Psychiatric Quarterly (2019) 90:431–445
https://doi.org/10.1007/s11126-019-09638-z

ORIGINAL PAPER

Enhancing Completion of Cognitive Processing Therapy for Posttraumatic Stress Disorder with Quetiapine in Veterans with Mild Traumatic Brain Injury: a Case Series

Muhammad R. Baig[1,2,3] · Jennifer L. Wilson[1,2] · Jennifer A. Lemmer[1,2] · Robert D. Beck[1,2] · Alan L. Peterson[1,3,4] · John D. Roache[3,5]

Published online: 4 May 2019

Abstract
To evaluate the outcomes of the antiarousal medications valproate, risperidone, and quetiapine on completion of treatment of cognitive processing therapy (CPT) for PTSD. A case series of fifty treatment-seeking adult (≥18 years) veterans with mild traumatic brain injury and combat-related PTSD who had unsuccessful trials of 2 or more first-line agents and previously declined treatment with trauma-focused therapy, seen at the psychiatric outpatient services of the local Polytrauma Rehabilitation Center from January 1, 2014, through December 31, 2017. Patients were prescribed valproate ($n = 8$), risperidone ($n = 17$), or quetiapine ($n = 25$) and were referred for individual weekly treatment with CPT. Outcome measurements of interest were measures of engagement and completion rate of CPT, PTSD Checklist total score (range, 0–80; higher scores indicate greater PTSD severity) and arousal subscale score (range, 0–24; higher scores indicate greater arousal severity), and clinical observations of sleep variables. Of the 50 patients included in the study, 48 (96%) were men; mean (SD) age was 36 (8) years. Eighteen (86%) patients initially receiving quetiapine and none taking valproate or risperidone became adequately engaged in and completed CPT. Among patients who completed CPT, the mean decrease in the PTSD Checklist score was 25 [95% CI, 30 to 20] and 9 (50%) patients no longer met criteria for PTSD. These preliminary findings support quetiapine as an adjunctive medication to facilitate CPT. A pragmatic trial is needed to evaluate the efficacy, safety, and feasibility of quetiapine to improve engagement in and completion rate of CPT.

Keywords Psychopharmacology · Evidence-based psychotherapy: Posttraumatic stress disorder · Mild traumatic brain injury

✉ Muhammad R. Baig
muhammad.baig@va.gov

Extended author information available on the last page of the article

Introduction

Mild traumatic brain injury (mTBI) is considered a signature wound among post-9/11veterans. [1] Most veterans have a concurrent diagnosis of posttraumatic stress disorder (PTSD) that results in diagnostic challenges given the overlap of symptoms with mTBI. [2–4] Unremitted PTSD interferes with rehabilitation outcomes [5, 6] and leads to persistent post-concussive symptoms and impaired functioning. [1, 7, 8]

Sertraline and paroxetine, both selective serotonin-reuptake inhibitors (SSRIs), are the only 2 medications approved by the US Food and Drug Administration for the treatment of PTSD. [9] The Department of Veterans Affairs (VA) and the Department of Defense clinical practice guidelines recommend SSRIs as a first-line treatment [10]. However, the limited effectiveness of SSRIs is evident in an Institute of Medicine review [11], which concluded that SSRI's efficacy is particularly limited for patients with PTSD due to military combat exposure. Limited SSRI efficacy results in multiple problems for veterans and the VA system by: (1) leading to the use of multiple medication polypharmacy practices that add the burden of adverse effects for veterans, (2) adding cost to the VA system even though still failing to achieve remission, and (3) exacerbating postconcussive mTBI symptoms, which make rehabilitation and recovery difficult. [12, 13] Thus, there is a need for the development of more effective medication approaches and the use of pragmatic trials to evaluate these approaches as conducted within the general VA population.

Trauma-focused therapies (i.e., cognitive processing therapy [CPT] and prolonged exposure therapy) have the most robust evidence bases for PTSD treatment and have gained wide acceptance as a standard of care in VA and Department of Defense practice settings. [14–16] Average dropout rates reported from trauma-focused therapies range from 20% to 44% and discomfort due to hyperarousal is the commonly reported cause of dropout. [17–23] A study of standard care in the South Texas Veterans Health Care System PTSD clinic [17] showed significant reduction in PTSD checklist scores with CPT for treatment completers, but dropout rates were high (32%–44%). Comparisons of treatment completers with dropouts in intent-to-treat samples consistently show superior outcomes when patients engage in and complete trauma-focused therapy. This suggests that failure to engage in and complete treatment is one factor preventing optimal outcomes of therapy [22, 24]. However, many patients express fear or concern regarding the potential of trauma-focused therapy to evoke arousal, which then prevents them from engaging in treatment. [25] Cognitive processing and fear extinction through deliberate, systematic confrontation with trauma-related feared beliefs, emotions, and stimuli during trauma-focused therapy are associated with substantial hyperarousal, which is associated with avoidance behavior leading to dropout from treatment and related disability. [17, 21–23, 26, 27] Therefore, trauma-focused therapy has a large effect size for patients adherent to therapy; however, there is room for improvement in the metrics of patient engagement, retention in treatment, and achievement of greater overall remission rates.

One possible approach, considered recently for the design of clinical trials focused on PTSD treatment, is to identify target systems involved in cognitive processing and fear extinction and explore medications that enhance the targeted approach of trauma-focused therapies. [28–35] A recent pilot trial of intranasal oxytocin compared with placebo showed lower PTSD symptoms and higher working alliance scores when combined with prolonged exposure therapy. [36] Emotional processing theory posits that fear activation is an essential component of successful PTSD treatment, and the extent of emotional reactions during trauma-focused therapy has been associated with the magnitude of clinical improvement.

[37] However, it is not clear whether physiologic arousal per se is a necessary component of fear extinction learning or is just a secondary consequence of the more critical component of extinction involving fear-related stimuli under the safe conditions of therapy. Indeed, biologic-based learning models posit that cue-induced amygdala activation is inhibited by the medial prefrontal cortex through learning expectancy violation rather than from habituation of physiologic arousal per se. [38] Therefore, we hypothesized that an antiarousal medication that reduces the physiologic arousal or distress associated with trauma-focused therapy treatment could reduce therapy-related avoidance behavior, thereby facilitating greater patient engagement, symptom reduction, and overall remission rates.

Previous work suggested that psychosedation of arousal with benzodiazepines may be counter-therapeutic because alprazolam impaired fear extinction learning during virtual reality-based exposure therapy. [39–41] However, countertherapeutic effects of benzodiazepines could be due to γ-aminobutyric acid (GABA)-mediated impairment of the fear-extinction learning that must occur with trauma-focused therapies. [41] In studies of psychopharmacologic treatment of PTSD, adjunctive use of risperidone [42] and valproate [43] did not show superior effects on lessening of PTSD symptoms compared with placebo. In contrast, a small, placebo-controlled trial of quetiapine reported reduced arousal and reexperiencing of PTSD symptoms in veterans [44], although few patients achieved remission. These data suggest that risperidone, valproate, and quetiapine may have limited value as the mainstay treatment, but their possible efficacy to facilitate trauma-focused therapy is less clear. This case series addresses this gap in the literature by examining the synergistic effects of antiarousal medications valproate, risperidone, and quetiapine to facilitate the benefits of a trauma-focused therapy.

Methods

Setting

Polytrauma Rehabilitation Center is housed within an urban Veterans Health Care System. The center provides a continuum of care for patients with TBI and other polytraumatic injuries, including the postacute phase of specialized rehabilitation services for those who have experienced an mTBI. The TBI clinic within the rehabilitation center has implemented a collaborative care model that includes a neuropsychiatrist to provide medication and clinical psychologists to provide trauma-focused therapy to the patients with PTSD, which is the most common psychiatric diagnosis (90%) within the clinic. Cognitive processing therapy (CPT) [45] is the trauma-focused therapy used for the treatment of PTSD in the TBI clinic as the standard of care.

The study was approved by the Institutional Review Board of the local academic institution, which serves as the institutional review board of record for the affiliated Veterans Health Care System.

Procedures

One of us has served as the assigned neuropsychiatrist within the TBI clinic since 2012. The present study was conducted from January 1, 2014, through December 31, 2017. He therefore had the opportunity to systematically evaluate the use of several antiarousal medications in patients with PTSD ($N = 73$) who were resistant to engage in CPT for PTSD as recommended

by the psychologist due to fear of hyperarousal. During neuropsychiatric evaluation, the most of these patients reported distressing hyperarousal symptoms as the primary reason for refusal to engage in CPT. Many patients agreed to reconsider CPT if arousal symptoms were stabilized by medication. Following the local VA treatment guidelines, antipsychotic medication can be used off-label only after at least 2 or 3 failed trials of SSRIs and serotonin-norepinephrine reuptake inhibitors. All of these patients also had failed several trials of standard psychopharmacologic treatment. Patients who had been taking other standard-of-care psychotropic medications had their medications tapered off as per clinical guidelines. We began by using valproate ($n = 15$), which did not improve engagement in CPT, and the sedating effect of the medication caused significant daytime fatigue, sleepiness, and cognitive slowing. We next tried risperidone ($n = 30$), which probably caused severe daytime sedation due to its long duration of action, and did not show any benefit to increase engagement of patients in CPT. Then, a small trial of quetiapine monotherapy in veterans showed reduced arousal and reexperiencing of PTSD symptoms [44], so we began using quetiapine ($n = 25$). Quetiapine monotherapy improved sleep measures and increased the willingness of veterans to engage in and complete CPT. After the benefits noted with quetiapine for CPT, we also tried quetiapine for patients ($n = 3$) referred for prolonged exposure therapy. After stabilization of arousal symptoms, a total of 8 patients receiving valproate, 17 patients receiving risperidone, and 25 patients receiving quetiapine agreed to begin trauma-focused therapy. The flow of patients through these procedures is reported in Fig. 1.

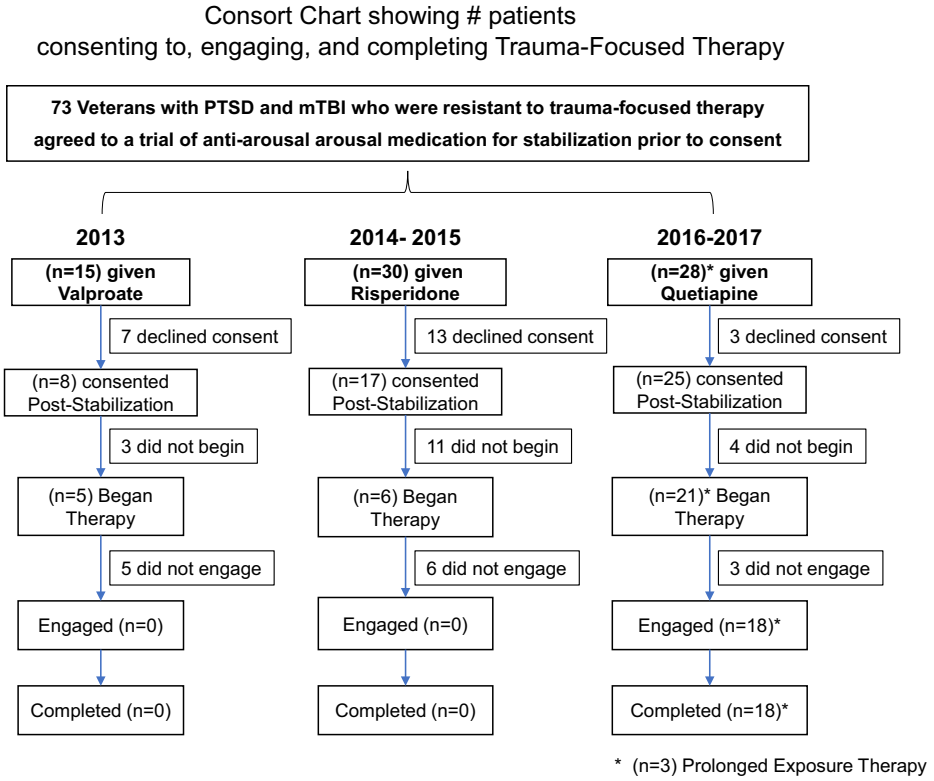

Fig. 1 Number of patients consenting to, engaging in, and completing trauma-focused therapy

Participants

Patients were initially evaluated by Rehabilitation Medicine and referred for comprehensive evaluation and treatment based on history and identification of persistent mTBI symptoms. Significant psychiatric and behavioral symptoms warranted psychiatric evaluation by the neuropsychiatrist who confirmed that patients met diagnostic criteria (*DSM-5*) for PTSD. All patients included in this case series were diagnosed with PTSD and mTBI and were found to have significant hyperarousal symptoms measured by the PTSD Checklist for *DSM-5* (PCL-5), which were affecting social and occupational functioning. Excluded from this case series were patients with (1) a lifetime history of psychosis, bipolar disorder, neurocognitive disorder, or current suicidal risk; (2) current substance use disorder severe enough to require medical detoxification or seizure disorder; (3) intolerance to valproate, risperidone, or quetiapine or current use of medications that could confound data (benzodiazepines, opioids); or (4) a history of clinically unstable heart, lung, liver, renal, or endocrinologic condition; diabetes; or current or known history of cardiac arrhythmia or QTc interval of 450 milliseconds or more. Also excluded were pregnant or lactating women and those of child-bearing potential not using a reliable method of contraception. Patients requiring other medications for general medical conditions that might have antiarousal effects, such as antihypertensive medications and β-blockers, for hypertension; antithyroid medications for hyperthyroidism; and/or antiepileptic medications, such as levetiracetam or carbamazepine, for a seizure disorder must have been on a stable dose for at least 1 month before beginning the treatment and maintain a stable dose throughout the treatment.

Medications

Valproate is an anticonvulsant used primarily to treat epilepsy and bipolar disorder and sometimes to prevent migraine headaches. Its mechanism of action includes increasing the amount of GABA production, blocking voltage-gated sodium channels, and inhibiting histone deacetylases. [46] Risperidone is an atypical antipsychotic medication with actions at multiple brain receptors, including dopaminergic, serotonergic, adrenergic, histaminic, and muscarinic. It is mainly used to treat schizophrenia and bipolar disorder. [47, 48] Quetiapine is also an atypical antipsychotic with a broad spectrum of actions similar to those of risperidone but shorter in duration (8–10 h). Quetiapine is approved by the US Food and Drug Administration for the treatment of schizophrenia [49] and bipolar disorder [50] and as an adjunct to treatment of major depressive disorder [51] when combined with another antidepressant.

Valproate, risperidone, or quetiapine monotherapy was initiated at a low dose at bedtime and then increased weekly as tolerated. Flexible dosing continued until patients were clinically stable on adequate therapeutic dosages without any significant adverse effects. Doses were adjusted using medical criteria, including response and clinical discretion, to achieve symptom control and minimize adverse effects. Medications were dispensed by the VA outpatient pharmacy. Adherence was assessed by pharmacy records.

Trauma-Focused Therapies

At the local Polytrauma Rehabilitation Program, CPT is delivered in twelve 60-min sessions following the model established by Resick et al. [45] and prolonged exposure therapy is delivered in ten 90-min sessions following the model established by Foa. [14]

Definitions of Begin, Engage, and Completion of Trauma-Focused Therapy

Begin Treatment Each patient was considered to begin treatment if they attended session 1 of therapy.

Engaged in Treatment With the CPT protocol, the participant is asked to write a full account of the most traumatic event with sensory details by session 4 and with the prolonged exposure therapy protocol, the first exposure sessions begin in session 3. We have established 2 measures of engagement in trauma-focused therapy treatment. The first is continuing treatment at least until session 4 (i.e., after writing trauma narrative in CPT or 2 exposure sessions in prolonged exposure therapy) and the second is being adherent to the treatment as per therapist's report in the medical record.

Completion of Treatment Treatment was considered complete when patients finished 12 sessions of CPT or 10 sessions of prolonged exposure.

Primary PTSD Measures and Secondary Arousal Measures

The PTSD Checklist for *DSM-5* (PCL-5) [52] is a 20-item self-report assessing PTSD severity (score range, 0–80; higher scores indicate greater PTSD severity). Patients completed the PCL-5 before every therapy session and total and symptom cluster scores are recorded by the treating psychologist. A PCL-5 score of 34 is considered as an optimal cutoff level for the diagnosis of PTSD. [53] Arousal cluster severity scores were obtained by summing the items 15–20 of PCL-5 (score range, 0–24; higher scores indicate greater arousal severity). We also collected patient self-reported disturbances in sleep onset, reduced sleep duration, interruptions, and nightmares as measures of arousal severity.

Throughout rehabilitation treatment, all of the patients continued to attend their visits with rehabilitation therapists, as well as the neuropsychiatrist and psychologists. Patients who either did not attend any trauma-focused therapy session or dropped out from therapy after attending at least 1 session continued to receive standard-of-care pharmacologic management and psychological treatment, including cognitive behavioral therapy focused on cognitive restructuring rather than focusing on the trauma.

Data Collection and Analysis

We collected demographic data (age, sex, race/ethnicity, and educational and marital status) and retained the participant's name and last 4 digits of their social security number for identification. From the VA's electronic health record maintained by the Polytrauma Rehabilitation Center, we collected self-reported PTSD symptom severity collected on the PCL-5 and self-reported sleep measures systematically documented by the neuropsychiatrist. We also extracted measures of therapy engagement and completion from the health record.

We analyzed data from the 50 patients who agreed to participate in therapy after an adequate course of treatment with antiarousal medication.

Statistical Analysis

Descriptive statistics were calculated for demographic variables and baseline clinical characteristics for the 3 treatment conditions. Data are expressed as the means (SDs) or proportions of patients. Statistical significance of the difference between before and after treatment means was determined using paired *t* tests. For all analyses, $P < .05$ was considered to be statistically significant.

Results

Demographics

Demographic characteristics are reported in Table 1. The mean (SD) age of the patients was 36 (8) years and 48 (96%) were male. Table 2 shows previous medications used at baseline that failed to manage psychiatric symptoms. Common medications were SSRIs (especially sertraline), trazodone, and prazosin**.**

Primary Outcome of Engagement and Completion Rate of CPT Treatment

The CONSORT chart is shown in Fig. 1. After initial interest to start therapy, many patients with initial quetiapine treatment began trauma-focused therapy (valproate, 5 [63%]; risperidone, 6 [35%]; and quetiapine, 21 [84%]; $p = 0.03$). Most patients who began treatment while in a quetiapine trial (18 [86%]; $p = .01$) were engaged in treatment and completed it compared with valproate (0) and risperidone (0). Three patients who were referred for prolonged exposure therapy began, became adequately engaged in, and completed it. Nine of the 18 completers had a history of failing to complete trauma-focused therapy.

PCL-5 Scores for Completers

PCL-5 scores decreased in the patients who completed CPT as shown in Fig. 2. Patients who completed CPT had lower mean PCL-5 scores at the end of treatment compared with baseline (37 vs 62, respectively; difference, 25; 95% CI, 30 to 20; $t_{34} = 9.61$; $p < .001$). There was a 50% decrease in the rate of PTSD diagnosis from baseline to end of treatment for treatment completers, and the completers also had significantly lower mean arousal subscale of PCL–5 scores at the end of treatment compared with baseline (10 vs 20, respectively; difference, 10; 95% CI, 12 to 8; $t_{34} = 9.90$; $p < .001$).

Sleep Outcomes

Patients taking quetiapine reported more improvement in sleep interruptions (16 [73%]) compared with valproate ($n = 0$) and risperidone (2 [12%]). Similarly, patients taking quetiapine reported more improvement in nightmares (19 [79%]) compared with valproate ($n = 0$) and risperidone (1 [6%]). Sleep latency and duration improved with all the 3 antiarousal treatments, as shown in Table 3.

Table 1 Demographic and clinical characteristics of patients by treatment condition

Characteristics	Antiarousal Monotherapy, No. (%)		
	Valproate ($n = 8$)	Risperidone ($n = 17$)	Quetiapine ($n = 25$)
Demographic			
Age, mean (SD), y	34 (7)	36 (10)	37 (8)
Sex			
Men	8 (100)	16 (94)	24 (96)
Women	0	1 (6)	1 (4)
Marital Status			
Not Married	3 (38)	14 (82)	18 (72)
Married or Cohabiting	5 (63)	3 (18)	7 (28)
Educational status			
GED	1 (13)	3 (18)	2 (8)
High School Diploma	5 (63)	5 (29)	13 (52)
Some College	0	5 (29)	7 (28)
College Degree	2 (25)	4 (24)	3 (12)
Employment Status			
Full time	3 (38)	5 (29)	12 (48)
Part time	1 (13)	1 (6)	0
Not employed	4 (50)	11 (65)	13 (52)
Ethnicity			
Hispanic	3 (38)	6 (35)	8 (32)
Non-Hispanic	5 (63)	11 (65)	17 (68)
Race			
Asian	0	0	2 (8)
Black	0	4 (24)	5 (20)
White	8 (100)	13 (76)	18 (72)
Military			
No. of times deployed			
1 or 2	5 (63)	8 (47)	14 (56)
≥ 3	3 (38)	9 (53)	11 (44)
Baseline			
Time since diagnosis of PTSD, mean (SD), y	3 (3)	2 (2)	3 (2)
PCL-5, mean (SD)[a]	61 (9) ($n = 6$)	62 (13) ($n = 15$)	63 (19) ($n = 22$)
Arousal subscale, mean (SD)[a]	19 (3) ($n = 6$)	19 (04) ($n = 15$)	20 (03) ($n = 22$)
Depressive symptoms	8 (100)	13 (76)	17 (68)
Substance Use Disorder	6 (75)	7 (41)	13 (52)
No. of failed TFTs	2 (25)	3 (18)	11 (44)
No. of psychotropic medications in use per day at baseline			
0	3 (38)	4 (24)	3 (12)
1	1 (13)	1 (6)	1 (4)
2	2 (25)	5 (29)	8 (32)
≥ 3	2 (25)	7 (41)	13 (52)
Treatment dosage, mean (range), mg	1625 (1500–2000)	2 (1–4)	180 (50–400)

Abbreviations: *GED* General educational development, *PCL-5* PTSD Checklist for *DSM-5, PTSD* Posttraumatic stress disorder, *TFT*, Treatment-focused therapies

[a] Sample sizes were different as these scores are taken from the standard-of-care assessment found in the electronic health record

Discussion

The results of the current clinical case series show that it is possible to use antiarousal psychiatric medication as an adjunct to help mTBI patients with PTSD to engage in trauma-focused therapy, even though they were initially resistant to such

Table 2 Past failed medications and medications at baseline for the 3 treatment conditions

Medication	Past Failed Medication Trials, No.			Medications at Baseline, No.		
	Valproate	Risperidone	Quetiapine	Valproate	Risperidone	Quetiapine
Antidepressants						
Sertraline	4	7	15	1	7	3
Other SSRIs, SNRIs	10	5	20	3	3	8
Others	8	6	17	3	4	10
Sympatholytic						
Prazosin	5	3	11	1	4	11
Sleep aids						
Trazodone	3	7	9	2	6	13
Nonbenzodiazepine	5	5	14	2	3	7
Mood stabilizers	1	5	6			2
Benzodiazepines		5	3			4
Hydroxyzine			1	1	2	7

Abbreviations: *SNRIs* Serotonin-norepinephrine reuptake inhibitors, *SSRIs* Selective serotonin-reuptake inhibitors

treatment and had several trials of standard psychopharmacologic treatment had failed. Quetiapine monotherapy, but not risperidone or valproate, was successful in helping patients in our polytrauma rehabilitation program to engage in and complete standard-of-care treatment with trauma-focused therapy (primarily CPT). After discontinuation of other psychiatric treatments, quetiapine monotherapy helped 72% of patients to engage in and complete a standard course of therapy. Although some patients who were receiving risperidone or valproate (35% and 63%, respectively) consented to therapy, none of them engaged sufficiently to progress to session 4 of CPT where full a written narrative of their trauma was discussed.

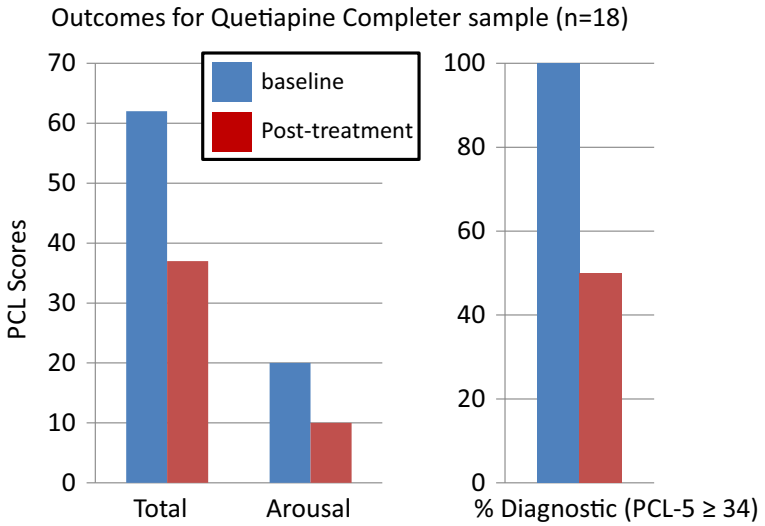

Fig. 2 Outcomes for quietapine completer sample

Table 3 Improvement in sleep for the 3 treatment conditions

	No. / n (%)		
	Antiarousal Monotherapy		
	VALPROATE	RISPERIDONE	QUETIAPINE
Latency	4/8 (50)	10/16 (63)	14/16 (88)
Total Sleep Time	2/8 (25)	10/17 (59)	19/23 (83)
Interruption	0/8	2/17 (12)	16/22 (73)
Nightmares	0/8	1/17 (6)	19/24 (79)

Consistent with previous findings that patients who engage in therapy demonstrate clinically significant improvements, [22] using before to after treatment standard-of-care assessments, we found that patients who received quetiapine treatment and completed therapy had significantly reduced PCL total scores and arousal subscale scores, and 50% of these veterans achieved a remission criterion of PCL score less than 34. [53] Although all 3 medications were shown to improve some patient self-reported sleep variables, quetiapine generally was superior to risperidone and valproate and this was particularly true for nightmares and sleep interruption reports. Adverse effects of quetiapine were generally tolerable, but both risperidone and valproate caused daytime sedative effects that were clinically significant and yet without showing any increase in patient engagement in therapy.

This preliminary work suggests that psychosedation per se is not necessarily beneficial, but that quetiapine exerted anti-arousal effects that reduced PCL scores, improved sleep, and enhanced patient engagement and retention in trauma-focused therapy. This challenges the presumption that antiarousal effects of psychiatric medication may be countertherapeutic. We suggest that the broad spectrum of quetiapine's neuropharmacologic effects having antiarousal and sleep promoting effects [54] could have promoted therapy engagement by ameliorating the unpleasant arousal associated with trauma-focused therapy. More particularly, its absence of effects on GABA and GABA receptors [55] may have allowed the fear extinction learning required for effective treatment without any amnestic effects. Quetiapine also allows reduction of sleep disruption without impairing sleep architecture [56] that might have benefited patients undergoing the new learning occurring in trauma-focused therapies compared with other medications used. [57]

These results make quetiapine well suited to repurpose an already approved drug for a randomized clinical trial using a pragmatic effectiveness approach to evaluate it for the treatment of PTSD in veterans with mTBI. These future studies will be critical to advance our understanding of how adequate management of arousal disturbance can safely and effectively improve engagement and retention in treatment-seeking participants and hence achieve greater remission rates for veterans experiencing this chronic and debilitating illness. It will also be a very significant step in the management of mTBI by showing that certain medications can effectively improve remission rate from PTSD within the VA standards of care programs and minimize polypharmacy practices. Improved patient engagement and retention in more effective treatments will ensure that dedicated resources achieve the best possible outcomes and thereby benefit the VA by reducing the ongoing demands of an unremitted chronic disease in veterans.

Quetiapine has risks and adverse effects, although none of these should prevent its effective use in PTSD treatment for 10 to12 weeks of trauma-focused therapy. Quetiapine may cause

sedation, which can be used to benefit regularization of circadian rhythm by starting a low dose scheduled at bedtime and slowly adjusting as tolerated to desired effects. When prescribed at high doses for longer durations of treatment in patients with severe mentally illness, quetiapine increases a dose-dependent risk for diabetes and heart diseases by causing metabolic dysregulation. Whereas, quetiapine monotherapy was well tolerated in a previous trial ($n = 80$) and showed no significant differences among groups in weight and metabolic parameters. [44] This medication has also been shown to cause prolongation of the QTc interval. This complication can be avoided by screening out veterans with prolonged QTc intervals (≥450 milliseconds) by a pre-initiation electrocardiogram. Antipsychotic medications, typical more so than atypical agents, are known to cause extrapyramidal symptoms due to dopamine blockade properties. Extrapyramidal symptoms are generally least common with quetiapine compared with other antipsychotics.

Limitations

The first and foremost limitation of this study is that it is a stepwise and sequential trial of open-label medication as we tried antiarousal medications following VA guidelines for restricted drug request in a clinical setting. Another limitation of this study is the use of CPT in most of the patients, as CPT is used as a standard-of-care trauma-focused therapy in our clinic. Prolonged exposure therapy, which we could use in only 3 patients, has the strongest evidence and is considered the most effective treatment. However, prolonged exposure therapy is one of the greatest concerns that patients and clinicians express because of its potential to evoke arousal contributing to avoidance, which initially may curtail engagement and later may cause discontinuation of treatment. [25] These findings warrant the need for wider-scale, randomized, placebo-controlled, pragmatic trials conducted in conjunction with concurrent TBI-related rehabilitation services to evaluate the efficacy of quetiapine monotherapy as an adjunct to facilitate prolonged exposure therapy compared with the treatment as usual psychiatric polypharmacy medication practice, which prohibits quetiapine use.

Conclusions

This case series evaluating antiarousal medication treatment demonstrated preliminary data to support our hypothesis that quetiapine monotherapy can facilitate rehabilitation and recovery for veterans with mTBI and PTSD by enhancing engagement and completion rate of CPT for PTSD and can do so without the complications of other standard-of-care polypharmacy practices.

Compliance with Ethical Standards

Conflict of Interest The authors report no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was not required for this retrospective chart review study.

References

1. Swanson TM, Isaacson BM, Cyborski CM, French LM, Tsao JW, Pasquina PF. Traumatic brain injury incidence, clinical overview, and policies in the US military health system since 2000. Public Health Rep. 2017;132(2):251–9.
2. Cohen BE, et al. Mental health diagnoses and utilization of VA non-mental health medical services among returning Iraq and Afghanistan veterans. J Gen Intern Med. 2010;25(1):18–24.
3. Tsan JY, et al. Primary care-mental health integration and treatment retention among Iraq and Afghanistan war veterans. Psychol Serv. 2012;9(4):336–48.
4. Diagnostic and statistical manual of mental disorders , fifth edition: American Psychiatric Association; 2013.
5. Cabana MD, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. Jama. 1999;282(15):1458–65.
6. Duff J, Walker K, Omari A. Translating venous thromboembolism (VTE) prevention evidence into practice: a multidisciplinary evidence implementation project. Worldviews Evid-Based Nurs. 2011;8(1):30–9.
7. Hoge CW, et al. Mild traumatic brain injury in U.S. soldiers returning from Iraq. N Engl J Med. 2008;358(5):453–63.
8. Chew E, Zafonte RD. Pharmacological management of neurobehavioral disorders following traumatic brain injury–a state-of-the-art review. J Rehabil Res Dev. 2009;46(6):851–79.
9. Krystal JH, et al. It is time to address the crisis in the pharmacotherapy of posttraumatic stress disorder: a consensus statement of the PTSD psychopharmacology working group. Biol Psychiatry. 2017.
10. Asnis GM, et al. SSRIs versus non-SSRIs in post-traumatic stress disorder: an update with recommendations. Drugs. 2004;64(4):383–404.
11. *Treatment of Posttraumatic Stress Disorder in Military and Veteran Populations: Final Assessment*. 2014, Committee on Treatment of Posttraumatic Stress Disorder. Institute of Medicine.: Washington, DC.
12. Collett GA, et al. Prevalence of central nervous system polypharmacy and associations with overdose and suicide-related behaviors in Iraq and Afghanistan war veterans in VA care 2010-2011. Drugs Real World Outcomes. 2016;3(1):45–52.
13. Kennedy JE, et al. Posttraumatic stress symptoms in OIF/OEF service members with blast-related and non-blast-related mild TBI. NeuroRehabilitation. 2010;26(3):223–31.
14. Foa EB. Prolonged exposure therapy: past, present, and future. Depress Anxiety. 2011;28(12):1043–7.
15. Goodson JT, et al. Outcomes of prolonged exposure therapy for veterans with posttraumatic stress disorder. J Trauma Stress. 2013;26(4):419–25.
16. Powers MB, et al. A meta-analytic review of prolonged exposure for posttraumatic stress disorder. Clin Psychol Rev. 2010;30(6):635–41.
17. Jeffreys MD, et al. Evaluating treatment of posttraumatic stress disorder with cognitive processing therapy and prolonged exposure therapy in a VHA specialty clinic. J Anxiety Disord. 2014;28(1):108–14.
18. Kilpatrick D.G., B CL , *Behavior Therapy* Some cautionary remarks on treating sexual assault victims with implosion . Vol. 15. 1984. 4.
19. Pitman RK, et al. Psychiatric complications during flooding therapy for posttraumatic stress disorder. J Clin Psychiatry. 1991;52(1):17–20.
20. Pitman RK, et al. Emotional processing during eye movement desensitization and reprocessing therapy of Vietnam veterans with chronic posttraumatic stress disorder. Compr Psychiatry. 1996;37(6):419–29.
21. Tarrier N, et al. A randomized trial of cognitive therapy and imaginal exposure in the treatment of chronic posttraumatic stress disorder. J Consult Clin Psychol. 1999;67(1):13–8.
22. Imel ZE, et al. Meta-analysis of dropout in treatments for posttraumatic stress disorder. J Consult Clin Psychol. 2013;81(3):394–404.
23. Steenkamp MM, et al. Psychotherapy for military-related PTSD: a review of randomized clinical trials. Jama. 2015;314(5):489–500.
24. Hembree EA, et al. Do patients drop out prematurely from exposure therapy for PTSD? J Trauma Stress. 2003;16(6):555–62.
25. Becker CB, Zayfert C, Anderson E. A survey of psychologists' attitudes towards and utilization of exposure therapy for PTSD. Behav Res Ther. 2004;42(3):277–92.
26. Hing M, et al. Special operations forces and incidence of post-traumatic stress disorder symptoms. J Spec Oper Med. 2012;12(3):23–35.
27. Jaeger JA, et al. Factors associated with choice of exposure therapy for PTSD. Int J Behav Consult Ther. 2009;5(3–4):294–310.
28. Matsumoto Y, et al. Vorinostat ameliorates impaired fear extinction possibly via the hippocampal NMDA-CaMKII pathway in an animal model of posttraumatic stress disorder. Psychopharmacology. 2013;229(1):51–62.

29. Acheson D, et al. The effect of intranasal oxytocin treatment on conditioned fear extinction and recall in a healthy human sample. Psychopharmacology. 2013;229(1):199–208.
30. Popiel A, et al. Prolonged exposure, paroxetine and the combination in the treatment of PTSD following a motor vehicle accident. A randomized clinical trial - the "TRAKT" study. J Behav Ther Exp Psychiatry. 2015;48:17–26.
31. Schneier FR, et al. Combined prolonged exposure therapy and paroxetine for PTSD related to the world trade center attack: a randomized controlled trial. Am J Psychiatry. 2012;169(1):80–8.
32. Simon NM, et al. Paroxetine CR augmentation for posttraumatic stress disorder refractory to prolonged exposure therapy. J Clin Psychiatry. 2008;69(3):400–5.
33. Echiverri-Cohen A, et al. Changes in temporal attention inhibition following prolonged exposure and sertraline in the treatment of PTSD. J Consult Clin Psychol. 2016;84(5):415–26.
34. Jun JJ, Zoellner LA, Feeny NC. Sudden gains in prolonged exposure and sertraline for chronic PTSD. Depress Anxiety. 2013;30(7):607–13.
35. Jerud AB, et al. The effects of prolonged exposure and sertraline on emotion regulation in individuals with posttraumatic stress disorder. Behav Res Ther. 2016;77:62–7.
36. Flanagan JC, et al. Augmenting prolonged exposure therapy for PTSD with intranasal oxytocin: a randomized, placebo-controlled pilot trial. J Psychiatr Res. 2017;98:64–9.
37. Rauch SA, et al. Imagery vividness and perceived anxious arousal in prolonged exposure treatment for PTSD. J Trauma Stress. 2004;17(6):461–5.
38. Deacon B, et al. Maximizing the efficacy of interoceptive exposure by optimizing inhibitory learning: a randomized controlled trial. Behav Res Ther. 2013;51(9):588–96.
39. Lund BC, et al. Declining benzodiazepine use in veterans with posttraumatic stress disorder. J Clin Psychiatry. 2012;73(3):292–6.
40. Viola J, et al. Pharmacological management of post-traumatic stress disorder: clinical summary of a five-year retrospective study, 1990-1995. Mil Med. 1997;162(9):616–9.
41. Rothbaum BO, et al. A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan war veterans. Am J Psychiatry. 2014;171(6):640–8.
42. Krystal JH, et al. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. Jama. 2011;306(5):493–502.
43. Davis LL, et al. Divalproex in the treatment of posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial in a veteran population. J Clin Psychopharmacol. 2008;28(1):84–8.
44. Villarreal G, et al. Efficacy of quetiapine monotherapy in posttraumatic stress disorder: a randomized, placebo-controlled trial. Am J Psychiatry. 2016;173(12):1205–12.
45. Patricia A, Resick PD, Candice M. Monson, Ph.D., Kathleen M. chard, Ph.D., *Cognitive Processing Therapy: Veterans/Military Version: Therapist's manual*. Washington, DC: Department of Veterans's Affairs; 2014.
46. Ghodke-Puranik Y, et al. Valproic acid pathway: pharmacokinetics and pharmacodynamics. Pharmacogenet Genomics. 2013;23(4):236–41.
47. Dold M, et al. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. Int J Neuropsychopharmacol. 2013;16(3):557–74.
48. Leucht S, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382(9896):951–62.
49. Borison RL, Arvanitis LA, Miller BG. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. *US SEROQUEL Study Group*. J Clin Psychopharmacol. 1996;16(2):158–69.
50. Sachs G, et al. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. Bipolar Disord. 2004;6(3):213–23.
51. El-Khalili N, et al. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. Int J Neuropsychopharmacol. 2010;13(7):917–32.
52. Weathers, F.W., Litz, B. T., Keane, T. M., Palmieri, P. A., Marx, B. P., & Schnurr, P. P. National Center for PTSD, *The PTSD Checklist for DSM-5 (PCL-5) – [Measurement instrument]*. 2013.
53. Murphy D, et al. Exploring optimum cut-off scores to screen for probable posttraumatic stress disorder within a sample of UK treatment-seeking veterans. Eur J Psychotraumatol. 2017;8(1):1398001.
54. Galovski TE, et al. Augmenting cognitive processing therapy to improve sleep impairment in PTSD: a randomized controlled trial. J Consult Clin Psychol. 2016;84(2):167–77.

55. Horacek J, et al. Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. CNS Drugs. 2006;20(5):389–409.
56. Robert S, et al. Quetiapine improves sleep disturbances in combat veterans with PTSD: sleep data from a prospective, open-label study. J Clin Psychopharmacol. 2005;25(4):387–8.
57. Wiegand MH, et al. Quetiapine in primary insomnia: a pilot study. Psychopharmacology. 2008;196(2):337–8.

Muhammad Rais Baig, M.D., is a clinical neuropsychiatrist at the Polytrauma Rehabilitation Center (PRC), South Texas Veterans Health Care System (STVHCS) and Research Instructor in the Department of Psychiatry, University of Texas Health San Antonio (UTHSA). He is board certified in General Adult Psychiatry, Brain Injury Medicine and Psychosomatic Medicine. In his early career, he completed graduate school education in Clinical Investigation and received initial experience in clinical trials. He then started research track psychiatry residency training at UTHSA and completed it at *Yale University School of Medicine*. During this period, he won the prestigious *NIMH Outstanding Resident Award*, a resident paper competition, and several training grants, and fellowships. Each of these experiences prepared him for his current position where he is dedicated to the evaluation and treatment of Veterans with Traumatic Brain Injury (TBI) and Posttraumatic Stress Disorder (PTSD) at the PRC. He is striving to identify, test and confirm the most effective pharmacological treatment for patients. Since, his residency, he established himself as a VA Neuropsychiatrist with plans to design and conduct clinical trials to overcome the shortcomings in psychopharmacological approaches for the management of Veterans with Traumatic Brain Injury (TBI) and Posttraumatic Stress Disorder (PTSD).

Jennifer L. Wilson, Ph.D., was trained under a social psychologist who not only gave her a passion for understanding how psychological research undergirds psychological theory, but also how quantitative and qualitative research is useful in explaining psychological phenomena. She studied the role of religiosity, anxiety, and anger in domestic violence, female to male directed domestic violence, and psychological abuse.

Jennifer A. Lemmer, Ph.D., identifies herself professionally as a scholar-practitioner in the fields of clinical psychology and public health with a primary focus on translating research into effective prevention and intervention efforts for trauma survivors across the lifespan. Her clinical training throughout graduate school, internship, and postdoctoral work focused on the assessment and treatment of PTSD and associated co-morbidities in the US military and veteran populations. She worked throughout graduate school in a laboratory for Posttraumatic Stress Disorder and Stress-Related Disorders Research (PI: Dewleen Baker, MD) at the Veterans Affairs San Diego Healthcare System. She completed VA funded training and consultation in Cognitive Processing Therapy (CPT) and Prolonged Exposure (PE) and routinely use these modalities to treat veterans. Since 2015, she has expanded her interests to include mental health care for individuals who sustained polytraumatic injuries most notably TBI and ABI.

Robert D. Beck, Ph.D., is a licensed and practicing clinical psychologist currently employed by the Department of Veterans Affairs (VA). His academic training and research background is primarily in the anxiety disorders, with particular emphasis on the role of cognitive biases in exacerbating and maintaining pathological anxiety responses. He completed intensive clinical training with VA as a predoctoral intern and a postdoctoral fellow. His primary area of focus was the assessment and treatment of Posttraumatic Stress Disorder (PTSD) in combat Veterans, with special focus on Veterans of the OEF/OIF/OND military campaigns in Afghanistan and Iraq. Following completion of his postdoctoral training and acquisition of professional licensure in 2011, he accepted a position at the South Texas VA in San Antonio, TX as the outpatient clinical psychologist for their newly expanded Polytrauma site, and have been in that capacity since that time. His clinic is tasked with providing outpatient care to severely injured OEF/OIF/OND combat Veterans as well as evaluating and treating Veterans with suspected traumatic brain injury (TBI). He works as a member of an interdisciplinary team of rehabilitation providers, including medical doctors, physical therapists, and a psychiatrist, in providing collaborative care. He provides clinical assessments and individual psychotherapy to aid patient population in addressing mental health barriers to their rehabilitation and reintegration goals, with particular emphasis on PTSD, depression, insomnia, and adjustment-related issues. He is proficient in a number of evidence-based treatments for mental health concerns which are common in the returning Veteran population and have a deep and abiding interest in ensuring that patient care is informed by high-quality empirical research.

Alan L. Peterson, Ph.D., has served as a member of the *Long-Term Effects of Blast Exposure* Committee for the Institute of Medicine (2014). He has significant clinical and research experience in traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) in active duty military personnel and veterans. He is a board certified clinical health psychologist, endowed Professor, and Chief of the Division of Behavioral Medicine in the Department of Psychiatry and School of Medicine at the University of Texas Health Science Center at San Antonio. He is the Director of the STRONG STAR Consortium and the Consortium to Alleviate PTSD. These research consortia include the collaboration of over 40 academic institutions and 150 investigators with peer-reviewed funding from the DoD, VA, NIH, and private agencies. He served previously as an active duty Air Force clinical psychologist and retired 2005 after 21 years of service including deployments in support of Operations Noble Eagle, Enduring Freedom, and Iraqi Freedom. He also served in the Air Force as the Chair of the Department of Psychology and the Director of the Clinical Health Psychology Postdoctoral Fellowship Program at Wilford Hall Medical Center. He has clinical and research expertise in the areas of behavioral medicine (chronic pain, tobacco cessation, weight management, sleep disorders, tic disorders, etc.) and military health psychology (PTSD, TBI, suicide, psychological resiliency, etc.). He has over 25 years of research experience in clinical trials evaluating behavioral interventions in civilian and military populations and have been the PI, Co-PI, or Co-Investigator on over 45 clinical trials.

John D. Roache, Ph.D., is an experimental and clinical psychopharmacologist and a Professor in the Departments of Psychiatry and Pharmacology at the UT Health Science Center in San Antonio. He has been engaged in NIH-funded research dedicated to understanding the causes, consequences, and treatments for drug and alcohol addiction for 30 years. In the Department of Psychiatry, he serves as Chief of the Division of Alcohol and Drug Addiction and as the Deputy Director of STRONG STAR and the Consortium to Alleviate PTSD (CAP) which is funded by the DoD and VA. Within that consortium, he has recently been privileged to conduct or collaborate in the conduct of several clinical trials treating PTSD in active-duty service members and Veterans.

Affiliations

Muhammad R. Baig[1,2,3] · Jennifer L. Wilson[1,2] · Jennifer A. Lemmer[1,2] · Robert D. Beck[1,2] · Alan L. Peterson[1,3,4] · John D. Roache[3,5]

[1] Mental Health, South Texas Veterans Healthcare System, San Antonio, TX, USA

[2] Polytrauma Rehabilitation Center, South Texas Veterans Healthcare System, San Antonio, TX, USA

[3] Department of Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

[4] Department of Psychology, University of Texas at San Antonio, San Antonio, TX, USA

[5] Department of Pharmacology, University of Texas Health San Antonio, San Antonio, TX, USA