Drug Utilization Trends in Patients With Posttraumatic Stress Disorder in a Postconflict Setting: Consistency With Clinical Practice Guidelines

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ABSTRACT

Objective: The objective of this study was to compare observed patterns of drug utilization among patients with posttraumatic stress disorder (PTSD) in a postconflict setting with current guidelines and to present baseline period prevalence and change in period prevalence from 2 time periods, 2002 and 2012.

Method: The study provides details of the annual number of patients with PTSD with at least 1 redeemed prescription containing the diagnostic code F43.1 according to *International Classification of Diseases* (*ICD-10*) for fiscal years 2002 through 2012 in Croatia. Using longitudinal data analysis, overall change in medication use frequency was calculated for each medication and therapeutic subgroup classified by the Anatomic Therapeutic Chemical classification system according to absolute frequency.

Results: Over the 11-year study period, the number of patients receiving pharmacotherapy associated with PTSD increased 7-fold. The annual frequency of drug use was highest for anxiolytics, with use of anxiolytics increasing from 73.32% in 2002 to 75.83% in 2012; antidepressants, from 44.56% to 61.36%; hypnotics, from 18.67% to 35.68%; and antipsychotics, from 21.81% to 30.21%. Overall change in drug utilization frequency was most prominent for hypnotics (17.01%), antidepressants (16.80%), and antipsychotics (8.40%) during the period 2002–2012.

Conclusions: Drug utilization trends in our postconflict setting were predominantly inconsistent with current guidelines for treatment of PTSD due to excessive anxiolytic use, implying that psychopharmacotherapy was used mainly for tranquilizing properties to address non–diagnosis-specific symptoms. Promising rising trends in utilization of antidepressants were not followed with compensatory reductions in anxiolytic use. These data revealed areas of inconsistent use of drugs, generating suggestions for interventions to improve drug use and also hypotheses for additional research.

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Data from different parts of the world indicate increasing prescriptions for drugs used for all mental disorders. Considering posttraumatic stress disorder (PTSD), the number of US veterans seeking help for this disorder, for example, has increased dramatically,[1] and studies indicate that over 80% of veterans treated for PTSD receive at least 1 medication.[2] Without knowledge of how drugs are being prescribed and used, it is difficult to initiate a discussion on rational drug use.

A number of well-designed randomized controlled trials of pharmacologic and psychotherapeutic interventions for PTSD have been conducted. As the evidence base for the treatment of PTSD grows, there is an increasing need to present an optimal approach to treatment to clinicians providing care to trauma survivors and patients with stress disorders. In recent years, several evidence-derived and expert consensus practice guidelines have been published to inform clinical work in the assessment and treatment of PTSD.[3–18] Most of these documents highlight antidepressants as first-line pharmacotherapeutic agents in the management of PTSD, particularly selective serotonin reuptake inhibitors (SSRIs)[3,5–8] and serotonin-norepinephrine reuptake inhibitors (SNRIs).[9,11–13,16,18] There is another important concordance between guidelines in discouraging providers in prescribing of benzodiazepines for management of core symptoms of PTSD because of lack of efficacy data and growing evidence for the potential risk of harm.[3–5,13] Other pharmacotherapeutic agents are considered a second-line option when SSRIs and SNRIs fail to alleviate PTSD symptoms or are recommended as add-on or adjunctive therapy (tricyclic antidepressants,[3,5,6,13,16] monoamine oxidase inhibitors,[3,5,6,8,13] newer antidepressants,[3,6,8,9,13] second-generation antipsychotics,[5,6,9,11–13,18] mood stabilizers[5,9]) for treatment of the core PTSD symptoms. Some of the pharmacotherapeutic agents are recommended in a targeted manner, such as the α-adrenergic antagonist prazosin for treatment of insomnia and nightmares,[5,9,11,13,18] short-term application of hypnotics for insomnia,[3,6,15] and mood stabilizers for irritability and aggressiveness.[18]

Study Background

The war in Croatia (1991–1995), because of its high level of political violence and terror,[19] has had numerous adverse effects on the mental health of Croatia's citizens. Among war survivors, there is a strong association between war experience and increased levels of mental disorders.[20–23] The most frequent mental disorders are PTSD and major depressive disorder.[24] Generally, war-related PTSD is associated with a higher rate of physical and mental health service use.[25] Although war-related PTSD is not necessarily a combat-related disorder, Croatian war veterans have been highly

Clinical Points

- Studies that compare drug utilization in patients with posttraumatic stress disorder (PTSD) and clinical practice guidelines provide insight into the consistency of use trends with recommended treatment options.
- Among PTSD patients in a postconflict setting, utilization of antidepressants is consistent with, but excessive utilization of anxiolytics is inconsistent with, clinical practice guidelines calling for specific strategies to improve drug use.

prevalent among those treated in health facilities for years after the war.[26–28] In spite of increasing drug consumption and development of guidelines, inadequate efficiency and effectiveness of the treatment of veterans with a PTSD diagnosis were recognized in previous studies revealing sparse symptom improvements after the treatment.[29,30] Although Croatian mental health researchers and experts contributed substantially to the rising body of scientific work in the field of PTSD diagnosis and treatment, we still lack Croatian clinical practice guidelines for PTSD.

The objective of this study was to evaluate drug utilization trends among patients with PTSD in Croatia and to compare the observed patterns of drug use with current guidelines for the treatment of patients with PTSD.

METHODS

Data Source

The data from the Croatian Health Insurance Fund (CHIF) were examined. The CHIF database contains details of annual outpatient prescription drug claims of 4,356,486 persons (97% of Croatia residents in 2012) covered by the national social health insurance system.[31] This study was approved by the Ethics Committee of the School of Medicine, University of Rijeka, Rijeka, Croatia.

Patients

The study provided details of the annual number of patients with PTSD with at least 1 redeemed prescription containing the diagnostic code F43.1 for PTSD according to the *International Classification of Diseases* (*ICD-10*)[32] dispensed through the outpatient service covered by CHIF over an 11-year time period (fiscal years 2002–2012) in Croatia. A prescription item was defined as a single drug package prescribed by a general practitioner on a prescription form, regardless of quantity per package, days' supply, or dosage form. The data do not give insight as to whether the drug was recommended by a psychiatrist and also do not cover items dispensed in the hospital or in private prescriptions.

ATC Classification System

Use data of medications for ambulatory care of patients with PTSD for the period 2002–2012, aggregated at the level of the active substance, were collected in accordance with the Anatomic Therapeutic Chemical (ATC) classification.[33] In brief, the ATC system classifies therapeutic drugs. The purpose of the system is to serve as a tool for drug utilization research in order to improve quality of drug use. In the ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacologic, and therapeutic properties. Drugs are classified into 5 different levels.

For the purpose of this study, drug consumption statistics were presented on the level of the pharmacologic subgroup (ATC-3 level) and chemical substance (ATC-5 level). On the third level, the following pharmacologic subgroups were included: N03A—Antiepileptics, N05A—Antipsychotics, N05B—Anxiolytics, N05C—Hypnotics and sedatives, N06A Antidepressants. All of the chemical substances included in these groups were analyzed.

Analysis

Medication utilization frequency was reported as the annual number of patients with PTSD who received at least 1 medication. Using longitudinal data analysis, overall change in medication use frequency was calculated for each medication and therapeutic class according to absolute frequency. According to our clinical experience, we are almost certain that there was only 1 medication registered in Croatia that was used by a substantial proportion of PTSD patients and was not included in this analysis: the hypnotic flurazepam, which is registered in Croatia but not included on the CHIF list of medicines and is completely distributed on private receipts. We assume that the frequency of its utilization was approximate to that of nitrazepam (7.1%). Other possible medications used in the PTSD population were the anxiolytic bromazepam and the hypnotic midazolam, but we assume that utilization of these drugs did not reach 1% of the patients with PTSD during the study period.

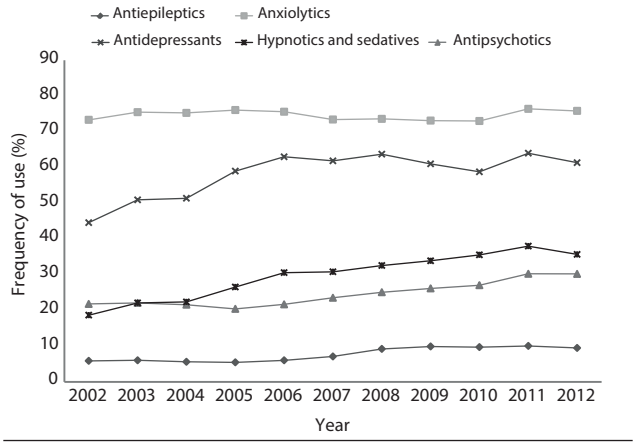
Several commonly prescribed medications were introduced on the official CHIF list of drugs after the study was initiated in 2002: quetiapine in 2002; citalopram, escitalopram, mirtazapine, and venlafaxine in 2005; duloxetine in 2007; bupropion in 2009; and agomelatine in 2010.[34] For these drugs, overall change in medication use frequency was calculated from the third year after the introduction on the list.

RESULTS

Over the 11-year study period, the number of patients receiving pharmacotherapy for PTSD through the CHIF system increased 7-fold, from 4.677 in 2002 to 33.113 in 2012. The proportion of the medication users with PTSD in total number of persons covered by CHIF health insurance increased in the same period from 0.11% to 0.76%. The proportion of female patients decreased from 19.86% (929) in 2002 to 7.37% (2,440) in 2012.

Among these patients, there was no change over time in the rankings of the most commonly utilized drug groups, with the exception of hypnotics, which overtook antipsychotics for third place. The annual frequency of use in 2012 was

Figure 1. Trends in Utilization of the 5 Most Commonly Used Classes of Psychiatric Medications, 2002–2012



highest for anxiolytics (75.83%), followed by antidepressants (61.36%), hypnotics (35.68%), antipsychotics, (30.21%), and antiepileptics–mood stabilizers (9.49%). Overall change in drug utilization frequency was most prominent for hypnotics (17.01%), antidepressants (16.80%), and antipsychotics (8.40%) during the period 2002–2012. Figure 1 illustrates trends in use of the 5 most commonly used classes of psychiatric drugs during the study period, and Table 1 illustrates yearly outpatient utilization of the most commonly used medications in PTSD population involved in pharmacotherapeutic treatment in 2002 and 2012.

Anxiolytics

Anxiolytics remained widely used drugs among pharmacologically treated PTSD patients, with an overall increase during the 11-year period of 2.51% (from 73.32% in 2002 to 75.83% in 2012). Alprazolam remained the most commonly used medication, with an increase from 33.40% in 2002 to 40.17% in 2012. Diazepam showed the most prominent increase in use, with 12.43%, and oxazepam showed the most prominent decrease over time (–15.58%).

Hypnotics

Hypnotics showed meaningful increase in use during the study time (17.01%), and a high proportion of patients with PTSD received at least 1 hypnotic during 1 year (35.68% in 2012). The increase in use of a "Z-drug"—zolpidem—(19.10%) is salient.

Antidepressants

There was a continuing increase in antidepressant utilization, from 44.56% in 2002 to 61.36% in 2012. In 2002, fluoxetine (15.42%), paroxetine (10.65%), and amitriptyline (6.78%) were the most-used medications. In 2012, sertraline overtook first place (15.63%), followed by mirtazapine (11.50%) and paroxetine (9.91%). There was a substantial increase in the frequency of utilization of sertraline (12.19%) and also a substantial decrease in fluoxetine use (–13.03%) over time.

Table 1. The Most Commonly Used Individual Drugs Among Patients With PTSD in 2002 and 2012

	2002 (N = 4,677)		2012 (N = 33,113)	
Ranking	Drug	n (%)	Drug	n (%)
1	Alprazolam	1,562 (33.4)	Alprazolam	13,302 (40.2)
2	Diazepam	1,183 (25.3)	Diazepam	12,490 (37.7)
3	Oxazepam	950 (20.3)	Zolpidem	9,872 (29.8)
4	Fluoxetine	720 (15.4)	Sertraline	5,177 (15.6)
5	Promazine	520 (10.7)	Promazine	4,441 (13.4)
6	Zolpidem	501 (10.7)	Mirtazapine	3,808 (11.5)
7	Paroxetine	498 (10.6)	Paroxetine	3,281 (9.9)
8	Nitrazepam	407 (8.7)	Venlafaxine	3,131 (9.5)
9	Amitriptyline	317 (6.8)	Escitalopram	2,855 (8.6)
10	Sulpiride	234 (5.0)	Fluvoxamine	2,593 (7.8)

Abbreviation: PTSD = posttraumatic stress disorder.

Antipsychotics

The annual frequency of antipsychotic use increased from 21.81% in 2002 to 30.21% in 2012. The most commonly used antipsychotics in 2002 were promazine (10.73%) and sulpiride (5.00%). That ranking changed with the inclusion of quetiapine in 2002. So, in 2012, promazine (13.41%) was still the most commonly used drug, followed by quetiapine (7.53%), which showed the most prominent increase from 2005 to 2012 (7.17%).

Antiepileptics–Mood Stabilizers

Mood stabilizers were the most rarely used drugs but also showed increase in utilization during the study period (3.61%). The most commonly prescribed drug in this class in 2002, carbamazepine, showed substantial decrease during the study period (–2.52%), and the benzodiazepine derivate clonazepam overtook first place (3.14%) in 2012.

DISCUSSION

The main finding in this study is that anxiolytics were used by the highest proportion of patients with PTSD (75.83% in 2012) and kept that primacy during the entire study period, even though such treatment is completely inconsistent with all relevant guidelines for treatment of PTSD.[4–9,11,13–18] The most comprehensive research examining the trends in benzodiazepine prescribing among veterans with PTSD in the United States revealed promising decline of use over time[35] but still raised concerns about the fact that more than 30% of veterans with PTSD continued to receive benzodiazepines. Another study[36] that evaluated prescribing patterns for persons with PTSD in a community-based nonveteran sample in which women were well represented revealed discrepancies between actual prescribing patterns and prescribing guidelines, particularly in frequent use of benzodiazepines (41%–54% depending on comorbidity). Clinical trials of benzodiazepines showing no significant benefit in treating PTSD are small and not very recent[37,38] relative to SSRI/SNRI trials in PTSD. On the other hand, there is a growing body of scientific evidence of potential risk of harm, including deterioration of the clinical condition of patients with PTSD, development of tolerance and dependence, abuse among patients with substance

use disorders, disinhibition effects among patients with traumatic brain injury,[2,3,13,39] and recent concerns about generally increased risk of Alzheimer's disease,[40] dementia,[41] and mortality,[42,43] which warrants recommendations against the use of benzodiazepines. Similar concerns are present when considering benzodiazepine hypnotic use. Some of the guidelines recommend cautious short-term use of hypnotic medication when sleep is a major problem for an adult PTSD sufferer.[6,15] Nonbenzodiazepine hypnotics, so-called *Z*-drugs, are preferred in that context (2–4 week treatment) because of their shorter half-life, slower development of tolerance, lower risk for withdrawal reactions, and lower risk for dependence.[13,44] Our study revealed the most prominent increase of hypnotic use during the study time (17.01%), mostly due to the increase in use of *Z*-drugs, which would be consistent with guidelines only if we could be sure of the short-term use of these drugs in appropriate, recommended doses. Considering treatment of sleep disturbances in PTSD, 1 important thing should be noted. Marketing authorization for the α-adrenergic antagonist prazosin, which is a highly recommended pharmacotherapeutic agent[7,9,12–14] with prominent expansion in prescribing and utilization, was withdrawn/revoked from the Croatian market before 2009.[45] After that, Croatia lacked an inexpensive ($5–$10 per month) and efficacious drug[46–48] for treatment of PTSD-related sleep disturbances and global PTSD. Bernardy et al,[2] in their research on prescribing trends, concluded that the decline in benzodiazepine prescribing among PTSD veterans tracked best with increases in prazosin use.

Antidepressant use rose subsequently over time, reaching almost two thirds of patients receiving pharmacotherapy for PTSD in Croatia. This increase was certainly due to the knowledge and experience of psychiatrists and general practitioners in the treatment of PTSD patients, but also to better compliance and adherence of patients to treatment. Among antidepressants, SSRIs[3,5–8] and in more recent guidelines SSRIs and SNRIs[9,11–13,16,18] are recommended as first-line pharmacotherapeutic intervention for PTSD. Unfortunately, promising rising trends in utilization of antidepressants were not followed with compensatory reduction in benzodiazepine use. The various SSRIs are often prescribed interchangeably for treatment of PTSD because it is usually believed that there is no scientific evidence for selective recommendation of one medication over another. On the other hand, it should also be noted that only sertraline and paroxetine have been approved by the Croatian Agency for Medicinal Products and Medical Devices for this indication and particularly recommended by some of the guidelines. The same agents have been approved by the US Food and Drug Administration for this use. These 2 drugs were the first and third most used medications among antidepressants in PTSD patients in 2012 in Croatia. Venlafaxine has been found to be effective and safe in PTSD and is highly recommended by most current guidelines.[9,11,13,18] In Croatia, it was the most prominent SNRI, showing promising trends during the study period (rising 4.20%) and pursuing paroxetine for third place, with only 0.45% (150 patients) difference in frequency of use in 2012. The study confirmed our clinical experience of a high representation of mirtazapine among other antidepressants in the PTSD population. It is recommended specifically by some guidelines as a first[8] or second[8,9,11–13] pharmacotherapeutic option. In Croatia, war veterans are highly represented in the PTSD population, and mirtazapine is a common therapeutic choice meeting these individuals' specific therapeutic needs, with its sedating effects, bedtime dosing, positive impact on insomnia, and relatively lower incidence of sexual dysfunction.[49]

Overall annual frequency of antipsychotic use slightly decreased from 2002 to 2005; this was followed by continuous expansion during the rest of the study period. Clinical guidelines predominantly recommend adjunctive, augmentative, add-on use of antipsychotics when patients with PTSD fail to respond to initial pharmacologic treatment.[6–9,11–13] Most of the guidelines recommend adjuvant therapy with olanzapine,[6–9,13] risperidone,[7–9] and, with a lower grade of recommendation (level C), quetiapine.[13] The most recent overview and revision of guidelines consider risperidone to be contraindicated for use as an adjunctive agent following the recent large-scale multisite trial[50] and emphasize insufficient evidence to recommend any other atypical antipsychotic as an adjunctive agent for PTSD.[51] Even if we assume that antipsychotics were used rigorously as adjunctive therapy in our sample, we still must recognize that half of the patients treated with antidepressants in our study also used antipsychotics. A possible reason for these findings is the high prevalence of chronic and combat-related PTSD patients with accompanying irritability, aggression, and sleeping difficulties. Monotherapy with antipsychotics would be completely inconsistent with current guidelines, but the methodology of our study does not allow such an insight. High representation of antipsychotics was certainly due to introduction of quetiapine on the official CHIF list. Quetiapine showed the most prominent increase among antipsychotics from 2005 to 2012. Data from other parts of the world and specifically from the United States showed that quetiapine was the most commonly prescribed second-generation antipsychotic in the PTSD population.[2,52,53] Antipsychotic utilization in Croatia substantially differed from these recommendations, with promazine as the antipsychotic used most often among PTSD patients. This finding, as well as increasing quetiapine utilization, suggests predominant use of antipsychotics as sedative-hypnotic agents and consequently possible monotherapy utilization.

Mood stabilizers were the most rarely used drugs. Such agents are not considered a first-line option in the pharmacotherapy of PTSD, and they are mentioned in one guideline as an augmentative treatment option.[18] In our sample, the most used medication from this group was the benzodiazepine derivate clonazepam, which we assume was used like other benzodiazepines for the treatment of PTSD-related sleep disturbances, irritability, and anxiety.

Several noteworthy strengths and limitations should be discussed. As far as we know, this is the first comprehensive

study of drug utilization trends among patients with PTSD in postwar countries with comparison of the observed patterns of drug use with current guidelines for the treatment of patients with PTSD. Coverage of 97% residents of Croatia by the CHIF database enables optimal generalizability of the results in our setting. Given the substantial nonadherence to drug prescription, these utilization data give much more accurate insight into drug use among PTSD patients than prescription data. Retrospective studies are inexpensive, can be conducted rapidly, and have easily accessible data but also have inherent limitations. We could not verify that coded diagnosis of PTSD conformed strictly to diagnostic criteria, and we had no insight into comorbidity. The study design precludes details about polypharmacy, applied dosages of medications, and length of time of treatment.

Drug utilization trends in our postconflict setting are predominantly inconsistent with current guidelines for treatment of PTSD due to excessive anxiolytic use, implying that psychopharmacotherapy was used mainly for tranquilizing properties for non–diagnosis-specific symptoms. The promising trends in rising utilization of antidepressants, which are first-line drugs for treatment of PTSD, and the relatively high proportion of PTSD patients treated with these drugs, which is completely consistent with current guidelines, were not accompanied by a compensatory reduction in anxiolytic use. According to recent studies,[54,55] patient education could be one of the effective public health interventions for successful reduction of benzodiazepine use. Regulatory policies such as a centralized prescription network,[56] discontinuation of reimbursement for benzodiazepines,[57] and particularly efforts directed to introduction of proven therapeutic options for treatment of PTSD such as prazosin can help in implementation of evidence-based treatment options. There is a need for additional research, which should be oriented toward determining the weakness in the patient–general practitioner–psychiatrist–PTSD centers–health insurance chain, with a primary goal of improving treatment of PTSD patients.

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Drug names: alprazolam (Xanax, Niravam, and others), bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clonazepam (Klonopin and others), diazepam (Diastat, Valium, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), flurazepam (Dalmane and others), fluvoxamine (Luvox and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), prazosin (Minipress and others), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), zolpidem (Ambien, Edluar, and others).

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