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# An Examination of Co-Occurring Conditions and Management of Psychotropic Medication Use in Soldiers With Traumatic Brain Injury

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## ABSTRACT

There are approximately 1.4 million cases of traumatic brain injury (TBI) per year in the United States, with about 23 000 survivors requiring hospitalization. The incidence of TBI has increased in the patient population of the Department of Defense and Veterans Healthcare Administration as a result of injuries suffered during recent military and combat operations. Within the past few years, TBI has emerged as a common form of injury in service members with a subset of patients experiencing postinjury symptoms that greatly affect their quality of life. Traumatic brain injury can occur when sudden trauma (ie, penetration blast or blunt) causes damage to the brain. Traumatic brain injury produces a cascade of potentially injurious processes that include focal contusions and cytotoxic damage. The results of TBI can include impaired physical, cognitive, emotional, and behavioral functioning, which may or may not require the initiation of pharmacological and nonpharmacological interventions when deemed appropriate. Associated outcomes of TBI include alterations in mental state at the time of injury (confusion, disorientation, slowed thinking, and alteration of consciousness). Neurological deficits include loss of balance, praxis, aphasia, change in vision that may or may not be transient. Individuals who sustain a TBI are more likely to have or developed co-occurring conditions (ie, sleep problems, headaches, depression, anxiety, and posttraumatic stress disorder) that may require the administration of multiple medications. It has been identified that veterans being discharged on central nervous system and muscular skeletal drug classes can develop addiction and experience medication misadventures. With the severity of TBI being highly variable but typically categorized as either mild, moderate, or severe, it can assist health care providers in determining which patients are more susceptible to medication misadventures compared with others. The unique development of cognitive and emotional symptoms of TBI can lead to significant impairments, so it is important for all health care providers, including pharmacists, to promote proper use of high-risk psychotropic medications among this patient population by providing effective medication education.



## Key Words

Medication misadventures, Psychotropic medications, Safety concerns, Soldiers, Traumatic brain injury


In the United States, about 1.4 million cases of traumatic brain injury (TBI) are registered annually, with 230 000 survivors of this inquiry requiring hospitalization.[1] Within the Department of Defense and Veterans Healthcare Administration, the incidence of TBI has increased because of injuries during military operation and combats.[2] Over the last decade, TBI has emerged as a common form of injury in service members with a subset of patients experiencing continued symptoms that significantly affect their quality of life and functioning.[2] Traumatic brain injury occurs when a sudden trauma (ie, penetration blast or blunt force) causes the brain to collide with the skull and results in a cascade of potentially injurious processes that include focal contusions and cytotoxic damage.[3] Such injuries can result in impaired physical, cognitive, and behavioral functioning, which require pharmacological and nonpharmacological interventions.[4] Examples of some types of impairments are provided in Table 1.

## SIGNS/SYMPTOMS OF TRAUMATIC BRAIN INJURY

The potential outcomes of TBI, from injury to onset of symptoms, can include alterations in mental state at the time of injury (confusion, disorientation, slowed thinking, and alteration of consciousness). Other neurological deficits include loss of balance, praxis, aphasia, and changes in vision that may or may not be transient.[5] Individuals who sustain this type of injury are likely to develop comorbid

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**TABLE 1 Types of Impairments[4]**

| Physical Impairments | Cognitive Impairments | Behavioral Impairments |
|---|---|---|
| Headache complaints | Delayed reaction time (diminished alertness) | Development of behaviors (new to the patient) |
| Muscle fatigue | Loss of memory | Recklessness |
| Musculoskeletal pain | Poor executive functioning | Yelling/screaming |

conditions (ie, sleep problems, headaches, depression, anxiety, or posttraumatic stress disorder) that often lead to prescription of multiple medications.[5] According to a review of 2 years of national medication records of Operations Enduring Freedom and Iraqi Freedom veterans on blast-related injuries, it has been determined that veterans being discharged on central nervous system agents (eg, antidepressants, antipsychotics, and sedative/hypnotics) and musculoskeletal medications (eg, baclofen, cyclobenzaprine, and dantrolene) are at greater risk for development of drug addiction, and are at increased risk of injury related to the drug's central nervous system effects.[6] The medication management of blast-related injuries has revealed that many of these veterans are prescribed antidepressants and/or benzodiazepines to manage their subsequent mental health-related effects, which may require long-term treatment.[6] The length and degree of treatment can vary from one soldier to another, so a focused approach to management is highly recommended.

The severity of TBI is highly variable and is categorized as mild, moderate, or severe. These classifications aid health care providers in determining which patients may be susceptible to medication misadventures. This enables clinicians to be aware of the requirement for increased monitoring parameters for those soldiers who may be at high risk.[7] The development of cognitive and behavioral symptoms is frequently associated with TBI, which can lead to observable impairments, so it is important for health care providers to promote proper use of psychotropic medications (ie, benzodiazepine-derived sedative hypnotics, tricyclic antidepressants, and antipsychotics) to name a few among this unique patient population.[7]

## Medication Misadventures and Safety Concerns

Medication misadventures consist of medication errors as well as medication-related adverse events. Medication-related adverse events are increasingly becoming viewed as public health issue, particularly in soldiers with TBIs.[8] Along with the potential for medication-related adverse events such as medication overdose, inappropriate medication administration, subtherapeutic effects, or therapeutic failures, medication withdrawal events can also occur in soldiers with TBIs.[9] One specific factor that is often not considered in soldiers with TBI is the ability to adequately administer and monitor these medications once they are dispensed. In most cases, an assumption is made that patients understand how to appropriately take their medications. Cognitive impairments such as forgetfulness, concentration difficulties, and a decreased ability to perform specific mental tasks, which require alertness (such as construction and utilization of combat weapons), among soldiers with TBIs increase the risk for these patients to take their medications incorrectly. For example, a soldier who is prescribed once daily dose of amitriptyline 10 mg at bedtime for neuropathic pain may inadvertently take the medication 2 to 3 times a day if instructed that the dose may be increased by 10 mg every 2 to 3 days with continued treatment. The direction for the appropriate medication administration may be unclear or considered to be too complicated, which may lead to the incorrect use of the medication.

The potential for medication abuse, prescription drug overdoses, and toxic drug combinations can be found among young soldiers.[10] In 2004, the Food and Drug Administration urged drug makers to expand on the black box warning for antidepressants to include the increased risk of suicide in children and adolescents, but the question that still exists whether there is an absolute link between the use of antidepressants in Iraqi and Afghanistan solders and the rates of suicide. At least 115 soldiers killed themselves in 2007, including 36 in Iraq and Afghanistan.[11] Approximately 40% of the persons who committed suicide in the Army in 2006 and 2007 took psychotropic medications, with a large majority of the victims being on selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and sertraline. There has been a long-standing controversy related to the possibility that SSRIs might induce suicidality in some patients. The original clinical studies that raised concerns about SSRIs and suicide induction demonstrated evidence of a dose-dependent link on a challenge-dechallenge and rechallenge basis between SSRIs and both agitation and suicidality. The meta-analysis indicated that SSRIs may reduce suicidal ideations in some patients while increasing suicidal acts on active treatment compared with placebo (odds ratio: 2.4; confidence interval: 1.6-3.7).[11] On the basis of the established potential risk, it is critically important that soldiers are also monitored for suicidal ideations while on antidepressant therapy, particularly those with TBI.[12] Although studies have been carried out on the impact of antidepressant use on cognitive performance in the elderly or on health volunteers, little research exists on the association between SSRIs and cognitive performance in soldiers with TBI.

## Use of Cognitive Enhancers

The use of acetylcholinesterase inhibitors, such as donepezil, may assist with cognitive deficits in patients with TBI. The selectivity of donepezil for central nervous system cholinesterase seems to demonstrate increased alertness and awareness of cognitive impairments compared with other acetylcholinesterase inhibitors in individuals with TBI.[13] In a retrospective study conducted by Walker and colleagues, an evaluation of the effect of donepezil was performed in 36 patients with moderate to severe TBI who were admitted to an acute rehabilitation unit within 90 days of injury.[14] Matched control groups were selected on the basis of the same criteria used for the donepezil group. Some of the promising results from this retrospective study were that patients started on donepezil during rehabilitation showed a greater rate of improvement in global cognitive functioning compared with the matched control group, and a subset analysis indicated higher rates of cognitive improvement. The series of subset analyses were conducted on the donepezil treatment group to examine whether difference in the administration of donepezil was related to functional independence measure (FIM). Cognitive total scores and rehabilitation length of stay were also assessed. The group of patients whose donepezil dose was increased from 5 to 10 mg did not perform significantly better on FIM cognitive total scores compared with patients who were treated with a donepezil dose of 5 mg throughout their rehabilitation stay ($P = .430$). This same group did not show significantly better FIM cognitive change scores (mean = 19.4) compared with patients who were treated with a dose of 5 mg throughout their rehabilitation length of stay (mean = 11.8; $P = .013$). When rehabilitation length of stay was controlled in the calculation of FIM cognitive efficient scores, no effect for donepezil dosage was observed ($P = .695$). Although the results of effectiveness of donepezil as examined in the previously discussed trial are inconclusive, there have been open-label reports of improved memory in persons with TBI who were treated with donepezil.[14]

## Review of Literature

Another study conducted by Whelan and colleagues assessed donepezil 5 and 10 mg per day in 53 individuals with TBI for 2 years. At the end of 2 years, assessments of cognition were performed with the Wechsler Adult Intelligence Scale-Revised and the Hooper Visual Organization Test on a subset of this sample (N = 22). The subset analysis results indicated an improvement in full-scale IQ with a paired test ($t = 2.5$; $P = .02$) score as well as clinician-based ratings ($t = 12.2$; $P < .0001$).[15,16] The findings suggest that the Wechsler Adult Intelligence Scale-Revised full-scale IQ score significantly improved with the donepezil treatment and the clinical assessment score significantly differed in the follow-up period as compared with the baseline assessment. The clinician assessment of functioning score was based on the observations of 2 raters that arrived at a single clinical assessment rating for each follow-up assessment. The score was based on an ordinal scale from −4 to +4 (−4 indicates very significant functional and +4 indicates very significant improvement in functional status) in comparison with baseline function before starting donepezil. The factors that were considered in the determination of the score consisted of improvement in mood, affect, energy, interest in daily activities, grooming, and social interaction, which were considered to be acceptable parameters for assessing the impact of donepezil treatment.[17] Recently, it has been observed that cholinesterase inhibitors are more likely to be prescribed alongside psychotropic medications, which can lead to an increase in the occurrence of inappropriate medication administration among soldiers with TBI.[18] Cholinesterase inhibitors have been hypothesized to have psychostimulant properties or other psychotropic effects, which are being explored for their beneficial effects. The potential issues that may occur with coadministration of psychotropic medications can include unintentional or intentional overmedication, errors in dosing frequencies, and negative effects such as increased blood levels of the medications, which may increase the impact of adverse events.[20]

## Treatment Interventions

Despite advances in medical treatment of active duty soldiers with TBIs, additional focus needs to be placed on the potential for medication misuse or abuse as these soldiers return to civilian life in the aftermath of their physical injuries.[18] Medication abuse can occur if soldiers proceed to take medication to alleviate the associated effects of their TBI. When addressing the medication misadventures that can occur among soldiers with TBI, a clinical pharmacist can prove to be instrumental in reducing the number of occurrences. Soldiers with TBI can present with cognitive dysfunction (eg, problems with memory, visual-spatial cognition, attention, and executive function), which may impact their ability to engage in medication management. Problems can arise from the management of some of the more commonly utilized psychotropic medications that can be used to treat accompanying problems of TBI such as sleep disturbances, agitation, posttraumatic stress, and psychosis.[21] Some of the drug-related problems include incorrect administration times or concurrent administration with other medications that can have a negative impact on cognition, alertness, and memory, which are required for soldiers to carry out their day-to-day duties. Soldiers must maintain a level of alertness to

undertake the duties that they are required to perform on a daily basis, but the use of medications such as antidepressants has the potential to impair cognition and memory.[12,19]

## Pharmacist Involvement With Medication Safety

The principles of medication therapy management can be implemented in soldiers to improve the understanding of their complex drug regimens and thus increase the likelihood of appropriate medication administration. Soldiers who experience traumatic brain injury are individuals who can significantly benefit from the adoption principles of this therapeutic service through promotion of medication management.[19,20] Once the reasons for nonadherence have been identified, pharmacists can intervene to achieve an improved therapeutic outcome.[21] It has been shown that the involvement of the patient in the decision-making process can lead to improved adherence.[22] For example, the simplification of the medication regimen with once-daily administration can result in as much as twice as many adherent days versus a complex dosing regimen. The ability to improve the patient–pharmacist relationship and patients' attitude about their medication regimen is a proposed mechanism for enhancing compliance and increasing the probability of proper medication administration.[23,24]

# CONCLUSIONS

A pharmacist practicing in a TBI clinic can become an active participant of the interprofessional team, and with regular follow-up with soldiers, a pharmacist can verify adherence to medication regimen.[25] Medication-related problems are considered significant public health issues within the health care system, and this concern is only magnified in soldiers with TBIs who may experience great difficulty with proper medication management. Clinical pharmacists have the potential to improve inappropriate medication administration, reduce polypharmacy and tablet burden, and prevention or management of adverse drug reactions in soldiers with TBIs.[26] The issue of TBI and medication-related events will continue to be that forefront of health care concerns if improvements in monitoring and appropriate identification of medication regimens are not implemented.

# REFERENCES


1. Twamley E, Noonan S, Savla GN, Schiehser D, Jak A. *Cognitive Symptom Management and Rehabilitation Therapy (CogSMART) for Traumatic Brain Injury*. San Diego: VA San Diego Healthcare System University of California; 2009:1-34.
2. Department of Veterans Affairs. Department of Defense. *VA/DoD Clinical Practice Guidelines: Management of Concussion/Mild Traumatic Brain Injury (Mtbi)*. 2009;1:1-112.
3. Waldron-Perrine B, Hanks RA, Perrine SA. Pharmacotherapy for postacute traumatic brain injury: a literature review for guidance in psychological practice. *Rehabil Psychol*. 2008;53(4):426-444.
4. Benedictus MR, Spikeman JM, Van der Naalt J. Cognitive and behavioral impairment in traumatic brain injury related to outcome and return to work. *Arch Phys Med Rehabil*. 2010;91(9):1436-1441.
5. Raskin SA, Mateet CA. *Neuropsychological Management of Mild Traumatic Brain Injury*. NY: Oxford University Press; 2000:65-68.
6. French DD, Siddharthan K, Bass E, Campbell RR. Benchmark data on the utilization and acquisition costs of central nervous system and muscular skeletal drugs among veterans with combat-related injuries. *Mil Med*. 2004;173(7):626-628.
7. French DD, Bair MJ, Bass E, Campbell R. Central nervous system and musculoskeletal medication profile of a veteran cohort with blast related injuries. *J Rehabil Res Dev*. 2009;46(4):463-468.
8. Girard P. Military and VA telemedicine systems for patients with traumatic brain injury. *J Rehabil Res Dev*. 2007;44:1071-1026.
9. Marcum Z, Handler S, Boyce R, Gellad W, Hanlon J. Medication misadventures in the elderly: a year in review. *Am J Geriatr Pharmacother*. 2010;8(1):77-83.
10. Welch B, Faulkner L. Texas vets dying young at an alarming rate. http://lubbockonline.com/filed-online/2012-09-30/report-texas-vets-dying-young-alarming-rate. Published 2012. Accessed March 18, 2014.
11. Healy D, Whitaker C. Antidepressants and suicide: risk-benefit conundrums. *J Psychiatry Neurosci*. 2003;28(5):331-337.
12. Wadsworth EJ, Moss SC, Simpson SA, Smith AP. SSRIs and cognitive performance in working sample. *Hum Psychopharmacol*. 2005;20(8):561-572.
13. Taverni J, Seliger G, Lichtman S. Donepezil mediated memory improvement in traumatic brain injury during post-acute rehabilitation. *Brain Inj*. 1998;12(1):77-80.
14. Walker W, Seel R, Silver T, et al. The effects of donepezil on traumatic brain injury acute rehabilitation outcomes. *Brain Inj*. 2004, 18(8):739-750.
15. Yoo J, Valdovinos M, Williams D. Relevance of donepezil in enhancing learning and memory in special populations: a review of the literature. *J Autism Dev Disord*. 2007;37(10):1883-1901.
16. Whelan FJ, Walker MS, Schultz SK. Donepezil in the treatment of cognitive dysfunction associated with traumatic brain injury. *Ann Clin Psychiatry*. 2000;12:131-135.
17. Bourgeis J, Bahadurm N, Minjares S. Donepezil for cognitive deficits following traumatic brain injury: a case report. *J Neuropsychiatry Clin Neurosci*. 2002;14:463-464.
18. Reichman W. Current pharmacologic options for patients with Alzheimer's disease. *Am Gen Hosp Psychiatry*. 2003;2:1-14.
19. Ritchie EC, Benedek D, Malone R, Carr-Malone R. Psychiatry and the military: an update. *Psychiatric Clin N Am*. 2006;29(3):695-707.
20. Halbauer JD, Ashford W, Zeiter JM, Adamson MM, Lew HL, Yesavage JA. Neuropsychiatric diagnosis and management of chronic sequelae of war-related mild to moderate traumatic brain injury. *J Rehabil Res Dev*. 2009;46:757-796.
21. Albanese NP, Rouse JR. Scope of contemporary pharmacy practice: roles, responsibilities, and functions of pharmacists and pharmacy technicians. *J Am Pharm Assoc*. 2010;50:134-139.
22. Touchette D. Improving adherence in the community and clinic pharmacy settings: an emerging opportunity. *Pharmacotherapy*. 2010;30:425-427.
23. Albrecht A. The pharmacist's role in medication adherence. *US Pharm*. 2011;36(5):45-48.
24. Edlin M. Medication therapy management bumps pharmacists' roles. Managed Health Care Executive. http://managedhealthcareexecutive.modernmedicine.com/mhe/Pharmacy+Best+Practices/Medication-therapy-management-

bumps-up-pharmacists/ArticleStandard/Article/detail/500104?contextCategoryId=971. Accessed August 30, 2013.
25. American Pharmacists Association and National Association of Chain Drug Stores Foundation. Medication therapy management in pharmacy practice: core elements of an MTM service model. *J Am Pharm Assoc*. 2008;48:1-18. http://www.accp.com/docs/positions/misc/CoreElements.pdf. Accessed September 7, 2012.
26. Rambhade S, Chakarborty A, Shrivastava A, Patil UK, Rambhade A. A survey on polypharmacy and use of inappropriate medications. *Toxicol Int*. 2012;19(1):68-73.