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Examining differences in clinical and demographic characteristics of patients with post-traumatic stress disorder across adult treatment subgroups based on the NeuroBlu database: a non-interventional, retrospective cohort study

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ABSTRACT

Background Post-traumatic stress disorder (PTSD) is a heterogeneous psychiatric disorder, with symptom variation between patients.

Objective We describe clinical and demographic characteristics of patients with PTSD based on real-world data.

Methods This non-interventional, retrospective cohort study analysed de-identified electronic health records of patients from the Holmusk NeuroBlu database in the USA. Patients with ≥2 PTSD diagnoses captured in the database within 30 days between 2001 and 2020 were included. The index date was defined as the date of the first recorded PTSD diagnosis. In patients who were aged ≥18 years, demographic and clinical characteristics at baseline (index date ±14 days), in the 6 months prior to baseline and 12 months after baseline were described. Patients were stratified into four mutually exclusive subgroups according to treatment received: psychotherapy only, pharmacotherapy only, psychotherapy and pharmacotherapy, and untreated. Natural language processing models were used to derive PTSD symptoms from unstructured clinician-documented mental state examination data. Data were analysed descriptively.

Findings A total of 37,449 patients had ≥2 PTSD diagnoses within 30 days between 2001 and 2020; 32,875 patients received care at clinical sites with both inpatient/outpatient units; 25,507 patients received psychotherapy and/or pharmacotherapy as per further prespecified criteria, and 17,234 were ≥18 years old and included in this analysis. Most patients (84.9%) received psychotherapy, pharmacotherapy or both during the first year post-baseline. Mean age (SD) was 37.7 (12.4) years, 73.4% of patients were female and 59.6% were White. At baseline, 98% of patients had ≥1 psychiatric comorbidity; major depressive disorder (42.2%), substance use disorder (35%) and anxiety disorder (30.7%) were most frequently reported. Reported suicidal ideation/attempts were most frequent in the pharmacotherapy only group compared with other subgroups at baseline. The most frequently prescribed drug classes were antidepressants (51.8%), second-generation antipsychotics (29.9%) and anxiolytics (23.3%) at baseline. Trazodone, clonazepam, quetiapine and sertraline were the most frequently prescribed medications.

Conclusion In the overall study population, most patients were female, with a high prevalence of psychiatric comorbidities. Demographic and clinical characteristics observed in this study varied across treatment subgroups. These insights may support patient-specific treatment planning and inform health-economic decision models in PTSD.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The data analysed in this study included a large cohort of patients.
⇒ Data extraction covered a broad geographical area which may be considered representative of patients receiving mental healthcare in a real-world setting in the USA.
⇒ However, the current dataset only includes clinician-recorded electronic health records and no patient-reported outcomes.
⇒ Additionally, data extraction via the use of the natural language processing models have inherent limitations.

BACKGROUND

Post-traumatic stress disorder (PTSD) has a lifetime prevalence in the USA of about 5% for adults, with higher rates observed in females (8%) compared with males (3%), and develops following exposure to isolated

or prolonged traumatic circumstances.[1 2] PTSD symptoms typically develop within 3 months following the traumatic event; however, onset may be delayed.[1] Symptoms may include re-experiencing the event or events through intrusive memories, dreams or dissociative flashbacks, avoidance of triggers associated with the traumatic event, emotional and cognitive disturbances, and alterations in arousal or reactivity following the traumatic event.[1] However, PTSD is a highly heterogeneous disorder, with substantial variation in possible symptomology and symptom trajectories among individuals.[3 4] Additionally, psychiatric comorbidities are common among patients diagnosed with PTSD, with a significant association found between PTSD and depression.[4–6] Other psychiatric disorders that may co-occur with PTSD include anxiety disorders, mood disorders and substance abuse disorders.[4 5]

Treatment strategies for PTSD generally include psychotherapy and/or pharmacotherapy.[7] The most recent guidelines from the American Psychological Association (APA) include a strong recommendation for the use of trauma-focused cognitive behavioural therapy including cognitive processing therapy and prolonged exposure therapy in first-line care.[7] Both cognitive processing therapy and prolonged exposure therapy include safely confronting triggering stimuli either by prolonged incremental exposure (exposure therapy) or through learning to modify contextual beliefs associated with the trauma (cognitive processing therapy).[8] In regard to pharmacological interventions, only a conditional recommendation is provided for the use of selective serotonin reuptake inhibitors, including fluoxetine, sertraline and paroxetine, or the serotonin-norepinephrine reuptake inhibitor venlafaxine in second-line care.[7] Importantly, only sertraline and paroxetine are approved by the US Food and Drug Administration (FDA) for the treatment of PTSD in adults,[9 10] although high rates of off-label medication use have been reported due to limited pharmacological treatment options specifically indicated for PTSD.[11]

The APA treatment guidelines also include outcomes focused on reducing comorbidities, such as decreasing depression symptoms, controlling substance use and regulating mood.[7] Furthermore, a recent meta-analysis provides support for the use of mindfulness and body-focused psychotherapies, prolonged exposure, narrative exposure therapy and cognitive processing therapy in individuals with PTSD and co-occurring depression.[12] The use of dialectical behaviour therapy has also been suggested for individuals with PTSD and co-morbid borderline personality disorder.[12] Notably, a previous real-world evidence study has demonstrated that individuals with PTSD and psychiatric comorbidities tend to receive more psychotherapy and a greater number of prescriptions compared with individuals with PTSD without psychiatric comorbidities.[11]

Given the prevalence of PTSD, observed difference in symptomology, variance in treatment response and limited pharmacological treatment options,[3 9 10 13 14] it may be beneficial for clinicians and involved healthcare providers to develop a thorough understanding of specific patient demographic and clinical characteristics in individuals with PTSD.

Objective

This real-world analysis describes the clinical and demographic characteristics of patients with PTSD at the time of first diagnosis captured in the NeuroBlu (Holmusk, New York, NY, USA) database. Improved understanding of these characteristics in patients with PTSD may help to inform future study designs and improve patient care. Additional insights into the clinical characteristics and demographics of patients with PTSD may help inform future clinical study approaches, leading to improved treatment options in this patient population.

METHODS

Study design and population

This non-interventional, retrospective cohort study analysed real-world de-identified electronic health records (EHR) from mental healthcare providers of USA operating the MindLinc system for Holmusk NeuroBlu (Holmusk, New York, NY, USA) (V.22R3), a longitudinal behavioural health database spanning 21 years between 1999 and 2020.[15] The study population was identified using diagnostic codes for PTSD from the International Classification of Diseases Clinical Modification (ICD-CM) V.9 (ICD-9; 309.81) and V.10 (ICD-10; F43.1, F43.10, F43.11, F43.12). Eligible patients had ≥2 PTSD diagnoses captured in the database within a 30-day period between 1 January 2001 and 31 December 2020, and received care at clinical sites with both inpatient and outpatient units. Patients included in this analysis were ≥18 years old. Patients were not involved with the research or writing process. The study index date was defined as the date of first PTSD diagnosis in the NeuroBlu database (online supplemental figure 1). In routine clinical care, the frequency and timing of patient visits and data recording within the EHR may be highly variable. To account for this variation in frequency and timing of patient visits and documentation, and to ensure adequate data capture, a ±14-day window was applied to the index date, which allowed for extraction of relative data and identified as the baseline period.

Subgroup stratification

Patients were stratified into four mutually exclusive subgroups according to treatment received. The psychotherapy-only subgroup included patients who had a record of psychotherapy, based on specified procedural codes (online supplemental table 1), within 90 days following the index date, had ≥2 records of psychotherapy within a 30-day period and no documented evidence of receiving subsequent pharmacotherapy anytime within the period from index date up to 12 months following the index

date. The pharmacotherapy-only subgroup included patients who had a record of pharmacotherapy within 90 days following the index date, were prescribed ≥1 pharmacotherapeutic medication for ≥14 consecutive days, and had no documented evidence of receiving subsequent psychotherapy anytime within the period from index date up to 12 months following the index date. The psychotherapy and pharmacotherapy subgroup included patients who had a record of psychotherapy or pharmacotherapy within 90 days following the index date, concurrent treatment of pharmacotherapy and psychotherapy occurring less than 90 days apart, ≥2 records of psychotherapy within a 30-day period and were prescribed ≥1 pharmacotherapy for ≥14 consecutive days. The untreated subgroup included patients without any record of psychotherapy or pharmacotherapy anytime within the period from the index date up to 12 months after. Patients were excluded from the analysis if they had ≥1 record of psychotherapy but did not have ≥2 records of psychotherapy within a 30-day period or were prescribed ≥1 pharmacotherapy in the first 90 days but for <14 days or received psychotherapy and pharmacotherapy >90 days apart.

Study outcomes and data capture

Structured patient-level data for demographic features (eg, age), prescription medications and clinical variables (eg, Clinical Global Impression-Severity (CGI-S) score) at the time of first PTSD diagnosis captured in the NeuroBlu database (ie, at baseline including the ±14 days from index) were extracted from the EHR. The CGI-S is a clinician-rated scale which assesses global illness severity over time on a 7-point scale as follows: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=among the most extremely ill patients.[16] These scores were aggregated to form three categories used in this study; score of 1–3=normal to mildly ill, 4–5=moderately to markedly ill, and 6–7=severely to most ill.

Unstructured patient-level clinical data documented as free text during patient mental state examinations (MSE), including clinician-documented information on patient social history and clinical presentation, was extracted using natural language processing (NLP) models. The full details and validation of these NLP models have been previously published.[17] Briefly, pre-specified text strings were extracted from the free text of the clinician's note and mapped to identify clinical characteristics and social stressors.[17] A total of 27 different MSE categories with 241 binary labels (online supplemental table 2) were identified and used to determine the presence (defined as a '1') or absence (defined as a '0') of a label.[17] In this study, 11 of the MSE labels were considered PTSD-related symptom categories. Samples of text strings from clinical notes and their associated PTSD-related MSE labels are provided in online supplemental table 3). Additionally, 9 different social stressor categories representing the majority of environmental conditions present in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and 61 clinician-verified labels were extracted from the EHR (online supplemental table 4). These included personal, family, financial, occupational, environment, social, legal, housing and academic factors and were recorded as a positive or negative stressor based on whether they had a positive or negative impact on treatment, respectively. Psychiatric comorbidities within 6 months pre-baseline, at baseline (±14 days from index) and at 12 months post-baseline were recorded.

Data analysis

Descriptive statistics were generated for clinical and demographic features at the time of first PTSD diagnosis. Continuous variables were summarised using mean (SD) and/or median (IQR). Categorical variables were summarised by both count and frequency. Descriptive statistics were calculated for each baseline characteristic as well as the percentage of missing data. Hypothesis tests (ie, Kruskal-Wallis test, χ^2 test or Fisher's exact test) were used to evaluate between-subgroup differences in distribution. A significance level of 0.05 was used for all analyses. Statistical analyses were performed using Python 3.8.9 (Python Software Foundation, Wilmington, DE, USA).

Ethical considerations

This study was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments. A waiver of Health Insurance Portability and Accountability Act (HIPAA) authorisation was obtained prior to study conduct and covers data originating from all sites represented. Approval was granted by the WCG IRB (The Holmusk Real-World Evidence Parent Protocol; IRB registration number 1-1470336-1; Protocol ID HolmuskRWE_1.0).

Patient and public involvement

This non-interventional, retrospective cohort study analysed de-identified EHR of patients from the Holmusk NeuroBlu database in the USA. The patients included in this study were not actively engaged in the designing the study or subject to recruitment.

Findings

A total of 46,383 patients with a diagnosis of PTSD were identified in the NeuroBlu database; 37,449 patients had ≥2 PTSD diagnoses within 30 days between 2001 and 2020. Of these, 32,875 patients received care at clinical sites with both inpatient and outpatient units, 25,507 patients received psychotherapy and/or pharmacotherapy according to further prespecified criteria and 17,234 were adults ≥18 years old and included in this analysis (online supplemental figure 2).

Of the 17,234 included in this analysis, 42.5% (n=7319) received psychotherapy and pharmacotherapy, 27.7% (n=4776) received pharmacotherapy only, 15.1% (n=2599) were untreated and 14.7%

(n=2540) received psychotherapy only. Overall, most patients (84.9%; n=14,635) were treated and received psychotherapy, pharmacotherapy or both during the first year post-baseline.

Patient demographics and clinical characteristics

For the overall population, the mean age (SD) was 37.7 (12.4) years, the majority (73.4%) of patients were female and most patients were White (59.6%) and not Hispanic or Latino (56.1%; table 1). However, race was unknown in 22.7% of patients and ethnicity unknown in 33% of patients. In terms of treatment subgroups, the mean age (SD) was lowest in the psychotherapy-only treatment group (36 (12.4) years) and highest in the psychotherapy and pharmacotherapy group (38.3 (12) years). Each treatment group had a substantially higher proportion of females than males. The group treated with both pharmacotherapy and psychotherapy had the highest proportion of females (77.2%) while the untreated group had the lowest proportion of females (65%).

Most patients (88.4%) received their first PTSD diagnosis in an outpatient setting. Individuals treated with psychotherapy only had the highest proportion of diagnosis in an outpatient setting (95.3%), while the group treated with pharmacotherapy only had the lowest proportion (78.7%). The mean (SD) time between diagnosis and treatment was 9.8 (15.8) days for the overall population. The mean (SD) time between diagnosis and treatment was longest for the psychotherapy-only treatment group (15.6 (16.5) days) followed by psychotherapy and pharmacotherapy (8.9 (13.7) days) and pharmacotherapy only (8.3 (17.6) days). The majority of patients (68.1%) had a baseline CGI-S score of 4–5. Across all treatment subgroups, the baseline median CGI-S was 5. However, the pharmacotherapy-only subgroup had a higher proportion (20.7%) of patients, indicating severe disease at baseline compared with patients who were untreated (15.8%) or who received only psychotherapy (13.9%).

Family history of a psychiatric disorder was reported by 37.6% of patients at baseline. The most frequently reported psychiatric disorders in family history were substance abuse (24.2%), major depressive disorder (MDD, 16.4%), bipolar disorder (11.6%) and anxiety disorder (6.5%). Of patients with PTSD-related symptoms at baseline as identified from the MSE, 21.4% of patients reported emotional dysregulation and 16.9% of patients reported suicidal intent/ideation. 'Other symptoms', which included anxious/tense mood, anxious/fearful affect and agitated, tense, restless psychomotor symptoms, were reported by 49.1% of patients (table 2). Treatment subgroups varied in terms of clinical symptoms reported. In patients who only received pharmacotherapy, 'other symptoms' (59.6%), emotional dysregulation (29.5%), suicidal ideation (26.6%) and suicidal attempts (8.4%) were reported by a greater proportion compared with other treatment groups ('other symptoms', 39.2%–49.2%; emotional dysregulation, 12.4%–21%; suicidal ideation, 7.8%–13.7%; and suicidal attempts, 2.8%–5.1%). These proportions were also higher compared with the untreated patient subgroup ('other symptoms', 39.6%; emotional dysregulation, 16.8%; suicidal ideation, 16.9%; and suicidal attempts, 4.7%). PTSD-related clinical symptoms at baseline were recorded least frequently in the psychotherapy-only subgroup. Patients who reported symptoms of emotional dysregulation, suicidal intent or attempts or self-injury were more likely to be treated with pharmacotherapy, with or without psychotherapy.

Psychosocial stressors and comorbidities

Psychosocial stressors were frequently reported with 72.6% of patients having ≥1 recorded psychosocial stressor at baseline. Nine categories of psychosocial stressors were defined (table 3). The most frequently recorded negative psychosocial stressors included personal stressors (44%), family stressors (41.9%), financial stressors (28.6%), occupational stressors (27.4%) and environmental stressors (21.5%). Patients who received only pharmacotherapy reported higher negative psychosocial stressors; personal (46.8%), financial (33.6%), occupational (34.9%) and environmental (24.3%), compared with other subgroups (personal, 39.1%–45%; financial, 22.7%–29%; occupational, 21.2%–26.1% and environmental, 19.4%–22.3%). Positive factors were described as positive psychosocial stressors. Among these, family (18.9%) and personal (10.6%) were reported by the greatest proportion of patients. However, patients in the untreated subgroup had the lowest proportion of positive family stressors (14.3%) and positive personal stressors (7.7%) compared with other subgroups (family, 19.5%–20%; personal, 10%–11.7%).

During the 6-month period prior to baseline, 36.6% of patients had ≥1 psychiatric comorbidity, with substance use disorder (10.1%) the most frequently reported, followed by MDD (9.4%) and anxiety disorder (7.6%; table 4). The proportions of patients with substance use disorder, MDD and anxiety disorder were highest in the subgroup receiving psychotherapy with pharmacotherapy compared with other subgroups (substance use disorder, 12.9% vs 5.2%–10.8%; MDD, 12.8% vs 2.8%–10.4%; anxiety disorder, 10.7% vs 1.9%–7.7%).

More patients had ≥1 psychiatric comorbidity at baseline (98%) compared with the period 6 months prior to baseline (36.6%). The most frequently reported comorbidities at baseline were MDD (42.2%), substance use disorder (35%) and anxiety disorder (30.7%). The proportion of patients with MDD or substance use disorder was highest in the subgroup receiving pharmacotherapy only compared with other subgroups (MDD, 47.7% vs 33.7%–43.2%; substance use disorder, 38.4% vs 30.4%–35.2%). These observations remained fairly consistent at 12 months post-baseline, with 93.5% of patients having at ≥1 psychiatric comorbidity recorded, and MDD (42.3%), substance use disorder (36.2%) and anxiety disorder (30.2%) remained the most frequently

Table 1 Baseline demographics of patients with PTSD in the overall population and by treatment subgroup

	Overall (n=17,234)	Psychotherapy only (n=2540)	Pharmacotherapy only (n=4776)	Psychotherapy and pharmacotherapy (n=7319)	Untreated (n=2599)	P value*
Age at index date, years						<0.01
Mean (SD)	37.7 (12.4)	36 (12.4)	38 (12.7)	38.3 (12)	36.7 (12.9)	
Median (IQR)	36 (20)	34 (19)	37 (19)	38 (18)	34 (20)	
Gender, n (%)						<0.01
Female	12,641 (73.4)	1907 (75.1)	3397 (71.1)	5647 (77.2)	1690 (65)	
Male	4575 (26.6)	627 (24.7)	1373 (28.8)	1669 (22.8)	906 (34.9)	
Unknown	18 (0.1)	6 (0.2)	6 (0.1)	3 (<0.1)	3 (0.1)	
Race, n (%)						<0.01
White	10,271 (59.6)	1413 (55.6)	3207 (67.2)	4343 (59.3)	1308 (50.3)	
Black or African American	2356 (13.7)	257 (10.1)	730 (15.3)	979 (13.4)	390 (15)	
Other race†	701 (4.1)	80 (3.1)	245 (5.1)	215 (2.9)	161 (6.2)	
Unknown	3906 (22.7)	790 (31.1)	594 (12.4)	1782 (24.4)	740 (28.5)	
Ethnicity, n (%)						<0.01
Hispanic or Latino	1885 (10.9)	256 (10.1)	248 (5.2)	1147 (15.7)	234 (9)	
Not Hispanic or Latino	9666 (56.1)	1477 (58.2)	2335 (48.9)	4645 (63.5)	1209 (46.5)	
Unknown	5683 (33)	807 (31.8)	2193 (45.9)	1527 (20.9)	1156 (44.5)	
CGI-S at baseline (categories), n (%)						<0.01
1–3 (normal to mildly ill)	1834 (10.6)	261 (10.3)	419 (8.8)	852 (11.6)	302 (11.6)	
4–5 (moderately to markedly ill)	11,736 (68.1)	1879 (74)	3132 (65.6)	5121 (70)	1604 (61.7)	
6–7 (severely to most extremely ill)	2901 (16.8)	354 (13.9)	988 (20.7)	1149 (15.7)	410 (15.8)	
CGI-S recorded at baseline (yes)	16,471 (95.6)	2494 (98.2)	4539 (95)	7122 (97.3)	2316 (89.1)	
CGI-S recorded at baseline (no)	763 (4.4)	46 (1.8)	237 (5)	197 (2.7)	283 (10.9)	
CGI-S at baseline						<0.01
Mean (SD)	4.6 (1.1)	4.5 (1.1)	4.7 (1.1)	4.5 (1.1)	4.5 (1.2)	
Median (IQR)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)	
Clinical setting of first PTSD diagnosis, n (%)						<0.01
Outpatient	15,231 (88.4)	2230 (95.3)	3862 (78.7)	6652 (93.4)	2489 (87.5)	
Emergency room/inpatient	1895 (11)	106 (4.2)	1002 (21)	455 (6.2)	332 (12.8)	
Unknown	102 (0.6)	14 (0.6)	25 (0.5)	48 (0.7)	15 (0.6)	
Time between first diagnosis and first treatment, days						<0.01

Continued

Table 1 Continued

	Overall (n=17,234)	Psychotherapy only (n=2540)	Pharmacotherapy only (n=4776)	Psychotherapy and pharmacotherapy (n=7319)	Untreated (n=2599)	P value*
Mean (SD)	9.8 (15.8)	15.6 (16.5)	8.3 (17.6)	8.9 (13.7)	NA	
Median (IQR)	1 (14)	12 (16)	0 (6)	1 (14)	NA	
Most frequently recorded psychiatric disorder indicated in family history, n (%)						
Substance abuse	4163 (24.2)	500 (19.7)	1450 (30.4)	1753 (24)	460 (17.7)	<0.01
Major depressive disorder	2821 (16.4)	230 (9.1)	997 (20.9)	1336 (18.3)	258 (9.9)	<0.01
Bipolar disorder	2004 (11.6)	191 (7.5)	681 (14.3)	977 (13.4)	155 (6)	<0.01
Anxiety disorder	1112 (6.5)	77 (3)	396 (8.3)	530 (7.2)	109 (4.2)	<0.01
Schizophrenia	1024 (5.9)	89 (3.5)	321 (6.7)	518 (7.1)	96 (3.7)	<0.01
Family history of psychiatric disorder, n (%)						
Family history of psychiatric disorder (yes)	6478 (37.6)	698 (27.5)	2190 (45.9)	2915 (39.8)	675 (26)	NA
Family history of psychiatric disorder (no)	7542 (43.8)	1392 (54.8)	1484 (31.1)	3235 (44.2)	1431 (55.1)	NA
Family history of psychiatric disorder (unknown)	3088 (17.9)	443 (17.4)	1062 (22.2)	1099 (15)	484 (18.6)	NA
Family history of non-psychiatric disorder	126 (0.7)	7 (0.3)	40 (0.8)	70 (1)	9 (0.4)	<0.01

*For age: Kruskal-Wallis test was performed; for gender, race, ethnicity, family history and clinical setting: χ^2 test was performed when all subgroups had ≥5 counts, whereas Fisher's exact test was performed when any subgroup had <5 counts.
†Other race includes: Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander and all other uncategorised race.
CGI-S, Clinical Global Impression-Severity; NA, not available; PTSD, post-traumatic stress disorder.

Table 2 Baseline clinical characteristics of patients in the overall population and by treatment subgroup

	Overall (n=17,234)	Psychotherapy only (n=2540)	Pharmacotherapy only (n=4776)	Psychotherapy and pharmacotherapy (n=7319)	Untreated (n=2599)	P value*
PTSD-related symptoms at baseline, n (%)						
Other symptoms	8468 (49.1)	996 (39.2)	2846 (59.6)	3597 (49.2)	1029 (39.6)	<0.01
Mood—anxious/tense	6732 (39.1)	809 (31.9)	2275 (47.6)	2854 (39)	794 (30.6)	<0.01
Affect—anxious/fearful	3615 (21)	474 (18.7)	1063 (22.3)	1672 (22.8)	406 (15.6)	<0.01
Psychomotor—agitated, tense, restless	2452 (14.2)	207 (8.2)	801 (16.8)	1156 (15.8)	288 (11.1)	<0.01
Memory—issues/impaired	1260 (7.3)	7 (0.3)	919 (19.2)	156 (2.1)	178 (6.9)	<0.01
Impulse control—limited/some issues	99 (0.6)	17 (0.7)	14 (0.3)	51 (0.7)	17 (0.7)	0.03
Impulse control—poor/serious issues	91 (0.5)	12 (0.5)	11 (0.2)	48 (0.7)	20 (0.8)	<0.01
Affect—reactive	60 (0.4)	3 (0.1)	33 (0.7)	23 (0.3)	1 (<0.1)	<0.01
Sleep—maintenance issues (can't stay asleep)	47 (0.3)	7 (0.4)	21 (0.4)	13 (0.2)	6 (0.2)	0.06
Sleep—onset issues (unable to fall asleep)	39 (0.2)	8 (0.3)	14 (0.3)	11 (0.2)	6 (0.2)	0.30
Violent thoughts—violent/aggressive behaviour	18 (0.1)	0 (0)	12 (0.3)	3 (<0.1)	3 (0.1)	<0.01
Sleep—hypersomnia	5 (<0.1)	2 (0.1)	2 (<0.1)	1 (<0.1)	0 (0)	0.23
Emotional dysregulation	3694 (21.4)	314 (12.4)	1408 (29.5)	1536 (21)	436 (16.8)	<0.01
Mood—irritable, angry	2274 (13.2)	176 (6.9)	847 (17.7)	956 (13.1)	295 (11.4)	<0.01
Affect—labile	1098 (6.4)	75 (3)	548 (11.5)	358 (4.9)	117 (4.5)	<0.01
Affect—irritable/angry	928 (5.4)	76 (3)	384 (8)	344 (4.7)	124 (4.8)	<0.01
Affect—intense	371 (2.2)	39 (1.5)	89 (1.9)	205 (2.8)	38 (1.5)	<0.01
Affect—aggressive	366 (2.1)	11 (0.4)	182 (3.8)	132 (1.8)	41 (1.6)	<0.01
Mood—labile	327 (1.9)	21 (0.8)	120 (2.5)	163 (2.2)	23 (0.9)	<0.01
Suicidal intent/ideation	2909 (16.9)	198 (7.8)	1271 (26.6)	1001 (13.7)	439 (16.9)	<0.01
Suicidality—suicidal ideation	2732 (15.9)	187 (7.4)	1193 (25)	955 (13.1)	397 (15.3)	<0.01
Suicidality—suicidal with plan	502 (2.9)	14 (0.6)	293 (6.1)	107 (1.5)	88 (3.4)	<0.01
Suicidality—suicidal with intent	306 (1.8)	8 (0.3)	175 (3.7)	65 (0.9)	58 (2.2)	<0.01

Continued

Table 2 Continued

	Overall (n=17,234)	Psychotherapy only (n=2540)	Pharmacotherapy only (n=4776)	Psychotherapy and pharmacotherapy (n=7319)	Untreated (n=2599)	P value*
Suicidality—suicidal ideation with means	100 (0.6)	8 (0.3)	54 (1.1)	22 (0.3)	16 (0.6)	<0.01
Mood—suicidal	32 (0.2)	1 (<0.1)	20 (0.4)	4 (0.1)	7 (0.3)	<0.01
Suicidality—history of ideation	29 (0.2)	3 (0.1)	6 (0.1)	14 (0.2)	6 (0.2)	0.65
Suicidal attempt	968 (5.6)	71 (2.8)	399 (8.4)	375 (5.1)	123 (4.7)	<0.01
Suicidality—history of attempt	844 (4.9)	71 (2.8)	316 (6.6)	344 (4.7)	113 (4.4)	<0.01
Suicidality—suicide attempt	135 (0.8)	0 (0)	88 (1.8)	37 (0.5)	10 (0.4)	<0.01
Self-injury	157 (0.9)	5 (0.2)	71 (1.5)	56 (0.8)	25 (1)	<0.01
Suicidality—self-injurious	157 (0.9)	5 (0.2)	71 (1.5)	56 (0.8)	25 (1)	<0.01
PTSD-related symptoms at baseline (yes)	10,299 (59.8)	1188 (46.8)	3414 (71.5)	4369 (59.7)	1328 (51.1)	NA
PTSD-related symptoms at baseline (no)	5277 (30.6)	1019 (40.1)	1023 (21.4)	2459 (33.6)	776 (29.9)	NA
No MSE data recorded at baseline	1658 (9.6)	333 (13.1)	339 (7.1)	491 (6.7)	495 (19.1)	NA

*For PTSD-related symptoms, the χ^2 test was performed when all subgroups had ≥5 counts, whereas the Fisher's exact test was performed when any subgroup had <5 counts.
MSE, Mental Status Examination; NA, not available; PTSD, post-traumatic stress disorder.

documented among all patients, irrespective of treatment subgroup.

Substance use disorder involving alcohol or cannabis was the most frequently reported comorbidity in the overall population at all time points. The proportion of patients reporting use of these substances increased substantially from the 6-month period prior to baseline (alcohol (4.9%); cannabis (2.4%); figure 1A) to baseline (alcohol (16.6%); cannabis (9.7%); figure 1B) and continued to demonstrate a slight increase from baseline to the 12-month period following baseline (alcohol (17.1%); cannabis (10.3%); figure 1C). Substance use disorder involving the use of opioids was highest for patients who received pharmacotherapy only compared with other subgroups.

Baseline pharmacotherapeutics

At baseline, among patients who received pharmacotherapy, 69.4% were prescribed ≥1 medication within the following classes: antidepressant, second-generation antipsychotic, anxiolytic, mood stabiliser, anticonvulsant, analgesic, sedative-hypnotic drug, substance abuse drug, stimulant, lithium, first-generation antipsychotic or other relevant drug (clonidine, dexamethasone and guanfacine; online supplemental table 5). Antidepressants (51.8%), second-generation antipsychotics (29.9%) and anxiolytics (23.3%) were the most prescribed medication classes at baseline (figure 2).

Prescriptions of psychotropic medications at baseline were common. Trazodone, clonazepam, quetiapine and sertraline were prescribed to the greatest proportion of patients in both the overall population and in both treatment subgroups. However, the proportion of patients prescribed these medications was consistently higher in patients who received pharmacotherapy only compared with those who received psychotherapy with pharmacotherapy.

DISCUSSION

This non-interventional, retrospective cohort study analysed real-world de-identified EHR data to assess the demographic and clinical characteristics of a large cohort of patients with PTSD in the USA stratified by treatment in order to gain real-world insights into the disorder.

In this study, the mean age of patients at diagnosis was 37.7 years and was similar across treatment groups. These findings align with results from another recent real-world evidence study in individuals with PTSD, reporting mean

Table 3 Psychosocial stressors in adult patients at baseline by treatment subgroups

Psychosocial stressors, n (%)	Overall (n=17,234)	Psychotherapy only (n=2540)	Pharmacotherapy only (n=4776)	Psychotherapy and pharmacotherapy (n=7319)	Untreated (n=2599)	P value*
Negative psychosocial stressors						
Personal†	7585 (44)	1144 (45)	2233 (46.8)	3193 (43.6)	1015 (39.1)	<0.01
Family‡	7215 (41.9)	1110 (43.7)	1979 (41.4)	3223 (44)	903 (34.7)	<0.01
Financial§	4929 (28.6)	617 (24.3)	1603 (33.6)	2120 (29)	589 (22.7)	<0.01
Occupational¶	4711 (27.4)	538 (21.2)	1668 (34.9)	1912 (26.1)	593 (22.8)	<0.01
Environment**	3708 (21.5)	566 (22.3)	1160 (24.3)	1479 (20.2)	503 (19.4)	<0.01
Social factors††	3618 (21)	482 (19)	1075 (22.5)	1635 (22.3)	426 (16.4)	<0.01
Legal factors‡‡	2583 (15)	404 (15.9)	658 (13.8)	1131 (15.5)	390 (15)	0.04
Housing factors§§	1891 (11)	235 (9.3)	614 (12.9)	746 (10.2)	296 (11.4)	<0.01
Academic factors¶¶	477 (2.8)	58 (2.3)	173 (3.6)	197 (2.7)	49 (1.9)	<0.01
Positive psychosocial stressors						
Personal***	1826 (10.6)	292 (11.5)	479 (10)	854 (11.7)	201 (7.7)	<0.01
Family†††	3254 (18.9)	508 (20)	948 (19.9)	1427 (19.5)	371 (14.3)	<0.01
Financial‡‡‡	14 (0.1)	3 (0.1)	3 (0.1)	6 (0.1)	2 (0.1)	0.85
Occupational§§§	366 (2.1)	68 (2.7)	109 (2.3)	160 (2.2)	29 (1.1)	<0.01
Environment¶¶¶	517 (3)	80 (3.2)	168 (3.5)	221 (3)	48 (1.9)	<0.01
Social factors****	583 (3.4)	102 (4)	131 (2.7)	273 (3.7)	77 (3)	<0.01
Academic factors††††	52 (0.3)	2 (0.1)	21 (0.4)	23 (0.3)	6 (0.2)	0.04
Social stressors at baseline, n (%)						
Social stressors at baseline (yes)	12,517 (72.6)	1854 (73)	3559 (74.5)	5447 (74.4)	1657 (63.8)	NA
Social stressors at baseline (no)	4717 (27.4)	686 (27)	1217 (25.5)	1872 (25.6)	942 (36.2)	NA

*χ^2 test was performed when all subgroups had ≥5 counts, whereas Fisher's exact test was performed when any subgroup had <5 counts.
†Victim of crime, physical abuse, sexual abuse, emotional abuse, relationship distress with spouse or intimate partner, major life events, involuntary treatment and target of adverse discrimination.
‡Disruption of family by separation or divorce, isolated family including lack of family support, substance abuse in family, bereavement, problems in parent–child relationships and in-laws, anxiety about sick person in family or dependent relative needing care at home, parenting situation, sibling relational problem, inadequate or distorted communication within family and legal problem in the family.
§Extreme poverty/low income, inadequate health/social insurance or welfare support, poor money management/no savings and problems related to loan/creditors.
¶Unemployment, occupational stress, fired, threat of job loss or underperformance at work, unstable job, job dissatisfaction and change of job.
**Problem related to living alone, exposure to disaster war or other hostilities, abusive environment at home, chaotic atmosphere/stressful home environment, inadequate care, migration/acculturation difficulty and cultural conflicts/issues.
††Lack of social circles, inadequate social support and conflictual social relationships.
‡‡Arrest or imprisonment and other incarceration, problems with legal personnels, offence/charges, child custody or support proceedings, litigation/legal proceedings and restraining order.
§§Homelessness, inadequate housing, isolated dwelling/lack of transportation, unstable housing arrangement and discord with neighbour.
¶¶Underachievement in school, suspension/expulsion, discord with teachers and classmates, and illiteracy/low-level literacy.
***Sense of meaning and support from belief.
†††Supportive family, love and respect in the family.
‡‡‡Financial stability.
§§§Job satisfaction.
¶¶¶Stable living situation.
****Supportive friends.
††††Good achievement in school.
NA, not available.

age of 38.4 years.[11] There was also a high proportion of female patients (73.4%) compared with males observed in the current study, consistent with other published findings indicating higher rates of PTSD in females compared with males.[2 18] While proportions of females to males were similar across treatment groups, the untreated group had the lowest proportion of female patients (65%). These results are also reflective of the DSM-5 Text Revision (DSM-5-TR), which indicates higher prevalence in females compared with males.[1]

More than half (59.6%) of the patients identified in this study were White. This contrasts with results from other studies, as well as the DSM-5-TR, which states higher prevalence of PTSD has been reported in African Americans compared with non-Latino Whites.[1 19] It is important to note, however, that over 20% of patients in this study had unknown race data. Additionally, nearly half (49.1%) of the entire NeuroBlu database population was White,[15] which may influence the results demonstrated here and may not be representative of the broader population. In the dataset

Table 4 Psychiatric comorbidities occurring in ≥10% of patients at baseline at specified time period and by treatment subgroups

Comorbidities, n (%)	Overall (n=17,234)	Psychotherapy only (n=2540)	Pharmacotherapy only (n=4776)	Psychotherapy+pharmacotherapy (n=7319)	Untreated (n=2599)	P value*
Six months prior to baseline						
Major depressive disorder	1621 (9.4)	112 (4.4)	496 (10.4)	940 (12.8)	73 (2.8)	<0.01
Substance use disorder	1745 (10.1)	153 (6)	514 (10.8)	942 (12.9)	136 (5.2)	<0.01
Anxiety disorder	1307 (7.6)	105 (4.1)	369 (7.7)	783 (10.7)	50 (1.9)	<0.01
Other mood disorder	1156 (6.7)	84 (3.3)	352 (7.4)	658 (9)	62 (2.4)	<0.01
Other bipolar disorder	687 (4)	32 (1.3)	222 (4.7)	415 (5.7)	18 (0.7)	<0.01
Bipolar I disorder	630 (3.7)	27 (1.1)	191 (4)	395 (5.4)	17 (0.7)	<0.01
Borderline personality disorder	384 (2.2)	23 (0.9)	112 (2.4)	239 (3.3)	10 (0.4)	<0.01
Comorbidities 6 months prior to baseline (yes)	6302 (36.6)	887 (34.9)	1607 (33.6)	3293 (45)	515 (19.8)	NA
Comorbidities 6 months prior to baseline (no)	10,932 (63.4)	1653 (65.1)	3169 (66.4)	4026 (55)	2084 (80.2)	NA
Baseline						
Major depressive disorder	7277 (42.2)	857 (33.7)	2276 (47.7)	3160 (43.2)	984 (37.9)	<0.01
Substance use disorder	6029 (35)	772 (30.4)	1835 (38.4)	2573 (35.2)	849 (32.7)	<0.01
Anxiety disorder	5284 (30.7)	656 (25.8)	1573 (32.9)	2451 (33.5)	604 (23.2)	<0.01
Other mood disorder	3844 (22.3)	440 (17.3)	1190 (24.9)	1695 (23.2)	519 (20)	<0.01
Other bipolar disorder	2506 (14.5)	233 (9.2)	811 (17)	1221 (16.7)	241 (9.3)	<0.01
Bipolar I disorder	2312 (13.4)	163 (6.4)	784 (16.4)	1151 (15.7)	214 (8.2)	<0.01
Borderline personality disorder	1806 (10.5)	173 (6.8)	588 (12.3)	877 (12)	168 (6.5)	<0.01
Comorbidities at baseline (yes)	16,886 (98)	2458 (96.8)	4713 (98.7)	7256 (99.1)	2459 (94.6)	NA

Continued

Table 4 Continued

Comorbidities, n (%)	Overall (n=17,234)	Psychotherapy only (n=2540)	Pharmacotherapy only (n=4776)	Psychotherapy+pharmacotherapy (n=7319)	Untreated (n=2599)	P value*
Comorbidities at baseline (no)	348 (2)	82 (3.2)	63 (1.3)	63 (0.9)	140 (5.4)	NA
12 months after baseline						
Major depressive disorder	7286 (42.3)	878 (34.6)	2252 (47.2)	3443 (47)	713 (27.4)	<0.01
Substance use disorder	6246 (36.2)	793 (31.2)	1877 (39.3)	2923 (39.9)	653 (25.1)	<0.01
Anxiety disorder	5205 (30.2)	632 (24.9)	1560 (32.7)	2566 (35.1)	447 (17.2)	<0.01
Other mood disorder	3636 (21.1)	443 (17.4)	1068 (22.4)	1746 (23.9)	379 (14.6)	<0.01
Other bipolar disorder	2749 (16)	248 (9.8)	829 (17.4)	1484 (20.3)	188 (7.2)	<0.01
Bipolar I disorder	2323 (13.5)	165 (6.5)	784 (16.4)	1231 (16.8)	143 (5.5)	<0.01
Borderline personality disorder	2146 (12.5)	203 (8)	692 (14.5)	1118 (15.3)	133 (5.1)	<0.01
Comorbidities 12 months after baseline (yes)	16,116 (93.5)	2392 (94.2)	4613 (96.6)	7264 (99.2)	1847 (71.1)	NA
Comorbidities 12 months after baseline (no)	1118 (6.5)	148 (5.8)	163 (3.4)	55 (0.8)	752 (28.9)	NA

*χ^2 test was performed on all subgroups presented.
NA, not available.

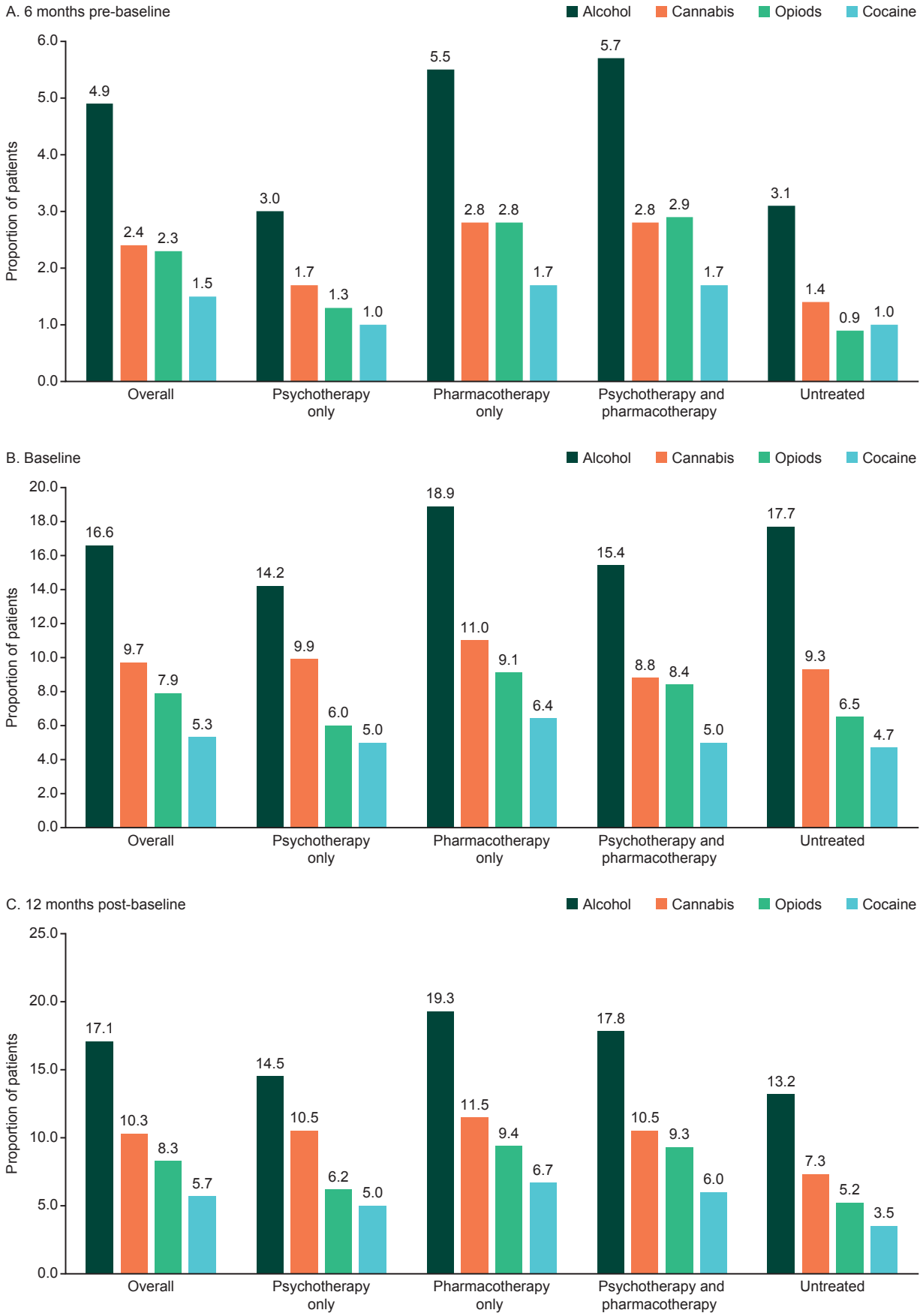

Figure 1 Proportion of patients reporting use of common substances at (A) 6 months prior to baseline, (B) baseline and (C) 12 months after baseline in patients with post-traumatic stress disorder in the overall population and treatment subgroups p value <0.01 for all; χ^2 test was performed on all subgroups presented.

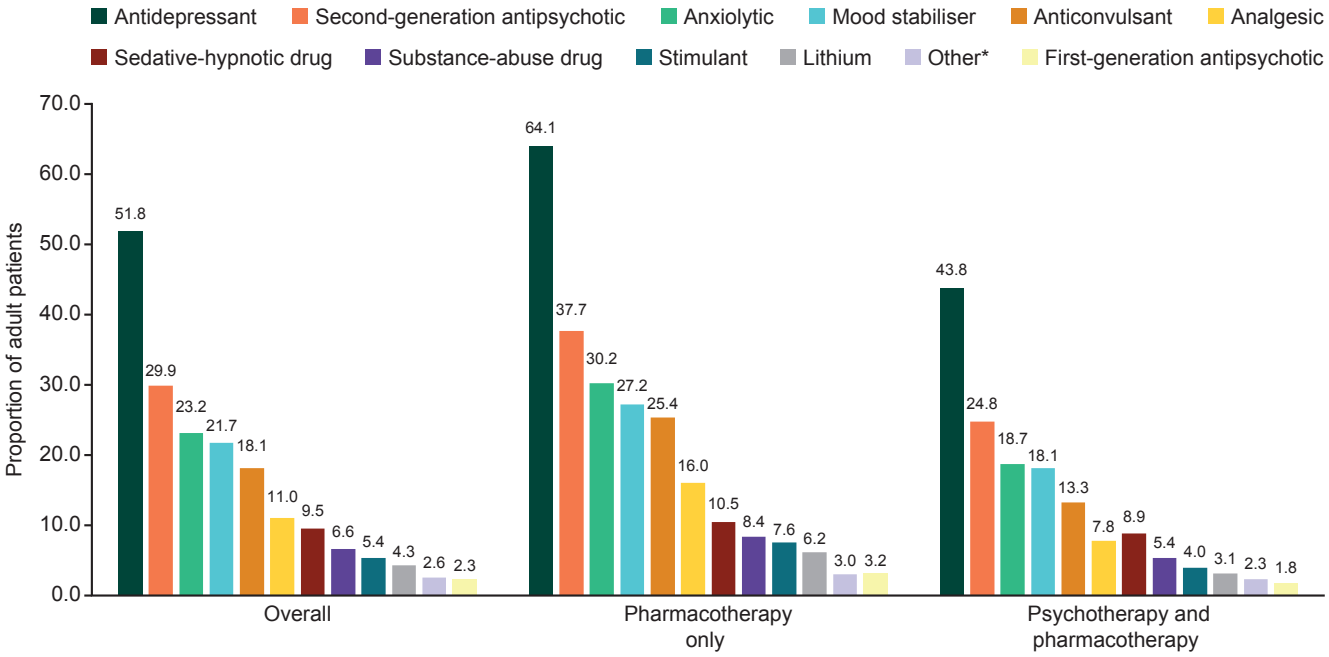

Figure 2 Most common medication class prescribed at baseline in patients with post-traumatic stress disorder for the overall adult population, pharmacotherapy only, and psychotherapy and pharmacotherapy treatment subgroups. P value <0.01 for all except p=0.02 for Other; χ^2 tests were performed on all subgroups presented. *Other includes clonidine, dexamethasone and guanfacine.

analysed, PTSD was found to be diagnosed most often in an outpatient setting. However, the NeuroBlu database includes more outpatient facilities compared with inpatient or hospital facilities,[15] and therefore these findings may not be generalisable to a wider patient population. The time between diagnosis and treatment was longest for patients who only received psychotherapy, compared with other treatment subgroups, which may reflect a difficulty in accessing psychotherapy due to a shortage of psychotherapists. Alternatively, this finding may indicate that patients who received psychotherapy had less severe disease and may not have required immediate treatment. Other factors such as scheduling difficulties or insurance pre-authorisation may also have contributed to the longer time from diagnosis to treatment in this group. Across all treatment subgroups, the majority of patients had a baseline CGI-S score of 4–5 indicating moderate to marked illness presentation, suggesting their illness was significantly impairing their functioning at the time of diagnosis.[16] Furthermore, the pharmacotherapy-only subgroup had the highest proportion of patients present with severe disease at baseline, which may suggest that prescribers start pharmacotherapy earlier for patients with more severe disease compared with patients with more mild presentation.

More than one third (37.6%) of patients identified in this study indicated a family history of psychiatric disorder. This finding supports results from a previous systematic literature review that suggested an association between individuals with a family history of psychopathology and higher rates of PTSD or more PTSD symptoms compared with individuals without a family history.[20] Symptoms of emotional dysregulation, or more serious symptoms such as suicidal intent/attempt or self-injury, were more commonly seen in the pharmacotherapy-only subgroup compared with the psychotherapy alone or untreated subgroups. Considering the methodology and data capture used in this study, it remains unclear if pharmacotherapy was specifically prescribed for patients with suicidal symptoms. Personal psychosocial stressors and family psychosocial stressors were both the most common positive and negative psychosocial stressors across all treatment groups. Importantly though, a greater proportion of patients indicated these as negative psychosocial stressors compared with positive psychosocial stressors. Improved understanding of psychosocial stressors may offer useful insight for patient screening purposes, especially as some studies in US veterans have suggested greater social support may be predictive of decreased PTSD severity.[21]

The presence of psychiatric comorbidities was common at all time points, with 98% of patients in this study having ≥1 psychiatric comorbidity recorded at baseline. Numerous other studies have also demonstrated the co-presence or association of other pre-existing psychiatric disorders in individuals with PTSD.[4 6 19 20 22] The specific psychiatric comorbidities seen in this study were largely expected and in line with previous findings.[4 6 19 20 22] Substance use disorder was the second most common psychiatric comorbidity reported, with 35% of patients reporting this disorder at baseline. This proportion was higher than observed in another study which reported substance use disorder occurring in 14.1% of individuals with PTSD.[22] It is possible the timing of data collection

could have been a factor causing this discrepancy, as only 10.1% of patients in this study had substance use disorder recorded in the 6 months prior to baseline, which is more aligned with the finding from the prior study of 14.1%.[22]

The most common medication classes prescribed were antidepressants, second-generation antipsychotics and anxiolytics. Despite the availability of two FDA-approved medications for PTSD in adults (sertraline and paroxetine),[9 10] and current evidence supporting the use of sertraline, paroxetine and venlafaxine,[23] prescriptions for these were less frequent than for other medications (trazodone, clonazepam and quetiapine) at baseline. However, when considering the prescribing trends described in this study, it is important to remember the dataset analysed did not provide information on the indication for which a medication was prescribed. The difficulty in understanding if prescription medications are specific to a PTSD diagnosis or due to the co-presence of other psychiatric comorbidities has been reported previously.[19] Furthermore, longitudinal analysis of treatment, including prescribing patterns, is beyond the scope of this analysis and will be reported separately.

While these data provide additional insights into the characteristics of patients with PTSD, there are strengths and limitations associated with this retrospective observational study. The data analysed in this study included a large cohort of patients (n=17,234). The database from which the data was extracted covered a broad geographical area across the USA. As such, the data analysed may be considered representative of patients receiving mental healthcare in a real-world setting in the USA. However, the current dataset only includes clinician-recorded EHR and no patient-reported outcomes.[15] Also, while stratification into the psychotherapy treatment group was based on a record of psychotherapy in the EHR, the precise modality of psychotherapy received by patients was not captured. Therefore, when interpreting the results, it cannot be assumed that the psychotherapy provided to patients included one of the APA-recommended modalities (eg, cognitive processing therapy or prolonged exposure therapy);[7] patients who received less efficacious therapies for PTSD were likely included in this subgroup. Furthermore, while patients were stratified by treatment regimen, cohorts were not matched based on demographics and other baseline characteristics. As such, any differences between the cohorts in these characteristics may have impacted study outcomes. Additionally, EHR data recorded in a real-world setting may not be recorded as consistently as data collected during a clinical trial. Furthermore, data extraction via the use of the NLP models has inherent limitations because it is not possible to capture all clinical notes written in free text by the provider.[17] Additionally, while this dataset provides insight into medications prescribed and treatment from providers in the NeuroBlu MindLinc EHR, insights on medications prescribed and treatments by providers outside the database were not captured.[15] These limitations should be considered while interpreting the findings of this study.

CONCLUSION

This retrospective, observational study of real-world data from the NeuroBlu health database of patients with PTSD confirmed previous understanding of PTSD demographics and clinical characteristics. The majority of patients were female, with a high prevalence of psychiatric comorbidities, including MDD and substance use disorder. Overall, the pharmacotherapy-only subgroup had the highest proportion of patients indicating severe illness at baseline based on the CGI-S, higher rates of suicidal ideation and suicidal attempts, and higher rates of negative psychosocial stressors and comorbidities compared with other treatment subgroups. These findings will enhance understanding of the clinical characteristics of patients with PTSD and may support patient-specific treatment planning and inform health-economic decision models in PTSD. The design of future clinical trials may be informed by the high frequency of comorbidities among patients with PTSD and the potential risk factors that may indicate patients likely to experience more severe disease and the challenges of treating this subgroup of patients.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Ethics approval This study was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments. A waiver of Health Insurance Portability and Accountability Act authorisation was obtained prior to study conduct and covers data originating from all sites represented. This study

involves human participants, but the NeuroBlu platform has received a waiver of authorisation for analysis of deidentified healthcare data from the Western-Copernicus Group (WCG) Institutional Review Board. Approval was granted by the WCG IRB (The Holmusk Real-World Evidence Parent Protocol; IRB registration number 1-1470336-1; Protocol ID HolmuskRWE_1.0).

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