Use of pharmacological treatment for posttraumatic stress disorder: analysis of a psychiatric population in Switzerland and comparison with international guidelines.

Traitement pharmacologique de l'état de stress post-traumatique : analyse d'une population en Suisse et comparaison avec les recommandations internationales.

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Abstract

Objectives: Several international guidelines for the pharmacological treatment of posttraumatic stress disorder (PTSD) have been published. However, it is unclear whether clinicians use these procedures in their daily practice. We compared the psychopharmacological prescription patterns in a Swiss adult psychiatric center with international clinical guidelines at admission and discharge.

Methods: Retrospective chart review study between 2005 and 2015 of adult patients with PTSD and no other documented psychiatric comorbidity.

Results: 52 outpatients and 21 inpatients were included; 47% had at least one psychopharmacological treatment at admission. Among them, 47% had one or several antidepressants, mainly escitalopram (31%, n=5) or citalopram. At discharge, 68% had at least one psychopharmacological treatment. Among them, 76% had at least one antidepressant, mainly escitalopram (34%, n=13) or mirtazapine (21%, n=8). They were compared to the guidelines of the Department of Veterans Affairs and Department of Defense (VA/DoD), showing 19% of the patients treated with antidepressants at admission were in agreement to the guidelines (sertraline, fluoxetine, paroxetine, venlafaxine), and 26% at discharge. In addition, we found prescriptions of benzodiazepines (62% at admission and 50% at discharge), antipsychotics (12% and 22%), Z-drugs (zolpidem, zopiclone: 15 and 40%) and a few pregabalin prescriptions (n = 4).

Conclusions: Clinicians in this study prescribed frequently antidepressants to treat PTSD, as recommended. However, most of the antidepressants used were not recommended in the VA/DoD guidelines. Benzodiazepines and Z-drugs remained widely used, although they are not recommended.

Keywords: psychiatry; posttraumatic stress disorder; psychopharmacological treatment; guideline.

Résumé

Objectifs: Il existe plusieurs recommandations internationales concernant le traitement de l'état de stress post-traumatique (ESPT). Cependant, leur utilisation dans la pratique clinique reste rarement évaluée. Nous avons comparé les prescriptions pharmacologiques effectuées dans un centre public suisse avec les recommandations internationales.

Méthodes: Etude rétrospective sur dossier des prescriptions pharmacologiques effectuées entre 2005 et 2015 chez des patients adultes avec un état de stress post-traumatique sans autre comorbidité. Les traitements présents à l'entrée et à la sortie d'unités ambulatoires et hospitalières ont été pris en compte. Nous avons analysé différentes classes de traitements, dont les antidépresseurs, les antipsychotiques, les stabilisateurs d'humeur (antiépileptiques), les benzodiazépines et leurs analogues.

Résultats: 52 patients ambulatoires et 21 patients hospitalisés ont rempli les critères d'inclusion. A l'entrée, 47% des patients avaient un traitement pharmacologique. Parmi ceux-ci, 47% avaient un ou plusieurs antidépresseurs, principalement escitalopram (31%, n=5) ou citalopram. A la sortie, 68% des patients avaient un traitement pharmacologique, parmi lesquels 76% avaient au moins un antidépresseur, principalement escitalopram (34%, n=13) ou mirtazapine (21%, n=8). La comparaison avec les recommandations du Département de la Défense américaine et des Vétérans (VA/DoD) montre 19% de concordance à l'admission (sertraline, fluoxétine, paroxétine, venlafaxine), et 26% à la sortie. Nous avons constaté également la présence de benzodiazépines (62% à l'admission et 50% à la sortie), d'antipsychotiques (12% et 22%), d'analogues aux benzodiazépines (zolpidem, zopiclone: 15 et 40%) et quelques prescriptions de prégabaline (n=4).

Conclusions: Les cliniciens ont prescrit fréquemment des antidépresseurs pour l'ESPT, comme recommandé. Toutefois, la plupart des antidépresseurs utilisés ne correspondaient pas aux recommandations. Les prescriptions de benzodiazépines et analogues restaient fréquentes, bien que non-recommandées.

Mots clés: psychiatrie; état de stress post-traumatique ; traitement psychopharmacologique ; recommandations internationales

Introduction

Although posttraumatic stress disorder (PTSD) has been observed throughout history, it was first introduced in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1980, and a burgeoning amount of literature on this topic has appeared ever since (1). The core features of PTSD are the persistence of intense, distressing, and fearfully avoided reactions to reminders of the triggering event, alteration of mood and cognition, a pervasive sense of imminent threat, disturbed sleep, and hypervigilance (2). The current diagnostic criteria, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) from the American Psychiatric Association (3) and the International Classification of Diseases from the World Health Organization (ICD-10 and the forthcoming ICD-11) (4), are summarized in Supplementary Table 1.

Numerous authors have highlighted the increasing role of clinical practice guidelines in both physical and mental healthcare (5). Currently, several international guidelines exist for the treatment of PTSD (6-14). Most of them give recommendations for psychopharmacological, as well as for psychotherapeutic treatments. Globally, 4 antidepressants (sertraline, paroxetine, fluoxetine, venlafaxine) are recommended, while psychotherapy remain the first-line treatment, if available. Although there is a high level of consensus across the guidelines, there are apparent differences that may lead to confusion (15). Guidelines can differ based on constitution of the expert group (psychiatrists only or multidisciplinary experts), the nature of studies examined (only randomized controlled trials or also studies with lower levels of evidence), the focus of the evidence review (e.g., literature search or key questions determined at the outset), the nature of the evidence review conducted to determine intervention (e.g., expert review or meta-analysis) and/or other characteristics.

To have an overview of the current recommendations, we summarized seven international guidelines, including both aspects of prevention and treatment: the Canadian Clinical Guidelines for the Management of Anxiety, Posttraumatic Stress and Obsessive-Compulsive Disorders (6); the National Institute for Health and Care Excellence (7); the American Psychological Association Guidelines (8); the World Health Organization (WHO) Guidelines (9); the Department of Veterans Affairs and Department of Defense Guidelines (10); the Australian Guidelines for the Treatment of Acute Stress Disorders and Posttraumatic Stress Disorder (11) and the International Society for Traumatic Stress Studies (12). The World Federation of Biological Psychiatry (13) and the American Psychiatric Association Guidelines (14) were not included as they are considerably older (published in 2010 or before).

The guidelines mention psychotherapy as an acknowledged treatment for PTSD: Trauma-focused psychotherapies are widely recommended (6-12), and some guidelines mention them as first-line treatment before pharmacotherapy (7, 9-11), whereas other guidelines (6, 8, 12) consider pharmacotherapy and psychotherapy separately, without giving preference to one over the other. The main pharmacological recommendations are as follows: for prevention of PTSD, pharmacotherapy is not indicated (7, 10), including the use of benzodiazepines (7). The latter may even increase the risk of developing PTSD (6).

The American Psychological Association guideline mentions moderate strength of evidence for fluoxetine and paroxetine in preventing comorbid depression for patients with PTSD (8). Regarding the treatment of PTSD, almost all the considered guidelines recommend a selective serotonin reuptake inhibitor (SSRI), like fluoxetine, paroxetine or sertraline, or recommend venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI). Only the WHO Guidelines recommend a SSRI without being more specific. Other antidepressants are not recommended due to insufficient evidence (e.g., mirtazapine, escitalopram), are 2nd or 3rd line, or are not mentioned. Of note, two guidelines specifically do not recommend citalopram (6, 10). Benzodiazepines are not mentioned (7-9, 11, 12), or not recommended (6, 10). There is more heterogeneity for antipsychotics, particularly for risperidone, which can either be strongly not recommended (10), exhibit insufficient evidence to recommend (8), can be recommended as 2nd line or 3rd line (6, 7), or can be recommended in 2nd line as adjunctive therapy (6). Mood stabilizers (anticonvulsants) are either not recommended (10), not mentioned (7, 9), have insufficient evidence (8, 11, 12) or are 3rd line (6). Prazosin has recommendation in one guideline for nightmares (6), while another mentions insufficient evidence (10). However, only sertraline and paroxetine have marketing authorization, for example in Switzerland (Swissmedic), in Europe (European Medicines Agency, EMA) and in the United States (Food and Drug Administration, FDA). To the best of our knowledge, fluoxetine and venlafaxine are not approved for PTSD in any regulatory agencies. Psychopharmacological recommendations of these guidelines are given in Supplementary Table 2.

Two studies examined the concordance between treatment guidelines and treatment prescription in US male combat veteran cohorts. In the first study including 482 veterans, first-line SSRIs or SNRIs were prescribed in more than 70% of the patients having at least one prescription. In the absence of a clearly indicated co-occurring psychiatric diagnosis, long-term benzodiazepines were prescribed to 14%, second-generation antipsychotics to 15%, and mood stabilizers to 18% of veterans with PTSD. Benzodiazepine prescribing was associated with symptoms of insomnia. The authors found a tendency to prescribe mood stabilizers and benzodiazepines without first-line SSRIs or SNRIs (16). The second study, a cross-sectional study of 356,958 veterans with PTSD and including other psychiatric comorbidities, found that 65.7% of veterans were prescribed SSRI/SNRIs. Second-generation antipsychotics and benzodiazepines were prescribed for 25.6% and 37%, respectively (17). Two other studies included a general population cohort. In the first one, psychopharmacological treatment utilization was examined among patients treated by general practitioners in Croatia (postconflict setting); 75.8% of the patients were treated with benzodiazepines (mostly alprazolam, diazepam and zolpidem) and 61% received antidepressants (mostly sertraline, paroxetine, mirtazapine). The authors concluded that there was excessive anxiolytic use (18). The second cross-sectional study compared the prescription pattern between patients with PTSD and/or major depression diagnosis. SSRIs were prescribed more to the depressed patients (32% versus 23%, $p<0.05$). Inversely, PTSD patients had more often atypical antipsychotics than depressed patients (17% versus 9% respectively, $p<0.001$) (19).

To the best of our knowledge, there are no recent studies comparing prescription patterns for PTSD patients without psychiatric comorbidities. Moreover, most of the studies concern veterans, which may not represent the general psychiatric population who can suffer from trauma not related to war. The aim of the present study was to examine the prescription patterns of psychopharmacological treatment in an adult cohort having a diagnosis of PTSD without other documented psychiatric comorbidities, and to compare such prescriptions with the recommendations of international published guidelines.

Methods

Study design

A retrospective review of psychopharmacological treatment prescribed between 01.01.2005 and 31.12.2015 was conducted in the Department of Psychiatry of the Lausanne University Hospital, Switzerland. This study took place in one of the three areas of the Department, called "North Sector", which covers a population of about 170,000 people, near the city of Lausanne. Five outpatient units (three general outpatient units, one emergency-crisis unit and one liaison-psychiatry unit) and three general psychiatric inpatient units were included. None of them is specialized in treating PTSD and most therapists were residents in psychiatry without specific training in PTSD therapies. The primary outcome was to assess prescriptions for PTSD at admission and at discharge, and to compare them to the VA/DoD guidelines (year 2017): These guidelines are often used in similar studies, allowing easier international comparison, and show a good level of consensus with other guidelines, especially concerning antidepressants, which are the first pharmacological treatment option for PTSD. We also included the Swissmedic official authorizations in our comparison (which are similar to the FDA official authorizations for antidepressants). We reviewed the medical charts individually after data extraction for better accuracy of the results (e.g. allowing to assess that the patients had PTSD and no comorbidities in their medical file).

Inclusion and exclusion criteria

Patients presenting a diagnosis of PTSD according to the ICD-10 classification (F43.1) without other psychiatric comorbidities were included. Diagnosis was made on a clinical basis by the therapist in charge of the patient. No specific structured or semi-structured interviews were used to establish a diagnosis of PTSD. Factors influencing health status and contact with health services (Z00 - Z99) were allowed because they did not imply a prescription of a psychopharmacological treatment. Somatic comorbidities were not considered as exclusion criteria. For outpatients, inclusion criteria were a PTSD diagnosis at admission and a follow-up duration of at least 30 days. A minimum follow-up duration of 30 days was arbitrarily defined to ensure that the medication titration period was over and that the treatment was tolerated and effective. Diagnosis was made typically after an investigation period of 4 interviews. Treatment was usually set up after that period. For inpatients, the inclusion criterion was a PTSD diagnosis at discharge. Because the duration of follow-up in hospital is typically 2 to 3 weeks and because medication is usually set up quickly after admission, no minimum follow-up duration was considered. Diagnosis was made in the first days of stay. Treatment was typically set up after diagnosis' confirmation. In case of multiple follow-ups for the same patient, the most recent outpatient and/or inpatient follow-up was included. The Ethics Committee of the Lausanne University Hospital approved the study. There was no request for informed consent due to the retrospective non-interventional study design. However, patients whose medical records included some mention of disapproval of participation in scientific research were not included in the study.

Data collection

All patients with a PTSD diagnosis and no other comorbidity were extracted from our hospital healthcare information database. The principal investigator (FM) individually reviewed the medical charts of identified subjects, including only patients meeting the above-mentioned inclusion criteria. Drug names and doses at admission, during follow-up and at discharge were recorded from the medical files. Additional data such as type of trauma (civil or war), country and date of trauma were considered. Type of treatment performed was categorized as pharmacotherapy, trauma-focused psychotherapy, both, or no specific treatment. Psychopharmacological treatments were categorized as antidepressants, benzodiazepines, antipsychotics, anticonvulsants (mood stabilizers), Z-drugs or “others” (all other categories). Treatment at admission was defined as a treatment present at take up, generally already set up by another physician (e.g. a general practitioner or another psychiatrist).

Statistical analysis

Descriptive statistics were calculated by presenting median and interquartile range (IQR) for continuous variables and numbers and percentages for categorical variables. Mann-Whitney tests for continuous variables and Fisher’s exact test for categorical variables were used. Both tests were two-sided, with p-values ≤0.05 considered as statistically significant.

Results

Cohort description

222 patients corresponding to 260 follow-ups were identified. After applying the above-mentioned inclusion and exclusion criteria, 52 outpatients and 21 inpatients were included for analysis (Figure 1). 53% were males and the median age was 31 years (Table 1). Gender and age were similar between inpatients and outpatients (p=0.44 and p=0.20 respectively). 74% were victims of civil trauma (defined as not related directly to war) and 26% of war trauma. This ratio was similar between outpatients and inpatients (p=0.39). Mean time from trauma until admission was 79 days (IQR 528 days) and was similar between outpatients and inpatients (p=0.97). As expected, mean follow-up duration was significantly shorter for inpatients than for outpatients (6 days vs 90 days respectively, p<0.001).

Prescriptions at admission and discharge

Figure 2 (left panel) shows treatment prescriptions at admission and discharge for all treatment categories. At admission, about half of the patients (47%) had at least one psychopharmacological treatment. Among them, 47% were given one or several antidepressants, 62% benzodiazepines, 12% antipsychotics, 15% Z-drugs and 3% others (pregabalin). At discharge, 68% of patients had at least one psychopharmacological treatment. Among them, the rate of antidepressants was 76%, benzodiazepines 50%, antipsychotics 22%, Z-drugs 40% and others 8% (pregabalin). The exact number of treatments at admission and discharge and p-values are available in Supplementary Table 3. Overall prescription increased between admission and discharge (47% vs 68% respectively, p=0.001), with a significant increase in the prescription of escitalopram in monotherapy (9% vs 26%, p=0.014) and a borderline increase in the prescription of mirtazapine in monotherapy (9% vs 14%, p=0.08). No significant differences in the prescription of other drugs could be shown between admission and discharge, with a borderline increase in the prescription of antipsychotics and Z drugs at discharge (12% vs 22%, p=0.08; respectively 15% vs 40%, p=0.06).

During follow-up itself (defined as the period between admission and discharge), 79% of the patients received pharmacological treatment, 3% had trauma-focused psychotherapy (and no pharmacological treatment), 18% had no specific treatment for trauma (neither pharmacological nor specific psychotherapy). For the 2 patients with trauma-focused psychotherapy, one had Eye Movement Desensitization and Reprocessing (EMDR) and the other had debriefing.

Antidepressants

Figure 2 (right panel) shows the specific prescriptions among patients treated with antidepressants. At admission, we found mainly prescriptions of escitalopram (31%, n=5) and citalopram (together resulting in 50% of prescriptions), followed by mirtazapine and trazodone (twice in combination with escitalopram). At discharge, escitalopram was again the most frequent prescription (34%, n=13), followed by mirtazapine (21%, n=8; once in combination with sertraline). Trazodone and mirtazapine were prescribed at low dosages

(100 mg and 15 mg respectively). The patients had often other psychopharmacological treatment in addition to antidepressants (described below).

Benzodiazepines, antipsychotics, anticonvulsants, Z-drugs and others

For the 21 patients with benzodiazepines at admission, lorazepam (48%) and clorazepate (24%) were the most frequent prescriptions. Seven were co-prescribed with other classes, including at least an antidepressant. For the 25 patients with benzodiazepines at discharge, lorazepam was again the most common prescription (64%). The rate of benzodiazepine use for inpatients at discharge was 74%, and 35% for outpatients. Benzodiazepines were frequently prescribed with another class of treatment (6 times alone and 19 times combined), usually an antidepressant, sometimes with the addition of an antipsychotic or a Z-drug. Rates of antipsychotics showed 12% at admission and 22% at discharge among treated patients, all combined with other psychotropic drugs. At admission, we found risperidone (50% of antipsychotics, n=2) and quetiapine (50%, n=2). At discharge, we found risperidone (45%, n=5), quetiapine (27%, n=3), olanzapine (18%, n=2) and chlorprothixene (9%, n=1). Reasons for prescribing antipsychotics were “hallucinations”, “flashbacks with hallucinations”, “anxiety” or “ruminations”. Of note, quetiapine dosage for the 2 patients at admission was 25 mg/d, one was increased at 150 mg/d and the second one was stopped. New prescriptions at discharge concerned 2 patients, with a dosage of 200 mg/d and 400 mg/d. Pregabalin was prescribed in one patient at admission and in 4 patients at discharge for its anxiolytic properties; most prescriptions were combined with an antidepressant.

Comparison with the VA/DoD guidelines and the FDA/Swissmedic labels

Among the 16 patients with antidepressants at admission, three were given treatment in agreement with the VA/DoD guidelines (sertraline, fluoxetine and venlafaxine), resulting in 19% compliance with the guidelines for antidepressants. Only venlafaxine was prescribed in monotherapy; the two other treatments were combined with a benzodiazepine and a Z-drug, treatments not recommended for augmentation therapy. Only one treatment (sertraline) was in agreement with the official indication of the FDA or Swissmedic.

Among the 38 patients with antidepressants at discharge, 11 were treated in agreement with the VA/DoD guidelines (sertraline: 6, paroxetine: 2, fluoxetine: 1, venlafaxine: 2), but one was a combination therapy of sertraline and mirtazapine, the latter displaying insufficient evidence of following the guideline. Therefore, we counted 10 treatments, resulting in 26% compliance with the guidelines for antidepressants. Again, only 1 treatment of venlafaxine was prescribed in monotherapy. All other patients also had a benzodiazepine and/or an antipsychotic and/or a Z-drug. None of these associations is recommended in the VA/DoD guidelines. Pregabalin, prescribed twice with escitalopram and once with duloxetine (and once alone), is not recommended for augmentation therapy. Seven prescriptions were in agreement with the FDA/Swissmedic labels (sertraline: 5, paroxetine: 2).

Discussion

In the present study, we noted that the rate of antidepressant prescription was significantly higher at discharge comparing to admission (47% and 76%, p=0.011). In the same way, prescription of treatments following the guidelines and the FDA/Swissmedic labels was higher at discharge. However, the proportion of treated patients receiving an antidepressant in agreement with the VA/DoD guidelines (sertraline, venlafaxine, paroxetine or fluoxetine) or the FDA/Swissmedic (sertraline, paroxetine) remained quite low (26% and 18%). This rate is even lower when considering all patients of the cohort and not only patients with a treatment. We found a wide use of escitalopram and mirtazapine, treatments that are not recommended or currently show insufficient evidence. The present results are in agreement with a previously published study (18), showing almost two-thirds of patients were treated with antidepressants, sertraline and mirtazapine being often used. Some explanations can tentatively be proposed for the wide use of escitalopram in our cohort. The latter is a frequent treatment for depressive and anxious states, largely prescribed in Switzerland, probably in relation to its wide spectrum of psychiatric indications and good tolerance. Thus, PTSD patients can present a few depressive or anxious symptoms simultaneously, without criteria for a co-occurring diagnosis, and therapists can choose to treat the global symptoms rather than PTSD specifically. Of note, a switch to another antidepressant occurred in a minority of patients, which, for inpatients, could be explained by a very short duration of hospital stay. Mirtazapine was prescribed at low dosages (15 mg), suggesting it was used for a sedative purpose.

The prevalence of prescription of benzodiazepines observed in our cohort (62% of treated patients at admission, 50% at discharge) is comparable with the prevalence of 30% to 74% reported in the literature (20, 21). As the length of stay for inpatients is often short, and benzodiazepines were mainly not prescribed alone at discharge, their use could hopefully be temporary, for example when initiating antidepressant treatment. However, their frequent use (and the tendency of prescribing mirtazapine for a sedative purpose) shows that treating anxious states or sleeping disorders in PTSD remains challenging, the options without benzodiazepines being sparse. Benzodiazepines present a high risk of dependence and tolerance and are associated with specific problems in patients suffering from PTSD such as worsening of overall severity, worse psychotherapy outcomes, aggression, depression and substance use. Moreover, benzodiazepine use after a recent trauma was found to increase the risk of developing PTSD symptoms (22). This shows the necessity of finding different options for the treatment of anxiety and sleep disturbances, especially for the patients with PTSD. As observed in the present cohort, we can speculate that some therapists could try to replace the use of benzodiazepines with pregabalin, as we observed that all patients treated with pregabalin are benzodiazepine-free at discharge. This drug is approved for Generalized Anxiety Disorder in Switzerland (Swissmedic) and Europe (EMA), and seems to develop less dependence and/or tolerance, except in patients with a history of substance abuse (23).

Z-drugs were also widely used in our cohort, most probably for treating sleep disorders. As for anxious states and the prescriptions of benzodiazepines, it can be challenging to treat sleep disorders in PTSD following the recommendations. Regarding the VA/DoD guidelines, no treatment is currently acknowledged.

Despite the small cohort, we can note that antipsychotic prescription showed an increase at discharge compared to admission, often for “psychotic” symptoms. In PTSD, it can be difficult to distinguish psychotic features from flashbacks (24), and therapists can therefore prescribe antipsychotics, trying to lower these symptoms. Moreover, some outpatients in our cohort were probably resistant to previous multiple treatments, which could explain why antipsychotics were prescribed. Antipsychotics were not prescribed for psychosis, as this diagnosis was an exclusion criterion in our study. For quetiapine, the doses were generally too low to have an antipsychotic action (below 600 mg/d), suggesting prescriptions were aimed more for an antidepressive and/or sedative than antipsychotic effect. However, we cannot exclude that some patients did not develop psychosis later.

Although some studies indicating a prescription of anticonvulsants ranging between 3% and 18% (16, 18), we found no prescription of this therapeutic class in our cohort, probably explained in part by the small sample size. Anticonvulsants (divalproex, lamotrigine, and carbamazepine, for example) are widely used for treating bipolar disorder and personality disorders. Due to their use as mood stabilizers, they could possibly show utility in the future for complex PTSD, a new feature in the ICD-11 classification, characterized by problems in affect regulation (25).

The strength of this study was the investigation of the treatment of a very specific population (PTSD without comorbidity), with individual chart review, allowing to verify the contents of the database provided (diagnosis, absence of comorbidities). Therefore, the proportion of false-positive for PTSD without comorbidity is almost absent. It should be mentioned that diagnosis of PTSD is generally straightforward, at least for PTSD with no comorbidities. As comorbidities were an exclusion factor, under-diagnosis of PTSD in our cohort was unlikely but cannot be excluded. Regarding the chart review, it should be mentioned that these data have been reviewed by the principal investigator only, which may increase the risk of reporting errors. Another limitation is the small sample size due to the specific population. Therefore, it can be difficult to extend the results to large populations. However, our results show global similarity with other studies. A last limitation is the exclusion of comorbidities, as we know that 75% of patients with PTSD have other comorbid psychiatric disorders (6). Therefore, this study concerns a minority of patients with PTSD. This fact should not minimize the importance of being aware of international recommendations for treating patients with PTSD.

Conclusion

PTSD is a condition of growing importance and specific guidelines are regularly updated. Our study is in accordance with previous research, showing tendency to prescribe antidepressants and benzodiazepines. However, only a small proportion of the prescribed antidepressants is in agreement with international recommendations, and benzodiazepines remain often prescribed. It remains challenging to find treatments for anxiety and sleep disorders in patients with PTSD, and some therapists could try to use benzodiazepines, Z-drugs or pregabalin. Although guidelines provide only recommendations and cannot substitute for clinical evaluation, clinicians should be aware of these recommendations without keeping away the personal history and preferences of the patient.

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Table 1: Demographic comparison of inpatients and outpatients

Variable	Total patients (73)	Inpatients (21)	Outpatients (52)	p-value
age, median (IQR), years	31.2 (15)	29.5 (7.8)	33 (17.3)	0.20
male, % (n)	53 (39)	62 (13)	50 (26)	0.44
Swiss citizenship, % (n)	21 (15)	10 (2)	25 (13)	0.20
civil status, % (n)				
divorced	8 (6)	10 (2)	8 (4)	1.00
married	48 (35)	33 (7)	54 (28)	0.13
separated	4 (3)	5 (1)	4 (2)	1.00
single	37 (27)	52 (11)	31 (16)	0.11
widowed	3 (2)	0 (0)	4 (2)	1.00
trauma localization, % (n)				
trauma inside Switzerland	55 (40)	33 (7)	63 (33)	0.04
trauma outside Switzerland	42 (31)	62 (13)	35 (18)	0.04
unknown localization	3 (2)	5 (1)	2 (1)	0.50
war trauma, % (n)	26 (19)	33 (7)	23 (12)	0.39
civil trauma, % (n)	74 (54)	67 (14)	77 (40)	0.39
time between trauma and medical care, median (IQR), days	79.4 (528.2)	47.1 (481.6)	83.5 (492)	0.97
duration of care, median (IQR), days	64.4 (102.6)	5.9 (6)	90.6 (102.8)	<0.0001
specific PTSD treatment during follow-up, % (n)*				
pharmaceutical	79 (58)	95 (20)	73 (38)	0.05
psychological	3 (2)	0 (0)	4 (2)	1.00
none	18 (13)	5 (1)	23 (12)	0.09

IQR: Inter quartile range. * No patient had a combined pharmaceutical and psychological PTSD treatment.

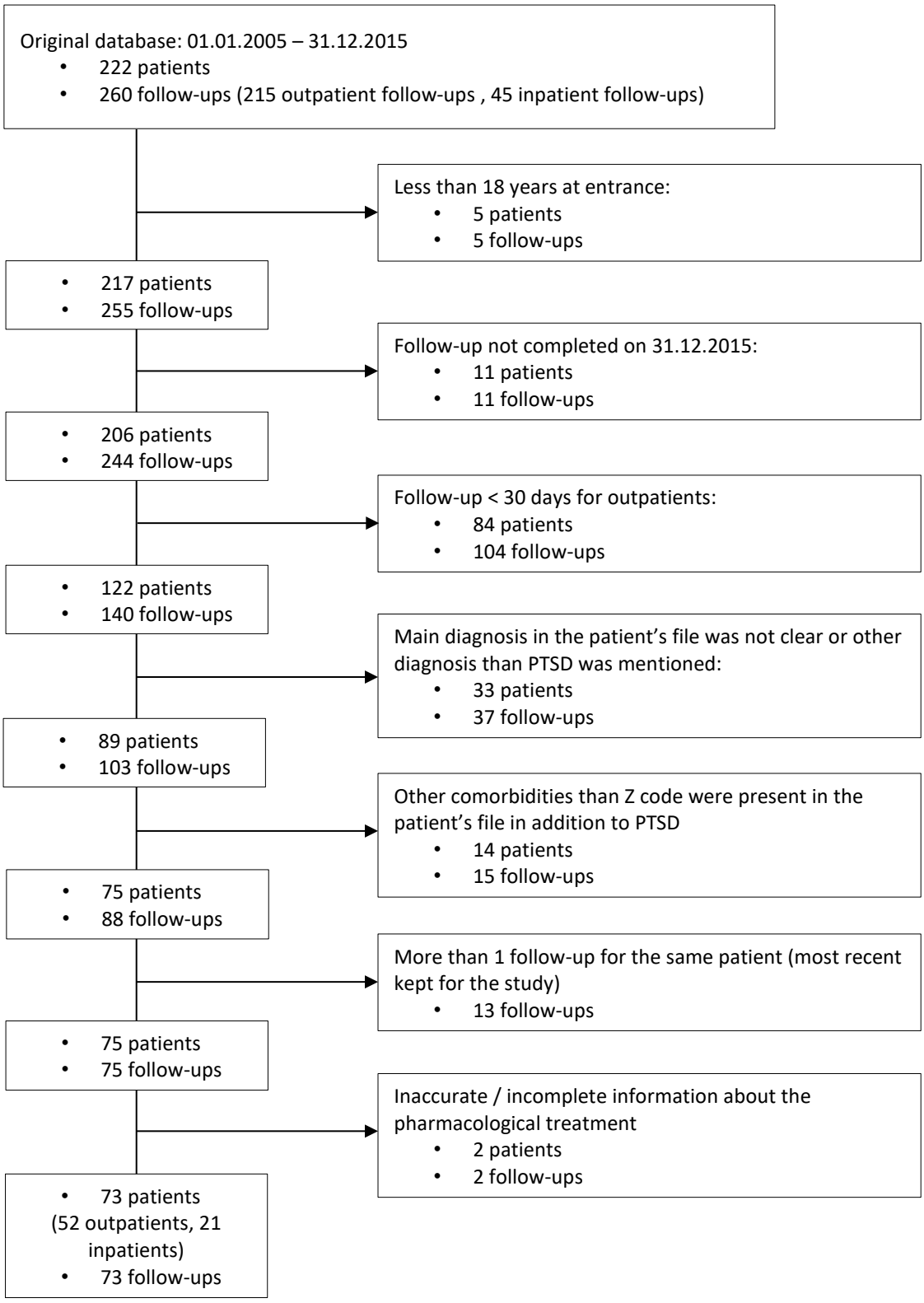

Figure 1: Flowchart of the inclusion / exclusion of patients.

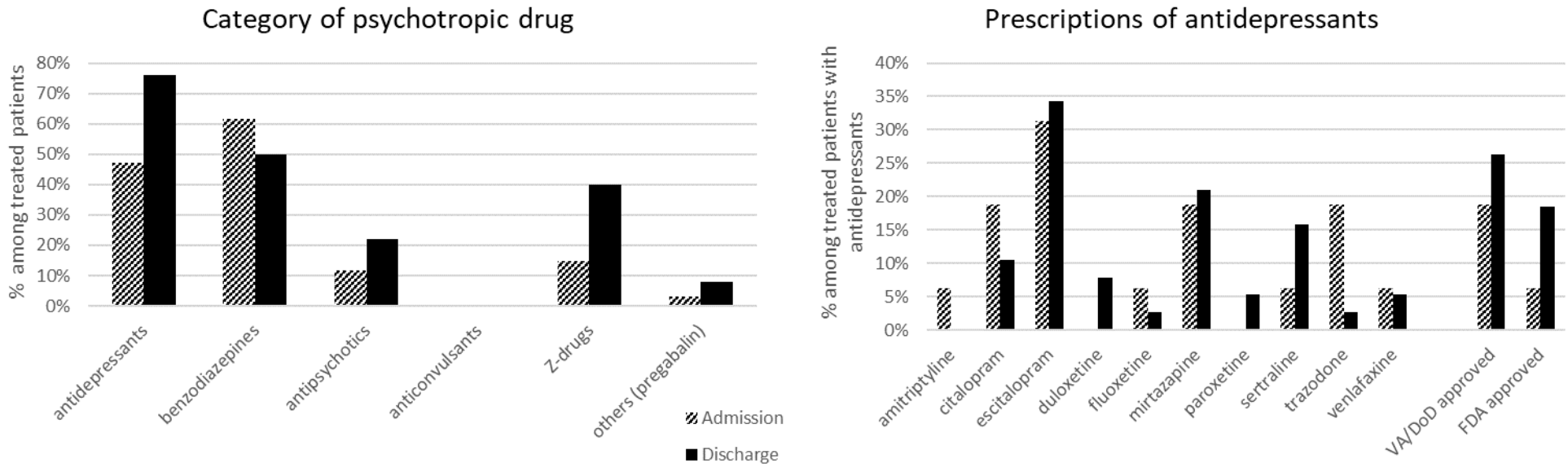

Figure 2: Comparison of psychotropic drugs (left) and antidepressants (right) prescriptions at admission (black hatched bar) and discharge (black bar).

Supplementary Table 1: International diagnostic criteria for Posttraumatic Stress Disorder (Adapted from Shalev, 2017). ICD-10 and ICD-11 criteria from ICD website, DSM-5 criteria from Katzman, 2014.

DSM-5 Criteria (309.81) (from Katzman, adapted from DSM-5)	ICD-10 Criteria (F43.1)	ICD-11 Criteria (6B40)
The person has been **exposed** to actual or threatened death, serious injury, or sexual violation in ≥1 of the following ways: - Directly experienced or witnessed the traumatic event, learned that trauma occurred to close family member or friend (actual or threatened death must have been violent or accidental), experienced repeated exposure to aversive details of trauma	A. Exposure to a stressful event or situation (either short or long lasting) of exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone.	Exposure to an extremely threatening or horrific event or series of events and all of the following:
Presence of ≥1 of the following **intrusion** symptoms associated with the trauma: - Recurrent, involuntary, and intrusive distressing memories, distressing dreams, dissociative reactions (e.g., flashbacks), psychological or physiological distress at reminders of trauma	B. Intrusion symptoms: Persistent remembering or "reliving" the stressor - by intrusive flashbacks, vivid memories, recurring dreams, or: - by experiencing distress when exposed to circumstances resembling or associated with the stressor.	Intrusion symptoms: - Re-experiencing the traumatic event or events in the present in the form of vivid intrusive memories, flashbacks, or nightmares. - Typically accompanied by strong or overwhelming emotions, particularly fear or horror, and strong physical sensations
Persistent **avoidance** of stimuli associated with the trauma, including ≥1 of the following: - Avoidance of distressing memories or feelings and external reminders (e.g., people, places) of the trauma	Avoidance: C. Actual or preferred avoidance of circumstances resembling or associated with the stressor (not present before exposure to the stressor).	Avoidance: - Avoidance of thoughts and memories of the event or events, or: - Avoidance of activities, situations, or people reminiscent of the event or events
Negative alterations in **cognitions and mood** associated with the trauma, including ≥2 of the following: - Inability to recall important aspect of the trauma, diminished interest or participation in activities, feeling of detachment or estrangement from others, persistent negative beliefs, distorted blame, and negative emotional state	D. Either 1) or 2) 1) Inability to recall, either partially or completely, some important aspects of the period of exposure to the stressor or:	

Marked alterations in **arousal and reactivity** associated with the trauma, including ≥2 of the following: - Irritable or aggressive behavior, reckless or self-destructive behavior, hypervigilance, exaggerated startle response, problems with concentration, sleep disturbance	2)	Persistent symptoms of increased psychological sensitivity and arousal (not present before exposure to the stressor) shown by any two of the following: difficulty in falling or staying asleep; irritability or outbursts of anger; difficulty in concentrating; hyper-vigilance; exaggerated startle response	Persistent perceptions of heightened current threat: - Hypervigilance, for example, or: - Enhanced startle reaction to stimuli such as unexpected noises
Duration of disturbance >1 month	E.	Criteria B, C and D all occurred within six months of the stressful event, or the end of a period of stress. (For some purposes, onset delayed more than six months may be included but this should be clearly specified separately	The symptoms persist for at least several weeks
Symptoms cause clinically significant **distress or impaired functioning**			The symptoms cause significant impairment in personal, family, social, educational, occupational or other important areas of functioning.
Specify whether with dissociative symptoms (depersonalization or derealization) or with delayed expression (full criteria not met until at least 6 months after the event)			

References:
Shalev, A., et al. (2017). "Post-Traumatic Stress Disorder." N Engl J Med **376**(25): 2459-2469.
Katzman, M. A., et al. (2014). "Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders." BMC Psychiatry **14**(1): S1.
ICD-10 online, Version 2010: https://icd.who.int/browse10/2010/en#/F43.1
ICD-10, Diagnostic criteria for research: https://www.who.int/classifications/icd/en/GRNBOOK.pdf
ICD-11 online: https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f2070699808

Supplementary table 2: Summary of the pharmacological treatment recommendations for PTSD (including prevention in some cases) of various international guidelines.

- World Health Organization (WHO) – Guidelines for the Management of Conditions Specifically Related to Stress (year 2013)
- Australian Guidelines for the Treatment of Acute Stress Disorders, Posttraumatic Stress Disorder, and Complex Posttraumatic Stress Disorder (year 2020)
- Canadian Clinical Guidelines for the Management of Anxiety, Posttraumatic Stress and Obsessive-Compulsive Disorders (year 2014)
- VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder (year 2017)
- American Psychological Association (APA) - Clinical Practice Guideline for the Treatment of PTSD (year 2017)
- International Society for Traumatic Stress Studies (ISTSS) – Posttraumatic Stress Disorder Prevention and Treatment Guidelines (year 2018)
- National Institute for Health and Care Excellence (NICE) – Post-Traumatic Stress Disorder Guideline (year 2019)

Recommended treatments are in green font, treatments not recommended are in red and treatments with insufficient evidence (or emerging evidence) are in purple. For the VA/DoD guidelines, strength of recommendation is available: strong recommendations are in **bold**, weak or N/A recommendations are in normal font.

	WHO[i] 2013	Australian 2020	Canadian 2014	VA/DoD 2017	American. Psychol. Assn 2019	ISTSS 2019	NICE 2018	FDA or Swissmedic label indication
Antidepressants	SSRI and TCA[ii]	SSRI[iii] sertraline paroxetine fluoxetine venlafaxine[iv] IE: mirtazapine amitriptyline imipramine brofaromine phenelzine Insufficient evidence for PTSD symptoms *in the first three months after exposure*: escitalopram	1st line: paroxetine fluoxetine sertraline venlafaxine XR 2nd line: fluvoxamine mirtazapine phenelzine 3rd line: amitriptyline bupropion SR desipramine duloxetine escitalopram imipramine moclobemide reboxetine tianeptine trazodone	Monotherapy: **sertraline** **paroxetine** **fluoxetine** **venlafaxine** (doses available in "Appendix C") Monotherapy 2nd line: nefazodone[v] imipramine phenelzine[vi] NR, monotherapy: amitriptyline citalopram IEFA, monotherapy or augmentation therapy: bupropion[vii] desipramine	sertraline paroxetine fluoxetine venlafaxine[viii] [ix]	Interventions with low effect: fluoxetine paroxetine sertraline venlafaxine IE: amitriptyline brofaromine imipramine mirtazapine phenelzine IE for *prevention* within the first 3 months: escitalopram	SSRI[x] venlafaxine	sertraline paroxetine

			NR: citalopram Adjunctive therapy, NR: bupropion SR	doxepin duloxetine desvenlafaxine escitalopram fluvoxamine levomilnacipran mirtazapine nortriptyline trazodone vilazodone vortioxetine				
Benzodiazepines and anxiolytics	Not mentioned for PTSD Negative recommendation for acute stress disorder, insomnia and bereavement[xi]	Not mentioned	NR: alprazolam clonazepam 3rd line: buspirone	NR, monotherapy and augmentation therapy: **benzodiazepines** (evidence based only on alprazolam and clonazepam) IEFA, monotherapy and augmentation therapy: zaleplon[xii]	Not mentioned	Not mentioned	Not mentioned for treatment[xiii] Negative recommendation for prevention	None
Antipsychotics	Not mentioned	Emerging evidence: quetiapine[xiv] IE: olanzapine	3rd line: aripiprazole quetiapine risperidone Adjunctive therapy, 2nd line: olanzapine risperidone Adjunctive therapy, 3rd line: aripiprazole quetiapine	NR, monotherapy: **risperidone** quetiapine[xv] olanzapine and other atypical antipsychotics IEFA, monotherapy or augmentation therapy: buspirone[xvi]	IEFA: risperidone	Emerging evidence: quetiapine IE: olanzapine	2nd line, as monotherapy or adjunctive therapy, in addition to psychological therapies: antipsychotics (for example risperidone), if disabling symptoms and no response to other treatment	None

			NR: olanzapine	NR, augmentation therapy: **atypical antipsychotics**				
Mood stabilizers/ Anticonvulsants	Not mentioned	divalproex lamotrigine tiagabine topiramate ganaxolone Insufficient evidence for PTSD symptoms *in the first three months after exposure*: gabapentin	3rd line: carbamazepine lamotrigine topiramate Adjunctive therapy, 3rd line: gabapentin levetiracetam tiagabine (monotherapy) NR: divalproex tiagabine Adjunctive therapy, NR: topiramate	NR, monotherapy: **divalproex** **tiagabine** NR, monotherapy: lamotrigine topiramate NR, augmentation therapy: **divalproex** NR, augmentation therapy: topiramate	IEFA: topiramate	IE: divalproex lamotrigine tiagabine topiramate IE for *prevention* within the first 3 months: gabapentin	Not mentioned	None
Z-drugs and others	Not mentioned	Emerging evidence: ketamine[xvii] IE: neurokinin-1 antagonist Emerging evidence for PTSD symptoms *in the first three months after exposure*: hydrocortisone	3rd line: memantine Adjunctive therapy, 2nd line: eszopiclone Adjunctive therapy, 3rd line: clonidine pregabalin Adjunctive therapy, NR: guanfacine zolpidem	NR, monotherapy: **guanfacine** **ketamine** **hydrocortisone** **D-cycloserine** NR: **Cannabis or derivatives** NR, augmentation therapy: baclofen pregabalin	Not mentioned	IE: ketamine neurokinin-1 antagonist Emerging evidence for *prevention* within the first 3 months: hydrocortisone IE for *prevention* within the first 3 months: docosahexaenoic acid oxytocin propanolol	Not mentioned	None

		Insufficient evidence for PTSD symptoms *in the first three months after exposure*: docosahexaenoic acid oxytocin propanolol	Nightmares: prazosin cyproheptadine Flashbacks (in the main text): naltrexone Improving trauma re-experiencing symptoms (in the main text): fluphenazine	NR, for global symptoms of PTSD, as monotherapy or augmentation therapy (except for nightmares): prazosin IEFA, monotherapy and augmentation therapy: eszopiclone[xviii] zolpidem D-serine hydroxyzine cyproheptadine IEFA, for nightmares associated with PTSD, as monotherapy or augmentation therapy: prazosin[xix]				

SSRI: selective serotonin re-uptake inhibitors, TCA: tricyclic antidepressants
IE: insufficient evidence to recommend, IEFA: insufficient evidence to recommend for or against, NR: not recommended

Note that the definition of “first/second/third-line” definitions can differ in each guideline.
Adjunctive therapy or a combination of drugs is called “augmentation therapy” in the VA/DoD guideline.
The various guidelines do not give dose recommendations. Only the VA/DoD guideline has a pharmacotherapy-dosing table in its “Appendix C”.
Most guidelines recommend psychotherapy before drug treatment (NICE, WHO, VA/DoD, Australian guidelines), and the other ones make separate recommendations.

[i] The primary audience is non-specialized specialized health-care providers working at first- and second-level health-care facilities […]. A secondary audience is those tasked with the organization of health care at the district or sub-district level […] (p.3).

[ii] SSRIs and TCAs should be considered if a) stress management, cognitive-behavioral therapy with a trauma focus and/or EMDR have failed or are not available, or b) if there is concurrent moderate-severe depression. Strength of recommendation: standard. Quality of evidence: low. (Recommendation 16 p.9). Of note, no recommendation is set for specific molecules within these groups.
[iii] Weak recommendation. If the following conditions apply: The person is unwilling or not in a position to engage in or access recommended psychological therapy (TF-CBT, PE, CT, CPT or EMDR). The person has a comorbid condition or associated symptoms (e.g., clinically significant depression and high levels of dissociation) where SSRIs are indicated. The person's circumstances are not sufficiently stable to commence recommended psychological therapy (as a result, for example, of significant ongoing life stress such as domestic violence). The person has not gained significant benefit from recommended psychological therapy. There is a significant wait time before psychological treatment is available.
[iv] Same as iii.
[v] Serious potential toxicity, should be managed carefully
[vi] Same as v
[vii] Strength of recommendation: N/A for all 13
[viii] Strength of recommendation: conditional for all 4.
[ix] The panel recommends clinicians offering either venlafaxine ER or sertraline when both are being considered. Strength of recommendation: Strong.
[x] There was no evidence for significant differential efficacy of specific SSRIs (sertraline, fluoxetine and paroxetine), so the committee agreed to allow prescribers to decide which SSRI to use.
[xi] Benzodiazepines and antidepressants should not be offered to adults to reduce *acute traumatic stress* symptoms associated with significant impairment in daily functioning in the first month after a potentially traumatic event. Strength of recommendation for benzodiazepines: strong, for antidepressants: standard. Quality of evidence: very low. (Recommendation 3 p. 6)
Benzodiazepines should not be offered to adults with *insomnia* within the first month after a potentially traumatic event. Strength of recommendation: standard. Quality of evidence: moderate. (Recommendation 7 p. 7)
Benzodiazepines should not be offered to *bereaved* adults who do not meet criteria for a mental disorder. Strength of recommendation: strong. Quality of evidence: very low. (Recommendation 20 p. 10).
[xii] Strength of recommendation: N/A
[xiii] Given the limited evidence of benefits and the potential harms, including side effects, the committee agreed that drug treatments should not be offered to *prevent* PTSD in adults. The committee specifically referred to benzodiazepines because of the lack of benefit in the evidence, concerns about harm and their clinical experience of these drugs being prescribed in practice.
[xiv] Research recommendation. Where medication is indicated for the treatment of PTSD we suggest an SSRI or SNRI antidepressant. There is emerging evidence for the use of quetiapine in the treatment of PTSD and it could be used in a research context.
[xv] Strength of recommendation: weakly against for all 3
[xvi] Strength of recommendation: N/A
[xvii] Research recommendation. Where medication is indicated for the treatment of PTSD we suggest an SSRI or SNRI antidepressant. There is emerging evidence for the use of ketamine in the treatment of PTSD and it could be used in a research context.
[xviii] Strength of recommendation: N/A for all 5
[xix] Strength of recommendation: N/A

Supplementary Table 3: Treatment of included patients

	Inpatient (21)		Outpatient (52)		Total (73)		
	Admission	Discharge	Admission	Discharge	Admission	Discharge	p-value[#]
At least one treatment*	13 (62%)	19 (90%)	21 (40%)	31 (60%)	34 (47%)	50 (68%)	0.001
Any antidepressant[&]	6 (46%)	14 (74%)	10 (48%)	24 (77%)	16 (47%)	38 (76%)	0.011
Amitriptyline	0	0	1	0	1	0	NA
Citalopram	1	2	2	2	3	4	1.00
Duloxetine (monotherapy)	0	0	0	2	0	2	NA
Duloxetine + trazodone	0	0	0	1	0	1	NA
Escitalopram (monotherapy)	2	4	1	9	3	13	0.014
Escitalopram + trazodone	0	0	2	0	2	0	NA
Fluoxetine	1	1	0	0	1	1	1.00
Mirtazapine (monotherapy)	1	4	2	3	3	7	0.08
Paroxetine	0	1	0	1	0	2	NA
Sertraline (monotherapy)	1	2	0	3	1	5	0.32
Sertraline + mirtazapine	0	0	0	1	0	1	NA
Trazodone	0	0	1	0	1	0	NA
Venlafaxine	0	0	1	2	1	2	1.00
Recommendations							
VA/DoD	2	4	1	6	3	10	0.32
FDA	1	3	0	4	1	7	0.32
Any benzodiazepine[&]	9 (69%)	14 (74%)	12 (57%)	11 (35%)	21 (62%)	25 (50%)	0.26
Alprazolam	1	1	1	1	2	2	0.32
Bromazepam	0	0	3	1	3	1	0.16
Clorazepate	2	2	3	2	5	4	0.56
Flurazepam	0	2	0	0	0	2	NA
Lorazepam	6	9	4	7	10	16	0.71
Oxazepam	0	0	1	0	1	0	NA
Any antipsychotic[&]	3 (23%)	4 (21%)	1 (5%)	7 (23%)	4 (12%)	11 (22%)	0.08
Chlorprothixene	0	0	0	1	0	1	NA
Olanzapine	0	0	0	2	0	2	NA
Quetiapine	1	1	1	2	2	3	0.32
Risperidone	2	3	0	2	2	5	1.00
Any anticonvulsant/mood stabilizer	0	0	0	0	0	0	NA
Any Z drug[&]	2 (15%)	8 (42%)	3 (14%)	12 (39%)	5 (15%)	20 (40%)	0.06
Zolpidem	1	7	3	11	4	18	0.06
Zopiclone	1	1	0	1	1	2	1.00
Other[&]							
Pregabalin	1 (8%)	1 (5%)	0	3 (10%)	1 (3%)	4 (8%)	0.16

[*]Percentage of patients among the total cohort. [&] Percentage of patients among patients with at least one treatment. [#]McNemar's chi-squared test was used to compare prescription rate between admission and discharge.