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Treatment of Generalized War-Related Health Concerns
Placing TBI and PTSD in Context

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Association Between Traumatic Brain Injury and Risk of Posttraumatic Stress Disorder in Active-Duty Marines

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IMPORTANCE Whether traumatic brain injury (TBI) is a risk factor for posttraumatic stress disorder (PTSD) has been difficult to determine because of the prevalence of comorbid conditions, overlapping symptoms, and cross-sectional samples.

OBJECTIVE To examine the extent to which self-reported predeployment and deployment-related TBI confers increased risk of PTSD when accounting for combat intensity and predeployment mental health symptoms.

DESIGN, SETTING, AND PARTICIPANTS As part of the prospective, longitudinal Marine Resiliency Study (June 2008 to May 2012), structured clinical interviews and self-report assessments were administered approximately 1 month before a 7-month deployment to Iraq or Afghanistan and again 3 to 6 months after deployment. The study was conducted at training areas on a Marine Corps base in southern California or at Veterans Affairs San Diego Medical Center. Participants for the final analytic sample were 1648 active-duty Marine and Navy servicemen who completed predeployment and postdeployment assessments. Reasons for exclusions were nondeployment (n = 34), missing data (n = 181), and rank of noncommissioned and commissioned officers (n = 66).

MAIN OUTCOMES AND MEASURES The primary outcome was the total score on the Clinician-Administered PTSD Scale (CAPS) 3 months after deployment.

RESULTS At the predeployment assessment, 56.8% of the participants reported prior TBI; at postdeployment assessment, 19.8% reported sustaining TBI between predeployment and postdeployment assessments (ie, deployment-related TBI). Approximately 87.2% of deployment-related TBIs were mild; 250 of 287 participants (87.1%) who reported posttraumatic amnesia reported less than 24 hours of posttraumatic amnesia (37 reported ≥24 hours), and 111 of 117 of those who lost consciousness (94.9%) reported less than 30 minutes of unconsciousness. Predeployment CAPS score and combat intensity score raised predicted 3-month postdeployment CAPS scores by factors of 1.02 ($P < .001$; 95% CI, 1.02-1.02) and 1.02 ($P < .001$; 95% CI, 1.01-1.02) per unit increase, respectively. Deployment-related mild TBI raised predicted CAPS scores by a factor of 1.23 ($P < .001$; 95% CI, 1.11-1.36), and moderate/severe TBI raised predicted scores by a factor of 1.71 ($P < .001$; 95% CI, 1.37-2.12). Probability of PTSD was highest for participants with severe predeployment symptoms, high combat intensity, and deployment-related TBI. Traumatic brain injury doubled or nearly doubled the PTSD rates for participants with less severe predeployment PTSD symptoms.

CONCLUSIONS AND RELEVANCE Even when accounting for predeployment symptoms, prior TBI, and combat intensity, TBI during the most recent deployment is the strongest predictor of postdeployment PTSD symptoms.

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A consistent experience across generations of veterans has been the generalized nature of postwar symptoms, often involving headaches, fatigue, musculoskeletal pain, concentration/memory problems, sleep disturbance, dizziness/imbalance, palpitations, gastrointestinal symptoms, irritability, and anxiety.[1] Also consistent across the years has been the intensity of debate as to etiology and relative contribution of physical, neurological, psychological, or environmental causes.

Service members returning from Iraq or Afghanistan have experienced health concerns comparable with those of prior wars,[1-3] and for better or worse, the focus of attention (and debate) has narrowed on 2 conditions, posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI). The majority of TBIs are mild, also known as concussions, and extensive screening, treatment, and research efforts have revolved around the presumed interaction of concussions and PTSD after blast exposure or other combat events.

Much of the epidemiological research has relied on cross-sectional surveys.[2,4] The recent study in *JAMA Psychiatry* by Yurgil et al[5] provides one of the only longitudinal assessments of the association of battlefield TBI (mostly concussions) with PTSD (assessed 3 months after return from deployment), controlling for predeployment health status. Despite an unusually low PTSD prevalence in this sample (2.4%), the authors confirmed the association observed in prior studies. Predeployment PTSD (full or partial) was most strongly associated with the presence of postdeployment PTSD. However, both high combat exposure and deployment-related concussions were also independently associated with postdeployment PTSD.

Applying Sir Austin Bradford Hill's 1965 foundational principles of epidemiological causation, a causal link between battlefield concussions and PTSD is suggested by the strength and consistency of this association across studies. However, Hill's other principles limit the ability to draw causal inferences.

For biological plausibility, researchers have suggested TBI may result in structural or functional damage to prefrontal, temporal, or limbic pathways involved in fear conditioning. However, this is largely theo-

retical. Concussions occurring in non–life-threatening situations (eg, sports) are not known to predispose to PTSD, and no direct concussion-related neurological mechanisms explain PTSD. Many other war-related conditions also can affect prefrontal functioning (eg, alcohol misuse, sleep deprivation). Although Yurgil et al[5] report evidence of dose response, the authors acknowledge this could be related to physical injury severity and is inconsistent with other studies that found paradoxically lower risk of PTSD after moderate or severe TBI compared with concussion. Paradoxical temporal associations have also been observed, with development of chronic postconcussive symptoms not present shortly after injury and strong associations with factors unrelated to injury (eg, negative expectations, psychological factors).[4,6,7] The specificity and coherence of associations have been challenged, including concerns with the validity of concussion and postconcussion syndrome definitions, and nonspecificity of postdeployment screening approaches.[8,9] The only clinical trial intervention shown to be effective in preventing persistent symptoms after concussion is education to foster recovery expectations,[8] and there is evidence that current care delivery models may reinforce symptom attribution and lead to iatrogenic outcomes.[7-9]

Multiple studies have shown that PTSD and depression are much more strongly associated with persistent postconcussive symptoms than concussions.[4,6,7] These findings do not mean that battlefield concussions (many of which are blast-related) are unimportant. Loss of consciousness and multiple concussions, in particular, are independently associated with some postdeployment symptoms, such as headaches,[4] but the relative strength of associations tends to be comparatively weak. Studies involving neuroimaging, hormonal measurements, or putative biomarkers often make the mistake of attributing abnormalities to blast or TBI that are likely explained by uncontrolled confounders (eg, injury severity, combat intensity, other injuries, comorbid conditions).

At this point, the best explanation for the findings from the report by Yurgil et al[5] and other studies is that context matters. Being knocked unconscious or even momentarily dazed from a concussion during direct combat or after exposure to devastating effects of an explosive device is an extremely close call on one's life and is often paired with other severely traumatic experiences (eg, death or dismemberment involving a team member). Such an experience cannot be adequately assessed using a typical combat exposure scale, and it is no surprise this is strongly associated with PTSD.

However, PTSD is not the most critical outcome. The service member's or veteran's general health, social functioning, and occupational functioning are most important, irrespective of etiology. Posttraumatic stress disorder may be the best available clinical marker for neuroendocrine and autonomic dysregulation resulting from trauma, and concussion contributes to some degree, but many other factors also combine to produce postdeployment symptoms that impair functioning, including depression, physical injuries, chronic pain, sleep deprivation (sleep has been documented during deployment to average 5 hours/24 hours in many units), substance use, and lack of social support. One study showed that grief is as strongly associated with postdeployment physical health outcomes as PTSD and depression, with concussion contributing much lower risk comparable with that of other injuries.[3]

Given multiple coexisting war-related conditions, treatment strategies are unlikely to be optimized until the aperture is widened beyond PTSD and TBI, the structure of care reassessed, and the intensity of debate itself accepted as emblematic of the problem. Targeted and effective strategies will likely never be optimized as long as dissimilar injuries remain grouped under the "TBI" diagnostic umbrella—ie, mild concussions with transient alteration in consciousness (eg, dazed for a few seconds/min) together with permanent coma from severe closed or penetrating brain injuries. This is akin to lumping an ankle sprain with an above-the-knee traumatic amputation under the rubric "traumatic leg injury—TLI."

Clinical approaches should draw on as wide a field of knowledge as possible, including lessons learned from treating other multisymptom conditions for which specific etiology is elusive. The most promising strategies include coordination of care, regularly scheduled primary care visits (with a brief physical examination at each), collaborative step-care approaches that protect patients from unnecessary diagnostic tests and specialty referrals, motivational interviewing, and cognitive behavioral therapy.[1,4,8]

Many of these approaches are beginning to be incorporated into existing practice, but the structure of care still remains largely specialty driven, with veterans at risk of iatrogenic effects from having their generalized health concerns misattributed to TBI. Harmful effects may result from negative expectations perpetuating symptom persistence (reinforced, for instance, by equivocal neuropsychological or neuroimaging test results), inconsistent clinical opinions from different specialists, poorly coordinated care, polypharmacy, and medication interactions.[7-9] It is essential to respect the historical context and take a broader view on what will be necessary to effectively address multiple overlapping health needs of combat veterans.

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