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## *Naval Health Research Center*


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*This research was conducted in compliance with all applicable federal regulations governing the protection of human subjects in research.*


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# Prescription Stimulants and the Development of Post-Traumatic Stress Disorder Among U.S. Service Members

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ABSTRACT

**Background**

Post-traumatic stress disorder (PTSD) occurs among both civilians and military personnel after traumatic events, and has become a signature wound of the recent conflicts in Iraq and Afghanistan. The relationship between novel risk factors, such as prescription stimulants, and the subsequent development of PTSD is unknown.

**Methods**

We studied 25910 military members from a large prospective cohort that began enrollment prior to September 11th, 2001. Medication prescriptions were obtained from the military Pharmacy Data Transaction Service, and PTSD was based on a validated survey instrument (PTSD Checklist–Civilian Version) during the study period (2001–2008). The risk of incident PTSD with stimulant use was estimated using survival analyses, while adjusting for sociodemographic factors, military service characteristics, baseline mental and physical health status, deployment experiences (e.g., combat), and physical/sexual trauma.

**Results**

Overall, 1368 (5.3%) persons developed incident PTSD during follow-up. Prescription stimulants were significantly associated with incident PTSD (hazard ratio [HR], 3.66; 95% confidence interval [CI], 2.48–5.41; $p<0.001$) in the adjusted model. The magnitude of this association exceeded that of a combat deployment and incident PTSD (HR, 1.61; 95% CI, 1.41–1.83; $p<0.001$). A dose-related relationship between the days' supply and number of stimulant prescriptions with PTSD was noted (p trend <0.001).

**Conclusions**

The findings suggest that prescription stimulants may increase the risk of subsequent development of PTSD. These data may inform the underlying pathogenesis of and preventive strategies for PTSD.

Post-traumatic stress disorder (PTSD) has been increasingly reported among U.S. service members in association with the recent conflicts in Iraq and Afghanistan, with an estimated post-deployment prevalence of 5.5% in population samples and 13.2% in operational infantry units.[1] With over 2.5 million service members having deployed at least once to the recent conflicts, the number of PTSD cases and their associated costs are substantial.[2,3] Further, PTSD represents an important health condition in the general population, with a reported lifetime prevalence of 4–10%.[4]

Traumatic experiences predate the onset of PTSD. Among military personnel, the most potent risk factor identified to date has been combat experiences, such as handling dead bodies, knowing someone who was killed, or killing enemy combatants.[5,6] Although several other pre-, during, and post-event risk factors have been identified,[7] the development of PTSD is not completely explained by these factors.

A recent report suggested a potential link between the increasing use of stimulants and the rising incidence of PTSD[8]; however, scientific research data are lacking. In both military and civilian settings, prescription stimulants may be used for conditions such as attention deficit disorder (ADD)/attention deficit hyperactivity disorder (ADHD) or to enhance performance, and such use has increased in recent decades.[9,10] In select military groups, stimulants may also be prescribed to reduce fatigue and improve cognitive abilities during periods of sleep deprivation.[11-13]

Pathophysiological relationships may exist between stimulant medications and the development of PTSD. Exposure to a traumatic event leads to an increase in adrenergic (e.g., norepinephrine) levels and activation of the amygdala, creating memories of the event.[14,15] Increased norepinephrine levels prior to, or shortly after, a traumatic event have been shown to result in more vivid, long-lasting memories.[16,17] Hence, the use of stimulants, which are known

to increase norepinephrine levels in the brain, could result in an increased incidence of PTSD following traumatic exposures. Unlike adrenergic mediators, centrally acting beta blockers, which inhibit norepinephrine, had a protective effect in some, but not all, studies.[18-20]

Although PTSD is one of the most important mental health conditions and a signature wound of the post-2001 Iraq and Afghanistan conflicts, to our knowledge there is no prospective research on the relationship between prescription stimulants and the subsequent development of PTSD. We utilized the Millennium Cohort Study, the largest prospective epidemiologic study in U.S. military history, to examine the association between prescription stimulants and subsequent PTSD, while controlling for multiple covariates including deployment experiences and prior sexual/physical trauma. This study was undertaken to potentially identify a novel risk factor for the development of PTSD, and to inform existing policies on the use of stimulants.

## METHODS

### Study Population

The Millennium Cohort Study began in 2001, just prior to the start of the conflicts in Iraq and Afghanistan. The study was approved by the Naval Health Research Center institutional review board, and all participants provided voluntary informed consent. Invited participants (n=256,400) to the first panel were randomly selected from U.S. military personnel serving in October 2000, with an oversampling of women, Reserve and National Guard, and members previously deployed to Bosnia, Kosovo, or Southwest Asia. Participants completed a comprehensive baseline survey as well as follow-up surveys approximately every 3 years thereafter. A detailed description of study methodology has been previously reported.[21] The first enrollment panel consisted of 77,047 participants (2001–2003), of whom 55,021 (71%)

completed the first follow-up questionnaire (2004–2006) and 54,790 (71%) completed the second follow-up questionnaire (2007–2008).

The study population for this analysis included participants who were active-duty members at baseline survey completion, completed at least the first follow-up survey, and had data within the military electronic medical record (EMR) system (n=28,952). Further exclusions included missing baseline covariate data (n=1480), missing combat experience from follow-up surveys (n=14), single stimulant prescriptions of <30 days' supply (n=31) since the accuracy in these limited pharmacy transactions could not be verified, and receipt of a non-stimulant ADD/ADHD medication (atomoxetine, n=61). To evaluate incident PTSD, those who had a positive PTSD screen or reported a prior diagnosis on the baseline survey (n=1456) were excluded (study population, n=25,910). To evaluate the relationship between stimulants and PTSD, independent of underlying ADD/ADHD diagnosis, analyses were repeated excluding participants with ADD/ADHD (study population, n=25,658).

**Outcome**

Due to the complexity of diagnosing PTSD and the underdiagnosis of this condition in military personnel, PTSD was assessed using the PTSD Checklist–Civilian Version. This 17-item measure of PTSD symptoms was interpreted according to *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, criteria.[22,23] This instrument has been validated, used extensively in military populations, and has demonstrated good internal consistency in this cohort.[22,24,25] Incident PTSD was defined as meeting the criteria at follow-up among those who both screened negative for PTSD and did not report a history of health professional-diagnosed PTSD at baseline.

In a subanalysis, EMR data were evaluated (including visits to military medical treatment facilities [MTFs] and other reimbursable facilities [e.g., TRICARE, a Department of Defense

(DoD) program that provides health care coverage for medical services and medications]) for the diagnosis of PTSD using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code 309.81.[26] The study population for this analysis consisted of active-duty members with complete survey data and excluded those with an ICD-9 diagnosis for PTSD prior to baseline survey (study population, n=27,835).

**Exposure of Interest**

Prescription stimulant data were obtained using the Pharmacy Data Transaction Service (PDTS), which records each prescription event within MTFs and TRICARE. Data included the medication name, date of dispensing event, number of days' supply, and number of refills. For this study, prescription stimulants were defined as a prescription for methylphenidate, dextroamphetamine, amphetamine, modafinil, armodafinil, methamphetamine, lisdexamfetamine, pemoline, dexmethylphenidate, and/or phentermine.

**Covariates**

Demographic and military-specific data, obtained from electronic military personnel files maintained by the Defense Manpower Data Center (DMDC), included sex, race/ethnicity, year of birth, highest education level, marital status, pay grade, military service branch and component, and duty occupation. Based on Millennium Cohort data on combat-like experiences (personal exposure to least one of the following: witnessing death, physical abuse, dead and/or decomposing bodies, maimed soldiers or civilians, or prisoners of war or refugees) and DMDC data on in- and out-of-theater dates, participants were categorized as nondeployed, deployed without combat-like experiences, or deployed with combat-like experiences. In addition, alcohol-related problems (using the Patient Health Questionnaire),[27] tobacco use, self-reported prior physical assault or sexual trauma, and physical component summary (PCS) and mental component summary (MCS) scores (from the Medical Outcomes Study Short Form 36-Item

Health Survey for Veterans) were included.[28] All covariates were assessed at baseline, while deployment and combat experiences were examined as time-varying covariates in the models.

**Statistical Analysis**

Characteristics of participants who did and did not receive a prescription stimulant medication were compared utilizing chi-square statistics and t-tests. Since incident PTSD symptoms were reported at the time the first or second follow-up survey was administered, rather than at the precise initiation of symptoms, discrete-time survival analysis[29] was used to investigate the association of stimulant medication prescription on incident PTSD. These analyses assumed an underlying continuous-time proportional hazards model, and a complementary log-log model using logistic regression was fitted. Person-years at risk were calculated from study entry (baseline survey completion) until development of the outcome (PTSD) or last completed survey. Estimates of the relationships between the exposure and the outcome were calculated as estimated hazard ratios (HRs) with 95% confidence intervals (CIs). The analysis was repeated excluding all participants with a diagnosis of ADD/ADHD (ICD-9 318.0–318.01).

In a subanalysis, PTSD diagnosis by an EMR ICD-9 code was examined using continuous-time survival analysis with Cox proportional hazards. Person-years at risk were calculated from the time of study entry until the earliest date of the occurrence of a PTSD code, military separation, death, or end of follow-up for this study (6 months after final survey completion). Data management and statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

## RESULTS

The study population consisted of 25,910 active-duty members, of whom 257 (1.0%) received a stimulant prescription during follow-up (mean, 5.0 years; standard deviation, 1.2). The most common type of stimulant initially prescribed was modafinil (n=99, 39%), followed by methylphenidate (n=83, 32%), dextroamphetamine (n=41, 16%), and other stimulants (n=34, 13%). Characteristics of military personnel who received a stimulant prescription are shown in Table 1.

Overall, 1368 (5.3%) persons developed incident PTSD during follow-up. Of those, 2% had received a prescription stimulant prior to PTSD symptom reporting. In the unadjusted analysis, receipt of a prescription stimulant was associated with incident PTSD (HR, 3.39; 95% CI, 2.10–5.46). In the final adjusted model, stimulants remained significantly associated with PTSD (Table 2; HR, 3.66; 95% CI, 2.48–5.41). Other factors associated with incident PTSD included combat deployment, female sex, non-white race/ethnicity, non-Air Force branch, enlisted pay grade, alcohol-related problems, being a current or past smoker, prior physical assault/sexual trauma, and lower baseline MCS and PCS scores (Table 2).

There was a dose relationship between the days' supply of a prescription stimulant and incident PTSD symptoms in adjusted models: 30–89 days versus 0 days (HR, 2.83; 95% CI, 1.45–5.48) and $\geq$90 days versus 0 days (HR, 4.29; 95% CI, 2.64–6.96). Similarly, the number of stimulant prescriptions was also associated with incident PTSD: 1–3 versus 0 prescriptions (HR, 2.91; 95% CI, 1.60–5.29) and $\geq$4 versus 0 prescriptions (HR, 4.46; 95% CI, 2.67–7.46). There was a significant trend for increasing risk of PTSD with increasing days supply and number of prescriptions (Table 3A, p trend <0.001).

In the adjusted model excluding participants with ADD/ADHD, the risk of incident PTSD was magnified in stimulant users (HR, 3.79; 95% CI, 2.33–6.15). A significant

relationship between cumulative days' supply and number of stimulant prescriptions with incident PTSD was also observed (Table 3B, p trend <0.001).

In the subanalysis, 441 (1.6%) had an ICD-9 code for PTSD. Among the 231 active-duty service members who received a prior stimulant prescription in this analysis, 6 (2.6%) were subsequently diagnosed with PTSD. The findings were in the same direction as the primary model (adjusted HR for stimulant use and incident PTSD: 1.48 [95% CI, 0.66–3.33]), although not statistically significant.

## DISCUSSION

This study is the first rigorous scientific investigation regarding the association between prescription stimulant medications and incident PTSD among U.S. military personnel during the post-2001 Iraq and Afghanistan conflicts. The findings show a strong and significant association between the receipt of a stimulant prescription and the development of incident PTSD, with the magnitude of association greater than described for combat deployment experiences and subsequent PTSD.

The rise in the number of PTSD cases during the past decade among military troops has been attributed to intense combat and other occupational exposures. Studies have consistently noted that combat experiences, such as killing enemy combatants and greater perceived threat, are related to post-deployment PTSD.[5,6] Whether an increasing use of stimulants during this past decade[9,10] is also related to the rising incidence of PTSD in the military has been hypothesized but previously unstudied.[8] Prior studies in the general population have largely been confined to evaluating PTSD as a risk factor for subsequent illicit drug use.[30-32] This study is the first to provide prospective evidence that prescription stimulants are associated with a higher risk of subsequent PTSD. While most cases of incident PTSD in our cohort were not prescribed

stimulants, our findings suggest that stimulants may be contributing to some of the PTSD cases among military personnel.

Stimulant medications (specifically dextroamphetamine and modafinil) have been used off label to heighten cognitive performance and reduce fatigue among select military troops, especially during operations that entail sleep deprivation (e.g., long flight missions).[11,12] The use of stimulant medications among military troops for these purposes dates back to World War II, and stimulants were utilized in Vietnam (at reportedly higher doses) and missions to Libya, the Falklands, and Operations Desert Shield and Desert Storm.[11] In the current era, stimulant prescriptions for fatigue reduction and/or performance enhancement is guided by specific military policies and only authorized for select aviation professionals,[12] with studies showing use during 57–96% of missions depending on the flight duration.[13] Use among other military personnel may also be occurring given a recent DoD survey finding stimulant misuse among 2-3% of personnel.[33]

Although no major problems have been reportedly attributed to stimulants in the military,[12] most studies were conducted in controlled settings and in-theater data are sparse. Further, no prior studies have specifically examined incident PTSD after stimulant use. Short-term side effects of stimulants include tachycardia, increased blood pressure, and jitteriness, likely the result of increased norepinephrine levels. Since increased noradrenergic (e.g., norepinephrine) levels at the time of a traumatic event create more vivid, long-lasting memories and fear of the event,[14,15] stimulants could potentially increase the incidence of PTSD following traumatic exposures.

The effect of stimulants on PTSD may vary both by the occurrence of subsequent traumatic exposures and by individual genetic characteristics. Among amphetamine users, those with specific single nucleotide polymorphisms in dopaminergic system genes have a heightened

risk for PTSD.[34] Further, specific polymorphisms (e.g., catechol-0-methyltransferase genes) have been associated with an individual's responsivity to stimulants during sleep loss.[35] Further research on potential gene–environmental interactions among service members who develop PTSD, especially in cases where stimulants were utilized, are needed.

Since stimulants are used to treat ADD/ADHD, and ADD/ADHD may increase the risk for PTSD[36,37] and these conditions may share a common pathophysiology,[38,39] analyses were repeated excluding service members with diagnosed ADD/ADHD. The strong relationship between stimulant prescriptions and PTSD persisted, suggesting that this relationship is independent of ADD/ADHD. While it is possible that ADD/ADHD diagnoses were not recorded, this is unlikely since we excluded anyone with a single ADD/ADHD ICD-9 code occurring anytime during the study period, and prescriptions for controlled medications are typically linked with specific medical codes.

This study highlights the potential risks of using stimulants in operational settings. Although the overall number of PTSD cases linked to stimulant use was small, the potential costs from this novel risk factor may be substantial. For example, if 5% of the ~2.5 million personnel deployed to Operations Iraqi Freedom and Enduring Freedom developed incident PTSD[1] and stimulants contributed to 2% of these cases, the cost would be nearly $26 million during a 2-year period, with an estimated lifetime cost of $3.8 billion.[2,3] Extending these findings to the general population would result in substantial health-related costs. In addition to the financial costs of PTSD, there are also important effects on quality of life and associated comorbidities among individuals with PTSD and their families. Given these potential health risks, the use of stimulants in settings where the risk of PTSD is elevated should be further studied and deliberated.

Limitations of this work include the small number of military members prescribed stimulants, the lack of data on actual use of the prescribed medication, and that the number of

PTSD cases attributable to stimulants may have been underestimated if medications were not recorded in the PDTS (e.g., obtained from non-military/TRICARE sources or missing from in-theater records). It is unlikely that any potential missed prescriptions accounted for our study's findings, since this would have likely resulted in a non-differential effect and a reduced magnitude of the association. PTSD symptoms were reported on the survey, thus we were not definitively able to ascertain the exact timing of symptom onset in relation to medication use; however, stimulants are rarely used to treat PTSD and are not part of the DoD/Department of Veterans Affairs PTSD management guidelines.[40] Further, additional analyses examined the date of ICD-9 diagnosis to confirm that PTSD occurred after the first prescription of the stimulant with findings in the same direction, albeit not significant possibly due to the small sample size. The primary model was based on PTSD by validated survey instruments as the majority of PTSD cases in the military are often not represented in the medical records due to stigma and the use of alternate codes. The Millennium Cohort represents a population-based sample of military members, and although potential biases may exist, previous studies have shown that participants self-report data reliably, well represent the U.S. military, and were not influenced to participate based on prior health.[21] Finally, in addition to stimulants, sedatives may be used to enhance sleep after missions ("go pills" and "no-go pills," respectively); we did not evaluate the use of sedatives, but it is possible that stimulants were used to counter the effects of sleep inducers, and vice versa, which should be investigated in future research.

This study provides critical information regarding the identification of a potential novel risk factor for the development of PTSD. These data may inform the underlying pathogenesis of and preventive strategies for PTSD, as well as inform future policies regarding the use of prescription stimulants in specific occupational settings.

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**Table 1. Stimulant Prescriptions among Military Members (N = 25,910).**

| | No Stimulant Rx N = 25,653 | | Stimulant Rx[†] N = 257 | |
|---|---|---|---|---|
| **Baseline Characteristics**[*] | n | % | n | % |
| Deployment experience[‡] | | | | |
| Non-deployed | 13,623 | 53.1 | 129 | 50.2 |
| Deployed with combat | 5412 | 21.1 | 57 | 22.2 |
| Deployed without combat | 6618 | 25.8 | 71 | 27.6 |
| Sex | | | | |
| Male | 19,828 | 77.3 | 192 | 74.7 |
| Female | 5825 | 22.7 | 65 | 25.3 |
| Birth cohort | | | | |
| Pre-1960 | 3224 | 12.6 | 37 | 14.4 |
| 1960–1969 | 11,445 | 44.6 | 124 | 48.2 |
| 1970–1979 | 9910 | 38.6 | 91 | 35.4 |
| 1980 and beyond | 1074 | 4.2 | 5 | 2.0 |
| Race/ethnicity | | | | |
| Non-Hispanic white | 16,447 | 64.1 | 193 | 75.1 |
| Non-Hispanic black | 3318 | 12.9 | 20 | 7.8 |
| Other | 5888 | 23.0 | 44 | 17.1 |
| Highest level of education | | | | |
| Some college or less | 17,677 | 68.9 | 142 | 55.3 |
| Bachelor's or higher | 7976 | 31.1 | 115 | 44.7 |
| Marital status | | | | |
| Never married | 6711 | 26.1 | 46 | 17.9 |
| Currently married | 17,690 | 69.0 | 198 | 77.0 |
| Separated, divorced, or widowed | 1252 | 4.9 | 13 | 5.1 |
| Service branch | | | | |
| Army | 10,205 | 39.8 | 86 | 33.5 |
| Navy/Coast Guard | 5919 | 23.1 | 45 | 15.5 |
| Marine Corps | 1391 | 5.4 | 6 | 2.3 |
| Air Force | 8138 | 31.7 | 120 | 46.7 |
| Military pay grade | | | | |
| Enlisted | 18,049 | 70.4 | 152 | 59.1 |
| Officer | 7604 | 29.6 | 105 | 40.9 |
| Occupation | | | | |
| Combat specialist | 5881 | 22.9 | 71 | 27.6 |
| Health care | 2650 | 10.3 | 39 | 15.2 |
| Other | 17,122 | 66.7 | 147 | 57.2 |
| Alcohol-related problems[§] | | | | |
| No | 23,399 | 91.2 | 240 | 93.4 |
| Yes | 2254 | 8.8 | 17 | 6.6 |
| Cigarette smoking[‖] | | | | |
| Non-smoker | 15,534 | 60.6 | 161 | 62.7 |
| Past smoker | 6029 | 23.5 | 63 | 24.5 |
| Current smoker | 4090 | 15.9 | 33 | 12.8 |

| | | | | |
|---|---|---|---|---|
| Prior physical assault/sexual trauma[¶] | | | | |
| No | 22,203 | 86.5 | 215 | 83.7 |
| Yes | 3450 | 13.4 | 42 | 16.3 |
| Mental component summary score[**] | | | | |
| <15th percentile | 2822 | 11.0 | 40 | 15.6 |
| 15th–85th percentile | 18,827 | 73.4 | 189 | 73.5 |
| >85th percentile | 4004 | 15.6 | 28 | 10.9 |
| Physical component summary score[**] | | | | |
| <15th percentile | 3500 | 13.6 | 45 | 17.5 |
| 15th–85th percentile | 18,595 | 72.5 | 172 | 66.9 |
| >85th percentile | 3558 | 13.9 | 40 | 15.6 |

[*] Characteristics were evaluated at the baseline survey, except for deployment experience. Using chi-square statistics to compare service members who received a stimulant prescription compared to those who did not, all characteristics were statistically significant different ($P < 0.05$) in the univariate analyses except for deployment experience, sex, birth year category, alcohol-related problems, smoking status, prior physical assault/sexual trauma, and physical component score (PCS).

[†] Obtained from pharmacy records, any prescription(s) for the following stimulants from 2002 to the date of the last follow-up survey were included: methylphenidate, dextroamphetamine, amphetamine, modafinil, armodafinil, methamphetamine, lisdexamfetamine, pemoline, dexmethylphenidate, and/or phentermine.

[‡] Deployment in support of the operations in Iraq and Afghanistan between baseline and the last completed follow-up.

[§] Assessed using five alcohol use questions from the Patient Health Questionnaire. Participants screened positive for alcohol-related problems if they endorsed at least one of the five items.

[‖] Smoking status was defined as never, former, or current based on questions of having used >100 cigarettes during their lifetime and the success of attempts to quit smoking.

[¶] Physical assault and sexual trauma were assessed using the questions, “Have you been hit, slapped, kicked, or otherwise physically hurt by someone?” and “Has anyone forced you to have an unwanted sexual act?”, respectively.

[**] Scoring metrics were derived from the Medical Outcomes Study Short Form 36-Item Health Survey for Veterans.

**Table 2. Adjusted[*] Hazard Ratios for Incident PTSD among Military Members (N = 25,910).**

| Characteristics | Adjusted HR | 95% CI | P Value |
|---|---|---|---|
| Stimulant prescription | | | |
| No | 1.00 | | |
| Yes | 3.66 | 2.48–5.41 | <0.001 |
| Deployment experience[†] | | | |
| Non-deployed | 1.00 | | |
| Deployed with combat | 1.61 | 1.41–1.83 | <0.001 |
| Deployed without combat | 0.75 | 0.63–0.90 | 0.002 |
| Sex | | | |
| Male | 1.00 | | |
| Female | 1.17 | 1.02–1.33 | 0.02 |
| Birth cohort | | | |
| Pre-1960 | 1.00 | | |
| 1960–1969 | 1.08 | 0.88–1.32 | 0.48 |
| 1970–1979 | 1.03 | 0.83–1.27 | 0.82 |
| 1980 and beyond | 1.24 | 0.92–1.68 | 0.15 |
| Race/ethnicity | | | |
| Non-Hispanic white | 1.00 | | |
| Non-Hispanic black | 1.35 | 1.15–1.58 | <0.001 |
| Other | 1.44 | 1.24–1.66 | <0.001 |
| Highest level of education | | | |
| Some college or less | 1.00 | | |
| Bachelor's or higher | 0.82 | 0.63–1.05 | 0.11 |
| Marital status | | | |
| Never married | 1.00 | | |
| Married | 0.93 | 0.82–1.07 | 0.32 |
| Divorced, separated, or widowed | 1.18 | 0.93–1.50 | 0.18 |
| Occupation | | | |
| Combat specialist | 1.00 | 0.87–1.15 | 0.97 |
| Health care professional | 0.79 | 0.65–0.97 | 0.02 |
| Other | 1.00 | | |
| Service branch | | | |
| Air Force | 1.00 | | |
| Army | 2.50 | 2.12–2.94 | <0.001 |
| Navy/Coast Guard | 1.61 | 1.33–1.95 | <0.001 |
| Marine Corps | 2.12 | 1.63–2.75 | <0.001 |
| Military pay grade | | | |
| Enlisted | 1.00 | | |
| Officer | 0.64 | 0.49–0.83 | 0.001 |
| Alcohol-related problems[‡] | | | |
| No | 1.00 | | |

| | | | |
|---|---|---|---|
| Yes | 1.24 | 1.06–1.45 | 0.006 |
| Cigarette smoking[§] | | | |
| Non-smoker | 1.00 | | |
| Past smoker | 1.25 | 1.09–1.43 | 0.001 |
| Current smoker | 1.50 | 1.31–1.72 | <0.001 |
| Prior physical assault/sexual trauma[‖] | | | |
| No | 1.00 | | |
| Yes | 1.98 | 1.75–2.23 | <0.001 |
| Mental component summary score[¶] | | | |
| <15th percentile | 3.08 | 2.73–3.49 | <0.001 |
| 15th–85th percentile | 1.00 | | |
| >85th percentile | 0.53 | 0.43–0.65 | <0.001 |
| Physical component summary score[¶] | | | |
| <15th percentile | 2.22 | 1.96–2.51 | <0.001 |
| 15th–85th percentile | 1.00 | | |
| >85th percentile | 0.82 | 0.69–0.97 | 0.02 |

CI, confidence interval; HR, hazard ratio; PTSD, post-traumatic stress disorder.

[*] Adjusted for all variables in the table.

[†] Deployment in support of the operations in Iraq and Afghanistan between baseline and the last completed follow-up.

[‡]Assessed using five alcohol use questions from the Patient Health Questionnaire. Participants screened positive for alcohol-related problems if they endorsed at least one of the five items.

[§] Smoking status was defined as never, former, or current based on questions of having used >100 cigarettes during their lifetime and the success of attempts to quit smoking.

[‖] Physical assault and sexual trauma were assessed using the questions, “Have you been hit, slapped, kicked, or otherwise physically hurt by someone?” and “Has anyone forced you to have an unwanted sexual act?”, respectively.

[¶] Scoring metrics were derived from the Medical Outcomes Study Short Form 36-Item Health Survey for Veterans.

**Table 3. Adjusted Associations[*] for Stimulant Use, Cumulative Days' Supply, and Total Number of Stimulant Prescriptions with Incident PTSD (A) and among Military Members without a Diagnosis ADD/ADHD (B).**

**A.**

| | **No PTSD n = 24,542** (%) | **Incident PTSD n = 1368** (%) | **Adjusted HR** | **95% CI** | **P Trend[†]** |
|---|---|---|---|---|---|
| Stimulant prescription | | | | | |
| No | 24,312 (99.1) | 1341 (98.0) | 1.00 | | |
| Yes | 230 (0.9) | 27 (2.0) | 3.66 | 2.48–5.41 | |
| Sum of days' supply of stimulants | | | | | <0.001 |
| No prescription | 24,312 (99.1) | 1341 (98.0) | 1.00 | | |
| 30–89 days | 110 (0.4) | 7 (0.5) | 2.83 | 1.45–5.48 | |
| 90+ days | 120 (0.5) | 20 (1.5) | 4.29 | 2.64–6.96 | |
| Number of stimulant prescriptions dispensed | | | | | <0.001 |
| None | 24,312 (99.1) | 1341 (98.0) | 1.00 | | |
| 1–3 prescriptions | 137 (0.5) | 11 (0.8) | 2.91 | 1.60–5.29 | |
| 4 or more prescriptions | 93 (0.4) | 16 (1.2) | 4.46 | 2.67–7.46 | |

**B.**

| | **No PTSD n = 24,311** (%) | **Incident PTSD n = 1347** (%) | **Adjusted HR** | **95% CI** | **P Trend**[†] |
|---|---|---|---|---|---|
| Stimulant prescription | | | | | |
| No | 24,149 (99.3) | 1330 (98.7) | 1.00 | | |
| Yes | 162 (0.7) | 17 (1.3) | 3.79 | 2.33–6.15 | |
| Sum of days' supply of stimulants | | | | | <0.001 |
| No prescription | 24,149 (99.3) | 1330 (98.7) | 1.00 | | |
| 30–89 days | 100 (0.4) | 6 (0.4) | 2.50 | 1.19–5.25 | |
| 90+ days | 62 (0.3) | 11 (0.9) | 5.94 | 3.15–11.18 | |
| Number of stimulant prescriptions dispensed | | | | | <0.001 |
| None | 24,149 (99.3) | 1330 (98.7) | 1.00 | | |
| 1–3 prescriptions | 118 (0.6) | 9 (1.0) | 3.03 | 1.57–5.86 | |
| 4 or more prescriptions | 44 (0.2) | 8 (0.7) | 5.26 | 2.60–10.67 | |

CI, confidence interval; HR, hazard ratio; PTSD, post-traumatic stress disorder.

[*] Adjusted for deployment experience, sex, birth year category, race/ethnicity, education, marital status, occupation, branch, pay grade, alcohol-related problems, smoking status, physical assault/sexual trauma, and mental and physical component summaries category.

[†] Wald's test with 1 df.

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**14. ABSTRACT**

Post-traumatic stress disorder (PTSD) occurs among both civilians and military personnel after traumatic events, and has become a signature wound of the recent conflicts in Iraq and Afghanistan. The relationship between novel risk factors, such as prescription stimulants, and the subsequent development of PTSD is unknown.

We studied 25,971 military members from a large prospective cohort that began enrollment prior to September 11th, 2001. Medication prescriptions were obtained from the military Pharmacy Data Transaction System, and PTSD diagnosis was based on a validated survey instrument (PTSD Checklist–Civilian Version). The risk of incident PTSD with stimulant use was estimated using survival analyses, while adjusting for sociodemographic factors, military service characteristics, baseline mental and physical health status, deployment experiences (e.g., combat), and physical/sexual trauma.

Overall, 1376 (5.3%) persons developed incident PTSD during follow-up. Prescription stimulants were significantly associated with incident PTSD (hazard ratio [HR], 3.34; 95% confidence interval [CI], 2.35–4.74; $p<0.001$) in the adjusted model. The magnitude of this association exceeded that of a combat deployment and incident PTSD (HR, 1.62; 95% CI, 1.42–1.84; $p<0.001$). A dose-related relationship between the days' supply and number of stimulant prescriptions with PTSD was noted.

The findings suggest that prescription stimulants may increase the risk of subsequent development of PTSD. These data may inform the underlying pathogenesis of and preventive strategies for PTSD.

**15. SUBJECT TERMS**
stimulant prescription medication, post-traumatic stress disorder, PTSD, military, deployment, prospective study, incidence

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