hard hit. A multi-institution team of researchers conducted a retrospective cohort analysis of 500 000 *K pneumoniae* cultures grown between 1999 and 2010 in 287 laboratories across the country (Braykov NP et al. *Infect Control Hosp Epidemiol.* 2013;34[3]:259-68). The researchers found that from 2002 to 2010, the proportion of *K pneumoniae* isolates that were resistant to carbapenems increased from about 0.1% to 4.5%, and the proportion of *Klebsiella* strains resistant to third-generation cephalosporins increased from 5.3% to 11% during the same period.

Resistant *Klebsiella* were about 3 times more common in samples collected from elderly patients than from pediatric patients. *Klebsiella* cultures from the Northeast were 9 times more likely to be carbapenem-resistant than those collected in the West, and they were 3 times more likely to be resistant to third-generation cephalosporins.

Although prevalence varies by region, 42 states have reported at least 1 case of carbapenem-resistant bacteria, according to the CDC. So far, these infections have occurred in medically complicated patients in health care facilities, but there is concern about the potential for spread into the community.

“This is something almost exclusively occurring in patients extensively exposed to health care,” said Arjun Srinivasan, MD, associate director for healthcare-associated infection prevention programs at the CDC. “It’s not yet an issue we face in the community.”

Daniel J. Diekema, MD, director of the division of infectious diseases at the University of Iowa Carver College of Medicine in Iowa City, said the selective pressure placed on these bacteria by the use of broad-spectrum antibiotics promotes the spread of genes that confer resistance to carbapenems, and the situation is likely to get worse.

“What we are seeing is the natural progression of the fight against increasingly resistant bacteria,” he said.

Diekema noted that few antibiotic options remain for combating these bacteria, and little is in the new drug pipeline, which raises the specter of a “post-antibiotic era.”

“The pipeline for antibiotics for superresistant gram-negative bacteria has dried up,” he said. “It’s a public health crisis.”

Neil Fishman, MD, an associate professor at the University of Pennsylvania and past president of the Society for Healthcare Epidemiology of America (SHEA), agreed about the urgent need for measures to stop the spread of these resistant bacteria and to take steps to preserve the usefulness of existing antibiotics. He estimated that it will take 5 to 8 years for new agents capable of treating CRE to become available.

“It’s important to grasp this opportunity, because it is going to be a long time before we have new antibiotics,” Fishman said.

#### Multipronged Approach

Preventing CRE from spreading further will take a multipronged and coordinated national effort, public health experts agree.

The CDC released a toolkit in 2012 to help hospitals curb the spread of CRE (<http://tinyurl.com/aupuv45>). At the press briefing, Frieden emphasized several key recommendations from the toolkit, including the following:

- Test patients for CRE and request immediate alerts from the laboratory when a case is found.

- Inform other facilities when transferring a patient infected with CRE, and ask about such infections in incoming patients.

- Use contact precautions to prevent the spread of CRE.

- Allocate specific rooms, equipment, and staff for the treatment of patients with CRE.

- Remove catheters and other devices as soon as possible.

Prescribe antibiotics carefully.

Srinivasan explained that the toolkit has specific recommendations for CRE screening protocols based on how frequently CRE has been detected in the surrounding community. Evidence suggests that facilities that implement the CDC's approach can help reduce CRE infections by about 50%. For example, a long-term care facility that implemented the guideline measures, including grouping together patients infected with CRE and having staff use dedicated equipment to treat them, reduced the prevalence of such infections from 49% to 8% and reduced the percentage of patients who screened positive from 44% to 0% (Chitnis AS et al. *Infect Control Hosp Epidemiol.* 2012;33[10]:984-992). This facility was also able to eliminate episodes of bacteremia, with a reduction from 2.5 episodes per 1000 patient days before the intervention to 0.0 per 1000 patient days after.

Fishman emphasized the importance of good antibiotic stewardship in preventing the emergence and spread of resistant bacteria. A statement from SHEA noted that one-third of antibiotics prescribed in hospitals are unnecessary.

But Fishman explained that good stewardship is more than just avoiding overuse of antibiotics. "Good antibiotic stewardship is making sure the correct patient gets the correct dose at the correct time," he said. "That's high-quality care, and it will limit the emergence of resistance."

Diekema urged clinicians and facilities not only to adopt the new CRE recommendations, but also to ensure that they are implementing all of the CDC's previous guidance on preventing the spread of multidrug-resistant organisms. He emphasized the importance of infection control basics such as ensuring a high rate of hand hygiene adherence among staff and making sure that surfaces and equipment are properly disinfected. Cleaning staff need adequate training, sufficient personnel, and the knowledge that they are essential members of the infection control team, he said.

"If you don't shore up those things, screening [for CRE] isn't going to help," Diekema said.

But Diekema noted there may be limits to what facilities can do to hold the line on CREs, which are a systemwide problem. Some colonized patients may slip through screening undetected, and many of the patients who are infected are transferred from facility to facility.

Less research has been done on preventing infections in long-term care settings, and some infection control approaches may not be practical or ethical in such a setting, Diekema noted. He said the onus is on acute care hospitals to know whether their local long-term care facilities have CRE cases and to be sure to isolate patients transferred from such facilities until the presence or absence of colonization can be established.

Fishman noted that many smaller hospitals may not be screening for CRE at all, and even when hospitals do test patients, they may not get test results back quickly enough. Rapid tests are needed, Fishman said.

An additional problem is the piecemeal approach to tracking these infections. Only 6 states require facilities to report CRE cases.

“We need a more coordinated response,” Diekema said. He explained that the CDC is doing as much as it can with the resources it has, but underfunding of public health at the national and state levels makes it difficult to mount a more coordinated national effort to contain the spread of these infections.

More research is also needed on the best strategies for environmental disinfection, ensuring adherence to hand hygiene and other measures that would prevent the spread of health care–acquired infections.

Srinivasan emphasized the importance of facilities taking immediate action to implement the recommendations and not waiting for new tools or information. He and Frieden acknowledged the challenges facilities face in ensuring compliance and implementing CRE-control programs.

“It is not cost-free to start these programs, but it will cost a lot more if [hospitals] don’t,” Frieden said.



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Bridget M. Koehn, MSJ

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Another analysis suggests that CRE make up a growing proportion of *Enterobacteriaceae* and that the Northeast has been particularly hard hit. A multi-institution team of researchers conducted a retrospective cohort

analysis of 500 000 *K. pneumoniae* cultures grown between 1999 and 2010 in 287 laboratories across the country (Braykov NP et al. *Infect Control Hosp Epidemiol*. 2013;34[3]:259-68). The researchers found that from 2002 to 2010, the proportion of *K. pneumoniae* isolates that were resistant to carbapenems increased from about 0.1% to 4.3%, and the proportion of *Klebsiella* strains resistant to third-generation cephalosporins increased from 5.3% to 11% during the same period.

Resistant *Klebsiella* were about 3 times more common in samples collected from elderly patients than from pediatric patients. *Klebsiella* cultures from the Northeast were 9 times more likely to be carbapenem-resistant than those collected in the West, and they were 3 times more likely to be resistant to third-generation cephalosporins.

Although prevalence varies by region, 42 states have reported at least 1 case of carbapenem-resistant bacteria, according to the CDC. So far, these infections have occurred in medically com-

plicated patients in health care facilities, but there is concern about the potential for spread into the community.

“This is something almost exclusively occurring in patients extensively exposed to health care,” said Arjun Srinivasan, MD, associate director for health-care-associated infection prevention programs at the CDC. “It’s not yet an issue we face in the community.”

Daniel J. Dickema, MD, director of the division of infectious diseases at the University of Iowa Carver College of Medicine in Iowa City, said the selective pressure placed on these bacteria by the use of broad-spectrum antibiotics promotes the spread of genes that confer resistance to carbapenems, and the situation is likely to get worse.

“What we are seeing is the natural progression of the fight against increasingly resistant bacteria,” he said. Dickema noted that few antibiotic options remain for combating these bacteria, and little is in the new drug pipeline, which raises the specter of a “post-antibiotic era.”



New data suggest that resistant strains of *Klebsiella pneumoniae* are becoming more common. A microbiologist at the Centers for Disease Control and Prevention examines some of the bacteria.

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## New System for Digital to Analog Transformation and Reconstruction of 12-Lead ECGs

PLOS one

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Abstract

Introduction

We describe initial validation of a new system for digital to analog conversion (DAC) and reconstruction of 12-lead ECGs. The system utilizes an open and optimized software format with a commensurately optimized DAC hardware configuration to accurately reproduce, from digital files, the original analog electrocardiographic signals of previously instrumented patients. By doing so, the system also ultimately allows for transmission of data collected on one manufacturer's 12-lead ECG hardware/software into that of any other.

## Materials and Methods

To initially validate the system, we compared original and post-DAC re-digitized 12-lead ECG data files (~5-minutes long) in two types of validation studies in 10 patients. The first type quantitatively compared the total waveform voltage differences between the original and re-digitized data while the second type qualitatively compared the automated electrocardiographic diagnostic statements generated by the original versus re-digitized data.

## Results

The grand-averaged difference in root mean squared voltage between the original and re-digitized data was 20.8  $\mu\text{V}$  per channel when re-digitization involved the same manufacturer's analog to digital converter (ADC) as the original digitization, and 28.4  $\mu\text{V}$  per channel when it involved a different manufacturer's ADC. Automated diagnostic statements generated by the original versus reconstructed data did not differ when using the diagnostic algorithm from the same manufacturer on whose device the original data were collected, and differed only slightly for just 1 of 10 patients when using a third-party diagnostic algorithm throughout.

## Conclusion

Original analog 12-lead ECG signals can be reconstructed from digital data files with accuracy sufficient for clinical use. Such reconstructions can readily enable automated second opinions for difficult-to-interpret 12-lead ECGs, either locally or remotely through the use of dedicated or cloud-based servers.

## Introduction

Most modern electrocardiogram (ECG) machines use built-in analog to digital converters (ADCs) to digitize patients' analog cardiac electrical signals for more efficient analysis, display, storage, printing, and sharing of data. While this common and intuitive method has heretofore been sufficient for most clinical uses, it typically "locks in" the practicing clinician to the often opaque and sometimes proprietary digital format(s) of the specific ECG machine(s) being employed. In contradistinction, and particularly for patients with a difficult-to-interpret 12-lead ECGs wherein the automated diagnosis from the "house machine" may be in question (no automated algorithm being error free), many clinicians might welcome the opportunity to readily obtain one or more additional opinions from other manufacturers' automated interpretive algorithms. Different algorithms for example are sometimes known to have widely varying diagnostic accuracies for common electrocardiographic conditions [1].

If through non-disclosure or other agreements with ECG manufacturers a researcher is given direct digital access into an automated interpretive program for 12-lead ECG that accepts a known digital format, then it is relatively straightforward to convert other known digital formats into that first known digital format to thereby gain access to the interpretive functionality. In principle therefore an "ideal" (albeit still non-universal) means for clinicians to obtain automated second opinions for 12-lead ECGs would involve a fully digital interchange wherein multiple manufacturers would allow for simultaneous digital access to their interpretive functionalities using a common digital format. In practice, however, such interchanges do

not exist for the general clinical community, one historical reason being the obstruction created by the manufacturers' naturally competing commercial interests. Thus while the previous starts that have been made toward such interchanges such as those of Bailey et al [2] in the 1970s and of Willems et al [1] in 1990s are of great interest, the fact that such starts have never germinated into a clinically useful, potentially lifesaving tool speaks to the inertia that can be generated when certain commercial forces persist that are not necessarily ideal from a patient-centered medicine standpoint. It was possibly this very non-ideality that in 1984 led Miyahara et al to take a slightly different approach of first collecting digital ECGs and then painstakingly regenerating analog signals – one complex at a time by means of magnetic tape and a specially constructed “generator” – that they then re-fed into 10 different interpretive ECG machines available in Japan [3]. However, the methods described by Miyahara et al are today obsolete, were unfortunately very cumbersome, and possibly also involved two serial (and thus clinically redundant) references to Wilson's central terminal (WCT).

Herein we describe a new digital to analog conversion system based on contemporary computer and electrical engineering technology that is readily available. It can reproduce with sufficient precision for clinical use the original analog ECG signals from any 12-lead ECG digital data file or stream of known format, thereby allowing for the complete reconstruction of the original ECG after “re-digitization” within any brand and model of receiving 12-lead ECG machine. It can do this either locally or remotely and without any requirement for manufacturer-adjudicated digital access into the receiving machine, thereby specifically allowing for the transmission of data collected on one manufacturer's ECG machine into that of any other for an automated diagnostic second opinion. Thus the system could be valuable for facilitating – by consensus among algorithms or physician judgment in conjunction with machine interpretation – the ultimately correct interpretation of difficult-to-interpret 12-lead ECGs and rhythms. Moreover because the system also performs its function with full “universality” (something that may never be practically possible for any purely digital interchange), over the short term it's also likely to better foster further improvements to all ECG manufacturers' (large and small) automated interpretive programs through provision to those manufacturers of multiple and repeatable input example cases that their diagnostic algorithms currently misdiagnose.

Although the concept of using a digital to analog converter (DAC) to retrieve original analog ECG waveforms is not novel (as described previously [3], plus it has been applied for decades in ECG simulator devices), we are aware of only one commercially available system (LifeSync®, Fort Lauderdale, FL) that presently applies the DAC concept to a patient-care setting. That system, however, utilizes a different type of technology to satisfy a different clinical need – i.e., it is designed to provide hospitalized, ECG-monitored patients with greater freedom of movement and less risk for hospital-acquired infections from otherwise reused and wall-tethered lead wires, certainly laudable goals themselves. Unfortunately the LifeSync DAC does not accept digitized ECG data from any ADC other than LifeSync's own, nor to our knowledge does it transmit digital data to remote locations. Instead, from an electronics standpoint, the LifeSync DAC functions as the “straight pass through” recipient of 9 channels of specially structured digital data (rather than the more reductionist and customary 8 channels) that can only originate from an accompanying LifeSync ADC device. Thus the LifeSync DAC procedure carries with it the absolute requirement not only for the presence of the LifeSync DAC device, but also for the use of the LifeSync ADC and all of its accoutrements during the original data collection.

The DAC system introduced herein is instead designed to begin with digital data, stored or streaming, collected on any ECG manufacturer's ADC. It is therefore independent of any particular manufacturer's 12-lead ECG hardware and can thus function in harmony with any 12-lead ECG machine used for data collection. The only requirement is that the digital format utilized by the given data collection machine must be known because that format will typically first undergo a purely digital (software-based) conversion to an optimal, open digital format (provided in Appendix S1) that is specifically designed to optimally reproduce (with the DAC hardware) the original analog ECG signals. Once the original analog signals are reproduced, the system can then move those signals forward into any other manufacturer's ECG machine(s) to be re-digitized (or “reconstructed”) there. Thus automated diagnostic interpretations from multiple manufacturers' ECG machines can be obtained for any ECG data

file or stream of known format collected by any other manufacturers' machine(s), either locally or remotely, and with any desired degree of fidelity dependent only on the specifications of the ADCs used for the original and reconstruction data collections.

The prototype system described herein was also specifically designed to expand automated analytical capabilities for 12-lead ECG data collected in certain remote places wherein the mass or volume of the ECG device must be constrained and/or wherein interpretive expertise is limited at the remote location. For example for 12-lead ECG data arriving from space or from remote terrestrial environments such as mobile military units, oil platforms or mountaineering, polar or other expedition areas.

## Methods

### The methodological problem

When collecting a standard 12-lead ECG, 10 electrodes placed on the patient are used to obtain (typically) up to 9 different analog voltages. These voltages are then most commonly stored digitally as 8 independent data channels (i.e., typically as channels that are equivalent to leads I and II plus leads V1–V6 as referenced to WCT [4]). Now if one defines the original 10 electrodes as follows: left arm electrode = EL; left leg electrode = EF; right arm electrode = ER; right leg electrode = N (reference neutral) and chest electrodes = EC<sub>i</sub> (where  $i = 1-6$ ), then the 8 independent data channels would most commonly be expressed as:

Thus the methodological problem the system must solve is as follows: How can one begin with 8 independent data channels in the original digital data and yet drive at least 9 DAC channels uncoupled from WCT (because the final receiving ECG machine is itself expected do such coupling) to produce these same data channels (leads I, II and V1–V6) at the receiving ECG machine? In other words how can one do this as if the channels ultimately outputted by the DAC had come from the usual 10 electrodes on a patient, and with the right leg electrode input remaining as DAC common? Figure 1 expresses this problem graphically by showing a generalized functional diagram for a typical 12-lead ECG system, but ignoring (as defined) the non-independent leads III, aVR, aVL and aVF.

### A methodological solution

For any 12-lead ECG system that uses a digital file format wherein the chest electrodes are referenced not to WCT, but instead to the right arm electrode (i.e., to ER, thereby producing CR<sub>i</sub> instead of V<sub>i</sub> chest lead data), the following applies:

Moreover, if in a DAC that is also associated with (receives digital data from) such a system, a “zero” voltage is imposed upon its right arm electrode input (i.e.,  $ER = 0$ ), then from that DAC:

Therefore, if the following conditions are assigned to the DAC, they should ultimately produce, on any ultimately receiving (re-digitizing) 12-lead ECG machine, the desired I, II, and V1–V6 data signals:

At least two other aspects of the above system are of interest. First, this system type where the chest electrodes are referenced not to WCT, but instead to the right arm electrode, was originally favored not only by Einthoven himself [5], but also by others even after the introduction of WCT [6], [7]. Second, algebraically it is also possible to accomplish the same fundamental end point through a digital format wherein all other electrodes are referenced to the left arm electrode while a zero voltage is simultaneously imposed on the DAC left arm electrode input, or through a digital

format wherein all other electrodes are referenced to the left leg electrode while a zero voltage is simultaneously imposed on the DAC left leg electrode input.

Optimized file format, hardware and software configuration, and data processing procedures

The format of any digital data inputted into the preferred (“right arm zeroed”) DAC described above must be compatible with that DAC's specific characteristics. Such an optimized data format, into which all other digital formats must therefore be converted before use with the DAC, is further detailed in Appendix S1. The specific hardware and software configuration of our prototype, including the details of how it currently processes ECG data, is outlined in Appendix S2. Figure 2 also provides a summary overview of all data processing procedures.

Initial validation studies

For the initial validation studies described herein, we used ten 12-lead ECG data files, each between 5 and 10 minutes in length, collected from five healthy and five diseased patients, respectively, who had given their written informed consent for participation in a larger study previously approved by the Johnson Space Center Institutional Review Board [8]. Their data were originally collected using a high-fidelity 12-lead PC-ECG device (Cardiax, IMED Ltd., Budapest, Hungary). The 12-lead ECGs were clinically normal in each of the five healthy patients chosen at random, whereas in the five diseased patients, the following electrocardiographic conditions were respectively selected (from affected individuals also chosen at random) to include a range of electrocardiographic pathologies: 1) coronary artery disease without prior myocardial infarction and with normal QRS interval; 2) coronary artery disease with prior myocardial infarction (i.e., ischemic cardiomyopathy) but with normal QRS interval; 3) non-ischemic (dilated) cardiomyopathy with normal QRS interval; 4) left bundle branch block of uncertain etiology; and 5) right bundle branch block of uncertain etiology.

Two types of validation studies were performed to compare the original digital ECG data to their reconstructed (i.e., after DAC and repeat ADC) counterpart data. The first type quantitatively compared the total-waveform voltage differences between the original and reconstructed data while the second type qualitatively compared the automated electrocardiographic (i.e., clinical) diagnostic statements generated by the original versus reconstructed data.

Quantitative validation

A MATLAB-based script was written to superimpose the data in the original and reconstructed files for each subject by using the corresponding R-wave fiducial point locations in the files to align the corresponding waveforms. For this purpose the original R-wave fiducial point locations were obtained directly, within exported files along with the raw data, from the hardware manufacturer's (Cardiax's) commercial software itself. Each test file had 250 to 500 PQRST complexes within a 5 to 10-minute data epoch. For each PQRST complex, a region about the R-wave fiducial point was used to define a window encompassing the PQRST segments with minimal amounts of pre-P and post-T baseline. The data in this window were linearly de-trended and the original versus reconstructed waveforms were overlaid and shifted to minimize the root mean square (RMS) difference. The standard deviation was used as a proxy because detrending alone ensures a near zero mean but not a perfectly zero mean. An average RMS difference estimate across all beats was then calculated for each channel in each patient, as was an overall average RMS difference for all channels combined. This same process was performed twice: once after having used the same model of ECG machine (Cardiax ADC; 1000 samples/s/channel) to collect the reconstructed (re-digitized) data that had also been used to collect the original data; and once after

having used a different manufacturer's ECG machine (BT12 ADC, CorScience, Erlangen, Germany; 500 samples/s/channel) to collect the re-digitized data.

#### Qualitative (automated clinical diagnostic) validation

A more qualitative (clinical) validation was also performed to further validate system performance. Specifically, the automated diagnostic statements, produced by commercial electrocardiographic software for the data within the first ~15 seconds in the original files, were compared in each case to the automated diagnostic statements produced for the same data in the post-DAC re-digitized files. Such analyses of potential changes in automated diagnostic statements were in turn performed in three separate ways: 1) by using the automated diagnostic program native to the Cardiac software program when a Cardiac ECG machine (ADC) had been used to collect both the original and re-digitized data; 2) by using the well-validated Leuven automated diagnostic algorithm [1] (see Program 16 in reference 1) for both the original data and the re-digitized data when a Cardiac ADC had been used to collect both the original and re-digitized data; and 3) by again using the Leuven automated diagnostic algorithm for both the original data and for the re-digitized data when a Cardiac ADC had been used to collect the original data but a CorScience BT12 ADC the re-digitized data.

#### Results

##### Quantitative validation: voltage comparison results

Table 1 shows the estimated RMS difference values for each of the 8 independent ECG channels (PQRST) when the same model of ECG machine (Cardiac ADC) that had been used to collect the original data was also used to collect the re-digitized data. Under these circumstances, the grand-average ( $\pm$ SEM) RMS difference value between the original and re-digitized data was  $8.5 \pm 0.05$  ADC counts per channel, or equivalently  $20.8 \pm 0.12$   $\mu$ V.

Table 2 shows the estimated RMS difference values for each of the 8 independent ECG channels (PQRST) when the re-digitized data were instead collected on an ADC (i.e., CorScience's) that was different from the ADC (Cardiac's) used to collect and store the original data. Under these circumstances, the grand-average RMS difference values between the original and re-digitized data was  $11.6 \pm 0.08$  ADC counts per channel, or equivalently  $28.4 \pm 0.21$   $\mu$ V.

As can be surmised from Tables 1 and 2, there were no clear trends in the differences generated by the original versus re-digitized files in the healthy versus diseased subjects when the QRS interval was within a clinically normal range. However, as might be expected, the presence of either left (subject 4D) or right (subject 5D) bundle branch block, wherein the QRS interval is relatively prolonged and the total voltage relatively increased, tended to increase the differences between the voltages in the original versus re-digitized files.

##### Qualitative validation: automated clinical diagnostic results

Table 3 shows the automated clinical diagnostic statements outputted by the commercial Cardiac software program for all 10 cases when both the original and re-digitized files were collected on the same model of Cardiac ADC. As can be surmised from Table 3, for all 10 cases under these circumstances, there were no differences in the clinical diagnostic statements outputted by Cardiac for the original versus the re-digitized files.

Table 4 shows the automated clinical diagnostic statements outputted by the commercial Leuven software program for all 10 cases when the original files were collected on the Cardiax ADC and when the re-digitized files were collected on either the Cardiax or CorScience ADC (i.e., the ultimate interpretive results from the Leuven program were the same under both of the above circumstances). Under either of these circumstances, the automated diagnostic statements outputted by the Leuven program for the original versus the re-digitized files differed for only one case (i.e., for healthy patient 2H). Specifically, within the Leuven program, criteria for “abnormal repolarization, possibly non-specific” were triggered for patient 2H’s re-digitized file whereas such criteria were not triggered for this same patient’s original file. While it is unclear whether this minor difference in the Leuven algorithm’s automated interpretation would have made any clinical difference (we suspect not), the original and re-digitized ECGs for this patient as interpreted by the Leuven algorithm are shown in Figure 3. Both Figure 3 and Figure 4 (which shows our corresponding “worst-case comparison” between original and re-digitized files as quantified by the greatest differences in RMS values; patient 4D) also aptly demonstrate the minor differences that typically occurred between all original versus re-digitized files with respect to the various electrocardiographic axes, intervals, and voltages that were outputted by the automated interpretive software.

## Discussion

Our results suggest that the system described herein can currently reproduce original analog signals from stored 12-lead ECG data files with a degree of fidelity likely sufficient for most clinical needs. In our formal study, one possible exception might have been when the system was used to reconstruct files that had bundle branch blocks, i.e., wherein quantitative reconstruction errors were at their highest (Tables 1 and 2 and Figure 4). In relation to this, it should be noted that the Cardiax and CorScience ADCs employed in our study use, like the majority of ADCs incorporated into other commercially available ECG devices, known non-optimal methods of sampling that implement “time interleaving”. Importantly, such methods alone, whether they implement “round robin” (e.g., Cardiax) or “pseudo-simultaneous” (e.g., CorScience) sampling, may introduce certain subtle distortions into any digitized data (and thus also into any re-digitized data) [9], [10]. For the first time, some of the newest ECG devices just introduced into the market now incorporate ADCs employing a more truly simultaneous method of sampling, made possible by new chips like Texas Instruments’ ADS1298. Thus digital data collected on devices employing such new chips may, with even greater fidelity, be re-convertible back to the original analog. Even more importantly, our own preliminary testing with one of these new devices (a new Cardiax device that now incorporates the ADS1298) for ultimate reconstruction rather than original data collection suggests that machines like it will notably further improve the quality of re-digitization (Figure 5). The substantial reduction in the quantitative RMS error values noted in Figure 5B (2–3 fold compared to the values shown in Tables 1 and 2) when using a device with “true simultaneous sampling” for ultimate re-digitization/reconstruction therefore provides evidence that files with bundle branch blocks can also be reproduced with clinically acceptable accuracy as long as the specifications of the ADC in the final recipient machine are sufficiently technologically advanced.

While our results further corroborate the utility of the one commercial device that to our knowledge currently applies DAC to ECG in a clinical setting—i.e., the aforementioned LifeSync® device utilized in hospitals—the overall greater utility, flexibility, universality, more open format, and “readiness for cloud computing” of our system potentially open up several new avenues for more widespread use of DAC devices in clinical electrocardiography. Specifically, without requiring manufacturer-adjudicated digital access into any automated interpretive functionality, systems such as ours might eventually allow for all of the following: 1) rapid second opinions from any number of automated interpretive programs, e.g., for difficult-to-interpret 12-lead ECGs and rhythms (not only locally, but also from dedicated remote central or cloud-based servers; 2) use of less expensive (i.e., commodity-grade) 12-lead ECG front ends (ADC hardware) in impoverished or underserved areas, because subsequent DAC will always permit use of any preferred (or any otherwise prohibitively-expensive) ECG machine or interpretive program only singly, on the back end; 3) use of less bulky ECG front ends during space flight or in other terrestrially remote environments; 4) improved performance of all automated ECG analytical software programs through the implementation by manufacturers of those “interpretive lessons learned” that will be more rapidly

ascertainable to them both through internal testing and through objective competitions enabled by the DAC; 5) better within-hospital consistency of automated ECG interpretations, e.g., when ECG machines from multiple different manufacturers are used in any single institution; and 6) better across-study consistency when large digital ECG databases are analyzed in epidemiological studies, as the DAC should allow for the same analytical programs to be used, when desired, across all such large studies, even when different collaborating groups don't all possess the same hardware and software.

It should be reemphasized that the only prerequisite for the use of the described system is that the format of the original digital data must be known – i.e., to permit pre-conversion into an optimal, open digital format for DAC such as the one described in Appendix S1—a functionality easily performed by either integrated or secondary software tailored to make such conversions. Once the data are converted to the optimized format either locally or remotely, then the hardware aspect of the system can also be readily employed either locally or remotely to convert the digital data to analog and then in turn to stream the analog data into any desired 12-lead ECG machine.

#### Limitations

The main limitation to this first proof-of-concept study is that it constitutes a limited initial validation wherein we have only formally analyzed a small number of stored digital files using hardware from two different ECG manufacturers. While non-formally we have also successfully employed the DAC to input data originally collected on several larger ECG manufacturers' machines into receiving machines from other large ECG manufacturers, future studies will ideally include the formal analyses of a larger number of files and electrocardiographic conditions and machines, and/or focus especially on those subtle ECG conditions that might be most susceptible to being “masked” (or to being spuriously introduced) in re-digitized recordings.

#### Conclusion

In conclusion, we have built a new system for digital to analog conversions of 12-lead ECG data and partially validated it through study of original versus re-digitized 12-lead ECG recordings from five healthy and five diseased individuals. Our results suggest that in the near future, systems like this will allow for rapid automated second opinions on difficult-to-interpret 12-lead ECGs and rhythms, for improvements to all manufacturers' automated 12-lead ECG interpretations, and for use of less expensive (or less bulky) ECG hardware front ends in impoverished, remote and other areas. Moreover the mere existence and availability of this new DAC system may provide an important stimulus to increase the willingness of all ECG manufacturers to participate in potentially more convenient, purely digital, multi-manufacturer interchanges for “automated 12-lead ECG second opinions”, to the further benefit of both patients and clinicians.

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#### **Obesity**

## **Compliance With Regulations on Weight Gain 6 Months After Delivery in Active Duty Military Women**

Military Medicine

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## Abstract

**Objective:** To determine factors associated with active duty military women being within Navy weight standards 6 months following childbirth. **Methods:** Inclusion criteria for this study were active duty women who delivered a nonanomalous fetus at a Naval Hospital and who remained in the area and their weight was recorded 6 months following childbirth. Multivariate logistic regressions, adjusted for 14 covariates, determined the factors for achieving acceptable weight. **Results:** Among 1,009 women who participated in this prospective cohort study, 68% began within Navy body weight standards and 52% had a normal body mass index (BMI) (<25). Six months after childbirth, 48% were within Navy body weight standards and 32% had a BMI <25. Only 2 factors, BMI at first visit and cesarean delivery, significantly influenced the percentage of women who met the weight standards at 6 months. **Conclusions:** Lowering the prepregnancy BMI and avoiding a cesarean delivery may improve the percentage of active duty women who meet weight standards 6 months after childbirth.

## Introduction

To optimize obstetric outcomes, women should gain weight during pregnancy. According to the Institute of Medicine (IOM), for obese women (body mass index [BMI] of 30 kg/m<sup>2</sup> or more), the gestational weight gain (GWG) should be 5 to 9 kg or 11 to 20 lbs; for underweight women (BMI < 18.5), it should be 12.5 to 18 kg or 28 to 40 lbs.<sup>1</sup> After childbirth, women need to lose the remaining GWG, as retention of that weight gain has been linked with long-term overweight or obesity issues and associated morbidity such as diabetes, hypertension, and heart disease. Studies that have followed women 10 to 15 years after childbirth have observed those who retained their GWG 6 months following childbirth were more likely to be obese later in life. Linne et al, for example, reported that 56% of women who were not overweight 15 years after childbirth were within 1.5 kg of their prepregnancy weight 6 months after delivery, compared to only 28% among those who were overweight. Rooney and Schaubberger<sup>4</sup> reported that 10 years after delivery, women who lost all of their GWG within 6 months were heavier by only 2. kg, whereas those who did not were heavier by over 8.3 kg. Thus, failure to lose intrapartum weight gain is associated with a long-term increase in weight. Since, only 37% of the women lose the GWG by 6 months, it is important to understand factors that affect weight loss after childbirth.

Pregnancies among active duty military women present a unique opportunity to evaluate the effects of weight gain and subsequent postpartum weight loss in a population of low-risk working women. U.S. Navy regulation (OPNAVINST 6110.1G) directs that all active duty women return to body weight standards within 6 months after childbirth. The evidence supporting this directive appears to be arbitrary. Weight standards for women not in the military, however, are based on guidelines from the IOM and American Congress of Obstetricians and Gynecologists (ACOG), with a BMI of ≥25 to 29.9 kg/m<sup>2</sup> being categorized as overweight and a BMI of ≥30 kg/m<sup>2</sup> as obese.

The primary purpose of this prospective cohort study was to determine the proportion of active duty women being within weight standards by 6 months postpartum and factors associated with this achievement. Secondly, we ascertained the factor(s) that influence whether the BMI was < vs.  $\geq 25$  kg/m<sup>2</sup> at 6 months postpartum and if the weight was within < or > 1.5 kg of prepregnancy weight.

## Materials and Methods

This study was approved by the Chief, Navy Bureau of Medicine and Surgery, Washington, DC, through the local Clinical Investigation Program (Naval Medical Center, Portsmouth; PO5-059). Patients were queried at the time of delivery to determine if they would still be within the Portsmouth area to answer additional questions about weight loss after the pregnancy and to be weighed at 6 months following the delivery. ACOG and IOM have made this marker follow-up criteria.<sup>6,7</sup> Women who met these criteria were invited to participate. Patients who would not be in the area for at least 6 months following delivery, delivered an anomalous fetus, had a multiple pregnancy, or refused participation were excluded.

Information collected on study participants included the demographics of age, race/ethnicity, gravidity, parity, prepregnancy weight, weight at delivery, weight gain during the pregnancy, maternal height, weight at 3 and 6 months postpartum, antepartum complications, self-reported level of exercise during the pregnancy and when it was altered, mode of delivery, gestational age at delivery, neonatal birth weight, postpartum complications, and if breastfeeding was initiated following delivery. All data were obtained from the electronic outpatient and inpatient records. Postdelivery information collected included the weight of active duty women at 3 and 6 months, when exercise was restarted, if that exercise was aerobic, how many days a week the women exercised, and if additional diets, dietary supplements, or formal dietary counseling was used to return within body weight standards.

The U.S. Navy regulation (OPNAVINST 6110.1G)<sup>5</sup> requires that 6 months after childbirth, active duty women be within weight standards, which ranges from 102 lbs for a height of 51 in to 263 lbs for 86 in, (BMI 24.9–27.6 kg/m<sup>2</sup>). To provide clinical correlation, the active duty participants (who are actually low-risk working women) were compared to other low-risk working women in the general population.<sup>1</sup> Another analysis compared active duty women with a BMI of < vs.  $\geq 25$  kg/m<sup>2</sup> based on a ACOG committee opinion, which classified women with a BMI of  $\geq 25$  kg/m<sup>2</sup> as being overweight vs. normal weight for BMI <25 kg/m<sup>2</sup>. The final analysis assessed the maternal weight at 6 months postpartum to determine if that weight was within 1.5 kg of the weight at the first prenatal visit. A weight within 1.5 kg of the weight recorded at the first prenatal visit has been shown to decrease the likelihood of being overweight 15 years later.

We included 14 covariates in the analyses. Each were categorized into several appropriate groups (i.e., BMI first visit, age  $\leq 19$ , 20–34, and  $\geq 35$  years, etc.) and are detailed in Tables I and II. Bivariate analyses were conducted to examine the relationship between each individual factor and the outcome variable.  $\chi^2$  tests or Fisher's exact tests were used to examine the group difference in proportion. Multivariate logistic regression models were conducted to examine the association between the risk factors and the outcomes. Results were presented as odds ratio (OR) and 95% confidence intervals (CIs). Statistical significance was defined as a p value <0.05. All statistical analyses were generated using SAS/STAT software, Version 9.2. (Cary, North Carolina).

## Results

During the 35 months of this study (July 2006 to May 2009), 1,009 women met our inclusion criteria and none declined participation in the study. Surprisingly at the onset of pregnancy, 68% (689) of the patients' weights were within the Navy standard, and by 6 months postpartum, less than half (49%) achieved this standard. Similarly, 53% (532) of the active duty populations had an initial BMI <25 kg/m<sup>2</sup>, and at the end of the study, only 32% (327) had a BMI <25 kg/m<sup>2</sup>. Finally, at 6 months after delivery, only 29% (297) of the active duty women were within 1.5 kg of their weight at the first prenatal visit. Based on the BMI at the start of the pregnancy, Figure 1 provides the percentage of women who at 6 months after childbirth, met Navy standards, had a BMI < 25, or were within 1.5 kg of their weight at the first visit.

Table I shows the sample characteristics. Of the 14 variables compared among women with weight within vs. not within the standard or BMI < vs. >25 kg/m<sup>2</sup>, seven were significantly different. These seven covariates were race/ethnicity (white), parity (0–1), BMI at the first prenatal visit (<25), mode of delivery (vaginal), episiotomy, birth weight (<4 kg), and additional methods used postpartum to reduce weight (none). The only variables significantly different among those who retained < vs. > 1.5 kg of their GWG were whether the delivery was vaginal and the birth weight of the newborns (<4 kg).

The result of multivariate analysis (Table II) indicates that there were three variables (BMI at the start of pregnancy (<25), vaginal delivery (vs. cesarean), and birth weight <4 kg that significantly influenced the proportion of parturients being within the Navy's standard at 6 months. Whether the women were < vs. > 25 kg/m<sup>2</sup> was not dependent on newborn weight but was reliant on the initial BMI, maternal age >35 years, and route of delivery. The only variable that differentiated achieving the Navy standard among women within 1.5 kg of their weight at first visit was whether they had vaginal or cesarean delivery.

## Discussion

Appropriate GWG during pregnancy is advisable, though excessive at times, whereas weight loss after childbirth is inevitable, but often insufficient. Inability to lose the weight gained during pregnancy contributes to long-term obesity, negatively influences outcomes of subsequent pregnancies, and is linked with the morbidity of being overweight. Thus, an understanding of factors related to achieving a desirable weight or not in the postpartum period is important. Earlier reports suggest that the following factors influence the extent to which weight gain during pregnancy is retained: ethnicity, maternal BMI before pregnancy, weight gained during pregnancy, counseling on diet and physical activities, breastfeeding, sleeping habits, postpartum depression, and nutritional knowledge. We sought to understand the factors associated with postpartum weight retention among active duty women because they are generally healthy, motivated, and incentivized.

There are several findings of this study. First, to our surprise one-third (32%) of the study participants began gestation over the Navy weight standard. This finding implies that the Navy weight standard is not rigorously adhered to during active duty. Furthermore, it imposes additional health risk on those parturients during future pregnancies, such as having an abdominal delivery, and makes it less likely that this group of women

can meet the postpartum weight requirement. In addition, 6 months after childbirth, about two-thirds (68%) healthy active duty women do not have normal BMI (<25) and 71% are not within 1.5 kg of the weight at the first prenatal visit. It is possible that many of these women will attain the preferred weight at 9 months or a year after childbirth, but a 15-year follow-up study by Linne et al<sup>3</sup> indicates that if a mother is not within 1.5 kg of their starting weight at 6 months, they are at increased risk of obesity and medical diseases such as hypertension and diabetes.

Even though the majority of the active duty women (68%) are within Navy standards at the start of the pregnancy, almost half (51%) do not return to Navy standards within 6 months after childbirth. If one in two women are unable to comply with the U.S. Navy regulation (OPNAVINST 6110.1G), then this regulation standard may need to be re-examined. The current Naval instruction does not calculate BMI to determine the desirable body weight composition and the use of weight/height accepts BMI ranging from 24.9 to 27.5 m/kg<sup>2</sup> (Fig. 1). Since ACOG, National Institutes of Health, and IOM<sup>1</sup>, recommends a BMI >25 as being unacceptable 6 months postpartum, should the U.S. Navy regulations also consider a change to this standard? Alternatively, if the current weight regulation persists, should it not be based on evidence similar to that in the current study?

The multivariate analysis (Table II) helps confirm our results as it removes factors not truly related to weight at 6 months postpartum, such as newborn birth weight and episiotomy. Understandably, being overweight at the start of pregnancy is a significant risk factor for not being able to meet Navy regulations (and having a BMI >25 m/kg<sup>2</sup>), 6 months after childbirth. Therefore, in a military population with a history of interpregnancy care, clinicians should have the opportunity to encourage women to achieve a normal weight preconceptually. Cesarean delivery was found, in this study, to significantly decrease the proportion of women who achieve a desired weight level after childbirth. This is important because isolated maternal obesity, without additional comorbidities, has been identified as an independent risk factor for cesarean delivery. The additional influence of weight gain during pregnancy is another factor that could affect the route of delivery, but our sample size was too small to determine its significance in this study. Unfortunately, the route of delivery was not related to our query on strategies to lose weight or other factors postpartum. Additional studies are needed to confirm this finding and to determine the influence of GWG gain along with or without prepregnancy obesity and interventions that would improve the weight loss for women who undergo cesarean delivery.

Lastly, there were factors that did not contribute to the desirable weight at 6 months. Surprisingly, breastfeeding, lack of exercise during pregnancy or postpartum period, nutritional support, and dietary counseling did not significantly influence the weight at 6 months. These negative findings are inconsistent with earlier reports because others have noted that counseling on diet, physical activities, and breastfeeding have a positive influence on weight loss. These studies, however, involved prescribed exercise routines and diets, whereas ours was based on patient perception and recall. Therefore, discrepancy between our findings and published reports among civilians may be due to methodology, sample size, or variables that do not influence the weight among active duty women.

There are limitations for this study. Principally, much of the data were self-reported in our study, thus making recall bias a significant concern that must be addressed by future studies with more strict criteria. Also, we only studied women in one branch of the Armed Forces. It is possible that these findings are not applicable to active duty women in the Air Force, the Army, or the Marine Corps, and additional studies are needed to confirm our results. It is also feasible that factors that influence weight loss for active duty women are not generalizable to the civilian population.

However, our findings may be applicable to low-risk working, civilian women, who are employed and whose work is similar to a large number of women who are active duty with their primary job being an administrative occupation. An additional shortcoming is that we did not assess some factors, such as weight gain during pregnancy, sleep habits, marital status, postpartum depression, smoking, and nutritional knowledge, which are all linked to weight loss after childbirth. In conclusion, among the active duty women in the U.S. Navy, at 6 months after delivery, the majority have not attained body weight within regulation nor a normal BMI. Preconceptional counseling regarding optimal weight at pregnancy onset, nutritional/exercise information, and the relationship of obesity to adverse outcomes may improve the likelihood of having a desirable weight after childbirth. A better understanding of factors and interventions that allow women to lose the weight gained during pregnancy is needed.

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## **Food production and obesity linked to climate change**

The Lancet Respiratory Medicine  
Bryant Furlow  
16 April 2013

Horse meat sold as beef has made headlines and provoked consumer outrage in the UK, but the contribution of global food production—and particularly meat—to climate change is the larger scandal, according to experts who spoke to The Lancet Respiratory Medicine.

“Meat and dairy are a hotspot for ecological public health”, notes Timothy Lang (Centre for Food Policy, City University London, London, UK). “About half the world's grain is fed to animals. The land and water use for such production systems are enormous. But this has created a situation where supposedly efficient modern agricultural systems have turned domestic animals as sources of cheap meat into direct competitors with humans for dominance in the ecological space.”

Although many people understand the threats that are posed to food systems by rising temperatures, extreme weather, and changing precipitation patterns, few seem to appreciate the degree to which human food production contributes to global climate change and the resulting health risks.

“It is bizarre that so many people in public health seem barely aware of food's massive contribution to climate change”, remarks Lang. “This is not just unfortunate but downright irresponsible.”

An estimated 14% of greenhouse gas emissions come directly from agriculture (putting it on par with transportation emissions). Increasing transportation distances to market worsens food's carbon footprint—a factor for which Lang coined the term “food miles.”

“A policy shift toward horticulture rather than animal-oriented agriculture is long overdue and is set to be a key challenge for the 21st century”, Lang believes. Public education campaigns to encourage people to eat less meat would seem to be the obvious direction for public health and environmental interventions meant to mitigate climate change. But public education is more easily advocated than implemented.

“In the past few years, several attempts to generate sustainable dietary advice for populations have come up against some big food-industry vested interests”, Lang says, citing recent controversies in Sweden, the UK, and Australia over proposed consumer advisories and nutritional guidelines. “Powerful interests will fight hard not to address the challenge of sustainability.”

Food production and agricultural and trade policies have been hijacked by a small number of large corporations in recent decades, agrees Wenonah Hauter (Food & Water Watch, Washington, DC, USA), whose father fled Oklahoma in the 1930s because of the so-called Dust Bowl—severe dust storms largely driven by agriculture.

In the USA, “20 large food processors own most brands on retail shelves”, notes Hauter. “Our political system is set up to allow companies to become larger and larger. During the Reagan administration, antitrust law was one of the main targets of the deregulatory agenda. They cut staff and enforcement budgets at regulatory agencies, and narrowed the definition of what constitutes an antitrust violation. Predictably, these companies became so large they're able to dictate food and farm policy on everything from what pesticides we're exposed to, to the way that food is made and labelled.”

US agriculture policy was further deregulated under the Clinton administration in the mid 1990s “to get in line with trade policy”, Hauter says. Deregulation of grain commodities during the 1990s saw increased corporate consolidation of corporate meat production, with the “factory farms” proportion of pork production, for example, rising from 30% in 1995 to 95% by 2005.

Under President Obama, efforts to curb junk food advertisements aimed at children yielded only “very weak voluntary guidelines”, Hauter says, which is testament to food industry lobbyists' sway in Washington DC.

“Governments don't govern; they follow”, cautions Lang. “Too often they are timid with regard to health and environment. The neoliberal perspective dominates: leave it to the consumer. But consumers are in the dark about the impact their food has on the planet, and the avalanche of cheap calories [in developed countries] acts as the model for what consumerism aspires to. But increasingly, scientists are aware that we need a new direction for food. We have to link human and environmental health.”

The burden of respiratory disease is expected to increase with global temperatures, and the link between respiratory disorders, such as asthma and sleep apnoea, could be compounded by the environmental consequences of climate change. Extreme heat, air pollutants such as ozone and particulate matter, and increased production of plant and fungal allergens, will all conspire to drive up respiratory morbidity and mortality rates.

Early modelling studies predict that concentrations of pollen from common tree species such as oak and birch, and weeds such as the highly-allergenic ragweed, will increase by 20—30% by 2020, and will continue climbing for decades to follow, notes Leonard Bielory (Center for Environmental Prediction, Rutgers University, Springfield, NJ, USA). The US Environmental Protection Agency is funding research at Rutgers University to assess the effect of climate change on allergenic airway disease, says Bielory.

The interactions between abundant cheap calories, obesity, and the environment can generate complex feedback loops between climate, food, and epidemiology. The industrial production and global transportation of food contributes to global climate change, which affects agriculture through changes in precipitation and temperature, and extreme weather events. The effects will be felt unevenly around the planet, further impoverishing Africa's agricultural base, for example. Overweight and obese people consume more food than others and rely disproportionately on travel by car, which together increases their carbon footprint to make obesity itself a serious global environmental problem, according to a 2009 study by scientists at the London School of Hygiene & Tropical Medicine.

Respiratory syncytial virus infections are more common when temperatures are higher. Prolonged drought and increased airborne levels of particulate matter from wildfire smoke and dust—including the intercontinental movement of dust from growing expanses of African desert—are expected to exacerbate asthma and COPD symptoms.

Concentrations of ground-level ozone, a highly oxidative air pollutant, are expected to rise in some regions and drop in others, leading to increased rates of respiratory distress, exacerbated airway diseases such as asthma, and respiratory infection risks, adds Hans Orru (Department of Public Health, University of Tartu, Estonia). Predicted increases in ground-level ozone will hit central and southern Europe harder than northern Europe, which is likely to see declines in ozone, Orru says.

“There are a number of interactions between plant biology, which will certainly be affected by rising CO<sub>2</sub> and increased temperature, and public health concerns. These interactions can run the gamut from aeroallergens to nutrition to pesticide use”, says Lewis H Ziska (Crop Systems and Global Change Laboratory, US Department of Agriculture, Beltsville, MD, USA). “There is initial evidence that all of these issues are already being affected.”

Recent and projected changes in atmospheric CO<sub>2</sub> have been shown to change yields of plant food proteins, antioxidants, and omega-3 fatty acids, Ziska points out. “One key question we have is whether or not rising CO<sub>2</sub> will also affect food allergies.” Ragweed pollen season has increased by as much as 13—27 days at higher latitudes since 1995, according to a 2011 study by Ziska, Bielory, and colleagues. Increased pollen seasons correspond to an increased number of frost-free days, Bielory notes.

Another key question is whether or not plant pollen might become more allergenic with changing temperatures or CO<sub>2</sub> levels. The effects of air pollutants on respiratory health can be compounded by the presence of respiratory allergens, Ziska notes. Pollen sticks to larger particulate matter associated, for example, with diesel fumes. “The particulate matter can act as a platform that attracts pollen and drives it further into the lungs”, Ziska explains. Sensitisation to common seasonal allergens has doubled over the past 20 years along with symptoms, Bielory has found.

In addition to airborne allergens, the effect of climate change on plant communities might lead to larger populations of disease vectors such as mosquitoes, whose larvae can feed on pollen.

AJ McMichael (National Centre for Epidemiology and Population Health, Australian National University, ACT, Australia) and others believe that major civilisational shifts, resulting in starvation, warfare, migration, and revolution, have accompanied abrupt climatic change in the past. A recent report even links droughts in wheat-producing regions of the globe with the Arab Spring uprisings in countries that are among the largest wheat importers.

Climate change will unveil complex interactions between plants and human physiology, Ziska concludes. “We are getting a sense of what some of those interactions are, and how significant they are, but we have a great deal more yet to do”. Untangling these interactions will be a major interdisciplinary endeavour.

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## ***PTSD***

# **Symptoms and Subjective Quality of Life in Post-Traumatic Stress Disorder: A Longitudinal Study**

Public Library of Science

Domenico Giacco, Aleksandra Matanov, Stefan Priebe

9 April 2013

Abstract

Background

Evidence suggests that post-traumatic stress disorder (PTSD) is associated with substantially reduced subjective quality of life (SQOL). This study aimed to explore whether and how changes in the levels of PTSD symptom clusters of intrusion, avoidance and hyperarousal are associated with changes in SQOL.

Methods

Two samples with PTSD following the war in former Yugoslavia were studied, i.e. a representative sample of 530 people in five Balkan countries and a non-representative sample of 215 refugees in three Western European countries. They were assessed on average eight years after the war and re-interviewed one year later. PTSD symptoms were assessed on the Impact of Event Scale - Revised and SQOL on the Manchester Short Assessment of Quality of Life. Linear regression and a two-wave cross lagged panel analysis were used to explore the association between PTSD symptom clusters and SQOL.

## Results

The findings in the two samples were consistent. Symptom reduction over time was associated with improved SQOL. In multivariable analyses adjusted for the influence of all three clusters, gender and time since war exposure, only changes in hyperarousal symptoms were significantly associated with changes in SQOL. The two-wave cross-lagged panel analysis suggested that the link between hyperarousal symptoms and SQOL is bidirectional.

## Conclusions

Low SQOL of patients with war-related PTSD is particularly associated with hyperarousal symptoms. The findings suggest a bidirectional influence: a reduction in hyperarousal symptoms may result in improved SQOL, and improvements in SQOL may lead to reduced hyperarousal symptoms.

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## Introduction

Patients with post-traumatic stress disorder (PTSD) report a poorer subjective quality of life (SQOL) than patients with other anxiety disorders.

In recent years, SQOL has become a widely established patient-reported outcome in severe mental disorders. The most established definition of SQOL is based on the Lehman's approach, which considers SQOL as the patient's satisfaction with life in general and with a number of major life domains.

The negative correlation between general PTSD symptom levels and subjective quality of life has been shown both in cross-sectional and longitudinal studies.

However, to our knowledge, only two studies, carried out in relatively small and non-representative samples, have investigated which symptom clusters of PTSD (defined according to DSM-IV as: intrusion, i.e. the persistent re-experience of the traumatic event with intrusive thoughts and images; avoidance, i.e. the persistent avoidance of stimuli associated with the traumatic event and "numbing" of general responsiveness; and hyperarousal, i.e. persistent symptoms of increased arousal) are particularly associated with poorer SQOL. The results were inconsistent. D'Ardenne and colleagues reported that lower levels of avoidance were cross-sectionally associated with poorer quality of life. In a longitudinal study, Loncar and colleagues found that changes in avoidance and hyperarousal clusters predicted changes in quality of life.

Our study assessed a large sample of people who met criteria for PTSD diagnosis following exposure to traumatic events during the war in former Yugoslavia. The data was collected within the CONNECT study, a multi-centre observational study on mental health consequences of war and migration. It assessed the prevalence of mental disorders in war-exposed people and the course of PTSD over time. The prevalence rate of PTSD in Balkan residents was 20% and in refugees 33%. In Balkan residents, risk factors for being diagnosed with PTSD were older age, female sex, more traumatic experiences during and after the war, and unemployment. In refugees, older age, a lower level of education, more traumatic experiences during and after the war, more migration-related stress, not feeling accepted by the host population, and having a temporary residence status were associated with having PTSD. People with PTSD generated significantly higher health and social care costs.

In this longitudinal study we explored, in a sample size providing a high statistical power, whether and how changes in the levels of PTSD symptom clusters of intrusion, avoidance and hyperarousal are associated with changes in SQOL. We also assessed the direction of possible associations, i.e. whether symptom improvement leads to better SQOL or if improved SQOL results in symptom reduction. Associations between PTSD symptoms and SQOL were separately investigated in two samples: a representative sample of people who still lived in the post-conflict areas in five Balkan countries and a non-representative sample of refugees in three Western European countries. The direction of associations between PTSD symptom clusters and SQOL was explored by pooling data from the two groups in a common dataset and conducting a cross-lagged panel analysis of the reciprocal associations between PTSD symptom clusters and SQOL.

## Materials and Methods

The data was collected within the CONNECT study, a multi-centre observational study on mental health consequences of war and migration. The observational study (funded by the Research Directorate of the European Community) was conducted in war-affected communities in five Balkan countries (Bosnia and Herzegovina, Croatia, Macedonia, Kosovo, Serbia) and among refugees in three Western European countries (Germany, Italy, United Kingdom, i.e. the three countries in Europe with the highest numbers of immigrants in the 1990s). CONNECT assessed the prevalence of mental disorders in war-exposed people and the course of PTSD over time. A detailed description of the rationale and methods of the CONNECT project is available in previous publications.

### Ethics Statement

Written informed consent was obtained from all participants prior to the interview. The study was approved by the Royal Free Medical School Research Ethics Committee (REC reference number 04/QO501/118) and conducted in compliance with the Code of the Ethics of the World Medical Association as reported in the Declaration of Helsinki (2004).

### Sampling Techniques and Participants

The assessments were carried out between January 2005 and November 2006. The global sample of the study included Balkan residents and refugees in Germany, Italy and United Kingdom.

A representative sample of residents in war-affected communities in five Balkan countries was recruited. Participants were chosen using a multi-stage probabilistic sampling frame and random walk approach in administrative regions that had been directly exposed to war activities. Areas and streets were randomly selected, and interviews were conducted in every fourth household. The eligible adult members of the identified households whose birthday was closest to the date of interviewing were asked to participate.

A sample of refugees from former Yugoslavia resettled in Germany, Italy and United Kingdom was also recruited in the study. For this sample a combination of random and non-random sampling approaches was adopted. In Germany and Italy, potential interviewees were identified through resident registers and snowball sampling. Due to the absence of such registers in the United Kingdom, potential interviewees were contacted through community organisations and snowball sampling.

The following inclusion criteria were applied: a) being born within the territory of former Yugoslavia; b) being between 18 and 65 years of age; c) having experienced at least one war-related potentially traumatic event and d) not having severe learning difficulty or mental impairment due to brain injury or other organic causes. Participants were excluded if they had experienced the last war-related event before 16 years of age.

Six hundred and sixty-five Balkan residents and 283 refugees met the criteria for PTSD on the MINI instrument at baseline. Out of these we attempted to follow up 620 Balkan residents (in Bosnia and Herzegovina the number of participants with baseline PTSD was too large to follow up all of them and 150 were randomly selected for re-interviews) and all of the refugees.

Numbers of eligible participants, those who were attempted to follow up, lost to follow up and interviewed in each country are reported in Table 1.

Table 1. Summary of recruitment and follow-up in each country.

#### Procedures and Measures

Socio-demographic characteristics of participants including their age, sex, marital status, educational level, and current employment status were obtained using a brief structured questionnaire.

Mental disorders were assessed on the Mini International Neuropsychiatric Interview (MINI), a structured and validated diagnostic interview. The symptom criteria in this instrument are assessed corresponding to the diagnosis Axis 1 of the DSM–IV. The instrument has been used previously in war-affected and refugee groups.

The level of post-traumatic stress symptoms was measured on the Impact of Events Scale-Revised (IES-R). This self-report instrument assesses 22 intrusion, avoidance and hyperarousal symptoms within the last 7 days with regard to a specific traumatic event. Each IES-R item is rated on a five-point scale of distress (0–4).

Manchester Short Assessment of Quality of Life (MANSA) was used to assess subjective quality of life. The MANSA contains 12 items on satisfaction with life in general and with various life domains (employment, financial situation, friendships, leisure activities, accommodation, personal safety, living situation, sex life, relationships with family, physical health, mental health) which are rated on a scale from 1, could not be worse, to 7, could not be better. The MANSA has shown good psychometric properties: Cronbach's alpha for MANSA items scores was 0.74 and MANSA mean score had a strong correlation with another established instrument for SQOL measurement, the Lancashire Quality of Life Profile, which has a much higher number of items. The mean score of the MANSA was taken as a measure of SQOL.

Post-traumatic symptoms and SQOL were reassessed after 12 months.

At both time points, interviews were conducted face-to-face by 33 trained interviewers, who were qualified psychologists, psychiatrists, sociologists or anthropologists. All those instruments for which there had been no validated translations in the relevant languages were translated and back-translated into English.

#### Statistical Analysis

Descriptive statistics were used to summarise the characteristics of participants who completed follow-up in the two samples. The differences in socio-demographic and clinical characteristics of participants who were followed-up and those who dropped out from the study were assessed

using two-tailed X2 tests and analysis of variance (ANOVA) tests, depending on the type of data. For one hundred and thirty-five participants who completed the follow-up (18.1%) a maximum number of two items was missing from IES-R and/or MANSA. To avoid potential problems of a list-wise deletion of incomplete cases a multiple imputation procedure was conducted.

Two-tailed paired t-tests were used to compare MANSA total score and IES-R subscales scores between baseline and follow-up.

Univariable linear regression models were used to explore, in the two groups (Balkan residents and refugees), associations between follow-up scores of PTSD symptom clusters of intrusion, avoidance and hyperarousal (IES-R) and SQOL. The univariable association of each cluster with SQOL at follow-up was adjusted for the scores of the given symptom cluster and SQOL at baseline. This type of analysis is commonly used for exploring changes over time although strictly speaking it does not use change scores.

Multivariable models were tested to adjust associations between symptom clusters and SQOL for confounding factors. With SQOL at follow up being the dependent variable again, scores of the three symptom clusters at follow-up were independent variables. The associations were adjusted for baseline scores of the three symptom clusters and SQOL as well as socio-demographic and clinical variables that were significantly associated with SQOL at follow up. As potentially relevant sociodemographic and clinical variables, age, gender, years in education, marital status, unemployment, living alone, comorbidity with other mental disorders, number of years since the exposure to traumatic events and country of residence were tested.

A two-wave cross lagged panel analysis was used to assess the direction (temporal ordering) of the association of the symptom clusters, which significantly covaried with SQOL over time, and SQOL. This method has been widely used to establish the direction of relationships between psychiatric symptoms and environmental factors. The cross-lagged panel analysis was carried out on the pooled dataset in order to achieve an adequate sample size. The Cronbach's alpha values of all the variables used (MANSA total score at baseline and follow-up; IES-R hyperarousal subscale at baseline and follow-up) were calculated to ensure that their internal consistency was sufficiently high to be included in the model, without creating latent variables.

Since we found a correlation between hyperarousal symptoms and SQOL ( $p < .01$ ) at baseline and at follow-up in Pearson's tests, the variables measured at the same time point were allowed to covary, resulting in a fully saturated model.

Stata 12 for Windows was used for all data analyses.

## Results

A summary of recruitment and follow up is reported in Table 1.

Seven hundred and forty-five subjects diagnosed with PTSD were included in the analysis, i.e. 530 Balkan residents (follow up rate: 85.5%) and 215 refugees (follow-up rate: 76%). The diagnosis was established according to the MINI. Rating agreement among interviewers was assessed for the MINI in 2 mock interviews. An agreement on an item was reached when all interviewers gave it the same answer. Among 251 items, the mean agreement rate across 2 sessions was 90.2%.

Overall, re-interviewed participants were significantly more often female (56% vs. 41%,  $X^2 = 11.475$ ,  $df = 1$ ,  $p < .001$ ), had experienced fewer traumatic war events (6.5 SD = 3.4 vs. 7.6 SD = 3.8,  $F = 14.210$ ,  $df = 1.902$ ,  $p < .001$ ), had less often participated in war activities (22% vs. 39%,  $X^2 = 12.253$ ,  $df = 1$ ,  $p < .001$ ), and had experienced the most traumatic war event a shorter time before the study (9.1 SD = 3.2 vs. 10.0 SD = 3.1,  $F = 17.854$ ,  $df = 902$ ,  $p < .001$ ). No significant differences in baseline PTSD symptoms and SQOL levels were found.

The main socio-demographic and clinical characteristics of the total sample and of the Balkan residents' and refugees' groups are summarized in Table 2.

Table 2. Patients' characteristics.

At the one year follow-up, the levels of SQOL were significantly improved in both samples and the scores of the IES-R subscales were significantly reduced ( $p < .001$  for all paired t-tests).

Linear regression models for association of changes in PTSD symptom clusters and SQOL in Balkan residents and refugees are reported in Table 3 and Table 4, respectively.

Table 3. Univariable and multivariable linear regression models<sup>b,c,d</sup> describing the relationship between subjective quality of life and PTSD symptoms in residents in war-affected countries ( $n = 530$ ).

Table 4. Univariable and multivariable<sup>b,c,d</sup> linear regression models describing the relationship between subjective quality of life and PTSD symptoms in refugees in western countries ( $n = 215$ ).

In the univariable models, reduction in all symptom clusters levels was associated with improvements in SQOL. Besides symptoms, only gender and number of years since the end of the exposure to traumatic events had a significant association with SQOL at follow up. These variables were entered in the multivariable model, adjusted for baseline scores of all symptom clusters and SQOL. In the multivariable models, only changes in hyperarousal symptoms were correlated with SQOL changes. The results were consistent in both samples.

The values of tests for multicollinearity for these multivariable models were in the acceptable range (all values of tolerance were above 0.1 and all values of VIF were less than 5).

The four variables used in the cross-lagged panel analysis (hyperarousal symptoms and SQOL both at baseline and at follow up) had a good internal consistency. Cronbach's alpha values were 0.861 for IES-R hyperarousal subscale at baseline, 0.910 for IES-R hyperarousal subscale at follow-up, 0.810 for SQOL at baseline and 0.857 for SQOL at follow-up. These variables were, therefore, used in the model as measured variables without a need for creating latent variables.

Figure 1 shows the results of the two-wave cross lagged panel analysis.

Figure 1. Cross-lagged panel analysis of relationship between hyperarousal and subjective quality of life in PTSD (n = 745).

SQOL and IES-R hyperarousal subscales scores had a significant inverse correlation at baseline (Pearson test's value:  $-.286$ ,  $p < .01$ ) and at follow-up (Pearson test's value:  $-.430$ ,  $p < .01$ ), hence the variables measured at the same time point were allowed to covariate in the model.

The association between hyperarousal symptoms and SQOL was bidirectional. A statistically significant negative beta coefficient was found for the path from hyperarousal symptoms at baseline to SQOL at one year-follow up ( $b = -.068$ ,  $p < .01$ ). Also the path for the reverse temporal ordering, from SQOL at baseline to hyperarousal symptoms at one year-follow up, was statistically significant ( $b = -.162$ ,  $p < .001$ ).

## Discussion

### Main Results

Changes in hyperarousal symptoms were associated with changes in SQOL over time in both univariable and multivariable models, controlled for other symptom clusters and main socio-demographic and trauma-related characteristics. Changes in intrusion and avoidance symptoms are linked with SQOL changes in univariable models only, in which they may just reflect the global severity of the PTSD symptomatology.

A cross-lagged panel analysis suggested a reciprocal influence between hyperarousal and SQOL. A reduction of hyperarousal symptoms may lead to improved SQOL, and – vice versa – an improved SQOL may also result in reduced PTSD symptoms.

### Strengths and Limitations

This is the largest longitudinal study to date assessing SQOL in people with PTSD. The sample of Balkan residents can be considered representative for war affected people in the participating countries. Consistent assessment methods were used across eight countries and the samples included both civilians and people who actively participated in the war. Standardized instruments for measuring PTSD symptoms and SQOL were administered face to face by trained researchers. Interrater reliability between research workers was excellent (90%). Findings in the two samples were consistent, although they differ in their characteristics and live in a different context.

There are also limitations: 1) Refugees' sample cannot be considered representative. However, the data protection legislation and the absence of complete data registers in the Western European countries do not allow for fully representative sampling of refugees, and the results in refugees are consistent with those in Balkan residents, indicating an overall validity; 2) The associations identified in this analysis might be explained by confounding factors that have not been assessed in the study (i.e. genetic and biological factors); 3) The cross-lagged analysis shows how different scores follow each other, but does not establish causality; 4) Not all participants interviewed at baseline were followed up and there is no data on the changes of PTSD symptoms and SQOL in those who were not followed up. We cannot rule out that a selection bias may have influenced the results, since subjects who dropped out were more frequently male and with a more intense exposure to war events. However, the levels of PTSD symptoms and SQOL at baseline did not differ between drop-out and people re-interviewed at follow-up; 5) PTSD symptoms are known to fluctuate over time and this might have influenced the results.

### Comparison with Literature

In our study, high levels of hyperarousal symptoms were associated with lower SQOL in people with war-related PTSD. Hyperarousal was the only symptom cluster that showed an association with SQOL when controlling for all the symptom clusters in multivariable models. The association of higher levels of hyperarousal symptoms with poorer SQOL has already been reported in smaller samples of people with PTSD. This association may be explained in light of the specific types of symptoms included in hyperarousal cluster. Sleeping difficulties and recurrent nightmares may significantly reduce levels of satisfaction with physical and psychological health and are particularly resistant to treatment. Hypervigilance and irritability could pose difficulties in family and social relationship and difficulties in concentration may reduce work and personal functioning. The findings of this study show that the improvement of these very distressing symptoms is associated with better SQOL, independently from changes in other symptom clusters.

On the other hand, in our study, avoidance and intrusion levels did not show a significant association with SQOL in multivariable models. Avoidance may even work as a coping strategy, temporarily reducing discomfort and limiting severe dissatisfaction with quality of life. Similarly, people with PTSD might deal with the recurrence of intrusive image or thoughts by avoiding "triggering" events or conditions, trying to distract themselves or even adopting unhealthy behaviours like alcohol and benzodiazepines abuse; this may reduce the impact of intrusion symptom cluster on subjective quality of life. The enduring discomfort related to high levels of hyperarousal symptoms and the related generalized anxiety may be more difficult to cope with than the more specific anxiety captured in some intrusion and avoidance symptoms and lead to a negative impact on SQOL.

Finally, our results suggest that a poorer SQOL, which may be due to psychosocial factors (unemployment, social isolation, economic problems, etc.), might influence the level of hyperarousal symptoms. The impact of poor living conditions on the level of anxiety symptoms has already been described in PTSD. As documented in patients with personality disorders, the sense of safety has a strong influence on SQOL. Precarious living conditions may be at least partially responsible for the persistence of higher levels of hyperarousal symptoms. On the other hand, a feeling of being unsafe, as reflected in hyperarousal symptoms, might impair a positive perception of living conditions and, therefore, reduce SQOL scores. SQOL and hyperarousal symptoms may reflect different but related aspects of feeling unsafe and threatened.

## Implications

Taking into account the association between hyperarousal symptoms and SQOL, hyperarousal symptoms should be a primary target for treatment aimed at improving SQOL in war related PTSD. Some evidence suggests that selective serotonin reuptake inhibitors, mood stabilizers and atypical anti-psychotics may be effective in reducing hyperarousal symptoms. Sympatholytic drugs appear to be particularly useful as an add-on therapy for treatment-resistant hyperarousal symptoms such as nightmares. Furthermore, several studies have documented the positive effects of psychological therapies such as trauma-focused cognitive behavioral therapy, eye movement desensitization and reprocessing, and in particular, of relaxation training on hyperarousal.

Our findings indicate a bidirectional association between hyperarousal symptoms and SQOL. Whilst symptom reduction may improve SQOL, improvements of SQOL may result in reduced hyperarousal symptoms. One can speculate as to whether social interventions improving life conditions of people with PTSD might ameliorate their hyperarousal symptoms. In fact, social support has been associated with a higher likelihood of recovery in PTSD patients whereas the presence of specific stressors, such as those related to migration, is associated with higher PTSD symptom levels. Identifying and meeting the psychosocial needs of people with PTSD may be important for improving SQOL and, as a consequence, lead to a remission of hyperarousal which reflects “core” symptoms of PTSD.

## Conclusions

The subjective quality of life of individuals with war related PTSD is particularly associated with their levels of hyperarousal symptoms. Experimental studies are required to explore whether the associations found in this large observational study reflect causal relationships that translate into direct treatment recommendations. These studies should test whether treatments targeting hyperarousal symptoms have a beneficial effect on SQOL, and whether effective social interventions specifically reduce hyperarousal symptoms.

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## **A Systematic Review of PTSD Prevalence and Trajectories in DSM-5 Defined Trauma Exposed Populations: Intentional and Non-Intentional Traumatic Events**

Public Library of Science

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11 April 2013

## Abstract

### Objective

We conducted a systematic review of the literature to explore the longitudinal course of PTSD in DSM-5-defined trauma exposed populations to identify the course of illness and recovery for individuals and populations experiencing PTSD.

### Methods

We reviewed the published literature from January 1, 1998 to December 31, 2010 for longitudinal studies of directly exposed trauma populations in order to: (1) review rates of PTSD in the first year after a traumatic event; (2) examine potential types of proposed DSM-5 direct trauma exposure (intentional and non-intentional); and (3) identify the clinical course of PTSD (early onset, later onset, chronicity, remission, and resilience). Of the 2537 identified articles, 58 articles representing 35 unique subject populations met the proposed DSM-5 criteria for experiencing a traumatic event, and assessed PTSD at two or more time points within 12 months of the traumatic event.

### Results

The mean prevalence of PTSD across all studies decreases from 28.8% (range = 3.1–87.5%) at 1 month to 17.0% (range = 0.6–43.8%) at 12 months. However, when traumatic events are classified into intentional and non-intentional, the median prevalences trend down for the non-intentional trauma exposed populations, while the median prevalences in the intentional trauma category steadily increase from 11.8% to 23.3%. Across five studies with sufficient data, 37.1% of those exposed to intentional trauma develop PTSD. Among those with PTSD, about one third (34.8%) remit after 3 months. Nearly 40% of those with PTSD (39.1%) have a chronic course, and only a very small fraction (3.5%) of new PTSD cases appears after three months.

### Conclusions

Understanding the trajectories of PTSD over time, and how it may vary by type of traumatic event (intentional vs. non-intentional) will assist public health planning and treatment.

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## Introduction

Longitudinal studies of responses to traumatic events document the course of illness and recovery in trauma-exposed populations confirming, as the Diagnostic and Statistical Manual (DSM) has written, that posttraumatic stress disorder has a variable course that can be acute or chronic, remitting after only three months, delayed after six months, or lasting for years. Other studies have longitudinally examined the effectiveness of treatment interventions, which highlight the advantage of early intervention to shorten the time to remission of symptoms. Data from control groups in these intervention studies often also reveal the natural course of PTSD. Studies using DSM-IV criteria have followed subjects to examine the epidemiology of PTSD after disasters, other traumatic events, and military deployment again finding substantial variability across different populations, traumatic events and community contexts. Knowing patterns of response after traumatic events can inform health system interventions after a disaster or traumatic event.

The proposed DSM-5 criteria highlight the importance of direct exposure as a specific category of traumatic experience and serve to narrow variation in the application of this criterion. Experiences that meet the DSM-IV and proposed DSM-5 traumatic events criterion range from direct exposure, such as motor vehicle accidents, mud slides, and terrorist attack, to witnessing a traumatic event. A number of studies have examined broad classifications of trauma exposures, including natural vs. human-made and intentional vs. non-intentional. The importance of differences between intentional and non-intentional traumatic events has been explored when examining treatment efficacy and attrition. Intentional traumas are those that involve the deliberate infliction of harm, and those exposed to intentional traumatic events had worse health outcomes than those who experienced harm that was inadvertent.

In order to better understand the course of PTSD during the first year after exposure, we conducted a systematic review of the empirical literature. We identified longitudinal studies reporting the prevalence of untreated PTSD in the same cohort or in a nationally representative sample, at two or more points in time within one year after direct exposure to a traumatic event that met the proposed DSM-5 criterion. We examined the longitudinal prevalence of PTSD in exposed populations, as well as the course of illness and recovery for individuals experiencing PTSD (early onset, later onset, chronicity, remission and resilience) in the first year after trauma exposure. This paper provides PTSD prevalence estimates,

including the differences in prevalence between intentional and non-intentional traumas, which may inform our understanding of both prognosis and recovery, as well as have implications for public health treatment needs.

## Methods

### Search Criteria

We reviewed the published literature from January 1, 1998 to December 31, 2010 for longitudinal studies of populations directly exposed to traumatic events. We chose 1998 to begin our review in order to update the literature since the review by Breslau et al (1998). We used the DSM-5 criteria for direct exposure PTSD to define a traumatic event and included studies published in English that measured PTSD prevalence using validated measures at two or more time points within twelve months post-trauma. Because we sought to identify patterns in the natural course of responses and recovery, we excluded studies if the subjects received treatment or other interventions, unless data from a control group were available. In addition, studies were excluded if they failed to meet the one-month duration criterion, if they measured only PTSD symptoms and not disorder, if the population of interest was children or adolescents under 18 years old, or if the study identified pregnancy or childbirth as a traumatic event (unless it was specified as a complicated or extraordinary event such as miscarriage). Finally, studies were excluded if the PTSD prevalence was not reported directly or was reported in a way that could not be calculated.

Our search strategy for this review involved three stages. First, we used PubMed and PILOTS databases to find abstracts using keyword combinations that included PTSD and each of the following: 'longitudinal', 'acute' and 'chronic', and key authors known to have conducted extensive research on the course of PTSD. Second, the citations were cross-referenced to eliminate duplicates prior to reviewing abstracts. Third, 2537 unique abstracts were reviewed. Those that explicitly stated inclusion criteria or provided information suggesting that the article may meet inclusion criteria were marked for further review.

### Analysis

In some studies, the desired information (prevalence of PTSD in the same cohort or in a representative sample at two or more time points) was not directly presented in the article. When possible, that information was calculated using other data presented in the article. In some cases, approximations were used to estimate time. For example, if a range of 4–8 months was provided for a time point, the midpoint (6 months) was used as the time point for the purpose of examining the course of illness for PTSD. Different articles with the same subject populations were combined as single studies. We grouped the data for each study into categories of 1, 3, 6, and 12 months post-trauma to allow comparison across studies and over time. Because the data are not symmetrically distributed, medians better represent the average values and were calculated at each of these time points.

All of the studies met the proposed DSM-5 criterion A. That is, the subject experienced "...one of the following event(s): death or threatened death, actual or threatened serious injury, or actual or threatened sexual violence...". To better understand the relationship between the nature of the

traumatic event and the course of PTSD, we classified the traumatic events into either intentional (e.g., assault, war) or non-intentional (e.g., earthquake, motor vehicle accident). This classification yielded 14 intentional and 21 non-intentional traumatic event studies.

Of the 2537 identified articles, 58 articles representing 35 unique subject populations met criteria of being assessed for PTSD at two or more time points within 12 months of a traumatic event and met the proposed DSM-5 criteria for experiencing a direct traumatic event. Those 35 populations were analyzed for this review (Table S1). The trauma exposures include: motor vehicle/plane crash (N = 8 studies), assault (N = 4), terrorism (N = 7), war as a combatant or civilian (N = 3), natural disaster (N = 4), severe injury warranting a hospital visit (N = 7), and serious, life-threatening medical condition (N = 2). For our analysis of trajectories, we identified studies that included a report of PTSD assessed in individual subjects in at least two time points within a year. This made possible identifying the course of PTSD in individual subjects. Among our examined studies, five of the 14 intentional trauma studies included sufficient information to examine the PTSD trajectory of individual subjects, allowing for calculation of the trajectories of PTSD within individuals. These studies reported PTSD at two different time points, where Time 1 was 1 to 1.5 months (4–6 weeks) post-trauma, and Time 2 was 3 to 12 months post trauma. Data was not sufficient to perform parallel analyses for non-intentional trauma. We calculated the percent of individuals who were never diagnosed with PTSD (were resilient), achieved remission during the first year, had a late onset of PTSD, and those who experienced chronic symptoms of PTSD.

## Results

### Longitudinal Prevalence of PTSD by Trauma Type

We examined medians of the PTSD prevalence at each time point (Table 1). In general, the trend of the means and medians are similar. The median prevalence of PTSD across all studies decreases from 28.8% (range = 3.1–87.5%) at 1 month to 17.0% (range = 0.6–43.8%) at 12 months (see Table 1). There is a drop in PTSD median prevalence between month 1 (28.8%) and month 3 (17.8%), after which the median prevalence appears to stabilize. These prevalences are similar to previously published rates across different types of traumatic events.

Table 1. Mean and median prevalence of PTSD in exposed populations meeting DSM-5 Direct Experiencing criteria (N = 35 studies). 1

Examination of PTSD prevalence across time (1, 3, 6 and 12 months) in the different traumatic event categories shows some differences by category (see Table 1). The trend in PTSD prevalence among those exposed to a non-intentional trauma is decreasing over time (30.1% at month 1 and 14.0% at month 12). The intentional trauma group shows a different course with the median prevalences increasing from 11.8% to 23.3%. This is particularly visible in the graphs of the median prevalence over time (Figure 1).

Figure 1. Median prevalence of PTSD in DSM-5-Experiencing categories of intentional and non-intentional trauma (N = 14 and 21 studies, respectively).

### Trajectory of PTSD

Of individuals exposed to intentional traumatic events, a median of 37.1% (range 6.5–87.5%) developed PTSD in the first year after exposure (Table 2). Therefore, 62.9% (range 12.5–93.5%) never developed PTSD. Among the exposed, a median of 12.9% (range 1.7–43.8%) had PTSD only at Time 1. This represents 34.8% of those ever diagnosed. Similarly, a median of 14.5% had PTSD at both Time 1 and Time 2 (39.0% of those diagnosed with PTSD) and 1.3% had PTSD onset after Time 1 (3.5% of those diagnosed with PTSD).

Table 2. Individual trajectories of PTSD prevalence in DSM-5-Direct Experiencing category with intentional trauma exposure (N = 5 studies).<sup>2</sup>

## Discussion

Overall, we found that when we separated intentional and non-intentional trauma, two population courses were suggested for the prevalence of PTSD across time. The prevalence of PTSD increased over time after intentional traumatic events and decreased after non-intentional traumatic events, indicating the overall public health burden of PTSD was greater in those exposed to intentional traumatic events. Of note, at one month, non-intentional traumatic events had a higher median prevalence of PTSD than intentional trauma. For public health planning, recognizing that the type of the traumatic event may mean a different natural course of the disorder can affect resource planning and treatment.

In order to examine the trajectory of PTSD, we examined studies of populations that had directly experienced traumatic events as listed in DSM-5, which are the most studied in the existing literature. Other proposed A criteria (i.e., witnessing an event, learning of an event, or experiencing repeated indirect exposures) may yield other courses and trajectories. There were only a small number of studies that met our criteria for addressing individual trajectories of PTSD over time, and all of these were for intentional traumatic events. The trajectories of PTSD after intentional traumatic events show wide variability, but on average, approximately one-third of those exposed developed PTSD in the first year. Importantly, nearly two-thirds did not. Among those with PTSD, about one third remitted within 3 months, while 39% of those with PTSD had a chronic course, supporting the notion that PTSD can spontaneously resolve or continue as a persistent disorder. Onset of PTSD after 3 months represented a small fraction (3.5%) of the total PTSD cases. Nevertheless, a “delayed expression” specifier to the diagnosis is supported by the data.

Our study did not examine predictors or risk factors that may modulate the different courses of PTSD in populations related to intentional and non-intentional exposures. These include genetic, dispositional, and recovery environment factors. Specifically, the types of populations exposed to intentional and non-intentional traumas can differ substantially in characteristics and contextual issues, due to socioeconomic factors, employment, cultural differences, and available resources. These factors can substantially contribute to the different courses of PTSD. A recent study of PTSD that examined multiple studies across different disaster types similarly found differences in rates of PTSD between intentional and non-intentional disasters (26% in “intentionally caused” disasters compared to 10% and 16% in “technological” and “natural” disasters, respectively). However, the differences were not present after controlling for pre-disaster conditions and sample characteristics. This is consistent with our findings and suggests that the difference in outcomes between intentional and non-intentional traumatic events is mediated by the severity of exposure, the characteristics of the populations exposed, and the recovery environment.

Few studies have followed participants for more than a year and with more than two assessments. This is unfortunate since it limits what one can investigate. For example, in the 20-year longitudinal study of Israeli veterans of the Lebanon War, which delineates the diagnostic patterns of 214 veterans at 1, 2, 3, and 20 years, a fluctuating course of PTSD (e.g., a variable pattern of remissions and relapses) was detected along with the remitting, persistent and delayed courses observed in the present study. In addition, studies of different disaster types and across cultures may yield different PTSD trajectories.

This study is limited by the relatively few studies available with longitudinal data. Our study is also focused only on directly experienced traumatic events. The broad set of categories originally delineated by the 1996 Detroit-area survey studying trauma and PTSD in the community grouped events as “assault,” “other injury or shocking experience,” “learning about trauma to others,” or “sudden unexpected death of a close friend or relative.” The latter two categories exemplify indirect traumatic exposure and, therefore, were not included in this review. In contrast, the two former categories map onto our broader terms of intentional and non-intentional traumatic events so they were included. This study also examined the literature from a specific 13-year period when the DSM-IV definition of PTSD was in use. We considered possible bias in the data in the studies we examined. Psychiatric epidemiology studies consistently report a lifetime prevalence of PTSD of approximately 8%, however, post-disaster rates of PTSD vary widely, and are similar to those found here. One could expect measurement bias in our study because of the different instruments used to obtain data in the different studies. However, this would not substantially affect the overall patterns found in this study, as the same instruments were used across time in individual studies. To further explore our finding of an increasing rate of PTSD in intentional traumas with an overall decreasing rate in non-intentional traumas, more detail on traumatic event characteristics, the degree of exposure and the context would be helpful. Systematically including this information in future studies will be required to address these issues.

Our results indicate that the type of events, whether being intentional or non-intentional, appear to affect both the prevalence of PTSD and its trajectories over time. Our findings reinforce the importance of longitudinal research in understanding the course, prognosis, and severity of PTSD. Such information is valuable for planning and implementing appropriate individual and population level interventions.

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## **Efficacy of Stellate Ganglion Block in the Treatment of Anxiety Symptoms From Combat-Related Post-Traumatic Stress Disorder: A Case Series**

Military Medicine

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Abstract

Objective: Report the efficacious use of stellate ganglion blocks (SGBs) in treating the anxiety symptoms of four patients diagnosed with combat-related post-traumatic stress disorder (PTSD) and discuss possible mechanisms of action to explain these findings. Background: Successful treatment of PTSD with SGB has been demonstrated and reported previously at Walter Reed Army Medical Center. An identical protocol was used at Tripler Army Medical Center to treat four service members diagnosed with combat-related PTSD. Methods: All patients reported received an SGB on the right side at the level of C6. The patient's PTSD symptoms were evaluated using the Post-traumatic Stress Disorder Checklist (PCL). This checklist was distributed one day before treatment and again the day following treatment. The patients were also given the PCL at subsequent follow-up visits to quantify sustained benefit. Results: SGB showed acute benefit for the symptoms of PTSD by markedly reduced PCL scores after the procedure. Benefits were also sustained during close outpatient follow-up. Conclusion: Selective blockade of the right stellate ganglion at C6 is a minimally invasive procedure with an excellent safety profile that may provide sustained relief of PTSD symptoms. The procedure may also provide benefit for those who are resistant to psychotropic intervention.

## Introduction

Post-traumatic stress disorder (PTSD) is a pathological symptomatology that can develop in certain individuals following exposure to an overwhelmingly traumatic event. The symptomatology includes patients reexperiencing the events of the trauma often through intense, intrusive, and vivid memories. Nightmares are common and often involve elements from the individual's memory of the trauma. Patients may also experience waking recollections of the trauma commonly called "flashbacks." During these recollections, the individual will act as if the original trauma is actually going on around them and may, in extreme cases, have perceptual disturbances including visual and/or auditory hallucinations. Other symptoms of the disease include avoidance of stimuli that may remind them of the trauma including activities, places, or people. They also may exhibit a general numbing of responsiveness marked by diminished interest in activities and general detachment from others. Along with detachment, individuals have symptoms of increased arousal as indicated by difficulty with sleep, increased irritability, problems in concentrating, and exaggerated startle response.

The underlying etiology of PTSD appears to be heavily influenced by one's autonomic susceptibility. Individuals diagnosed with PTSD have shown increased catecholamine levels, namely norepinephrine, in both cerebrospinal fluid and 24-hour urine levels. Further evidence for sympathetic involvement was shown when patients' symptoms worsened with the administration of yohimbine, a noradrenergic agonist. The hypothalamic–pituitary–adrenal axis also documented increased levels of corticotrophin-releasing hormone in cerebrospinal fluid, which is similar that seen in major depressive disorder. However, unlike individuals with depression, cortisol levels are not resistant to suppression with the administration of dexamethasone. Given the fact that corticotrophin-releasing hormone is stimulated by both glucocorticoids and catecholamines, this effect further supports the conclusion that the sympathetic system plays a strong role in the etiology of PTSD.

The prevalence of PTSD in military personnel has been rising steadily over the past decade. The reason for this is likely multifactorial with the ongoing psychiatric toll of combat trauma and recurring deployment cycles. Some of the most recent data collected by the Department of Defense survey showed that PTSD incidence rose from 7% to 11% (from 2005 to 2008). Along with increases in PTSD, attempted suicide rates doubled

from 1% to 2%. Studies have shown an increased risk of suicide in those diagnosed with PTSD. Given this fact, it is becoming increasingly important that more efficacious treatment modalities be used.

Recent medical treatment for PTSD has relied heavily on pharmacologic modalities. Conventional first-line treatments include selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and mirtazapine. These medications work by increasing the serotonin/norepinephrine available in the synaptic cleft and thereby, over the course of several weeks, changing the concentration of postsynaptic receptors. Although the safety and side-effect profiles of these medications are relatively benign, the response rate, discontinuation rate, and overall efficacy leave much to be desired.

SSRIs, despite the relatively low side-effect profile, have a high discontinuation rate ranging from 30% to 50%. All of these medications take anywhere from 4 to 8 weeks to take effect, which places individuals at increased risk of suicide during this latency period. The overall efficacy of these modalities have also proven to be moderate at best with a symptom rate of response averaging around 60%. Some research has indicated improvement with risperidone or olanzapine as augmentation agents with failed response to high-dose SSRI/SNRI. However, these medications also increase side effects including risks of extrapyramidal symptoms, metabolic abnormalities, and possible tardive dyskinesia with long-term use. Given these limitations, alternative treatment modalities targeting the sympathetic nervous system have developed in recent years.

Recent research has shown that the alpha-1 antagonist, prazosin is effective at reducing nightmares commonly seen in PTSD. Along with its effectiveness during sleep, there has been some suggestive work that it may also be beneficial when dosed during the day. Other successful treatments targeting the sympathetic nervous system include endoscopic sympathetic block and stellate ganglion block (SGB). Both of these treatments have reported improvement of anxiety symptoms; however, endoscopic sympathetic block is significantly more invasive, associated with more side effects, and is irreversible. A prior case series published in 2010 showed effective treatment of combat-related PTSD with SGB. The goal of this article is to advance the published data pertaining to PTSD successfully and safely treated with SGB. We will discuss four cases where individuals diagnosed with PTSD were able to obtain sustained benefit with SGB as well as minimal side effects. All of these patients failed several psychopharmacologic interventions and several even required prior hospitalization for their psychiatric symptoms. After the procedure, all of these individuals were able to return to some form of duty and also slowly titrated off many of their psychotropics.

## Methods

Patient was given information concerning the risk/benefits of the procedure and a consent form was completed. An intravenous line was started with a 22G IV in the left hand. The patient was positioned comfortably in the supine position and prepped and draped in the sterile fashion. Radiographic confirmation of the right C6 transverse process was obtained using c-arm X ray. For patient comfort, the skin was anesthetized with 1 cc of 2% lidocaine. Using an anterior paratracheal approach, a 25-gauge Quincke needle was passed under fluoroscopic guidance until it contacted the transverse process of the C6 vertebra and then was pulled back 1 mm. Appropriate needle position was then confirmed by injection of 2 cc of iohexol (180 mg/mL) radio-opaque dye to monitor its spread. After negative aspiration, 7 cc of 0.5% ropivacaine was slowly injected to produce a sympathetic block. We monitored the patient's right hand temperature for 15 minutes following the anesthetic administration to confirm

successful blockade of the cervical sympathetic ganglia as evidenced by an increase of at least 1.5°C. We also observed the patient for facial anhidrosis and Horner's syndrome symptoms (namely ptosis and miosis) for further confirmation.

## Psychometric Testing

The Post-traumatic Stress Disorder Checklist (PCL) is a 17-item psychometric test commonly used to screen, diagnose, and monitor symptom changes in individuals suspected/diagnosed with PTSD. A total symptom severity score (range 17–85) can be obtained by summing the scores from each of the 17 items. It was developed based on the symptoms criteria for PTSD from the Diagnostic and Statistical Manual of Mental Disorders.<sup>1</sup> There are three versions of the test: M (military), C (civilian), and S (specific). Given that our patients were all active duty military members with combat-induced symptoms, we used the M version for monitoring. Different cut-off scores have been suggested for both screening and diagnosis. One study of active duty members returning from combat recommended that a score of 28 was sensitive for the diagnosis of PTSD. Other studies have recommended a score of 50 to optimize both sensitivity and specificity. All patients included in this study had scores >50 before the procedure and were already diagnosed with PTSD.

## Case Reports

### Case 1

The patient was a 34-year-old male with two deployments to Iraq from 2006 to 2007 and 2009 to 2010 as a combat medic. He was exposed to combat trauma during both deployments witnessing several members of his unit killed with improvised explosive devices and having to recover the bodies. The patient's PTSD symptoms started during his first deployment taking the form of reexperiencing through nightmares (approximately 3 per week) and recurrent intrusive thoughts, avoidance of crowded areas, and increased arousal in the form of difficulty falling and staying asleep (2–3 hours per night), outbursts of anger, hypervigilance, and exaggerated startle response (started after second deployment, patient's children started startling him on purpose for fun until he broke his son's arm). Interventions by his mental health providers included trials of citalopram, buspirone, Prozac, Wellbutrin, Minipress and sertraline, and individual therapy. All of these treatments were unsuccessful at controlling his symptoms.

Approximately 4 months after his second deployment, in the context of marital discord stemming from his PTSD symptoms, the patient attempted to kill himself by cutting his wrists in a hot bath. He was found by his wife, brought to the Tripler Army Medical Center (TAMC) Emergency Department and eventually admitted to inpatient psychiatry. During his inpatient stay, patient was referred for SGB. PCL-M was administered immediately before the block and recorded at 64. PCL-M was then readministered 72 hours after the procedure and had decreased to 22. The patient and family noticed immediate improvement and reduction in symptoms. His PCL-M administered one month later was 35 and opted for a second SGB. His PCL-M measured 2 weeks after the second procedure was 29 with subjective improvement in his symptoms. The patient's records reviewed 3 months after the second procedure indicated continued sustained benefit with minimal anxiety symptoms that were being successfully controlled with low-dose Celexa and buspirone.

## Case 2

The patient was a 35-year-old male with 8 years time in service (Army) as a truck driver. He had two deployments to Iraq from 2004 to 2005 and 2007 to 2008. The patient also had significant history of childhood physical abuse. He was diagnosed with PTSD before entering the military related to an incident where he was beaten severely by his father with a large plank at the age of 12. The patient started drinking as a teenager and had a history of ethyl alcohol (ETOH) dependence. During his first deployment to Iraq, the patient was involved in 4 separate convoys hit by improvised explosive devices and was involved in 8 firefights. During this time the patient also reports psychological disturbance from seeing burning/dismembered bodies. He initially screened 41 out of 85 on his as PCL-C on March 16, 2009. He was admitted to the inpatient psychiatric ward 4 times between March 22, 2009 and November 15, 2010 for suicidality in the context of ETOH intoxication and PTSD symptoms. Stays were between 3 and 37 days with one discharge to a dual diagnosis program for 6 weeks. The patient's PCL-C score measured on December 31, 2009 was 85 out of 85. During this time, the patient had been in close contact with behavioral health and was attending PTSD groups. The patient had been tried on the following psychotropics with little improvement during the course of his treatment: trazodone, Remeron, Celexa, Zoloft, risperidone, naltrexone (ETOH), disulfiram (ETOH), and lithium.

During the patient's final say on the TAMC psychiatric inpatient ward, he scored 80 or 85 on his PCL-M. He was referred to anesthesiology for SGB on November 16, 2010. Two days after the procedure, he was discharged from the ward, his PCL-M having dropped to 18, and his suicidal ideation having completely resolved. The patient was unfortunately lost to follow-up after discharge.

## Case 3

The patient was a 46-year-old male with one deployment to Iraq (2008–2009). During his deployment he was hiding in a shack during a mortar attack. One of the mortars landed a few feet from the shack causing direct injury to the patient and others in his squad. Throughout the deployment, he was attacked by small arms fire requiring the patient to take cover and return fire. The patient admitted that during these times he experienced extreme fear and helplessness.

After returning from deployment, he was diagnosed with PTSD. His symptoms included mood swings; insomnia with recurrent nightmares, reliving the events; intense psychological and physiological reactivity when exposed to internal and external cues with exaggerated startle response; efforts to avoid thoughts, feelings and conversations, feeling detached and estranged from others, restricted range of affect; outbursts of anger, avoidance of crowds, crying spells; and generalized hypervigilance. Following deployment, the patient did not develop substance abuse, but did experience relational problems with his wife. He initially underwent a course of cognitive behavior therapy and prolonged exposure therapy for his symptoms, but was only minimally responsive to both. During his treatment he was tried on sertraline, bupropion, Paxil, Ativan, and clonazepam for anxiety and depressive symptoms as well as trazodone for sleep. All of these psychotropics proved ineffective at controlling his PTSD symptoms.

At the time of SGB the patient's PCL-M score was 69. He experienced significant relief of symptoms after the procedure though he had a cough for 3 to 4 hours afterward and only a partial Horner's syndrome. At one month follow-up, he acknowledged sustained benefit with a PCL-M of 34.

#### Case 4

The patient was a 29-year-old male with one deployment to Iraq from 2008 to 2009. While in Iraq, the patient was exposed to several firefights and was one of the primary members involved in casualty cleanup. During this time, he was exposed to dismembered bodies including several friends in his unit. On returning home in September 2009, the patient noticed that he started to increase his alcohol intake eventually becoming dependent. He went through outpatient substance abuse treatment, however, continued to drink in lesser amounts.

Shortly after his substance abuse treatment, he was seen by outpatient psychiatry for continued aggressive behavior and insomnia. He was started on medications including Zoloft and Ambien with little improvement in his symptoms. The patient admitted that during this time he had difficulty sleeping because of frequent nightmares and would often awaken with substantial diaphoresis. He also expressed avoidance symptoms including fear of crowds, diminished interest in previously pleasurable activities, and general detachment from others including his family and friends. He acknowledged increased startle response and frequent anger outburst. His symptoms continued until he self-presented to the outpatient clinic at TAMC complaining of homicidal ideation toward several members of his chain of command. He was subsequently admitted to the active duty inpatient ward and officially given the diagnosis of PTSD.

While on the ward, he displayed a general aversity to any medications and would become enraged at the thought of starting further medication. The patient was offered the option of receiving an SGB. He consented to the procedure and was given the PCL-M 3 days before the procedure. His initial PCL-M score was 76. He received the procedure with no prominent side effects. The patient acknowledged immediate improvement in his hyperarousal symptoms. The next day his PCL-M was readministered and the patient scored a 24.

#### Discussion

SGB is a relatively noninvasive procedure with few side effects that has been in use since the 1920s for the treatment of pain (migraines, herpes zoster, and sympathetic mediated pain to include complex regional pain syndrome). Recently, SGB has been used at Walter Reed Army Medical Center and TAMC for treatment of refractory PTSD. Although this case series shows efficacy of this treatment for some patients, it raises more questions than it answers.

First, the mechanism of action has yet to be elucidated. Although Maihöfner et al demonstrated activation of insular cortex during mechanical hyperesthesia (pain with light touch) with complex regional pain syndrome and Liberzon and Martis demonstrated insular cortex activation in PTSD patients, the mechanism of activation remains unclear for both conditions and insular deactivation remains to be shown in patients treated with SGB. Suggestions that the connection between the stellate ganglion and the hypothalamus is responsible for the changes based on Westerhaus and Loewy demonstration of connection are without foundation as they utilized a pseudorabies virus to show this connection (pseudorabies being a reverse axonal virus showing input from hypothalamus to stellate ganglion and not vice versa). Lipov et al hypothesize that after SGB the resulting decrease in nerve growth factor leads to reduction in norepinephrine, and deactivation of intracerebral pathologic states

shows the most promise at this point; however, the mechanism needs further elucidation and biochemical verification in patients treated specifically for PTSD.

More important than actual mechanism, however, are quantification of efficacy on a population level, comparison of efficacy to other treatments, better defining the duration of symptom relief, and discovering whether results separate from sham procedure. Given the dramatic results seen in this case series as well as the case series by Mulvaney et al, future studies into these variables are of paramount importance in defining the role of SGB in the treatment of PTSD.

#### Conclusion

As found in prior case studies, SGB appears to be not only safe but also efficacious in the treatment of PTSD symptoms. Given that none of the patients presented in this case series were psychotropic naive and indeed several were totally resistant, further weight can be given to the possibility that SGB may prove to be beneficial for medication of nonresponders. Although the mechanism of action for the procedure's efficacy remains unknown, the objective findings seem to argue the case of long-term neuronal changes. Further research, namely with larger double-blind randomized control trials from several geographic areas, will be needed to determine if these results are directly because of the procedure or secondary placebo effects. Given the results shown in these and other cases, we believe the prior to be the more likely scenario.

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#### ***Sexual Assault***

### **Military Sexual Trauma Increases Risk of Post-Traumatic Stress Disorder and Depression Thereby Amplifying the Possibility of Suicidal Ideation and Cardiovascular Disease**

Military Medicine

Nancy Lutwak, MD; Curt Dill, MD

April 2013

Military sexual trauma (MST) is a form of high betrayal trauma resulting in long-lasting physical and psychological problems. It is of major concern and must be a focus of all health care providers caring for Veterans. It is an issue requiring substantial resources, sensitivity, and compassion to ensure victims the proper requisite treatment. The victims of this abuse often times suffer from guilt, fear, anger, and shame. It creates a sense of sadness, loneliness, and anguish in many. Often sexual assault survivors are reluctant to discuss this experience because of the pain that emerges and the worry that they will be blamed or accused, thus becoming victims again.

The incidence of MST among female Veterans has been reported to be as high as 40%. The accurate number is uncertain, however, since MST is known to be underreported. What is certain, however, is that this form of high betrayal trauma results in several negative consequences.

It is clear that MST is a form of high betrayal trauma, meaning trauma in which depended-upon-for-survival individuals harm or violate a dependent person, thus breaking the social agreement of trust. The victim of the harm, who is in a dependent position, is unable to confront or break ties with the perpetrator of the violation. This damages the victim's well-being, self-concept, relationships, and view of the world. The dependent victim experiences a trauma where expectations and reality are incongruous. Because the victim is in a dependent position, escape is impossible and more violations may occur. Because MST is a form of high betrayal trauma, it results in significant devastating long-term consequences and profound anguish in the victims.

MST, sexual assault or multiple verbal episodes of sexual harassment, results in psychological and physical problems. Studies of MST among women Veterans report increased gynecological, urological, gastrointestinal, pulmonary, neurological, and cardiovascular problems among the victims. Furthermore, women who report sexual assault while in the military are more likely to report being treated for a "heart attack" in the past year than those who have no history of sexual assault.

MST, which is exceedingly distressing, leads to greater risk of posttraumatic stress disorder (PTSD). Women with MST have higher rates of PTSD than women who have experienced other types of trauma. Rape and interpersonal violence, which causes PTSD, is made even worse when it occurs in the military because of continued exposure and involvement with the perpetrator.<sup>6</sup> The resulting PTSD may lead to greater risk of heart disease from change in health behaviors such as smoking and decreased physical activity. Studies have also shown that there is a strong association between PTSD and worsening of physical health; greater physical limitations; poorer quality of life; and greater symptom burden of chest pain, angina, or chest tightness.

In addition, substance abuse and depression occur commonly in women after experiencing MST. There is a link between MST and suicide and intentional self-harm, as these negative reactions are over twice as common among women and men who report MST. In addition, the coexistence of PTSD and depression increases the risk of suicidal ideation. Depression is a major risk factor for cardiovascular disease and may lead to behaviors that increase other cardiac risk factors, as does PTSD. MST with resulting depression and PTSD, therefore, may lead to cardiovascular disease, a major killer of women as well as greater risk of suicide.

There is a definite association between abuse and health problems. Women who experienced abuse in childhood and/or adulthood are more likely to experience heart problems, diabetes, chronic fatigue, chronic pain, and asthma. There are strong associations between betrayal trauma and negative physical and psychological effects. Even among young adults, betrayal trauma results in psychological difficulties such as anxiety and depression as well as physical health complaints. These difficulties occur to a greater extent after high betrayal trauma than after other forms of trauma.

It is clear, then, that MST is associated with many physical problems and greater need for preventive care. Sexual assault in the military causes neurologic, musculoskeletal, genitourinary, and gastrointestinal symptoms. In addition, women with PTSD and MST are more likely to be depressed, as well as have anxiety and eating disorders compared to their male counterparts. The depression that results from MST may increase the risk for cardiovascular disease because depression is an independent risk factor. Thus, MST may lead to cerebral infarct or myocardial infarction, major killers of women. Depression is additionally associated with poorer adherence to prescribed treatment for lipid reduction, smoking cessation, and hypertension. It is also associated with poor diabetic control. Depression resulting from experiencing MST can therefore lead to extremely serious health problems. Cardiovascular disease is the leading cause of death in women and causes poorer quality of life with disability. MST, therefore, has numerous severe negative effects that are immediate as well as persistent.

The pathophysiology leading to the cardiovascular problems is now known. Depressed patients have higher levels of proinflammatory cytokines such as tumor necrosis factor and interleukin 6, which may cause the development and increase in amount of vasculature atherosclerosis. They also have neurohormonal alterations in the hypothalamic–pituitary–adrenal axis with increases in corticotropin-releasing factor, which may lead to injury of endothelial cells of the vasculature.

There is evidence, as well, that patients with depression have sympathoadrenal hyperactivity, and higher levels of circulating catecholamines which initiate the response of platelets causing their aggregation. Thus, depression is linked to hypercoagulability of platelets. Depression, anxiety, and pain all involve pathophysiological changes involving the balance of the sympathetic/parasympathetic and neuroendocrine systems causing dysfunction of the hypothalamic/pituitary/adrenal axis and increased production of proinflammatory cytokines.

MST, therefore, may lead to depression and a greater probability that its victims develop cardiac problems. This is significant since women, particularly postmenopausal women, are at high risk for cardiac disease. Furthermore, the incidence of heart disease in women is often underestimated and undertreated by health care providers. Its seriousness must be emphasized. The evidence that depressed patients are at greater risk of cardiovascular disease indicates that women who have experienced MST with resulting depression need to be evaluated for coronary artery disease and treated for modifiable risk factors. The importance of screening for MST is thus underscored. Veterans Health Administration (VA) has a significant responsibility to accomplish this screening so that those who need urgent care receive it in a timely manner.

Women who have experienced this high betrayal trauma, who may develop anxiety, depression, and poor health habits, require preventive care for lipid management, smoking cessation, exercise encouragement, diabetic control, and diet advice. Health care providers of women Veterans need to be cognizant of the importance of screening for MST with possible need for counseling, testing for depression, and evaluation for cardiovascular disease.

In addition, the fact that depression and coronary ischemia often times have overlapping symptomatology particularly in postmenopausal women underscores the vigilance with which clinicians must evaluate these patients. Women who have complaints of fatigue or insomnia perceived as isolated or lonely by clinicians may have anginal equivalents that are being underdiagnosed. VA health care providers need to have knowledge of

this issue to be excellent physicians and nurses, and to give women Veterans superb treatment. For these reasons, it is of utmost importance to screen women Veterans for MST as well as depression so that cardiac risk factors may be assessed.

VA has the responsibility to provide the extensive care needed to ameliorate the profound hurt and physical morbidities caused by MST. Multiple approaches may be needed. Survivors of betrayal trauma require corrective experiences during therapy that demonstrate what healthy loving relationships are like. Cognitive behavioral interventions are also efficacious after traumatic events. Returning military from Iraq and Afghanistan may not seek mental health care for depression and efforts should be made to destigmatize this type of care by using motivational interviewing techniques. Marital and family therapy are also useful, as social support is extremely helpful, particularly for improving PTSD. VA is obligated to assess the most effective methods to decrease the morbidities caused by MST and PTSD. Patient interviewing, surveys, and computer questionnaires should be ongoing to evaluate effectiveness of these therapies.

MST causes multiple devastating problems. Health care providers must have knowledge that women Veterans who have experienced this form of high betrayal trauma require comprehensive gender-sensitive care addressing the many physical and psychological difficulties that may result. It is also important to recognize that MST increases risk of PTSD and depression, thus amplifying the possibility of suicide and cardiovascular disease.

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## ***Sleep***

### **Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study**

The Lancet Neurology

Dr Alex Iranzo MD, Prof Eduard Tolosa MD, Ellen Gelpi MD, José Luis Molinuevo MD, Francesc Valldeoriola MD, Mónica Serradell BSc, Raquel Sanchez-Valle MD, Isabel Vilaseca MD, Francisco Lomeña MD, Dolores Vilas MD, Albert LLadó MD, Carles Gaig MD, Joan Santamaria MD  
03 April 2013

Summary

Background

We postulated that idiopathic rapid-eye-movement (REM) sleep behaviour disorder (IRBD) represents the prodromal phase of a Lewy body disorder and that, with sufficient follow-up, most cases would eventually be diagnosed with a clinical defined Lewy body disorder, such as Parkinson's disease (PD) or dementia with Lewy bodies (DLB).

## Methods

Patients from an IRBD cohort recruited between 1991 and 2003, and previously assessed in 2005, were followed up during an additional period of 7 years. In this original cohort, we sought to identify the nature and frequency of emerging defined neurodegenerative syndromes diagnosed by standard clinical criteria. We estimated rates of survival free from defined neurodegenerative disease by means of the Kaplan-Meier method. We further characterised individuals who remained diagnosed as having only IRBD, through dopamine transporter (DAT) imaging, transcranial sonography (TCS), and olfactory testing. We did a neuropathological assessment in three patients who died during follow-up and who had the antemortem diagnosis of PD or DLB.

## Findings

Of the 44 participants from the original cohort, 36 (82%) had developed a defined neurodegenerative syndrome by the 2012 assessment (16 patients were diagnosed with PD, with DLB, one with multiple system atrophy, and five with mild cognitive impairment). The rates of neurological-disease-free survival from time of IRBD diagnosis were 65.2% (95% CI 50.9 to 79.5) at 5 years, 26.6% (12.7 to 40.5) at 10 years, and 7.5% (-1.9 to 16.9) at 14 years. Of the four remaining neurological-disease-free individuals who underwent neuroimaging and olfactory tests, all four had decreased striatal DAT uptake, one had substantia nigra hyperechogenicity on TCS, and two had impaired olfaction. In three patients, the antemortem diagnoses of PD and DLB were confirmed by neuropathological examination showing widespread Lewy bodies in the brain, and  $\alpha$ -synuclein aggregates in the peripheral autonomic nervous system in one case. In these three patients, neuronal loss and Lewy pathology ( $\alpha$ -synuclein-containing Lewy bodies and Lewy neurites) were found in the brainstem nuclei that regulate REM sleep atonia.

## Interpretation

Most IRBD individuals from our cohort developed a Lewy body disorder with time. Patients who remained disease-free at follow-up showed markers of increased short-term risk for developing PD and DLB in IRBD, such as decreased striatal DAT binding. Our findings indicate that in most patients diagnosed with IRBD this parasomnia represents the prodromal phase of a Lewy body disorder. IRBD is a candidate for the study of early events and progression of this prodromal phase, and to test disease-modifying strategies to slow or stop the neurodegenerative process.

## Funding

None.

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## **Idiopathic REM sleep behaviour disorder in the development of Parkinson's disease**

The Lancet Neurology

Dr Bradley F Boeve MD  
09 April 2013

## Summary

Parkinson's disease is a progressive neurodegenerative disorder associated with Lewy body disease pathology in central and peripheral nervous system structures. Although the cause of Parkinson's disease is not fully understood, clinicopathological analyses have led to the development of a staging system for Lewy body disease-associated pathological changes. This system posits a predictable topography of progression of Lewy body disease in the CNS, beginning in olfactory structures and the medulla, then progressing rostrally from the medulla to the pons, then to midbrain and substantia nigra, limbic structures, and neocortical structures. If this topography and temporal evolution of Lewy body disease does occur, other manifestations of the disease as a result of degeneration of olfactory and pontomedullary structures could theoretically begin many years before the development of prominent nigral degeneration and the associated parkinsonian features of Parkinson's disease. One such manifestation of prodromal Parkinson's disease is rapid eye movement (REM) sleep behaviour disorder, which is a parasomnia manifested by vivid dreams associated with dream enactment behaviour during REM sleep. Findings from animal and human studies have suggested that lesions or dysfunction in REM sleep and motor control circuitry in the pontomedullary structures cause REM sleep behaviour disorder phenomenology, and degeneration of these structures might explain the presence of REM sleep behaviour disorder years or decades before the onset of parkinsonism in people who develop Parkinson's disease.

The full research was not able to be accessed.

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## **Neuroendocrine Regulation and Metabolism of Glucose and Lipids in Primary Chronic Insomnia: A Prospective Case-Control Study**

PLOS One

Eleonora Seelig mail, Ulrich Keller, Markus Klarhöfer, Klaus Scheffler, Serge Brand, Edith Holsboer-Trachsler, Martin Hatzinger, Stefan Bilz  
12 April 2013

## Introduction

Diabetes mellitus type 2 has an increasing prevalence in our society [1], [2]. Changes in dietary habits and diminished physical activity are important contributors to this development. Another behavioral change that has occurred during the same time period is the increased prevalence of sleep curtailment [3]. Both animal and clinical studies have established the importance of an intact circadian rhythm for the regulation of

metabolic processes and sleep deprivation has been linked to impaired glucose and lipid metabolism [3], [4], [5], [6], [7], [8]. The identification of so-called clock genes has further highlighted the importance of circadian rhythms for the regulation of metabolic processes. These genes promote the production of downstream transcription factors, which in turn regulate genes involved in metabolic pathways [4]. Interestingly, mice homozygous for a loss of function mutation in the clock genes develop features of the metabolic syndrome [5]. Several clinical studies in humans also suggested a relation between sleep deprivation and insulin resistance. Spiegel et al., for example, showed that short time sleep restriction promoted an impairment of glucose tolerance in healthy young men [6]. Sleep apnea has been identified as a common trait of the metabolic syndrome and its treatment led to improved insulin sensitivity in obese patients [7], [9]. Moreover, a recently published meta-analysis suggested that quantity and quality of sleep predicts the risk of developing diabetes [8]. The impact of acute sleep loss on metabolism has been thoroughly investigated, but the relation between chronic sleep loss and metabolism still needs further analysis [10].

The aim of the present investigation was therefore to assess whether (i) patients diagnosed with primary chronic insomnia show alterations of glucose and lipid metabolism when compared to age, sex and body mass index (BMI)-matched healthy controls, (ii) the potential metabolic alterations could promote the development of features of type 2 diabetes and its associated metabolic disorders, such as dyslipidaemia, visceral adiposity and non-alcoholic fatty liver disease. Moreover, we were interested to see (iii) whether the-pituitary-adrenal axis and the sympathoadrenal system, which play a role in the regulation of glucose metabolism, may be dysregulated in patients with primary insomnia. To this purpose we defined the metabolic alterations in patients with primary insomnia and compared them to age, BMI and menopausal status-matched healthy controls in a case-controlled, prospective trial.

## Materials and Methods

The protocol was approved by the Human Ethics Committee of Basel. All participants gave written informed consent prior to the study (Clinical Trial Registration Number: NCT00442624).

Patients with primary chronic insomnia were recruited from the Depression and Sleep Research Unit, Psychiatric University Clinics, Basel, and by advertisements in local newspapers. Participants responding to advertisements were screened by a structured telephone interview. Those deemed eligible were invited to join a screening visit in the outpatient department of the Division of Endocrinology, University Hospital Basel (see Fig 1). Written informed consent was obtained from all participants.

Age and BMI- matched healthy controls were recruited by internet advertisements from the local population and underwent the same screening procedures as patients. The inclusion criterion for insomniacs was diagnosis of primary chronic insomnia based on clinical history. Exclusion criteria for insomniacs were any other known sleeping disorders but primary chronic insomnia. Exclusion criteria for healthy controls were any kind of sleeping disorders. Importantly, controls and insomniacs with diabetes mellitus, dyslipidaemia (LDL cholesterol  $>4.9$  mmol/l and/or increased fasting triglycerides  $>1.7$  mmol/l), those taking medication interfering with glucose or lipid metabolism, or presenting with any other significant comorbidity and pregnant and breast feeding women were not eligible to participate.

The diagnosis of “primary chronic insomnia” was made using the Diagnostic and Statistic manual of Mental Disorders IV (DSM-IV) criteria [11]. This means the predominant complaint was difficulty initiating or maintaining sleep, or non-restorative sleep, for at least one month. Further on the sleep disturbance had to cause clinically significant distress. It did not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, parasomnia or a mental disorder. Additionally the disturbance was not due to the direct physiological effects of a substance or a general medical condition.

To exclude any organic cause for the sleeping disorder or a metabolic disease, a thorough clinical investigation was performed, and screening blood samples were drawn.

To exclude a psychiatric cause for the sleep disorder the Mini-international Neuropsychiatric Interview (M.I.N.I.) [12] and the Beck Depression Inventory (BDI) [13] were performed.

The M.I.N.I. is a short structured diagnostic interview designed to assess psychiatric diagnoses for clinical trials [12].

The BDI is a 21-question multiple choice self-report inventory for measuring the severity of depression [13]. On a global depression score with a possible range of 0-63, a score of >15 indicates the existence of depression.

Patients and controls eligible to participate in the study protocol based on the results of the screening visit were to undergo a polysomnographic study (PSG) with a portable monitoring system (Siesta®, Compumedics, Abbotsford, Australia) in order to analyze sleep continuity and architecture.

Participants were monitored for two non-consecutive nights in the course of one week. Electrodes for the electroencephalogram were placed according to the international 10/20-system using C3/ C4 positions occipital and A1/ A2 positions postauricular. The polysomnographic study further included a submental electromyogram for muscle tone, an electrooculogram for eye movement and an electrocardiogram for heart rate. Respiration was monitored using two elastic bands placed around abdomen and thorax registering respiratory excursion. Finger oxymetry provided information about blood oxygenation. Limb movements were measured with two electrodes applied to the Musculi tibialis anteriores.

After the PSG installation patients and controls were discharged to spend the night in their usual environment at home. The next morning patients and controls returned and the polysomnograph was removed.

After the first night all participants were manually scored for restless legs syndrome and sleep apnea using the ProFusion PSG software (Compumedics®, Abbotsford, Australia) according to standardized criteria [14].

Participants having a periodic limb movement index (PLM-index) exceeding 15 and those having a PLM-index with arousal exceeding 5 were excluded from our study, assuming the presence of a restless legs syndrome. Participants having a respiratory deficiency index (RDI) exceeding 5 were also excluded from our study since it indicates sleep apnea.

The second night of the patients was manually analysed regarding quality of sleep using the Profusion PSG software (Compumedics®, Abbotsford, Australia). The following items were evaluated: time of sleep, sleep efficiency ( $[\text{sleep time} \cdot 100 / \text{bed time}]$ ), number of arousals, wake up time after initiation of sleep, latency of REM-sleep (time between initiation of sleep and first REM epoch), percentage of the various sleep stages, PLM-index, PLM-index with arousal and RDI.

On the evening before the metabolic studies patients were admitted to the Clinical Research Center (CRC) of the University Hospital Basel. A standard dinner was served containing 30 g protein, 90 g carbohydrate and 30 g fat. Participants were asked to remain fasting until the end of the study. After receiving instructions for 12 h urine collection for catecholamine measurements and salivary samples for cortisol measurements at 11.30 p.m. and 06.00 a.m., patients were discharged.

All participants were readmitted to the outpatient department the next morning. Cortisol levels were determined employing a competitive solid phase time-resolved fluorescence immunoassay with fluorometric end point detection (DELFI; Wallac, Turku, Finland). Adrenaline and noradrenaline were measured in 12 h urine using high performance liquid chromatography (CoulArray HPLC system, ESA Biosciences, MA, USA).

Plasma metanephrine concentrations were measured in fasting blood samples using high performance liquid chromatography (CoulArray HPLC system, ESA Biosciences, MA, USA).

Magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy ( $^1\text{H}$  MRS) were performed to gain information about liver fat content, the quantity of adipose tissue and intracellular triglyceride concentrations [15], [16], [17].

For measurements of hepatic lipid accumulation and visceral adipose tissue MRI data were acquired on a 1.5 Tesla whole body system. (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany). A 6 element array coil placed over the right lateral abdomen of the patients and appropriate channels of an 8 element spine coil were used for signal reception.

Anatomical MRI was performed in order to position the  $2 \cdot 2 \cdot 2$  cm<sup>3</sup> voxel used in the localized spectroscopy experiment. Spectroscopic data were acquired using a double spin echo PRESS sequence without water suppression. RF-pulses with optimised excitation profiles were used in order to achieve good voxel localization and to avoid signal contamination from subcutaneous fat. Four signal averages were collected during one breath hold. Spectroscopic data was analysed using the software package NUTS (Acorn NMR Inc., Livermore, USA). The acquisition of six data sets with spin echo times of 30 ms, 40 ms, 50 ms, 60 ms, 70 ms and 80 ms allowed estimation of fat and water contributions and therefore excluded relaxation phenomena. The lipid signal results from chemically shifted proton resonances corresponding to methyl and methylene groups occupying different positions on lipid molecules with frequencies found in the range -140 Hz to -245 Hz with a major peak at about -220 Hz,

corresponding to methylene groups in (CH<sub>2</sub>)<sub>n</sub> acyl chains. The MRI liver fat percentage was then reported as the spin density of the aliphatic <sup>1</sup>H signal divided by the sum of the spin densities of aliphatic and water <sup>1</sup>H signals. To exclude outliers, the spectroscopic experiment described above was performed for two different voxels in each subject.

The amount of visceral adipose tissue was obtained from multislice T1-weighted MR imaging. Fatty tissue appears bright in T1-weighted MR images and can be easily segmented by thresholding. Subcutaneous fat was separated manually from visceral fat. Visceral and subcutaneous fat volumes were calculated by multiplying the number of voxels containing visceral and subcutaneous fat, respectively by the voxel volume.

To assess intramyocellular lipids (IMCL), spectroscopic MRI data were acquired on a 3.0 Tesla scanner (Magnetom Allegra, Siemens, Erlangen, Germany). Participants were placed in supine position; their right leg was positioned in the center of the radiofrequency headcoil. Anatomical T1-weighted MR imaging was performed in order to define the region of interest. Localized proton spectra were collected using a PRESS sequence. A voxel (10×10×12 mm<sup>3</sup>) was placed in the Musculus tibialis anterior trying to avoid macroscopic visible fat accumulations as well as vessel structures. To optimize the homogeneity of the magnetic field volume selective shimming was accomplished [18]. IMCL concentration was calculated as the ratio between the area under the IMCL peak and the area under the water line.

To assess body composition, body impedance analysis (Bodyimpedance Analyzer Model BIA 101, Akern Srl Florence Italy) was performed. Body composition was calculated using the Bodygram software (Akern Srl Florence Italy).

Indirect calorimetry (Deltatrac II, Datex) was used to examine rates of energy production and substrate oxidation. To assess oxygen consumption, carbon dioxide production and the respiratory quotient (RQ) indirect calorimetry (Deltatrac II, Datex) was performed.

An euglycaemic hyperinsulinemic clamp was performed to assess insulin sensitivity of glucose turnover [19].

An indwelling teflon catheter was placed into an antecubital vein for infusions and a retrograde cannula in a hand vein for blood collection. A 3 hour insulin-glucose clamp began with a primed/continuous insulin infusion (20 mU/m<sup>2</sup>/min) and a variable infusion of 20% dextrose to maintain plasma glucose levels at 5.5±0.5 mmol/l. Arterialized blood was collected during the clamp every 5 min for immediate determination of plasma glucose levels using an automated glucose analyzer (2300 STAT Plus, YSI Bioanalytical Products). The portion of metabolized glucose (M) was calculated as follows:  $M = \text{GINF} - s$ .

GINF was the glucose concentration in the infusate [mg/(kg×min)] and s the space correction factor. Total M ( μmol/ kg/min) was calculated from the means of the four 10 min periods from 150 to 180 min of the euglycaemic hyperinsulinaemic clamp.

The space correction factor (s) was calculated as follows:  $s = 3.795 \times (\text{SA}/\text{BW}) \times (\text{G1} - \text{G2})$  SA was the body surface area (m<sup>2</sup>), and BW the body weight (kg), G1 the initial plasma glucose concentration (mmol/l) and G2 the final plasma glucose concentration (mmol/l).

Plasma insulin levels were measured to ascertain a steady state during the euglycaemic hyperinsulinaemic clamp. Plasma C-peptide concentrations were measured to evaluate if the insulin concentration in the infusate was sufficient to suppress endogenous insulin production.

Insulin and C-peptide levels were determined employing solid-phase, two-site chemiluminescent immunometric assays (IMMULITE 2000 Insulin or C-peptide, respectively, from Siemens, UK).

Mann Whitney U tests and correlation analyses were performed using statistical software (JMP Statistical Software, SAS Institute Inc);  $p < 0.05$  was defined significant. Initially demographic variables were compared between patients with insomnia and healthy controls. In addition, sleep variables were compared to know if patients and healthy controls differed with respect to sleep. All data are expressed as means  $\pm$  SD.

## Results

### Baseline characteristics

Age, BMI, waist circumference, blood pressure, serum cholesterol, HDL-cholesterol, triglycerides, ASAT (aspartate transaminase), ALAT (alanine transaminase), GGT (Gamma-glutamyl transferase) and CRP (C-reactive protein) did not differ significantly between 13 women with chronic insomnia and 12 matched healthy control women. Thus, patients and healthy controls were well matched for demographic, anthropometric and biochemical characteristics.

The Mini- International Neuropsychiatric Interview showed throughout negative answers to all questions in all patients and controls enrolled in the study. Thus, a psychiatric disease was excluded in all participants of the study.

The BDI showed no statistically significant difference regarding depressive symptoms.

### Sleep assessment

All patients suffered from primary chronic insomnia according to DSM IV criteria while controls had a normal sleep-wake-cycle.

In the PSG study the wake time after sleep onset (Table 2) was longer in insomniacs than in controls ( $p = 0.05$ ) whereas no statistically significant differences were found between patients and controls with regard to dimensions of both the remaining sleep continuity and sleep architecture (Table 2).

### Salivary cortisol, urinary catecholamines, plasma metanephrines

Midnight salivary cortisol concentrations were higher in insomniacs compared to healthy controls ( $p = 0.02$ ). No significant differences were observed for morning salivary cortisol concentrations. Urinary 12 h excretion rates of noradrenaline were significantly higher in controls compared to insomniacs ( $p = 0.02$ ), whereas no significant difference was found in urinary excretion rates of adrenalin and dopamine, nor plasma

concentrations of metanephrines (Table 3, Fig. 2). No significant correlations between cortisol levels and baseline characteristics, parameters of sleep assessed by PSG, urinary catecholamines, visceral and subcutaneous adipose tissue volume, liver fat content, intramyocellular lipid content and insulin sensitivity in insomniacs alone and in all participants together were identified (Fig. 3).

#### MR spectroscopy of liver and muscle

No statistically significant differences of liver fat content, visceral and subcutaneous adipose tissue volume and intramyocellular lipids were found between insomniacs and controls (Table 4).

#### Euglycaemic hyperinsulinaemic clamp technique

No statistically significant difference of insulin-induced glucose uptake, i.e. no difference of insulin sensitivity between patients and controls was found (Table 4).

#### Body impedance analysis (BIA) and resting energy expenditure

Healthy controls had a significantly higher amount of total body water when compared to patients ( $p = 0.04$ ). No significant differences in cell mass, weight of fat and non-fat tissue, as well as muscle mass were detected. Respiratory quotients and resting energy expenditure were comparable between patients and controls (Table 5).

#### Discussion

The present study investigated whether primary chronic insomnia in otherwise healthy, normal weight women is associated with metabolic and neuroendocrine changes that promote the onset of diabetes. To this aim extensive metabolic phenotyping and sleep studies were performed in 13 women diagnosed with primary chronic insomnia and 12 healthy controls matched for gender, age, BMI, body composition and menopausal status.

Regarding features of the sleep disturbance, it was unexpected to observe that all patients with primary chronic insomnia according to DSM IV criteria showed no major differences in polysomnographic data compared to controls. We only found a significantly higher amount of wake time after sleep onset in patients. There was no significant group difference concerning the various sleep stages. Similar results were found in other studies where only 50–60% of individuals with established diagnostic criteria for insomnia actually showed differences in the polysomnographic studies compared to normal sleepers [20].

A possible explanation for this discrepancy could be the fact that for the traditional PSG scoring a vast amount of data collected during one PSG study is drastically reduced and artificially segmented during analysis. Therefore, the limited representation of sleep monitored by traditional PSG may not fully represent the quality of sleep [20].

Midnight salivary cortisol concentrations were significantly increased in patients with primary chronic insomnia when compared to controls, indicating dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis. Midnight as well as morning salivary cortisol levels were not associated with baseline characteristics, metabolism of glucose and lipids and catecholamines. Similar alterations in evening cortisol levels were observed previously in a study with 11 healthy young men after one night of sleep deprivation [21]. A correlation between elevated evening plasma cortisol levels and sleep deprivation has also been demonstrated in the Whitehall II study, where a cohort of nearly 7000 subjects recruited from the general population was investigated [22]. Further on in infants suffering from infantile colic, fragmented sleep patterns and increased saliva cortisol levels were related [23]. The results of these and our own studies suggest that dysregulation of HPA is a common feature of both acute and chronic sleep curtailment. However, the mechanisms involved are unclear. It is well known that corticotropin-releasing hormone and cortisol have adverse effects on sleep quality [24], [25]. Noteworthy, insomnia can also provoke a stress reaction, including the activation of the HPA-axis [26]. Therefore, it remains unknown whether sleep deprivation leads to increased cortisol levels or if the dysregulation of the HPA-axis causes primary chronic insomnia. Abnormal cortisol levels may precipitate more severe stages of insomnia. However, to proof this hypothesis, longitudinal studies are required.

Interestingly, we found a slightly increased urinary noradrenaline excretion in controls as compared to insomniacs while excretion rates of adrenaline and dopamine and plasma concentrations of metanephrines were not significantly different. These results suggest that the sympatho-adrenal system did not play a pathogenic role in the development of primary chronic insomnia in our patients. Despite extensive investigations employing glucose clamp and in vivo MRI techniques no metabolic features indicating increased diabetes risk or incipient diabetes, such as peripheral insulin resistance or increased intramyocellular or hepatic lipids could be detected in our study population. At a first glance this seems unexpected since several authors reported disturbed glucose metabolism or incident diabetes in patients with short sleep duration [27], [28], sleep disorders such as obstructive sleep apnea [29] and healthy subjects subjected to sleep deprivation [6], [10], [30]. In our study, healthy physically active women with primary chronic insomnia, i.e. subjects reporting difficulty initiating or maintaining sleep, or non-restorative sleep leading to subjective distress and increased wake time after sleep but normal sleep architecture were investigated. The presence of a relatively mild sleep disorder in otherwise healthy women may explain the absence of metabolic disturbances and agrees with the results of Keckeis et al. who could not find impaired glucose tolerance in patients with chronic primary insomnia [31]. Nevertheless, sleep curtailment in subjects having adopted to an unhealthy lifestyle with physical inactivity and ad libitum food intake resulting in weight gain may precipitate impaired glucose metabolism [32].

A limitation of our study may be the relatively small number of participants. However, the variances of the parameters measured were similar to previous studies, and according to our sample size calculation the chance for a statistical error type II was small.

In summary, we found that chronic primary insomnia is associated with dysregulation of the HPA-axis, as indicated by increased midnight salivary cortisol concentrations. Although elevated night time cortisol levels have been demonstrated to more profoundly impact glucose metabolism when compared to increased morning cortisol levels [33], we could not demonstrate any changes in glucose and lipid metabolism that may precede the onset of diabetes. Nevertheless, due to the well described detrimental metabolic effects of cortisol oversecretion, the increase in nocturnal cortisol levels may convey an increased risk to develop diabetes and dyslipidemia.

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## **Stress**

# **Proposals for mental disorders specifically associated with stress in the International Classification of Diseases-11**

The Lancet

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11 April 2013

Mental disorders specifically associated with stress are exceptional in needing external events to have caused psychiatric symptoms for a diagnosis to be made. The specialty of stress-associated disorders is characterised by lively debates, including about the extent to which human suffering should be medicalised,<sup>1</sup> and the purported overuse of the diagnosis of post-traumatic stress disorder (PTSD).<sup>2</sup> Most common mental disorders are potentiated or exacerbated by stress and childhood adversity.<sup>3, 4</sup> Moreover, the subjective narratives of many people with mental disorders emphasise such external events.<sup>5</sup> Clinicians might inadvertently gravitate towards diagnoses of disorders specifically associated with stress whenever a significant stressor can be identified, because this approach provides a way to understand the person's experience of symptoms, as a function of external events, that is more likely to be acceptable to the person.<sup>6</sup> What could be missed in such formulations is that mental disorders specifically associated with stress are characterised not only by an antecedent event, but also by a distinct clinical picture with core symptoms that differ from those of other mental disorders.

WHO is developing the International Classification of Diseases, version 11 (ICD-11), which is scheduled for approval in 2015. WHO is also responsible for the Mental Health Gap Action Programme (mhGAP), intended to assist with scaling up of mental health care, particularly in low-income and middle-income countries.<sup>7</sup> It has launched the mhGAP intervention guide, which provides assessment and management protocols for selected conditions in non-specialised health-care settings. In response to requests from health-care providers, WHO is developing a module for this guide with disorders specifically associated with stress that will use proposed ICD-11 definitions. These activities are also relevant to WHO's role in development of mental health policies related to humanitarian crises.

Changes in the category of mental disorders specifically associated with stress are important because of questions about the validity of surveys showing a high rate of these diagnoses in populations who have experienced natural or man-made disasters, and about whether these diagnoses are clinically useful in terms of leading to feasible and effective treatment. People with these disorders seek help in many health settings globally.<sup>8</sup>

The high level of overlap and co-occurrence with other mental disorders often challenges mental health specialists,<sup>9</sup> while general medical services often note co-occurring somatic problems.<sup>10</sup>

The ICD-11 Working Group on this topic was asked to review scientific evidence and other information about use, clinical utility (as termed by WHO), and experience with relevant ICD-10 diagnoses in various health-care settings; to review proposals for the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) and consider how these may be suitable/useful for global applications; and to assemble proposals for ICD-11 with a focus on improving clinical utility.

The Working Group has recommended a separate grouping of disorders specifically associated with stress for ICD-11, rather than combining them with anxiety disorders as in ICD-10 or DSM-IV. Disorders specifically associated with stress have two key characteristics: they are identifiable on the basis of different psychopathology that is distinct from other mental disorders; and they arise in specific association with a stressful event or series of events. For each disorder in the grouping, the stressor is a necessary, although not sufficient, causal factor. The stressor could range from negative life events within the normal range of experience (in the case of adjustment disorder) to traumatic stressors of exceptional severity (in the case of PTSD and complex PTSD).

Among the controversies about existing formulations of PTSD are concerns about its overuse in populations exposed to natural or man-made disasters.<sup>7, 8</sup> One problem has been the application of the diagnosis when populations are still being actively exposed to extreme stressors—eg, continuing conflict, uprooting to unsafe locations, or earthquake aftershocks—which makes differentiation between PTSD, adaptive fear reactions, and grief difficult, especially when the definition of PTSD includes non-specific symptoms. Moreover, there is a concern that an overemphasis on PTSD could contribute to clinicians failing to recognise other commonly occurring mental disorders, especially depression.<sup>11</sup> Nonetheless, the appropriate use of a clearly defined PTSD category is one aspect of progress in evidence-based mental health care in humanitarian settings.<sup>12</sup>

The Working Group has recommended a refocus on the diagnosis of PTSD on three core elements, and removal of non-specific symptoms that are also part of other disorders.<sup>13, 14</sup> The proposed diagnostic guidelines need re-experiencing of the traumatic event, in which the event is not only remembered but experienced as occurring again; avoidance of reminders likely to produce re-experiencing of the traumatic event(s); and a perception of heightened current threat, as indicated by various forms of arousal.<sup>15</sup> These elements must have developed after exposure to an event of an extremely threatening or horrific nature, but the diagnosis is mainly based on symptom presentation rather than on determination of whether or not the event constitutes an eligible traumatic stressor. By contrast with ICD-10, functional impairment (in addition to the duration of symptoms) would be needed to help to differentiate PTSD from normal reactions to extreme stressors. The intention is to simplify the diagnosis and direct clinicians' attention to its core elements, and to use functional impairment rather than specific classes of stressors to enhance the threshold for diagnosis. As in ICD-10, the diagnosis could be made within 1 month of the event.

Complex PTSD is a new proposed category, reserved for extensive reactions typically arising from severe and prolonged stressors usually involving several or repeated adverse events.<sup>16</sup> The proposed diagnosis comprises the three core elements of PTSD, accompanied by enduring disturbances in the domains of affect, self, and interpersonal relationships. This construct is drawn from studies of survivor populations identifying

symptom presentations that reflect sustained and pervasive disturbances in emotion regulation, in the experience of a diminished and defeated sense of self, and in difficulties maintaining relationships.<sup>17, 18</sup> Complex PTSD is distinguishable from personality disorders by its restricted symptom profile and its responsiveness to specific treatments that differ from those for personality disorders and from those for PTSD.<sup>19</sup>

Another new category proposed for ICD-11 is prolonged grief disorder, describing intensely painful, disabling, and persistent responses to bereavement with specific symptoms such as pervasive yearning or preoccupation with the deceased and associated emotional pain.<sup>20</sup> The duration of the symptoms is clearly prolonged compared with what would be considered a normative grief reaction in view of the individual's cultural and religious background.<sup>21</sup> There are well validated treatment programmes that are specific to these symptoms<sup>22</sup> and are not the same as treatment for depression,<sup>23</sup> which also has a different symptom profile; a separate diagnosis will provide a more precise diagnostic indication. The Working Group's conclusion is that there is sufficient evidence for the validity, specificity, and treatability of this disorder to include it, with appropriate caveats about cultural and individual variability in expressions of grief and mourning. The Working Group did not support a previous DSM-5 proposal to include a bereavement-related subtype of adjustment disorder,<sup>24</sup> which accords with guidance provided for ICD-10,<sup>25</sup> because the defining characteristics and duration requirements of prolonged grief disorder are incompatible with the timeframe of adjustment disorder.

Adjustment disorder is defined as an emotional disturbance arising as a consequence of a significant life event. It has often been used as a provisional diagnosis or residual category for people who do not meet thresholds for other disorders, particularly depressive and anxiety disorders. Although some commentators have advocated for elimination of this category,<sup>24</sup> the Working Group emphasised its significance within the range of disorders associated with stress, and as part of the continuum from normal to severe exposure. The Working Group noted that in a global sample of nearly 5000 psychiatrists, adjustment disorder was the seventh most frequently used category,<sup>26</sup> and that it ranked even higher among psychologists.<sup>27</sup> The ICD-11 proposal describes adjustment disorder more specifically as a maladaptive reaction to an identifiable stressor defined in terms of positive symptoms,<sup>28</sup> such as intrusive preoccupation with the stressor and inability to adapt. Symptoms typically emerge within a month of the onset of the stressor and tend to resolve in 6 months.

ICD-10 describes acute stress reaction as emotional, cognitive, and behavioural reactions that subside within days after an exceptionally stressful event, but implicitly labels it as pathological by placing it in the mental disorders chapter. The Working Group regarded such reactions as falling in the normal range, although they could merit clinical attention, and has recommended that acute stress reaction be moved to the ICD-11 chapter containing categories that represent reasons for clinical encounters that are not themselves disorders or diseases (the Z chapter in ICD-10). Humanitarian and other agencies could use this category to allocate immediate psychological assistance to people in need after traumatic events. In the context of many health systems, a diagnostic code in relation to provided health services is necessary, and this proposal is intended to facilitate short-term support without pathologising acute stress reactions.<sup>29</sup>

In conclusion, the Working Group has proposed the following changes from ICD-10: a separate grouping for disorders specifically associated with stress, tighter symptom requirements for PTSD, the addition of complex PTSD and prolonged grief disorder, and the description of adjustment

disorder in terms of specific symptoms. Acute stress reaction is classified as a non-pathological response to an exceptional stressor that may require therapeutic intervention.

There are important differences between the proposals for ICD-11 and those for DSM-5, stemming from WHO's emphasis on clinical usefulness. According to the DSM-5 proposal, PTSD is operationalised by 20 symptoms grouped into four clusters, yielding more than 10 000 combinations of symptoms by which a person can meet the minimum criteria for PTSD. The ICD-11 PTSD proposal is much simpler, and will be easier for clinicians to use and more feasible in low-resource and humanitarian settings. ICD-11 distinguishes a complex form of PTSD that could follow prolonged or multiple events. The American Psychiatric Association has decided against the inclusion of a separate diagnosis of Complex PTSD in DSM-5 but instead has expanded PTSD to include additional aspects of disturbed emotionality and behaviour. In contrast with DSM-5, ICD-11 proposes tightening of the diagnostic requirements for adjustment disorder and elimination of the different subtypes. The earlier DSM-5 proposal for bereavement-related adjustment disorder has been withdrawn, leaving the ICD-11 proposal for prolonged grief disorder as the only one focused on pathological consequences of bereavement.

All proposals for ICD-11, including categories, definitions, and diagnostic guidelines, will be made publicly available for review and comment,<sup>30</sup> and will be subjected to field testing. We wish to emphasise that the present proposals represent a starting point, and look forward to a rich global exchange about how best to address problems of nosology in this area and show greater clinical usefulness in diverse global settings, including humanitarian settings after man-made and natural disasters.

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### ***Substance Abuse***

## **Global Alcohol Use**

Journal of American Medical Association

M. J. Friedrich

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Having accurate information about patterns of alcohol consumption in different regions is necessary to develop policies and strategies to reduce the harms caused by alcohol, a leading risk factor for global disease burden. To gather such information, Canadian researchers examined data on the amount and patterns of alcohol consumption in 241 countries in 2005 and estimated those figures for 2010 (Shield KD et al. *Addiction*. doi:10.1111/add.12112 [published online January 24, 2013]).

The researchers found that worldwide, 40.6% of the adult population currently consumes alcohol, 45.8% are lifetime abstainers, and 13.6% are former drinkers. The prevalence of abstinence, amount of alcohol consumed, and patterns of drinking varied widely from region to region around the globe.

“As these indicators are correlated with alcohol-attributable harms, research on the factors that create variations in these indicators is required to understand more clearly the causes of these variations and how best to formulate and implement country- and regional-level alcohol strategies aimed at reducing consumption and its impact on public health,” the authors noted.



#### Congenital Syphilis Estimates

Syphilis continues to affect large numbers of women and their offspring worldwide, despite the feasibility of screening and treating such women, even in low-resource settings, report researchers from the World Health Organization (WHO) (Newman L et al. *PLoS Med*. 2013;10(12):e1001395).

The researchers developed a mathematical model to estimate global and regional prevalence of syphilis in pregnant women and adverse syphilis-associated pregnancy outcomes for 2008. They applied the model to information in WHO databases, including national syphilis seropositivity data from 97 of 193 countries and information on attendance at antenatal clinics from 147 countries.

The findings suggested that about 1.36 million pregnant women had a probable active syphilis infection, 80% of whom had attended an antenatal clinic. The authors estimate that more than 520,000 adverse pregnancy outcomes from syphilis occurred in 2008, including stillbirths or early fetal deaths, neonatal deaths, preterm or low-birth-weight infants, and infants born with congenital disease.

#### Global Alcohol Use

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time abstainers, and 13.6% are former drinkers. The prevalence of abstinence, amount of alcohol consumed, and patterns of drinking varied widely from region to region around the globe.



Global patterns of drinking alcohol, a leading factor for disease burden, vary widely.

“As these indicators are correlated with alcohol-attributable harms, research on the factors that create variations in these indicators is required to understand more clearly the causes of these variations and how best to formulate and implement country- and regional-level alcohol strategies aimed at reducing consumption and its impact on public health,” the authors noted.

#### Childhood Cancer in the Developing World

Many children in the developing world die of potentially curable cancers, and delivery of better care, research, and education of professionals is needed to reverse this trend, according to a new report (Sullivan R et al. *Lancet Oncol*. 2013;14(3):e123-135).

Rates of childhood cancer are increasing globally, and about 100,000 children die of cancer before the age of 15 years, more than 90% of them in low- and middle-income countries. Approximately

80% of children with cancer in high-income countries survive. However, in low-resource settings, many cases are detected too late for effective treatment.

Challenges in addressing the global burden of childhood cancer includes finding ways to disseminate effective standard-of-care treatments to children living in low- and middle-income countries. Investing in health care systems and capacity, increasing the number of health professionals and improving training, and establishing regional hospital networks are possible strategies to address the issue, write the authors, and collaboration between developed and developing countries could help provide mentoring, education, and access to standard treatments.

#### Endocrine-Disrupting Chemicals

Many endocrine-related diseases and disorders are increasing around the globe, highlighting the need for a better understanding of chemicals known or suspected to be capable of interfering with normal hormone function. A new report from the United Nations Environment Programme (UNEP) and the World Health Organization (WHO) provides information on the current scientific knowledge about exposure to endocrine-disrupting chemicals (EDCs) (<http://bit.ly/9gAaVf>).

Endocrine-disrupting chemicals are found in many household and industrial products and also may be additives or contaminants in food, cosmetics, and personal care products. Evidence from animal models and human studies supports the idea that exposure to EDCs during developmentally critical times plays a role in the rise of endocrine-related cancers, reproductive diseases, behavioral and learning problems, and obesity and diabetes. The report calls for more research to understand the effects and health implications of these substances for humans and wildlife. — M. J. Friedrich

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## Internet Versus In-Person Counseling for Patients Taking Varenicline for Smoking Cessation

Military Medicine

LTC Kent J. DeZee, MC USA; Jennifer S. Wink, MD; MAJ Christopher M. Cowan, MC USA  
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## Abstract

**Introduction:** Quit rates for smoking cessation attempts are maximized by using counseling with medication. Internet-based counseling might be a suitable replacement for in-person counseling. **Methods:** Patients in a military medical system in the active phase of quitting presented for study intake. They were randomized to in-person counseling (n = 44) or Internet counseling (n = 173). In-person counseling consisted of four 1.5 hour classes based on the American Cancer Society's Freshstart program. Internet counseling consisted of daily e-mails with recommended activities through Pfizer's GetQuit program. Both groups were concomitantly treated with standard dose varenicline. The primary outcome was the quit rate at 12 weeks, defined as abstinence and an exhaled carbon monoxide level <10 ppm at the 12-week visit. All those lost to follow-up were considered persistent smokers. **Results:** 217 smokers were randomized, of which 43% returned for the 12-week follow-up visit. Quit rates between the two groups were similar (Internet group: 21%, n = 36/173; in-person group: 18%, n = 8/44, p = 0.7). **Conclusions:** Internet-based counseling might be equivalent to in-person counseling for smoking cessation in patients taking varenicline. Additional studies with more complete and longer-term (≥1 year) follow-up are needed to confirm these findings.

## Introduction

Smoking tobacco has been linked to multiple health conditions and is a leading cause of preventable death in the world. Smoking cessation is the primary method to prevent the adverse health effects of smoking. The most effective techniques to achieve smoking cessation involve both intensive counseling and medication. Although counseling remains an important and effective method for smoking cessation, it requires the patient to report to a clinic or be available at designated times for telephone calls. The latest medication to aid in smoking cessation, varenicline, was approved for use in the United States based on two trials that showed efficacy of this medication when combined with counseling.

Internet-based counseling can be delivered virtually anywhere at any time. Two recent reviews summarized the previous studies of Internet-based counseling for smoking cessation and found inconsistent results. Only four trials have compared Internet to in-person or telephone-based counseling. Two of these were in adolescents and did not use medications, and two compared in-person counseling to in-person counseling plus Internet counseling. Only one of these four trials showed a difference in quit rates, where the telephone counseling was marginally better than the Internet counseling at 3 months (49% vs. 39%), but this difference did not persist at 6 months.

Thus, it is difficult to determine if Internet counseling with medication can be used in lieu of the best available treatment option, intense in-person counseling with medication, as no study has directly compared them to date. The goals of this study were (1) to determine if the GetQuit program, an Internet counseling program specifically designed for varenicline, was more effective than in-person counseling for smoking cessation with all participants taking varenicline; and (2) to determine if Internet counseling was associated with greater satisfaction for smoking cessation than standard in-person counseling.

## Methods

### Study Design

This trial was designed as a randomized controlled trial to compare quit rates between Internet and in-person counseling in patients taking varenicline for smoking cessation. Because of limitations in the number of participants that could be handled by in-person counseling sessions, one-fourth of the participants were randomized to in-person counseling. The remaining three-fourths received Internet counseling. In-person counseling consisted of four 1.5 hours group classes conducted once weekly for 4 consecutive weeks. A trained, experienced tobacco cessation counselor delivered the content of the classes (based on the American Cancer Society's Freshstart program), which emphasized motivational intervention activities, practical counseling (problem solving), social support, healthy eating, stress management, and education about medications and approaches to quitting. The Internet counseling group used the GetQuit web-based counseling program developed by Pfizer, the manufacturer of varenicline. Participants using Internet program received a daily e-mail and invitation to complete an activity. The activities included a detailed smoking history, motivations to quit smoking, quit date advice, smoking triggers and alternatives, support systems, coping strategies, avoiding weight gain, and medication education.

### Screening and Eligibility Criteria

Men and women at least 18 years old, who were entitled for care within the U.S. military medical system (includes active duty military, retired military, and family members of active duty and retired military) and smoked at least 10 cigarettes per day, were eligible for the study. In addition, participants were required to have used e-mail at least every other day, plan to be geographically stable for 4 months, and be in the active phase of quitting (defined as planning on quitting in the next 30 days). Exclusion criteria included glomerular filtration rate <30 ml/min (varenicline is renally excreted), not be currently pregnant or planning on becoming pregnant (varenicline is category C), life expectancy <12 months, and not have been hospitalized within the previous 30 days.

### Study Procedures

To recruit participants, we invited smokers at a single military medical center and surrounding clinics in the southwestern United States to participate in a smoking cessation study through general advertisements and notification of providers. Participants indicated their willingness to be considered for the study by reporting to a clinic at a specific date and time. Each eligible participant then completed an intake questionnaire that contained questions about demographics, smoking history, and a brief medical history. All patients were weighed and self-reported height was collected. Nicotine dependence was assessed using the Fagerstrom instrument. The last page of the questionnaire contained the Patient Health Questionnaire-8 (PHQ-8) for depression (this is the PHQ-9 without the suicidality question) and the Generalized Anxiety Disorder (GAD-7) for anxiety. Before completing the PHQ-8 and GAD-7, all participants were informed verbally and in writing that these questions would not be reviewed by the investigators until after the study was complete, would never be reviewed with them, and they should seek care with their primary

care provider if they felt they were depressed or anxious. The original intent to include these psychiatric scales was to determine if either helped predict quit rates. The study was initiated before psychiatric side effects of varenicline were identified.

After providing written informed consent, each participant received his/her randomly determined counseling assignment (Internet or in-person) by opening a sealed, opaque envelope. The randomization sequence was generated by an individual who was otherwise not involved in the study using a random number table, which was then enclosed in the consecutively numbered envelopes.

All patients who were enrolled in the study were prescribed standard dose varenicline (0.5 mg daily for 3 days, 0.5 mg twice daily for 3 days, then 1 mg twice daily to complete 12 weeks). In-person counseling groups were instructed to begin varenicline on the day of their first class, as the quit day was planned on the day of the second class (1 week later). Internet participants were instructed to begin taking varenicline 1 week before their self-selected quit date and to initiate the Internet counseling on the same day as starting varenicline. They were asked to pick a quit date between 8 days and 2 weeks after study enrollment. All participants were permitted to reduce the dose of varenicline to 1 mg daily if side effects were troublesome.

For the next 12 weeks, participants took varenicline and underwent their randomly assigned counseling as above. They were contacted via e-mail once a month to provide refills of varenicline and answer any questions. After 12 weeks, participants were expected to report for the exit assessment. For those that did not follow up, multiple attempts were made to contact the participant via e-mail and telephone. At this visit, they were asked to report "over the last 7 days, how many cigarettes have you smoked (even one puff of a cigarettes counts)?" Further questions included perceived medication side effects (headache, nausea, insomnia, more/vivid dreams, constipation, diarrhea), weight changes, whether or not they participated in counseling outside their randomization, and how frequently they underwent the assigned counseling. Finally, the exit questionnaire inquired about their overall satisfaction with the counseling program on a 9-point Likert scale, anchored with 1 "very unsatisfied," 5 "somewhat satisfied," and 9 "extremely satisfied." In addition to the questionnaire, exhaled carbon monoxide was measured using an EC50-Micro 4 Carbon Monoxide Monitor-Smokerlyzer (Bedfont Scientific, Medford, New Jersey) and participants were weighed. The investigator measuring carbon monoxide was masked to the randomization assignment.

All appointments, counseling, and medication were provided free of charge, as they would have been for all patients within this health system. The participants were not otherwise compensated for their participation.

Enrollment occurred between February 20, 2007 and May 27, 2008. The study was intended to enroll 600 participants to have 90% power to detect a difference in quit rate of 15% between the groups ( $\alpha = 0.05$ ). However, it was terminated early after the psychiatric side effects of varenicline became known in late 2007/early 2008 and enrollment subsequently dwindled.

Outcome Measures and Statistical Analysis

The primary outcome for this study was the point prevalence of smoking cessation at 12 weeks. Participants who self-reported no smoking in the previous 7 days (not even a puff) and had an exhaled carbon monoxide level less than 10 ppm at their 12-week appointment were considered to have successfully quit. All others, including those lost to follow-up, were considered persistent smokers. The prevalence of smoking cessation between the two counseling types was compared using  $\chi^2$  test. Other comparisons between categorical variables were made with  $\chi^2$  test or Fisher's exact test, as appropriate. All comparisons with continuous variables were made with a t-test or Wilcoxon rank-sum test, as appropriate. For all analyses, a p-value <0.05 was considered statistically significant. All analyses were based on the intention-to-treat principle. All calculations were performed with STATA 11.2 (STATA Corp, College Station, Texas). The study was approved by the local institutional review board. There was no external funding. The manufacturer of varenicline, Pfizer, had no role in the design, conduct, or interpretation of the results.

## Results

247 individuals attended an initial meeting to discuss the study with the investigators. Of these, 217 (88%) were enrolled into the study and were randomized to the Internet counseling group (n = 173) or the in-person counseling group (n = 44). Baseline characteristics were not significantly different between the two counseling groups (Table I).<sup>5,6</sup> There was minimal crossover between groups, as only 1 participant from each group reported counseling of the other assignment during the study.

Unfortunately, follow-up through study completion was poor, as only 93 (43%) reported for the 12-week follow-up and performed an exhaled carbon monoxide. Of the characteristics listed in the table, six predicted higher follow-up rates: older age, more pack-years of smoking, more years of smoking, having attended a smoking cessation class before the study, having cardiac disease or a risk factor for cardiac disease, and previous use of bupropion (p ≤ 0.007 for all comparing those who did and did not complete the study). This likely reflected older age as the main predictor for study completion, as all but one of these characteristics (previous use of bupropion) was associated with older age (p < 0.0001 for all except bupropion).

Participation in the counseling sessions seemed to be similar. Of the 74 participants in the Internet group who provided data on the exit survey, 51% (n = 38) reported reading all of the daily e-mails and 81% (n = 60) read at least half. Similarly, 53% (8 of the 15) respondents in the in-person group reported attending all the classes, and 87% (n = 13) reported attending at least half.

## Efficacy

There was no difference between the two groups with regard to quit rates (quit rate for all participants: 20% [n = 44]; Internet group: 21% [n = 36]; in-person group: 18% [n = 8]; p = 0.7,  $\chi^2$  test). As the study completion rate was poor, additional analyses were performed in patients aged 40 or older, as older patients were more likely to complete the study and 40 was the median age. Of the 108 study participants aged 40 or older, 60 (56%) completed the study. Within this group, quit rates were higher overall but still not different between the treatment groups (quit rate for all participants age 40 or older: 31% [n = 33]; Internet group: 31% [n = 27]; in-person group 30% [n = 6]; p = 0.95,  $\chi^2$  test). Finally, the subgroup of participants (n = 69) with cardiac disease or a risk factor for cardiac disease (defined as any self-reported heart disease, history of a myocardial infarction, diabetes mellitus, hypertension, or hyperlipidemia) had the highest return rate (65%, n = 45) and quit rate (32%, n = 22).

## Satisfaction With Counseling

Participants were asked to indicate their overall satisfaction with their counseling on a 9-point Likert scale, anchored with 1 “very unsatisfied,” 5 “somewhat satisfied,” and 9 “extremely satisfied.” Participants from the Internet group who provided a response ( $n = 71$ ) rated their satisfaction at a mean of 6.5 (SD 2.3). The in-person group participants who provided a response ( $n = 15$ ) were less satisfied (mean 5.5, SD 2.6) but not significantly so ( $p = 0.14$ , t-test).

For the Internet group, satisfaction varied by counseling preference at study onset. For those whose top choice of counseling at study onset was Internet counseling ( $n = 53$ ), satisfaction with the Internet counseling was higher than those ( $n = 18$ ) whose initial preference was either in-person or telephone (mean 6.9 vs. 5.3,  $p = 0.011$ , t-test). This same pattern was seen with the in-person group (mean satisfaction 6.8 for the 5 participants preferring in-person counseling vs. 4.8 in the 10 participants who did not prefer in-person counseling), but there was no statistical difference likely because of the small numbers of participants ( $p = 0.12$ , Wilcoxon rank-sum test).

## Side Effects

90 patients provided data on nonpsychiatric side effects. Nausea was the most common side effect (58%,  $n = 52$ ), followed by insomnia (39%,  $n = 35$ ), abnormal dreams (36%,  $n = 32$ ), headache (23%,  $n = 21$ ), constipation (14%,  $n = 13$ ), and diarrhea (12%,  $n = 11$ ). The average weight change ( $n = 80$ ) was a gain of 2.9 kg (SD 3.7). We did not collect data on cardiovascular side effects, as these potential adverse effects of varenicline were not known until long after our study's completion.

The psychiatric side effects have been previously reported. In brief, of the 72 patients successfully contacted 6 to 18 months after the study completion (when the psychiatric side effects became known), 6% ( $n = 4$ ) reported suicidal ideation either during or close to the time of varenicline usage. There were no known suicide attempts. In addition, 1 participant was admitted for psychosis within 30 days of starting varenicline, but the treating psychiatrist determined the symptoms were unrelated to varenicline.

## Discussion

For patients taking varenicline for smoking cessation, we found no difference in quit rates between Internet and in-person counseling. In addition, both counseling groups were generally satisfied with their counseling (particularly those who preferred Internet counseling and were randomized to that group), though it is possible our estimation of satisfaction might be overestimated as those who did not return might have been poorly satisfied.

Our study was the first to examine an Internet-based counseling method directly against in-person counseling in the setting of medication use for smoking cessation. Only four previous trials used a similar study design of comparing an Internet to a non-Internet counseling method, with two

differing from our study by not providing medications; two augmenting the Internet counseling with in-person counseling; and one substituting active telephone counseling for in-person counseling. Like our study, none of these trials found any difference in quit rates by the conclusion of study period. These studies lend support to our finding of Internet counseling being equivalent to in-person counseling for smoking cessation.

An Internet option for counseling is clearly important. As others have suggested, it is valuable to have another option besides telephone and in-person counseling for smokers who are attempting to quit. This is shown in our study, as Internet counseling was the preferred method for 67% of participants, compared to just 25% for in-person counseling. Thus, at least for our study population, there is a clear desire for this mode of counseling. This trend may continue to grow as more smokers become Internet savvy.

We found lower quit rates than published studies of varenicline. The primary explanation would be that our follow-up was poor and worse than previous studies despite multiple attempts to contact participants. This resulted in assigning more than half of our cohort as continued smokers as per our intention-to-treat analysis. For the subset of patients with the highest return rate in our study (those with risk factors for cardiovascular disease or having cardiovascular disease, return rate 65%), the quit rate was 32%, which is within 12% of the initial varenicline trials. Thus, it is possible that our quit rate would have approached the previous trials with better follow-up. Finally, poor follow-up is pervasive in Internet counseling studies for smoking cessation, with drop-out rates ranging from 20% to 46%.

There were limitations with this study. First and foremost, as discussed earlier, more than 50% of participants were lost to follow-up. Unfortunately, poor follow-up is sometimes the price for increased generalizability. Our study design resulted in nearly all participants who reported to the initial study meeting (88% of those screened subsequently enrolled) as we had a very limited number of inclusion and exclusion criteria. Also, we did not provide a financial reward for follow-up. Thus, although we appear to have selected participants representative of the study population (baseline demographics and smoking history were similar to the initial varenicline trials<sup>5,6</sup>) and motivated to quit (all were planning on quitting in the next 30 days), we may not have selected patients who were motivated to return for the final study session. The other major limitation is we did not meet our targeted study enrollment. Thus, we could have made a type II error (failing to find a difference when one exists). We should also balance these limitations against our studies strengths: a representative population, allocation concealment to prevent bias, negligible crossover, blinding of the outcome assessor (exhaled carbon monoxide), and similar amounts of counseling between the two groups.

In conclusion, our study suggests that smokers desiring to quit, who prefer Internet counseling, may use this format instead of in-person counseling without compromising quit rates. Additional studies, particularly with longer follow-up (more than 1 year), would be useful to confirm these findings.

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## **Conflicts and Compromises in Not Hiring Smokers**

The New England Journal of Medicine

David A. Asch, M.D., M.B.A., Ralph W. Muller, M.A., and Kevin G. Volpp, M.D., Ph.D.  
11 April 2013

Tobacco use is responsible for approximately 440,000 deaths in the United States each year — about one death out of every five. This number is more than the annual number of deaths caused by HIV infection, illegal drug use, alcohol use, motor vehicle injuries, suicides, and murders combined and more than the number of American servicemen who died during World War II.

A small but increasing number of employers — including health care systems such as the Cleveland Clinic, Geisinger, Baylor, and the University of Pennsylvania Health System — have established policies of no longer hiring tobacco users. These employers might justify such hiring policies in many ways — arguing, for instance, that they're taking a stand against a habit that causes death and disability, that they're sending an important message to young people and others within their communities about the harms of smoking, or that they're reducing their future costs, given that smokers, on average, cost employers several thousand dollars more each year than nonsmokers in health care expenses and lost productivity.

These policies engender controversy, and we recognize that they risk creating or perpetuating injustices. One set of concerns arises from the fact that tobacco use is more concentrated in groups with lower socioeconomic status. Hospitals do better than most institutions at creating employment and advancement opportunities for disadvantaged populations. So even though most members of lower socioeconomic groups do not use tobacco, and even though anti-tobacco hiring policies are not intended to reduce jobs for these populations, they are likely to do so inadvertently, at least somewhat.

However, these policies may also save lives, directly and through their potential effects on social norms, and these same disadvantaged populations are at greatest risk for smoking-related harms and ensuing disparities in health. Many Americans see it as perfectly acceptable that most workplaces are smoke-free and that smoking is prohibited in many bars and restaurants. We are reminded of how far we have come in our tolerance for restricting this activity only on visits to other countries, where public smoking is much less restricted, or when we recall the time when airplanes had smoking sections — a notion that seems absurd today.

To be sure, many of the restrictive policies we now take for granted were justified not by their effects on smokers but by the harm inflicted on nonsmokers by secondhand smoke. These policies also increased the stigma against smoking, so although there's debate over whether stigma can be used as a tool for good, ultimately these policies almost certainly contributed to the decrease in the prevalence of smoking, not just the limits on where it occurs. For example, the Cleveland Clinic moved to a smoke-free campus in 2005 and stopped hiring smokers in 2007. Reportedly, smoking rates decreased in Cuyahoga County (where the Cleveland Clinic is located) from 20.7% in 2005 to 15% in 2009, whereas the overall rate in the state decreased only from 22.4% to 20.3%.

Similarly, policies against hiring smokers shift the debate from the question of where one smokes to that of whether one smokes. Are these policies aimed at tobacco, which is harmful and destructive, or at people who are addicted to tobacco, who may be seen as victims? Do the policies target legally available products or people who make a personal choice that contributes to a social burden and could conceivably choose

otherwise? Are the rules designed to reduce smoking, which is a population health goal, or to fence out smokers, which may be an institutional financial goal? How, exactly, should we look at these policies?

We believe we should see them as one product of a growing recognition that changing behaviors is hard, that combating addiction is harder, and that behaviors that were once seen as exclusively private often have profound societal effects. As a result, many stakeholders are trying to change unhealthy behaviors through mechanisms as varied as legislative requirements for calorie labeling in some restaurants, bans on the sale of large servings of sugar-sweetened beverages, and Affordable Care Act provisions allowing employers to provide rewards or penalties worth up to 50% of employees' health insurance premiums on the basis of health assessments, including smoking status. Those policies would have seemed like hard paternalism back when no one questioned passengers' right to smoke on airplanes, but they might be seen as considerably softer now in light of social trends, and perhaps in the future we won't consider them paternalistic at all.

The Nuffield Council on Bioethics in the United Kingdom has proposed a conceptual ladder of progressively higher levels of interventions aimed at improving health-related behaviors. Finding the ladder useful in the context of smoking, we have laid out an anti-tobacco-intervention ladder that ranges from simply monitoring behavior, to guiding people's choices through increasingly aggressive means, and ultimately to eliminating choice (see figure).

Proposed Ladder of Interventions to Reduce Tobacco Use.

An important justification for climbing the ladder is that the gentler interventions that make up the lower rungs haven't resulted in adequate smoking-cessation rates, given tobacco's harms.

For example, we conducted a randomized trial comparing the use of employer-provided financial incentives for smoking cessation, aided by counseling, with an approach in which the same sorts of counseling programs were made available to employees but no incentives were given — effectively comparing enabling choice (rung 3) with guiding choice through incentives (rung 5). In one sense, the results were dramatic: during 12 to 18 months of follow-up, employees in the incentive group had a quit rate that was approximately three times that in the comparison group. But in absolute terms, even the incentive group had an 18-month quit rate of only about 9% — meaning that even with an aggressive system of rewards, 91% of employees who wanted to quit could not. We believe that the severe harms of smoking justify moving higher up on the ladder when lower-rung interventions don't achieve essential public health goals.

Not everyone will see a given approach as achieving the same balance between social goals and effects on individuals. Is it fair to penalize smokers even though the highly addictive nature of nicotine makes their behavior less than entirely voluntary? In many surveys, about 70% of smokers say they want to quit, but only 2 to 3% succeed each year. One reason for this huge gap is that smoking cessation has immediate costs in the form of nicotine withdrawal (i.e., the symptoms of withdrawal and the costs of antismoking treatments), but its benefits in terms of improved health are considerably delayed. Thus, although some people may see anti-tobacco hiring policies as adding economic injury to physical injury, we

would argue that such policies also make the benefits of smoking cessation more immediate and so help to counterbalance the immediate costs of quitting.

Do hospitals' anti-tobacco hiring policies send a signal to their patients? Many patients dislike the smell of smoke clinging to a health worker's clothing as he or she leans over them — or at least may see that odor as inconsistent with the values and goals hospitals are supposed to represent. Do hospitals' anti-tobacco hiring policies denormalize smoking and help communities escape tobacco's burden? Critics may argue that these claims are disingenuous, akin to a human resource director's saying to tobacco-using applicants, “Believe me, it's for your own good that I'm not hiring you.” But in the long run, such policies may indeed be for their own good.

We recognize that these hiring practices are controversial, reflecting a mix of intentions and offering a set of outcomes that may blend the bad with the good. We know that many companies will want merely to continue their current level of anti-tobacco efforts, but given the threats that tobacco presents to our communities and institutions, we believe it's time to climb another rung on the ladder.

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***TBI***

## **Guideline: Tailor Appraisal of Concussion During Sports**

The Journal of the American Medical Association

Mike Mitka, MSJ

17 April 2013

Use of traditional grading systems to evaluate the severity of a possible sport-related concussion should be eliminated in favor of more nuanced individualized assessment and follow-up care of injured athletes, according to an updated guideline from the American Academy of Neurology (Giza CC et al. *Neurology*. doi: 10.1212/WNL.0b013e31828d57dd [published online March 18, 2013]).

The update recommends immediately removing from play athletes with suspected concussion and returning them to play only after they have been assessed by a licensed health care professional trained in concussion assessment and treatment. Following a concussion, the athlete's return to play should be gradual and only after all acute symptoms are gone. In addition, athletes of high school age and younger who experience a concussion should be managed more conservatively, as evidence suggests it takes them longer to recover than college athletes.

“We've moved away from the concussion grading systems we first established in 1997 and are now recommending concussion and return to play be assessed in each athlete individually,” said guideline coauthor Christopher C. Giza, MD, of the David Geffen School of Medicine at the University of California, Los Angeles, in a release. “There is no set timeline for safe return to play.”

The guideline notes that athletes with a history of 1 or more concussions are at higher risk for being diagnosed with another such injury and that the first 10 days after a concussion appears to be the period of greatest risk for a subsequent concussion.

The risk of concussion in young male athletes is greatest in football, rugby, hockey, and soccer. The risk of concussion for young women and girls is greatest in soccer and basketball.

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***Other***

## **Alterations in Spontaneous Brain Oscillations during Stroke Recovery**

Public Library of Science

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Abstract

Amplitude or frequency alterations of spontaneous brain oscillations may reveal pathological phenomena in the brain or predict recovery from brain lesions, but the temporal evolution and the functional significance of these changes is not well known. We performed follow-up recordings of spontaneous brain oscillations with whole-head MEG in 16 patients with first-ever stroke in the middle cerebral artery territory, affecting upper limb motor function, 1–7 days (T0), 1 month (T1), and 3 months (T2) after stroke, with concomitant clinical examination. Clinical test results improved significantly from T0 to T1 or T2. During recovery (at T1 and T2), the strength of temporo–parietal ~10-Hz oscillations in the affected hemisphere (AH) was increased as compared with the unaffected hemisphere. Abnormal low-frequency magnetic activity (ALFMA) at ~1 Hz in the AH was detected in the perilesional cortex in seven patients at T0. In four of these, ALFMA persisted at T2. In patients with ALFMA, the lesion size was significantly larger than in the rest of the patients, and worse clinical outcome was observed in patients with persisting ALFMA. Our results indicate that temporo–parietal ~10-Hz oscillations are enhanced in the AH during recovery from stroke. Moreover, stroke causes ALFMA, which seems to persist in patients with worse clinical outcome.

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## Introduction

Magnetoencephalography (MEG) and electroencephalography (EEG) studies have shown that the human brain exhibits spontaneous intrinsic electrical oscillations at various frequencies. In healthy brain, the most prominent oscillations occur in the 8–30 Hz frequency range and their quantitative parameters such as frequency and power have been shown to be intraindividually rather stable across repeated measurements. Although the functional significance of these brain rhythms is not thoroughly understood, changes in the amplitude or frequency as well as alterations in task-related modulation of brain rhythms, have been linked with pathological phenomena of the brain.

Several EEG and MEG studies have reported changes in spontaneous brain oscillations after stroke. However, the results are highly variable: for example, both attenuation and enhancement of ipsilesional rolandic ~10-Hz activity has been observed, and the temporal evolution from the acute phase and the association of these findings with clinical recovery are unclear. Moreover, gamma-band power in the affected hemisphere and delta-band power in the unaffected hemisphere in the acute phase after stroke have been suggested to predict clinical outcome.

In addition to alterations in physiological brain oscillations, abnormal low-frequency magnetic activity (ALFMA, in the 0.5–6 Hz range) has been reported in patients with brain lesions such as traumatic brain injury and stroke. However, the association of ALFMA with clinical outcome is not yet known.

The aim of this study was to investigate 1) how the earlier reported alterations in rolandic ~10-Hz oscillations evolve during recovery from stroke and if these alterations are associated with functional recovery, 2) if alterations in spontaneous brain oscillations can predict recovery from stroke and 3) how ALFMA is associated with clinical recovery from stroke. To achieve this, we measured spontaneous resting state brain oscillations with a whole-head MEG in 20 first-ever stroke patients within one week and one and three months after stroke. Compared with EEG, MEG has the

advantage that the brain signals are practically unaffected by the conductivity differences of the brain and surrounding tissues, giving MEG a better spatial accuracy. With whole-head MEG, the activity of the two hemispheres can be recorded simultaneously and thus compared in exactly same conditions.

## Materials and Methods

### Patients and control subjects

Twenty patients with a first-ever acute stroke in the middle cerebral artery territory affecting upper limb motor function were recruited at the Department of Neurology, Helsinki University Central Hospital (HUCH), Helsinki, Finland. Exclusion criteria were earlier neurological diseases, head traumas or neurosurgical operations, severe psychiatric disorders, and unstable or poor general condition. Magnetoencephalographic (MEG) recordings were performed in the BioMag Laboratory, HUCH, within 1–7 (mean  $3.5 \pm 0.5$ ) days (T0) and after one (T1) and three (T2) months from stroke onset. One patient was excluded because of a recurrent infarction after the first measurement, and the MEG data of three patients had to be excluded because of technical problems in the recordings, preventing reliable analysis. Thus the data of 16 patients (8 females, 8 males; age 44–84 years, mean age  $66 \pm 3$  years; all right-handed) and ten healthy control subjects (5 females, 5 males; mean age  $61 \pm 2$  years, all right-handed) were used for further analysis. One of the included patients refused the third measurement (T2) because of claustrophobia, whereas the rest of the patients underwent successfully all three measurement sessions.

The study was approved by the Ethics Committees of the Helsinki and Uusimaa Hospital District. All patients and control subjects gave written informed consent. Somatosensory evoked fields (SEFs) to tactile finger stimulation and motor cortex excitability of the same patients and control subjects have been reported previously.

### Clinical and neuroradiological evaluation

Clinical examination was performed at T0, T1, and T2. It consisted of National Institutes of Health Stroke Scale (NIHSS; 0–42 points, with 0 being the best score), modified Rankin Scale (mRS; 0–5 points, with 0 being the best score), and Nine Hole Pegboard test (Peg; time measured to remove and replace nine pegs as fast as possible; upper limit set to 120 s) scoring. To evaluate the size and site of ischemic lesion, anatomical MRIs with T1 MPRAGE and T2 sequences were taken with a 3 T MR scanner (Philips) at T0 and T1.

### Magnetoencephalographic (MEG) recordings

Spontaneous brain activity during rest was recorded with a 306-channel whole-head MEG device (Elekta Neuromag®, Elekta Oy, Helsinki, Finland), housing 204 gradiometer and 102 magnetometer sensors, in a magnetically shielded room. During the recordings, the subjects were, according to their clinical condition and their own wish, either sitting or lying with the head resting on the sensor helmet. The subjects were asked to relax and not to move their head. During the recordings, a nurse inside the magnetically shielded room observed the patients' general condition.

The exact head position with respect to the sensor array was determined at the beginning of each measurement by detecting the magnetic fields produced by four indicator coils placed on the scalp. To align the MEG data with the coordinate system of anatomical MRIs, the locations of the indicator coils with respect to anatomical landmarks were determined with a three-dimensional digitizer before each measurement session. During the 6-min recording, subjects kept their eyes open/closed for 3 min each. The MEG signals were sampled at 941 Hz and band-pass filtered to 0.03–308 Hz.

#### Data analysis

To remove interference due to external and nearby artifact sources, the data were first processed with the temporal extension of the signal space separation method (tSSS) implemented in Maxfilter™ software (Elekta Oy) using a correlation window length of 16 s and a correlation limit of 0.98. In each patient, the data from measurements at T0 and T1 were transformed to correspond to the head position in the measurement at T2 allowing a more accurate sensor-level comparison of location and strength of spontaneous brain activity. To remove the cardiac contamination occurring at the frequency band of ALFMA, a signal-space projection was derived by averaging the MEG signals with respect to the magnetocardiographic QRS complex, applying principal component analysis to the average, and selecting the two principal components associated with the highest singular values. These components were projected out from the tSSS-processed continuous data.

After preprocessing the data, the amplitude spectra of spontaneous brain activity were calculated separately for the eyes-open and eyes-closed conditions by averaging the magnitudes of fast Fourier transforms (FFT) in half-overlapping windows over the whole measurement time. To estimate the amplitudes of spontaneous brain oscillations in the frequency range of 5–90 Hz, 2048-point FFTs, corresponding to a frequency resolution of ~0.5 Hz were used. A flat-top window was applied in conjunction with the FFTs to get accurate amplitude estimates from the spectra. To identify possible ALFMA (0–4 Hz), 8192-point FFTs, resulting in a frequency-resolution of ~0.1 Hz, with a Hanning window were used. A Hanning window was chosen for its better frequency resolution compared to the flat-top window. The amplitudes of the spectral peaks over the centroparietal (rolandic 10-Hz and beta rhythms) and parieto-occipital (alpha rhythm) regions were quantified from 5–9 MEG channels showing the largest amplitudes (see Fig. 1).

Figure 1. Amplitude spectra of one patient (gradiometers; eyes open).

Three channels from both hemispheres, showing peaks of rolandic ~10-Hz, rolandic beta, and occipital alpha activity. Rolandic ~10-Hz oscillations are clearly increased in the affected hemisphere (AH). UH; unaffected hemisphere. T0, 1 week; T1, 1 month; T2, 3 months after stroke.

Minimum current estimates in the frequency domain (fdMCE) were calculated to localize the sources of spontaneous brain oscillations. fdMCE for ~10-Hz activity was calculated for the eyes-open condition to avoid the contaminating effect of strong occipital alpha activity. In fdMCE, 2048-point Hanning windowed half-overlapping FFTs (frequency resolution of ~0.5 Hz) were computed across the recordings, and the frequency components in individual frequency windows (detected in the individual spectra) were source-modeled using L1 minimum norm estimation. A realistically-shaped standard brain volume with a uniform 10-mm grid was used as the source space, and a spherical conductor model was used for the

forward computations. The source locations were projected to the surface of the standard brain volume for visualization, and the strength of the ~10-Hz activity at each subjects' individual peak frequency was defined for each hemisphere in a region of interest (ROI) which excluded the parieto-occipital region. The same ROI was used for each subject and each measurement, and symmetrical (with respect to the interhemispheric plane) ROIs were used for the left and right hemispheres. The interhemispheric ratio of ~10-Hz oscillations was calculated with the formula  $(AH/UH)*100$  and compared between different time points and between patients and control subjects. The source locations of ALFMA were estimated from the eyes-closed condition to minimize possible artifacts due to eye blinks, which contaminate the same frequency band. The procedure was as above, except that 4096-point Hanning-windowed FFTs were computed to achieve a frequency resolution of ~0.2 Hz. For each patient, an individual ROI was defined to enclose the detected activity in all three measurements, and the same ROI was used within one patient to evaluate the persistence of ALFMA. The strength of ALFMA in the affected hemisphere was normalized by subtracting the strength in the mirrored ROI in the unaffected hemisphere. For comparison, the sources of ALFMA were modeled in two patients also with equivalent current dipoles (ECDs) fitted sequentially in 10-ms steps to band-pass-filtered (0–3 Hz) data using a subset of ~40 channels over the area with largest signals. Only ECDs that explained at least 92% of the measured field pattern were accepted.

Repeated-measures ANOVA with within-subject factors time (T0, T1, T2) and hemisphere (affected, AH; unaffected, UH), and for the beta-range a three-way ANOVA with the additional within-subject factor beta-range (beta1, beta2), were used to evaluate alterations of frequencies and amplitudes of spontaneous brain oscillations, and to analyze the clinical tests. When a significant main effect was detected, pair-wise comparisons were performed between different time points or between hemispheres. Bonferroni-corrected independent sample t-tests were used to compare the parameters between patients and control subjects. Clinical parameters between patients with vs. without ALFMA were compared with non-paired t-tests. A p-value <0.05 was considered statistically significant.

## Results

### Clinical outcome

Patients' clinical details are summarized in Table 1. The patients recovered well: all measured clinical parameters improved significantly from T0 to T1 or T2 (Peg:  $81\pm 10$  s vs.  $57\pm 10$  s and  $48\pm 8$  s; NIHSS:  $4\pm 1$  vs.  $2\pm 1$  and  $1\pm 0$ ; mRS:  $3\pm 0$  vs.  $2\pm 0$  and  $2\pm 0$ ,  $p<0.01$  for all). The improvement was steepest from T0 to T1. Although the overall clinical outcome, measured with NIHSS and mRS, improved still from T1 to T2 ( $p<0.05$ ), no significant improvement of hand dexterity, as measured with Peg, was observed from T1 to T2. However, the affected hand function did not reach the level of the healthy hand function during our three-month follow-up ( $48\pm 8$  s vs.  $26\pm 1$  s,  $p<0.05$ ).

Table 1. Clinical details of the patients.  
Spontaneous brain rhythms

Temporo-parietal area.

Figure 1 shows the spectra of spontaneous brain activity in gradiometers (0–60 Hz, eyes open) in one patient at T0, T1, and T2. Spectral peaks are observed at ~10 Hz and at ~20 Hz over the temporo–parietal region in both hemispheres and at ~10 Hz over the occipital region. In all patients and control subjects, 2 to 3 spectral peaks were observed over the temporo–parietal region in both hemispheres; around 9 Hz (corresponding to rolandic 10-Hz rhythm), around 15 Hz (beta1), and around 20 Hz (beta2; Table 2). However, distinct beta1 and beta2 peaks were not found in all patients and control subjects. No systematic spectral peaks at frequencies higher than ~20 Hz were observed in the control subjects or in the patients. No significant differences in any of the frequencies were found between the hemispheres of the control subjects. Neither were there differences in the peak frequencies over the temporo–parietal region between the hemispheres nor measurements of the patients, nor between patients and control subjects.

Table 2. Frequencies (Hz) and amplitudes of spectral peaks in the patients (fT/cm $\sqrt$ Hz) over the temporo-parietal (eyes open) and occipital (eyes closed) areas.

In the patients, at sensor level, the amplitude of the major spectral peak at ~10 Hz over the temporo–parietal region (eyes open) was significantly stronger in the AH than in the UH at T1 and T2. Repeated-measures ANOVA showed a significant main effect for the factor hemisphere [ $F(1,15) = 5.721$ ,  $p < 0.05$ ]. Pair-wise comparison showed that the amplitude of the ~10-Hz rhythm was significantly stronger in the AH than in the UH at T1 and at T2 ( $p < 0.05$  and  $p < 0.005$ , respectively; Table 2).

Figure 2 shows the averages of the source locations of ~10-Hz oscillations in the patients with a left hemispheric stroke and in the control subjects. The strongest sources for the eyes-open condition are in the temporo–parietal region, clearly distinct from occipital alpha sources, but slightly lateral to the typical location of rolandic ~10-Hz oscillations. In the patients' eyes-open condition, the sources of ~10-Hz oscillations are clearly stronger in the AH than in the UH. Such difference is not seen in the eyes-closed condition, or in the control subjects. Repeated-measures ANOVA showed a significant main effect for the factor hemisphere [ $F(1,12) = 5.590$ ,  $p < 0.05$ ] and an interaction between the factors time and hemisphere [ $F(2,24) = 3.556$ ,  $p < 0.05$ ] for the source strength. Pair-wise comparison showed that the mean strength of the sources of ~10-Hz oscillations was significantly stronger in the AH than in the UH at T1 and at T2 ( $p < 0.05$ , Figure 3, Table 3). The amplitude of the ~10-Hz sources seemed to increase in bursts (Figure 4), varying strongly in source localization and strength from time window to another, used in the spectral estimation. As fdMCE calculates the mean strength of all the FFT-windows, the absolute values for the ~10-Hz sources remain rather small.

Figure 2. Source localizations of ~10-Hz oscillations in patients with left hemispheric stroke and in control subjects. Averages of source localizations of ~10-Hz oscillations (arbitrary scale) estimated with fdMCE in the patients with left hemispheric stroke (eyes-open/eyes-closed) and in the control subjects (eyes-open).

Figure 3. Mean (+SEM) source strength of ~10-Hz oscillations over the temporo–parietal region (eyes open/eyes closed). AH, affected hemisphere. UH, unaffected hemisphere. T0, 1 week; T1, 1 month; T2, 3 months after stroke. \* $p < 0.05$ .

Figure 4. Spectrum and time-frequency representation of ~10-Hz oscillations from one channel over the temporo-parietal region in one patient (eyes open).

The amplitude spectrum of the channel is shown on the left (spectral density in arbitrary units). The burst-like nature of ~10-Hz oscillations is illustrated in the time-frequency representation on the right.

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Table 3. Source strength estimates (nAm) of ~10-Hz activity over the temporo-parietal region in all patients (mean  $\pm$  SEM), and low-frequency (~1-Hz) oscillations in the patients, in whom low-frequency oscillations were detected (mean  $\pm$  SEM).

ANOVA showed a main effect for the interhemispheric ratio (AH/UH) of the strength of ~10-Hz oscillations [ $F(2,24) = 3.865$ ,  $p < 0.05$ ]. Pair-wise comparison showed that the interhemispheric ratio was larger at T1 and T2 than at T0 (178% and 180% vs. 129%,  $p < 0.05$ , respectively). No significant differences in the strength of the temporo-parietal ~10-Hz rhythm was detected between the hemispheres of the control subjects or between patients and control subjects. However, the interhemispheric ratio (AH/UH) of the strength of ~10-Hz oscillations was significantly larger in the patients at T1 and T2 than in the control subjects (178% and 180% vs. 93%,  $p < 0.05$ , respectively). The source strength of the ~10-Hz rhythm for the eyes-closed condition did not differ between the hemispheres, or between the measurements. Peak amplitudes of the beta1 (~15 Hz) and beta2 (~20 Hz) rhythms, generated in the rolandic region, did not differ between the hemispheres, time points, or patients and control subjects (Table 2).

In summary, both amplitude spectra and fdMCE revealed that the strength of ~10-Hz oscillations in the AH was enhanced at T1 and T2 as compared with the UH.

Occipital area.

The spectral peaks over the occipital region (eyes closed, corresponding to occipital alpha) are listed in Table 2. For the peak frequency of the occipital alpha, ANOVA showed a significant main effect for the factor hemisphere [ $F(1,12) = 21.309$ ,  $p < 0.001$ ]. Pair-wise comparison showed that the peak frequency of the occipital alpha was significantly lower in the AH than in the UH at T2 ( $p < 0.05$ ). At T0 and T1, the difference was not significant ( $p = 0.12$  and  $p = 0.11$ , respectively). The amplitudes of the occipital ~10-Hz rhythm did not differ between the hemispheres, measurements, or patients and control subjects.

Abnormal low-frequency magnetic activity (ALFMA)

Figure 5A illustrates the frequency spectra of spontaneous 0–5 Hz brain oscillations from two gradiometer channels overlying the affected (AH) and unaffected hemispheres (UH) in one patient at T0, T1, and T2, and in one control subject. The spectra show a clear peak at ~1 Hz in the AH in the patient at T0 and T1, and an elevated level of ALFMA still at T2. ALFMA were detected in seven out of 16 patients at T0, and in six patients at T1. In four patients ALFMA persisted still at T2. In six of the patients with ALFMA the lesion included the cortex, whereas one of the patients had a pure subcortical stroke.

Figure 5. Spectrum and source localization of abnormal low-frequency magnetic activity (ALFMA).

A) Amplitude spectra (eyes closed) of spontaneous 0–5-Hz brain oscillations in one patient and one control subject. Two channels from the amplitude spectra of spontaneous 0–5-Hz brain oscillations in one patient at T0, T1, and T2 and in one control subject. AH, channel from the perilesional area in the affected hemisphere. UH, channel from the corresponding region in the unaffected hemisphere. T0, 1 week; T1, 1 month; T2, 3 months after stroke. B) Source localization of ALFMA in one patient above Source localization of ALFMA (arbitrary scale) projected on the surface of the standard brain volume (same patient as in A). below Source localizations of ALFMA projected on the MRI of the patient. Lesion localization is shown on the left.

Figure 5B illustrates the localization of the sources of ALFMA in one patient at T0, T1, and T2. Localization found with fdMCE corresponded well with the localization with ECDs. In patients with cortical lesions, the sources of ALFMA were localized in the perilesional cortex, whereas in the patient with a pure subcortical stroke the source was found in the cortical region overlying the lesion.

The lesion size was significantly larger in the patients showing ALFMA than in the rest of the patients ( $35 \pm 15$  cm<sup>3</sup> vs.  $2 \pm 1$  cm<sup>3</sup>,  $p < 0.05$ ). In addition, ALFMA seemed to be associated with worse clinical outcome. At T0, no statistically significant differences in the Peg test results or in the overall clinical outcome (measured with NIHSS) was detected between patients with or without ALFMA ( $101 \pm 13$  vs.  $75 \pm 16$ ,  $p = 0.09$  for Peg; and  $5 \pm 1$  vs.  $3 \pm 1$ ,  $p = 0.2$  for NIHSS). However, the four patients with persistence of ALFMA had a worse clinical outcome at T2 than the rest of the patients ( $88 \pm 21$  s vs.  $33 \pm 3$  s,  $p < 0.001$  for Peg;  $3 \pm 1$  vs.  $1 \pm 0$ ,  $p < 0.05$  for NIHSS).

In summary, ALFMA was detected in 7/16 patients at T0 and it persisted in four of these at T2. The patients with persistent ALFMA had a significantly worse clinical outcome at T2 than the rest of the patients.

## Discussion

### Temporo–parietal ~10-Hz oscillations

In the patients, the strength of temporo–parietal ~10-Hz oscillations was increased for the eyes-open condition in the AH at T1 and T2 as compared with the UH. In contrast, no such difference was observed for the eyes-closed condition. In the control subjects, no interhemispheric differences in the strength of temporo–parietal ~10-Hz oscillations was detected neither for the eyes-open nor the eyes-closed condition, indicating

that although the amplitude of spontaneous brain oscillations varies interindividually, the amplitude is rather similar in the two hemispheres in healthy subjects. Further, the interhemispheric ratio (AH/UH) of the strength of ~10-Hz oscillations was significantly larger in the patients than in the control subjects, indicating that this interhemispheric difference, detected only in the patients, is a pathological phenomenon. The strongest sources of ~10-Hz oscillations in the eyes-open condition were localized in the temporo–parietal region, clearly distinct from the occipital region, but slightly lateral to the typical rolandic area.

In addition to occipital and rolandic ~10-Hz oscillations, spontaneous oscillations at 7–10-Hz have been detected in the temporal lobe (auditory tau-rhythm) and in the parietal operculum, most likely in the secondary somatosensory cortex (SII; sigma rhythm) in healthy subjects. The strongest sources of our prominent ~10-Hz oscillations could agree with the location of the sigma rhythm. However, fdMCE analysis revealed that the amplitude of ~10-Hz oscillations increased in bursts and had generators both in the rolandic region and in the parietal operculum. As the source localization and strength of ~10-Hz oscillations varied strongly from time window to another used in spectral estimation, no exact separation between sources in the rolandic region and the parietal operculum could be made. Hence, we cannot rule out contributions of different temporo–parietal rhythms (such as the tau, sigma and rolandic ~10-Hz rhythms) to the observed ~10-Hz oscillations detected over the temporo–parietal region in our patients and control subjects, and thus we call this rhythm temporo–parietal ~10-Hz rhythm. The occipital alpha rhythm is known to be strongly modulated by opening or closing the eyes, and some of its activity may be detected also at sensors above the temporo–parietal region. However, the interhemispheric difference in the strength of the temporo–parietal ~10 Hz rhythm was detected only for the eyes-open condition, when the occipital alpha rhythm is dampened. Thus the increased temporo–parietal ~10-Hz activity, described in the AH, likely represents a rhythm clearly distinct from occipital alpha.

Earlier studies on the strength of spontaneous ~10-Hz oscillations after stroke have reported varying results: both decreases and increases of rolandic ~10-Hz oscillations in the AH have been reported. In these studies ~10-Hz oscillations were studied at the sensor level and no source modeling was performed; thus, non-rolandic contributions can not completely be ruled out.

No correlation between the strength of ~10-Hz oscillations in the AH and clinical outcome has been found in earlier stroke studies, in line with the findings of the present study. Earlier studies have shown that post-stroke recovery mechanisms may differ between patients with cortical vs. subcortical strokes. In the present study, seven patients had a subcortical, three a pure cortical, and six a cortico–subcortical stroke. It may be that the lesion site affects the amplitude of ~10-Hz oscillations, which could explain the lack of correlation between the strength of the ~10-Hz oscillations and clinical recovery in the present study. Unfortunately, we were not able to demonstrate different effects of cortical vs. subcortical strokes as the separate groups were rather small. However, Pfurtscheller et al. found enhanced ~10-Hz oscillations in the AH in the acute state in patients with mild or moderate neurological deficits and months later in patients with slow clinical recovery from a severe neurological deficit. This enhancement was interpreted as a favorable sign for recovery. In our patients, the steepest clinical improvement was observed from T0 to T1. Accordingly, the ipsilesional enhancement of temporo–parietal ~10-Hz was observed not earlier than at T1, suggesting that the enhanced rhythm may be linked with positive alterations in the somatosensory cortex. However, as no correlation between increased ~10-Hz oscillations and clinical recovery was observed, this suggestion remains speculative and future studies are needed to evaluate the functional significance of increased ~10-Hz oscillations during stroke recovery.

In healthy subjects, ~10-Hz oscillations have been shown to be involved in the engagement and disengagement of specific brain regions in tactile discrimination tasks and in somatosensory working memory performance; ~10-Hz activity has been shown to increase in task-irrelevant areas and to decrease in task-relevant areas. Thus ~10-Hz activity is suggested to filter the inflow of sensory input with respect to its anticipated relevance. The increase in ~10-Hz activity has been linked to active inhibition of neuronal firing. In the light of these findings, it may be that the enhancement of ~10-Hz oscillations in the AH of our stroke patients could possibly be engaged in allocating resources for recovery mechanisms. However, this remains hypothetical, and needs to be elucidated in future studies.

Earlier studies have suggested slowing of both occipital alpha rhythm and rolandic ~10-Hz rhythm in the affected hemisphere (AH) after thalamic and middle cerebral artery territory strokes. In line, we observed deceleration of the occipital alpha rhythm in the AH of our stroke patients at T2. However, at group level, no such deceleration was observed in the temporo–parietal ~10-Hz rhythm. This may be due to differences in sites of the lesions in the middle cerebral artery territory. Cortical rhythms are mainly generated in cortical areas. However, the thalamus has been suggested to play an essential role in driving the cortical rhythmic activity. Hence, disturbances in different sites of thalamocortical connections may affect the peak frequency of occipital alpha and temporo–parietal ~10-Hz activity differently. The differences in the amplitude and frequency behavior of the occipital alpha and the temporo–parietal ~10-Hz rhythm further emphasize the distinct generators and functional role of these rhythms.

#### ALFMA

Earlier studies have indicated that brain lesions are often accompanied by abnormal electromagnetic activity at 1–4 Hz that can be directly measured with MEG. Animal studies have indicated that this abnormal activity is caused by partial cortical deafferentation. This theory was supported in a recent study, which combined MEG and diffusion tensor imaging (DTI) in patients with traumatic brain injury, and found a co-occurrence of axonal injury with ALFMA. A combined MEG and proton magnetic resonance spectroscopic imaging study suggested an association between ALFMA and abnormal metabolic activity in preserved but dysfunctioning cortical neurons adjacent to the lesion. However, the functional significance of these oscillations is still poorly understood.

Perilesional ALFMA has also been detected in stroke patients, but the relationship between ALFMA and the site or size of the lesion has remained unclear. Vieth et al. detected ALFMA at 1–6-Hz range in patients with focal and superficial lesions. Similarly, Butz et al. detected perilesional ALFMA at 1–3 Hz in 15 out of 23 patients in different stages after cortical strokes. In the present longitudinal study, ALFMA was detected in the acute phase in the affected hemisphere (AH) in 7/16 patients; 6/9 patients with a lesion extending to the cortex and only in 1/7 patients with pure subcortical stroke, in line with the earlier observations. These results suggest that cortical damage may predispose to the generation of ALFMA after stroke.

In adult rat thermal-ischemic lesions of the sensorimotor cortex induced ALFMA that was strongly correlated with axonal sprouting. Both ALFMA and axonal sprouting were blocked with tetrodotoxin infusion, suggesting that ALFMA may have a role in anatomical reorganization after a brain lesion. In humans, no systematic relationship between the occurrence or persistence of ALFMA and clinical findings has been observed in earlier

studies. In the present study, the patients with persistence of ALFMA had a worse clinical outcome at T2 than the rest of the patients. However, as the patient number with persistence of ALFMA was very small (4 patients), no definitive conclusions on the correlation between persistence of ALFMA and clinical outcome can be drawn. Whether ALFMA is a sign of severity of neuronal damage or a signal of still ongoing plastic reorganization needs to be elucidated in future studies.

#### Predictive value of spontaneous brain oscillations

The strength of spontaneous gamma oscillations (>34 Hz) in the AH and the strength of delta (2.0–3.5 Hz) oscillations in the UH in the acute phase after stroke have been suggested to predict recovery. In the present study, no clear spectral peaks in the gamma range were detected in the patients or in the control subjects, neither did we detect delta peaks in the UH of the patients. As the MEG/EEG signal strength typically decreases with increasing frequency, it may be difficult to separate gamma band oscillations from the background and sensor noise and possible muscular artifacts, due to the low signal-to-noise ratio. Most reports of gamma oscillations have been associated with event-related phenomena such as visual processing or motor tasks that synchronize the envelope of gamma oscillations and thus increase their detectability. Resting-state gamma oscillations are more difficult to separate from background and sensor noise and were probably therefore not observed in our patients. In contrast, ~10-Hz activity is a very robust signal, which is detected practically in every subject. In 13/16 of our well-recovering patients, enhancement of AH ~10-Hz activity was detected at some time point. Thus increased ~10-Hz activity may have a functional role in stroke recovery. Future studies should aim at investigating if this enhancement could be used to predict the outcome from stroke.

In conclusion, our results show that stroke causes perilesional ALFMA, which persists in some patients and which may be associated with the severity of the stroke and poor recovery. Moreover, the temporo–parietal ~10-Hz oscillations were enhanced in the affected hemisphere during recovery of our patients, which may be a favorable sign for recovery. Future studies will show, whether temporo–parietal ~10-Hz oscillations can be used to predict the outcome from stroke.

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## Mapping the mind—smart thinking for brain health?

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On April 2, US President Barack Obama launched his most ambitious scientific research plan to date—the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative. The programme aims to accelerate the development of new tools to map comprehensively, for the first time, the activity of the human brain. The White House claims that the project will not only revolutionise our understanding of the human mind but also uncover new ways to treat, prevent, and cure brain disorders like Alzheimer's disease, schizophrenia, autism, epilepsy, and

traumatic brain injury. Obama has requested US\$100 million in federal funding for the initiative, which will be channelled through the National Institutes of Health (NIH), the Defense Advanced Research Projects Agency, and the National Science Foundation. He has also called for companies, universities, foundations, and philanthropists to join the project, which he hopes will generate thousands of jobs and provide a boost to America's economy.

Will the reality match the ambition? Reaction has been mixed. In its favour, the project's leaders recognise that the tools to map the complex neural circuits of the brain, and accurately and non-invasively record the activity of almost 100 billion neurons in real-time, do not yet exist. With its technological focus, the Initiative could therefore produce real advances in methods, such as brain imaging. The BRAIN Initiative also seems a sounder endeavour than its European counterpart, the Human Brain Project, which promises to build a supercomputer simulation that integrates everything known about the human brain, including the structures of ion channels in neural cell membranes. But detractors say that the data for such a reconstruction of the brain are inadequate.

The BRAIN Initiative certainly has high-level political and academic support and a coherent approach to tackle the task. The NIH will establish a high-level working group to shape and develop a plan for the project, including timetables, milestones, and cost estimates. But there are problems. Questions have been raised about how useful mapping the brain will be. Given that our brains change, learn, think, remember, and are shaped by our experiences, interactions with other people, and society, mapping the electrical spikes in the brain seems an overly restrictive biomedical approach to understanding the most complex organ in the human body. It is also doubtful that this approach will yield cures for conditions such as Parkinson's disease and Alzheimer's disease as purported, at least not for several decades to come. Furthermore, this high-level initiative might divert funds from other areas of brain research—eg, brain chemistry, physiology, and pharmacology—that are more likely to have clinical impact sooner.

There are also non-biomedical aspects of brain disorders that require urgent attention. For example, access to psychological treatments for depression worldwide is woefully inadequate and the costs and availability of social care for people with Alzheimer's disease is a growing concern in many countries.

Parallels have been made between the BRAIN Initiative and the Decade of the Brain (1990—1999), which was announced with a similar fanfare by then President George H W Bush. Yet, experts note that during the Decade there was neither a substantial increase in the rate of recovery from mental illness, nor a detectable decrease in suicide or homelessness—both of which are associated with a failure to recover from mental illness.

Additionally, concerns exist about the creation of a divide in brain science if equity and global health implications are not considered up front. Such divides arose with the development of digital and genomic technologies. Peter Singer, chief executive officer of Grand Challenges Canada, an organisation that funds innovative global health projects, told *The Lancet* that one of the most important ways to promote equity would be to focus on early child development. As many as 200 million children fail to reach their full potential as a result of exposure to risk factors—malnutrition,

infection, poor management of pregnancy, birth complications, and lack of stimulation and nurturing—in the first 1000 days of life. Protecting young brains from these threats in developing nations should be part of the BRAIN Initiative to ensure that the project has global impact, he says.

Ultimately, the BRAIN Initiative is a valiant attempt to unlock the mysteries of the human mind. But whether it is a wise move for better brain health globally is debatable.

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## **Dependent Adolescent Pregnancy Rates and Risk Factors for Pregnancy in the Military Health Care System**

Military Medicine

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### **ABSTRACT**

**Background:** We sought to determine the pregnancy rate of U.S. military-dependent adolescents enrolled in the military healthcare system.

**Methods:** We examined the age and insurance status of dependent adolescents, ages 12 to 23, and determined the incidence of new pregnancies in the military healthcare system from 2006 to 2010 in San Antonio, Texas. Adolescents not enrolled or only recently enrolled in TRICARE Prime at the time of pregnancy were analyzed separately. A Cox-Proportional Hazards model was used to determine risk factors for pregnancy (relationship to sponsor, age, and contraceptive prescription).

**Results:** 444 pregnancies were diagnosed among the 12,417 eligible subjects. For adolescents with continuous enrollment in TRICARE Prime, the pregnancy rate was 9.67/1,000 woman-years at risk, much lower than the national average. Cox-Proportional Hazards analysis showed age group (15–19 years), and history of oral contraceptive prescription were associated with a higher pregnancy rate. 59% of pregnancies occurred in women not enrolled or only briefly enrolled in TRICARE Prime at the time of pregnancy.

**Conclusion:** Dependent daughters enrolled in TRICARE Prime had a very low pregnancy rate. The majority of pregnancies occurred in adolescents not enrolled in TRICARE Prime at the time of pregnancy diagnosis, suggesting many adolescents sought health insurance after pregnancy was diagnosed.

## INTRODUCTION

Despite recent declines in national teen pregnancy rates, teen pregnancy continues to be a problem in the United States. Compared to other developed countries, the United States has a much higher rate of adolescent pregnancy, 3 to 6 times higher than European countries and a birth rate 4 to 9 times higher. Recent years, however, have shown a modest decline in the national teen birth rate. Although we should celebrate our success, it is clear continued efforts are needed to combat this problem, as current U.S. teen pregnancy rates are still twice that of the United Kingdom (41.5 vs. 26.7/1,000) and significantly higher than other industrialized nations such as Switzerland (4.3/1,000) and Japan (5.1/1,000).

The consequences of teen births are many and impact the teen parent, infants of teen parents, and society. Teens who give birth at young ages are more likely to drop out of school, have low educational attainment, and live in poverty. Infants of teen parents are more likely to drop out of high school, use public insurance, enter the foster care system, be at risk of abuse or neglect, and become a teen parent themselves. In society, teen births are costly; in 2004, U.S. taxpayers paid at least \$9.1 billion for teen childbearing. Texas, with one of the highest teen birth rates, had the highest individual state taxpayer bill.

The military healthcare system (MHS) is not immune to these problems. An average teen pregnancy costs the Department of Defense between \$3,900 and \$6,200 for prenatal visits, delivery, and immediate postdelivery care for mother and infant, based on TRICARE reimbursement rates. These figures likely underestimate the total cost per adolescent pregnancy, as they do not attempt to capture the added financial burden to the system of preterm and complicated births. These costs also do not capture the impact on military readiness or conflict between the parent and the teen during the pregnancy, delivery, and postpartum periods.

Many studies have examined teen pregnancy in the general population, but very few have addressed teen pregnancy in the MHS. Previous studies examining this issue have evaluated live birth rates to military dependents, but not pregnancy rates, nor examined the insurance status of these women at time of the pregnancy. The purpose of this study was to identify the pregnancy rate among dependent children enrolled in the MHS in the San Antonio, Texas area. Additional description of the demographic factors associated with pregnancy included insurance status at the time of diagnosis, parent-child relationship, age, and prior prescription of contraception.

## METHODS

We performed a retrospective cohort study examining military insurance and laboratory records of medical care performed for female-dependent children, ages 12 to 23, in the San Antonio military catchment area between January 1, 2006 and September 30, 2010.

First, we examined the age and insurance status of all dependent children, ages 12 to 23, and determined the incidence of new pregnancies. To be counted as a unique pregnancy diagnosis, there could be no positive pregnancy tests in the preceding 9 months. Positive pregnancy tests more than 9 months apart during the study period were recorded as a second pregnancy.

Our dataset allowed for examination of all positive pregnancy tests performed at military treatment facilities. We then parsed this data to assure only unmarried dependent daughters of active duty or retired military service members were included. Further, we examined the insurance status of these patients to confirm that they were enrolled in TRICARE Prime and recorded their age at diagnosis of pregnancy. We also examined the time period of enrollment in TRICARE Prime and how this related to the date of pregnancy. Data for pregnancies of subjects who were not included in our main cohort were analyzed separately (subjects not enrolled in TRICARE Prime or those enrolled for less than 9 months at the time of pregnancy diagnosis).

To determine the rate of pregnancy, we performed a life table analysis examining the rate of first pregnancy diagnosis among dependent females with continuous enrollment in TRICARE Prime insurance. The event under examination for the life table analysis was the time to first pregnancy, defined as the first appearance of a positive pregnancy test. To be eligible for inclusion, subjects needed to have at least 10 months of continuous enrollment to a TRICARE Prime clinic in the San Antonio area. This allowed us to strictly rule out all pregnancies that could have occurred before enrollment in TRICARE Prime. Subjects were excluded from the life table analysis at the time of the first interruption in TRICARE Prime coverage, once they became pregnant, or upon the end of the study period on September 30, 2010. The incidence of pregnancy was determined using Kaplan–Meier analysis. A Cox proportional hazards model was used to model time to first pregnancy as the event with covariates of subject status (relationship to sponsor), age, and contraceptive prescription.

Contraceptive prescriptions were measured via pharmacy records, which cover prescriptions at military pharmacies and at civilian network pharmacies. Positive responses included any prescription of emergency contraception, oral contraceptives, contraceptive patch, the vaginal ring, or subdermal implanted contraception during the study period. We also included prescription of oral contraceptives or the vaginal ring in the 1 year before entry into the cohort and prescription of subdermal contraception during the 3 years before entry into the cohort. We did not measure patient compliance with the contraceptive method.

Analyses were performed using STATA. This study was approved by the Institutional Review Board at the Brooke Army Medical Center. Investigators adhered to the policies for protection of human subjects as prescribed in 45 Code of Federal Regulation 46.

## RESULTS

There were 12,488 subjects, with at least 10 months of continuous enrollment in TRICARE Prime during our study period, who were eligible for inclusion in our analysis of pregnancy rates among TRICARE Prime enrollees. Seventy-one women had a positive pregnancy test in the first 9 months of enrollment and therefore were excluded from further analysis. The remaining 12,417 young women contributed a total of 16,338 woman-years at risk for pregnancy.

We identified 444 unique pregnancies during our study period. The majority of these pregnancies (59%) occurred among women who were either not enrolled or had <9 months of enrollment in TRICARE Prime at the time of diagnosis. Many of these patients were identified through testing in the emergency room or through subsequent follow-up at the military treatment facility. All of these women were eligible for enrollment in TRICARE

Prime before pregnancy, but their families had elected not to enroll them. Also, 5% of the pregnancies identified during the study period were second pregnancies.

The incidence of pregnancy for dependent adolescents who were enrolled in TRICARE Prime and met our inclusion criteria for the main analysis was 9.67/1,000 woman-years at risk. The highest incidence of pregnancy was among women who were ages 15 to 19 at entry into the study (15.8/1,000 woman-years at risk). Among these subjects, overall time to pregnancy, after the 9 month lead-in period, was 0.71 years (interquartile range 0.30–1.28 years).

As shown in Figure 1, there is a significant difference between the age categories with the women who were in the 15- to 19-year age group at entry to the study being most likely to become pregnant. Pregnancy rates for all age groups are listed in Figure 1. In Cox-Proportional Hazards analysis, age group (15–19 years) and a history of being prescribed oral contraceptives were associated with a higher incidence of a positive pregnancy test.

## DISCUSSION

This study shows that over half of teen pregnancies in the MHS occur in dependent adolescent daughters with no or only brief enrollment in TRICARE Prime at the time of diagnosis of pregnancy. Many of these adolescents enroll in insurance coverage after becoming pregnant. This suggests prior studies that have examined live birth rates in adolescent age mothers in the MHS have underestimated the effectiveness of pregnancy prevention efforts in the MHS, because many of these mothers will have had no access to preventative services from the military before becoming pregnant. The limitations of our study did not allow for examination of the reasons for lack of enrollment. However, we hypothesized that cost could have been an issue for retiree family members, as they have an enrollment fee of \$460 per year for all dependents in the family. Enrollment for dependents of active duty service members requires an administrative procedure, but there is no cost.

This study also shows that adolescent females who are enrolled in the MHS have markedly lower pregnancy rates than national and state rates. The rate of 0.8 pregnancies per 1,000 woman-years among adolescents ages 12 to 14 in this study compares favorably with the rate of 7.1 in the same age group in the U.S. population. In addition, the rate of 15.8 pregnancies per 1,000 woman-years for adolescent women ages 15 to 19 in this study also compares favorably with the rate of 71.5 in the same age group in the U.S. population. The pregnancy rate for women ages 15 to 19 is also significantly lower than the rate in our surrounding community (Texas at 88/1,000) and lower than the lowest state in the nation (New Hampshire at 33.0/1,000). This difference may be artificially high, especially in the older adolescents, as we are excluding married women, but it still represents a difference between patients seen in the MHS versus the general population. These differences may reflect socioeconomic and behavioral differences between military dependents and the general population but may also reflect the excellent access to care and low barriers to accessing reproductive health care in the MHS. Further research is needed to clarify the underlying reasons for the differences between military dependents and the general population.

As we expected, the 15- to 19-year-old age group had a higher risk of pregnancy than the 12- to 14-year-old age group. This is supported by adolescent pregnancy data from almost every source. Likely correlates include rates of sexual activity going up over time, and lack of responsible use of contraception whether it is barrier, hormonal methods, or the combination.

We were surprised by the lower pregnancy rate seen in the 20- to 23-year-old age group as compared to the 15- to 19-year-old age group in this study. Some possible reasons for the lower rates seen in the older adolescents include more mature use of contraceptives (both barrier and hormonal) and selection bias in our older population because only full-time college students were eligible for TRICARE Prime insurance after age 21. Additionally, when we compare this 20- to 23-year-old category to national rates (8.4/1,000 woman-years vs. 171.0/1,000 women-years in the U.S. population), we must take into consideration that none of the subjects enrolled in this study were married, as this would disqualify them from TRICARE Prime insurance as dependent daughters.

The association seen between prescribed oral contraceptives and increased risk of pregnancy was also surprising. We suspect that this reflects an association between being sexual active and being prescribed a contraceptive agent, and poor compliance with contraceptive methods requiring daily use. Our dataset only allowed us to measure if a woman was prescribed contraceptives but did not have information on compliance. We also measured the association between use of other contraceptive methods and pregnancy rate but did not have enough data to make meaningful inferences.

Additionally, second pregnancies, although a small number, present an additional opportunity to improve pregnancy prevention. This study shows that even with health insurance offering free contraception and excellent access to reproductive health care, approximately 18% of the total subjects in the dataset with a first pregnancy go on to a second. This is a population in which targeted intervention is paramount.

Although this is the largest study of teen pregnancy in military dependents, we recognize there were many limitations to the methods used. Our dataset lacked information about pregnancy test results and care received outside the MHS. Also, we do not have data on military dependents who did not access care at all in the MHS, so, we do not know if the lower pregnancy rate we found among the young women enrolled in the MHS reflects better outcomes among all military-dependent females or just among those enrolled in the MHS. Further study is required to determine if factors present in the MHS account for lower teen pregnancy rates and if these factors can be generalized to the U.S. health care system to improve outcomes for all adolescent and young adult women.

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## **Cypriot and Greek Army Military Boot Cushioning: Ground Reaction Forces and Subjective Responses**

Military Medicine

## ABSTRACT

Lower limb injuries are a continual and serious issue for military personnel. Such injuries have been associated with the requirement to train in military boots (MBs) and might be offset with commercial insoles. In this study, ground reaction forces were measured in seven male participants wearing running shoes (RS), MBs commonly used by Cypriot and Greek Army personnel, and the MBs with two types of shock-absorbing insole. The participants performed 4-min trials at walking pace ( $5 \text{ km}\cdot\text{h}^{-1}$ ) and running pace ( $10 \text{ km}\cdot\text{h}^{-1}$ ) at a 5% gradient on a treadmill under all four shod conditions. The treadmill incorporated two force plates under its belt, which provided measurements of key kinetic variables. During walking, RS showed significantly lower values for impact peak force ( $p < 0.01$ ), maximum force ( $p < 0.05$ ), and push-off rate ( $p < 0.05$ ) compared with other conditions, although no significant differences were found during running. Although the RS were rated significantly more comfortable than any other condition, neither insole made the MBs more comfortable to wear. With little evidence to support wholesale adoption of insoles in MBs, their use by military personnel can only be recommended on a case-by-case basis.

Overuse injuries of the lower extremities associated with military training are a serious and continual problem, resulting in loss of manpower and training time. The majority of musculoskeletal injuries associated with military training occur at or below the knee. For example, Havenetidis et al found that the most common injuries in Hellenic Army Academy recruits were to the ankle and foot. It has been suggested that the typical military boot (MB) worn during training may be a factor in these injuries, due partly to the inadequate cushioning they provide against shock transmission through the tissues of the lower limb. This is because the main role of MBs is to protect the foot from direct trauma (because of rough terrain, for example) and protect the ankle from inversion injury rather than providing shock absorbance. However, previous research has suggested that impact forces were decreased in MBs when using an additional insole and that by using such insoles the incidence of injuries can similarly be decreased. This is interesting given that athletic footwear and shock-absorbing insoles are often used by the civilian population to try to protect against injury by reducing the magnitude and rate of loading experienced during walking and running. However, other research has found that there was no benefit gained from using additional insoles in MBs, particularly when running and so their value to Army personnel is still unclear.

Although some studies have taken an epidemiological approach in assessing the role of insoles in reduction of injury risk, others have directly measured those factors associated with lower limb injury. For example, in comparing a standard British MB with and without a commercial insole, Dixon used a force plate to measure ground reaction forces (GRFs) from the right foot only during running trials along a 15-m runway. She found that peak impact force and peak rate of loading were both significantly reduced when using the insole. Similar experimental setups were adopted by Dixon et al and O'Leary et al, but a limitation of measuring kinetic variables in walking or running is the difficulty of obtaining multiple footstrikes. This is because normal gait patterns, and consequently GRF curves, can be affected by participants targeting the force plates rather than walking or running naturally at an appropriate, realistic pace. This drawback can be avoided with the use of an instrumented treadmill with in-dwelling force plates located under the treadmill belt. Such treadmills also have the advantage that running or walking speed can be controlled and multiple steps

can be measured during a single trial. These treadmills are not widely available and therefore offer a novel approach to analyze the effects of MBs on GRFs.

Although all Cypriot and Greek men are normally required to attend the Army forces for a period of between 1 and 2 years, few published data exist related to the shock properties of the MB that is used by Cypriot and Greek Army personnel. Army personnel might decide to use commercially available insoles as a means of protecting themselves from injury or pain. However, despite the enormity of the problem as reflected by the high incidence of lower limb injuries during basic training, no studies have examined the possible beneficial effects of improving shock absorption in MBs in Cypriot and Greek Army personnel. Therefore, the principal aim of this study was to investigate the GRFs generated during walking and running on an instrumented treadmill while wearing RS, MBs commonly used by Cypriot and Greek personnel, and MB with two different shock-absorbing commercial insoles in an attempt to understand the possible internal loading mechanics. The present study aimed to investigate the importance of comfort perception under these footwear conditions and how this information related to GRF data. Because of the employment of the instrumented treadmill, the findings of the study would provide valuable information not only to Cypriot and Greek Army personnel but also to other users of MBs.

## METHODS

### Participants

Seven healthy young adult male volunteers ( $24 \pm 3$  years;  $1.73 \pm 0.06$  m;  $79.2 \pm 9.4$  kg) took part in the study. The participants wore light clothing and were barefoot during the measurement of their anthropometric characteristics. All participants were normally heel strikers, free from injury on the day of testing, and experienced in treadmill running. The study was approved by the University Ethics Committee, and written informed consent was obtained from all participants before participation in the study.

### Description of the Boot and Insoles

The standard MB is a rigid boot composed of an upper made of leather and a rubber sole and its mass (individually) is 0.90 kg. This particular MB is used by Cypriot and Greek Army personnel (infantry). Two commercial pairs of insoles from different manufacturers were used in the present study. The specifications of the insoles are presented below:

#### Insole A

An ethyl vinyl acetate (EVA) insole, featuring a forefoot to aid flexibility and increased EVA heel thickness for comfort. It also has a sculpted heel area for support, an antislip texture on the underside for grip, and a toweling top surface for comfort.

#### Insole B

This insole was developed using Sorbothane technology and consists of 100% polyurethane foam for cushioning and covered in breathable polyester fabric to wick away moisture.

## Procedure

The research took place at the University Campus (Biomechanics Laboratory), where participants performed a test comprising both walking and running on the h/p/Cosmos Gaitway treadmill (Gaitway, Traunstein, Germany). This treadmill has two in-dwelling force plates with an eight-channel charge amplifier (Kistler, Winterthur, Switzerland), which can measure GRFs during locomotion. Its force range was set to 6,000 N for testing. All participants were given time to familiarize themselves with the treadmill during a separate visit. This was achieved by allowing the participants to walk and run on the treadmill at any desired speed for any period of time.

Each participant performed a warm-up at a steady pace. Afterwards, they performed stretching exercises of their preference. To imitate the kinds of training undertaken using the MBs, the participants then started either walking at  $5 \text{ km}\cdot\text{h}^{-1}$  ( $1.39 \text{ m}\cdot\text{s}^{-1}$ ) or running at  $10 \text{ km}\cdot\text{h}^{-1}$  ( $2.78 \text{ m}\cdot\text{s}^{-1}$ ) on the treadmill, at a 5% gradient, for 4 minutes. Each test was performed under the following conditions:

- — Wearing running shoes (RS)
- — Wearing the MB without insole (MB)
- — Wearing the MB with insole A (MBA)
- — Wearing the MB with insole B (MBB)

The order of testing was randomized to imitate the undefined nature of training and between each condition the participants had a rest of 4 minutes. It was decided to conduct each running and walking trial over 4 minutes to minimize any possible influence of fatigue over the course of testing and to minimize any discomfort felt in any particular shod condition. The participants wore their own RS, although the boots and both sets of insoles were newly acquired. Data were collected at 1,000 Hz during the last 30 seconds of walking and running in all four different conditions. This resulted in analysis of between 50 and 60 steps during walking and between 70 and 90 steps during running per participant during each condition. During data collection, the researcher ensured that each participant was striking the treadmill correctly; this was achieved by monitoring the participant's position on the treadmill and by checking that a full complement of force traces were recorded immediately after recording. The treadmill collected data from both left and right footstrikes. The kinetic variables that were collected and investigated included the impact peak force (IPF), the push-off rate (POR), maximum force (MF), and loading rate (LR). IPF was defined as the as highest recorded force recorded during the first 70 ms of contact with the treadmill and represented the passive peak. In conjunction with this, MF was defined as the highest force recorded during the contact phase. LR was defined as the slope of the force curve throughout the loading phase of the running cycle and is taken from the point of 10% of the IPF to the 90% point. POR was defined as the slope of the force curve during unloading, taken from the 90% of push-off peak to the point of 10%. To facilitate comparisons between participants, GRF peak magnitudes and LRs were divided by the participants' weights and expressed in bodyweights (BW) and BW per second ( $\text{BW}\cdot\text{s}^{-1}$ ), respectively.

Upon completion of each experimental condition, the participants answered a questionnaire (as described by House et al), which asked them to evaluate the comfort of the RS, MBs, and MBs with insoles, by marking a position on a line that ranged from very comfortable (+10) to very uncomfortable (-10).

### Statistical Analysis

Statistical analysis of the GRF variables was undertaken using PASW Statistics 18 (IBM SPSS, Chicago, Illinois, 2009). Means and standard deviations were computed for all variables. Analysis of variance and subsequent post hoc analysis (Tukey) were used to determine possible differences between footwear conditions with an  $\alpha$  level of 5%. A Friedman test was used to analyze the questionnaire data, and Spearman's rank correlation test was used to examine possible relationships between subjective (questionnaire) and objective (GRF) data.

## RESULTS

Analytical data for all variables during walking are presented in Table I.

During walking, IPF was lower when participants wore their own RS than when wearing the MBs either with or without the insoles. Furthermore, MF was lower in RS than in the MBA and MBB conditions, but it was not lower in RS than in the MB condition. This was despite there being a larger absolute difference between the RS and MB than between RS and MBA or MBB. This was because of the larger range (and therefore larger standard deviation) found in the MB condition for this variable.

Analytical data for conditions RS, MB, MBA, and MBB during running are shown in Table II; no significant differences were found for any of these variables.

The subjective comfort/discomfort data for each condition are presented in Figure 1.

All participants rated the RS as the most comfortable, and they were significantly different from other conditions (Friedman = 17.4,  $p < 0.001$ ). Mean ranks for RS, MB, MBA, and MBB were 3.9, 1.0, 2.7, and 2.4, respectively. The range of comfort–discomfort scores (-10 = very uncomfortable; 0 = neutral; 10 = very comfortable) for RS, MB, MBA, and MBB were from 5 to 10, from -10 to 4, from -7 to 8 and from -8 to 7, respectively. The number of participants who rated the RS, MB, MBA, and MBB conditions in the comfortable range (greater than 0) was 7 (100%), 1 (14%), 4 (57%), and 3 (43%), respectively. Alternatively, the number of participants who rated the RS, MB, MBA, and MBB conditions in the uncomfortable range (less than zero) was 0 (0%), 9 (86%), 3 (43%), and 4 (57%), respectively. No significant correlations were found between comfort/discomfort data and GRF data. Spearman rank test correlation values are presented in Table III.

## DISCUSSION

The aim of this study was to investigate the GRFs generated during walking and running while wearing RS, MBs, and MBs with two different shock-absorbing commercial insoles (MBA and MBB) in an attempt to understand the possible internal loading mechanics. The present data showed that during walking across all conditions, RS presented a lower GRF profile compared with MBs either with or without the shock-absorbing insoles. In particular, IPF was approximately four times greater in the three MB conditions compared with RS. However, despite the absolute values for MF, LR, and POR being higher for MBs than for RS, there were no significant differences between them. The values found for MF in both insole conditions (MBA and MBB) were found to be greater than in RS. The absence of a similar significant difference in the MB condition (despite higher absolute values) might have been due to the larger standard deviation found in the MB condition. Larger standard deviations were also found in the MB condition during the running trials for all GRF variables. These larger deviations in both forms of gait suggest that there is a wider range of individual adaptations to wearing MBs, which means that for some individuals (i.e., those encountering the greatest decrease in GRFs) the insoles might be more worthwhile and have an important benefit.

During the running trials, the study's overall results showed that no significant differences existed across all variables while wearing the running shoe compared with the three boot conditions. This might have been because of the participants adopting different running styles to accommodate the different footwear conditions so that GRFs were minimized. In particular, research suggests that individuals adapt their running style to different shoe-surface interactions so that changes in gait kinematics (e.g., footstrike pattern) occur to reduce impact variables, such as peak impact force, or any pain or discomfort experienced; it is possible that this may have occurred in the MB conditions. Whatever the reason, there was no advantage to either wearing RS or commercial insoles when running in terms of reducing GRF magnitudes. These results differ from those of some previous research, which did find reduced impact forces with some insoles in MBs. The present study measured impact forces using a instrumented treadmill rather than the more commonly used runway methodology as it eliminated the risk of participants targeting the force plate or varying their speed. It is possible that the differences in findings were a result of these different methodologies, and further research using instrumented treadmills is advised.

With regard to ratings of comfort, the findings of the present study suggested that commercially available insoles did not play a significant role in the perception of footwear comfort in the MBs. In particular, the results showed that even with an insole the MBs did not achieve the comfort perception of the RS. This is probably because of the fact that the MB provided extra weight to the foot, is much more rigid, and its general design and construction have other priorities than comfort. On an individual basis, all participants gave higher ratings to the two insole conditions than without the insoles, similar to earlier studies, but there was no significant difference overall and both insole conditions were still rated as uncomfortable by roughly half the participants. This suggests that the shock absorbance properties of the insoles were not sufficient to make the boots comfortable enough for walking and running across all individuals (as the RS were), and this is another aspect of fitting insoles, which needs to be assessed on a case-by-case basis. The low comfort scores found for the insole conditions might be because of the other properties of the MB, which make it uncomfortable (e.g., its rigidity) and therefore cannot be overcome with an insole alone. The perception of comfort scores showed that all participants preferred walking and running while wearing a running shoe and this suggests that changes in MB design, such as softer leather and wider shoe lasts, could be beneficial.

The results of the present study indicating that insoles did not have a significant role in comfort perception when wearing the MB contrasts with the findings of other studies, where boots with the best combination of shock-absorbing properties and stability were rated the most comfortable by the participants. However, even in these studies, there was no association between the sensitivity of cushioning and the GRFs, which was supported by the present study's data where comfort ranking was also not related with any of the force variables measured. This would seem to suggest that a boot which feels comfortable does not necessarily have reduced GRF magnitudes, and therefore any risk of injury to the lower limb from impact forces needs to be assessed separately. Although the lack of significance could be partly because of the limited number of participants, we would nonetheless suggest that the perception of comfort itself is not sufficient to provide evidence for the suitability of the insoles and for their promotion among recruits. Furthermore, since the insoles in the present study were rated under a very short-term trial, the clinical value of the present results is not certain; in particular, insoles which do make MBs comfortable on initial usage should be assessed over the course of many months of being worn to measure any depreciation in quality. The participants in the present study were required to run and walk for relatively short periods of time for each condition (4 minutes); this was to avoid fatigue or pain, which could have been exacerbated by performing in unusual shod conditions. However, it is possible that longer bouts of running and walking will provide useful insights into cushioning and comfort variables in MBs, and such future research is recommended.

The loss of manpower because of lower limb injury is a serious issue for professional armies. Basic infantry training has been changed in some armies to reduce the incidence of lower limb injury, for example with reduced marching. Nonetheless, army personnel are still required to march often considerable distances on foot while carrying heavy loads. With regard to GRF variables, program modifications may be needed so that long-term hiking with pack and equipment are performed in MBs, which resemble RS in terms of absorbance and comfort properties, rather than by just adding an insole to the MB. However, care must always be taken with new boot design as more comfortable boots are not necessarily better for injury prevention. The use of an instrumented treadmill for future studies on MBs is recommended because of the large number of footstrikes quickly available for analysis and the ability to record footstrikes from both right and left feet.

## CONCLUSIONS

The present study illustrated that the MBs used by the Cypriot and Greek Army personnel with the use of the two specific insoles did not significantly influence IPFs during walking and running. Participants found the MBs uncomfortable, and this was not significantly offset when using the insoles. Although commanders insist that recruits wear MBs in preparation for and during war and therefore there is a need to train in them beforehand, it should be noted that an injured recruit cannot fight as well as a healthy recruit. Therefore, because of interindividual differences in GRF patterns, it is worthwhile assessing each recruit on an individual basis for the appropriateness of inserting insoles into MBs.

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