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Short communication

Low-dose clonidine in veterans with Posttraumatic stress disorder

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ABSTRACT

Posttraumatic stress disorder (PTSD) symptoms of hyperarousal are mediated through sympathetic nervous system hyperactivity. PTSD symptoms, including distressing thoughts and memories, flashbacks, hyperarousal, and sleep disturbances, have been linked with elevated norepinephrine levels in the cerebrospinal fluid. Clonidine, an alpha2-adrenergic agonist, reduces the release of norepinephrine and has been suggested as a treatment for PTSD. However, literature for use of clonidine in PTSD is limited. The objective of this study was to evaluate clinical records of patients with PTSD treated with clonidine to assess reported efficacy and safety. A cohort of veterans with PTSD treated with clonidine at a midwestern VA hospital between July 2015 and January 2018 were studied retrospectively. Medical records of 79 patients with moderate to severe PTSD symptoms were reviewed by three independent clinicians using the Clinical Global Impressions (CGI) scale to quantify symptom severity (CGI-S) before starting clonidine and subjects' change in symptoms (CGI-I) after starting clonidine. Data on adverse events were also collected. Subgroup analyses were conducted on the impact of comorbid diagnoses, concurrent medications, and substance use. Mean CGI-S score at baseline was 4.8 (5 = markedly ill). After treatment with low-dose clonidine, 72% of patients experienced improvement, and 49% scored "much improved" or "very much improved." Adverse effects were reported by 18 out of 79 subjects. In this retrospective analysis of veterans prescribed clonidine for PTSD, CGI-I scores suggested improvement in PTSD symptoms, and minimal side effects were reported. In addition, some comorbid diagnoses and concurrent medications were correlated with variations in outcomes.

1. Introduction

Posttraumatic stress disorder (PTSD) is a highly disabling trauma- and stressor-related disorder, with reports of lifetime prevalence in US veterans ranging from 10% to 31% (Kulka et al., 1990; Norman et al., 2018). These symptoms can significantly and negatively impact the quality of life for veterans and their families. Veterans with PTSD are more likely to present with anger/aggression (Buchholz et al., 2017), substance use disorder (Norman et al., 2018), or greater life difficulties (e.g., mental health disorders, marriage instability, unemployment) (Kessler, 2000). Further, veterans with PTSD are significantly more likely to present with suicidal ideation or attempts than veterans without PTSD (Norman et al., 2018).

PTSD is characterized by four symptom clusters: re-experiencing, avoidance, negative alterations in cognition or mood, and/or hyperarousal. Hyperarousal may include insomnia or other sleep disturbances, irritability, angry outbursts, hypervigilance, exaggerated physiologic and startle responses, and poor concentration. Evidence suggests that many hyperarousal PTSD symptoms are mediated through hyperactivity of the sympathetic nervous system, through increased norepinephrine outflow or increased receptor responsiveness (Southwick et al., 1993). This is consistent with increased levels of norepinephrine in the cerebrospinal fluid correlating with PTSD severity scores (Geracioti et al., 2001) and other measures of dysregulation of noradrenergic tone in PTSD (Hendrickson and Raskind, 2016). PTSD symptoms are likely exacerbated by sleep disturbances, which are considered a prominent, yet difficult-to-treat feature of PTSD (Spoormaker and Montgomery, 2008). Sleep disturbances include difficulty falling or

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staying asleep and trauma-related nightmares and are thought to potentiate PTSD via associations with increased depression, heightened anxiety, unstable mood, decreased affect, and increased daytime PTSD symptoms (Short et al., 2017).

Treatments for PTSD typically include medications and psychotherapy, although there is significant variability in treatment response across individuals. First-line pharmacotherapies for PTSD include selective serotonin reuptake inhibitors (SSRI), although SSRIs have little impact on nighttime PTSD symptoms (Maher et al., 2006; Spoormaker and Montgomery, 2008; van Liempt et al., 2006) and appear less effective for veterans with PTSD than other populations with PTSD (Benedek et al., 2009). Interventions directly targeting sympathetic nervous system activity and sleep disturbance may be more efficacious. Specifically, targeting noradrenergic/adrenergic activity may improve PTSD nighttime symptoms (Belkin and Schwartz, 2015).

Clonidine, an FDA-approved antihypertensive, is a centrally acting alpha2-adrenergic agonist that reduces norepinephrine levels (Cubeddu et al., 1984) and thus has been recommended to treat PTSD nighttime symptoms (Boehnlein and Kinzie, 2007). Lofexidine, another alpha2-adrenergic agonist recently approved for opioid withdrawal, improved sleep during drug withdrawal (Beswick et al., 2003; Haney et al., 2008) although it has not been tested for use in PTSD. Prazosin is a similar medication targeting norepinephrine activity and has demonstrated some efficacy at improving PTSD nighttime symptoms (George et al., 2016; Raskind et al., 2013). Low-dose clonidine is hypothesized to produce similar outcomes to prazosin with a comparable side effect profile (Wendell and Maxwell, 2015). Though several reports have suggested the efficacy of clonidine for nighttime symptoms of PTSD in veterans (Detweiler et al., 2016; Wendell and Maxwell, 2015), those studies had small population sizes.

The primary study objective was to assess the reported efficacy of low-dose clonidine for treating veterans diagnosed with PTSD. Secondary objectives were to assess the safety of clonidine by describing the type and frequency of reported adverse effects and identify correlations of comorbidities or concurrent medications with treatment response.

2. Methods

2.1. Participants and procedure

This was a retrospective cohort study of veterans with PTSD treated at a large, midwestern Veterans Affairs (VA) hospital and was approved by the local VA institutional review board. The research team collected data from the VA electronic medical record (CPRS) to identify veterans with PTSD seen in mental health outpatient or urgent care clinics and treated with clonidine for mental health at a dosage as decided by their provider between July 1, 2015 and January 31, 2018. Subjects between 18 and 80 years old were included. Exclusion criteria included medication noncompliance, histories of psychotic disorders or poorly controlled bipolar I disorder, severe brain injury or organic mental syndromes, or severe substance use disorder within the past 3 months. A total of 79 patients met eligibility criteria.

2.2. Outcome measurement and interrater agreement

The primary outcome of medication effectiveness was assessed by scoring subject records on the Clinical Global Impression (CGI) scale (Guy, 1976). The CGI is commonly used in studies assessing medication efficacy for PTSD (Writer et al., 2014), as it is a simplified, empirical measure of the clinician's overall impression of the patient's condition and can measure general severity (CGI-S) or comparative improvement (CGI-I). The CGI-S scale is scored from 1 *(not at all ill)* to 7 *(among the most extremely ill patients)*, and the CGI-I is scored from 1 *(very much improved)* to 7 *(very much worse)*.

Progress notes were collected by the primary reviewer and provided to two co-reviewers for scoring. All reviewers were psychiatrists in a VA outpatient clinic with at least two years of experience assessing the relevant records and population. Reviewers independently reviewed patient notes and scored the CGI-S based on the baseline visit (first clonidine prescription) and the CGI-I from the next visit progress note containing enough information for scoring. If clonidine dosage was titrated over time, the CGI-I was scored at the next visit after clonidine dosage was maximized. Prior to scoring, reviewers discussed the CGI scale, proceduralized scoring, and completed a scoring agreement trial to assess rater consistency. Scoring was based only on clinical variables relevant to PTSD.

Mean CGI-S and CGI-I were calculated from the three interrater scores. Interrater agreement was calculated using intraclass correlation. Agreement for CGI-S was moderate at 0.74 (95% confidence interval [CI], 0.64 to 0.81) and for CGI-I was good at 0.88 (95% CI, 0.84 to 0.92). Additional data were captured from medical records including demographics, clonidine duration/dosage, comorbid diagnoses, and active medications. Comorbid diagnoses included physical disorders, substance use, and other psychiatric disorders. Medications were grouped by class (e.g., SSRIs, antipsychotics, benzodiazepines, beta-blockers).

2.3. Data analysis

Continuous variables were summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). For categorical variables, frequencies and percentages were examined by condition (response), comorbidities, treatment and concomitant medication class. Fisher exact tests and chi-squared tests were used to compare groups, where appropriate. Spearman rank correlation was used to examine potential correlation between numeric data and CGI-S and CGI-I scores. Mann-Whitney *U* Test was used for non-parametric variables. Associations between potential predictors and CGI-S and CGI-I scores were analyzed using logistic regression. Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC). P-values $\leq$.05 were considered significant.

3. Results

The study population consisted entirely of male veterans, with a mean age of 48 years (Table 1). Subjects had a range of concomitant physical and psychiatric diagnoses, with a mean of 4.7 comorbid diagnoses per person. At baseline (before starting clonidine) the mean CGI-S was 4.8 (markedly ill). At follow-up, mean CGI-I was 2.87 (between minimally and much improved), and no single CGI-I score was above 4.33 (CGI-I 4 = no change). Further, 39 (49%) subjects had CGI-I scores in the 1–2 range, indicating outcomes as "very much improved" or "improved". At least minimal improvement was seen in 57 subjects (72%).

A total of 18 subjects (22.8%) reported side effects (Table 1). Of those, nine (11.4%) discontinued clonidine. Seven subjects (8.9%) reported sleepiness/grogginess, four of which discontinued use. Five subjects (6.3%) reported lightheadedness/dizziness, two of which discontinued. Three subjects (3.8%) reported GI symptoms, of which two discontinued. Three subjects (3.8%) reported dry mouth, one discontinued. The mean age of patients reporting side effects was 54.1 years and was not significantly different from the age of those who discontinued ($F(1,78) = 3.35$, $p = .07$). Further, mean ages did not differ between patients who reported side effects versus those who did not ($F(1,78) = 3.94$, $p = .051$). No serious adverse events occurred during the study period.

Clonidine dosages ranged between 0.05 mg (qHS) and a total of 0.5 mg in divided doses (0.2 mg qAM, 0.3 mg qHS) with a mean total of 0.20 mg per day. Most common dosing was 0.1 mg qHS (N = 25), 0.1 mg BID (N = 9), 0.2 mg qHS (N = 8) and 0.1 mg qAM, 0.2 mg qHS (N = 23). The two subjects on 0.05 mg qHS reported no benefit. Of those taking 0.1 mg total per day or less, 15 of 29 (52%) had CGI-I indicating at least some improvement (Fig. 1). Subjects taking between 0.15 and 0.2 mg total per

Table 1
Patient demographics, clonidine use, and reported side effects.

Characteristic	N	%		
Gender				
Male	79	100%		
Race/Ethnicity				
African American	19	24.1%		
Asian	1	1.3%		
Hispanic	3	3.8%		
White	56	70.9%		
Characteristic	**Mean**	**Min.**	**Max.**	**SD**
Age (years)	48.0	26	76	15.1
Diagnoses Count				
Physical diagnoses	2.8	0	7	1.7
SUD diagnoses	0.6	0	3	0.84
Behavioral diagnoses	1.0	0	3	0.85
Misc. diagnoses	0.4	0	2	0.58
Total diagnoses	4.7	0	11	2.5
CGI Scores				
CGI-S	4.8	4	6.3	0.54
CGI-I	2.9	1	4.3	0.86
Clonidine Duration (days)	245.7	21	1011	217.6
Clonidine Dosage (mg/day)	0.2	0.05	0.4	0.1
Side Effects	**N**	**% of Population**	**Count Discontinued**	**% Discontinued**
No side effects noted	61	77.2%	-	-
Grogginess/ Drowsiness	7	8.9%	4	5.1%
Lightheadedness/ Dizziness	5	6.3%	2	2.5%
GI problems	3	3.8%	2	2.5%
Dry mouth	3	3.8%	1	1.3%

day 19 of 23 (83%) had improvement, and 12 (52%) scored as much improved or very much improved. For subjects on doses at or above 0.25 mg total per day, 23 of 27 (85%) had improvement, with 16 (59%) scoring as much improved or very much improved. Higher dosage of clonidine was correlated with superior CGI-I scores ($r = -0.27$; $p = .02$).

Subgroup analyses of CGI-S showed that subjects with history of traumatic brain injury, irritable bowel syndrome, or depression had significantly higher (worse) CGI-S scores than those without (Table 2). Regression analysis of these variables accounted for 35.2% of the variance in CGI-S scores. CGI-S was not significantly different between subjects with a single substance use disorder and those without. However, subjects having multiple substance use disorders correlated with worse CGI-S scores ($r = .23$; $p = .04$), meaning that subjects with multiple substance use disorders had worse baseline PTSD symptom severity than those with one or none.

When assessing CGI-I, subjects had significantly worse CGI-I scores if diagnosed with comorbid alcohol use disorder (3.1 vs. 2.7, $p = .04$), opioid use disorder (3.8 vs. 2.8, $p = .01$), or cocaine use disorder (3.8 vs. 2.8, $p = .01$) than those without (Table 2). CGI-I scores also were worse in subjects prescribed opioids (3.3 vs. 2.8, $p = .04$). In contrast, CGI-I suggested significantly greater improvement in subjects concomitantly taking SSRIs (2.6 vs 3.0, $p = .04$), but less improvement if previously prescribed prazosin (3.3 vs. 2.8, $p = .03$). Subjects with comorbid anxiety disorder as showed significantly greater improvement (2.3 vs. 2.7, $p = .05$) than those without. Similar to CGI-S, having multiple substance use disorders correlated with worse CGI-I ($r = 0.32$; $p = .004$), meaning less overall improvement. Subject age did not correlate with CGI-S or CGI-I.

4. Discussion

Overall, results indicated improvement of clinician-rated PTSD symptoms in veterans after prescription of clonidine. These results are consistent with previous studies in veteran populations (Detweiler et al., 2016; Wendell and Maxwell, 2015). Detweiler et al. (2016) found a 63% (17/20) partial response in veterans treated with clonidine for PTSD nightmares. Wendell and Maxwell (2015) found that 57% (24/42) of subjects had a positive response for nighttime PTSD symptoms. This study extends previous literature by assessing a larger cohort of subjects, analyzing overall clinical improvement beyond nighttime symptoms, incorporating interrater agreement, and evaluating other clinical

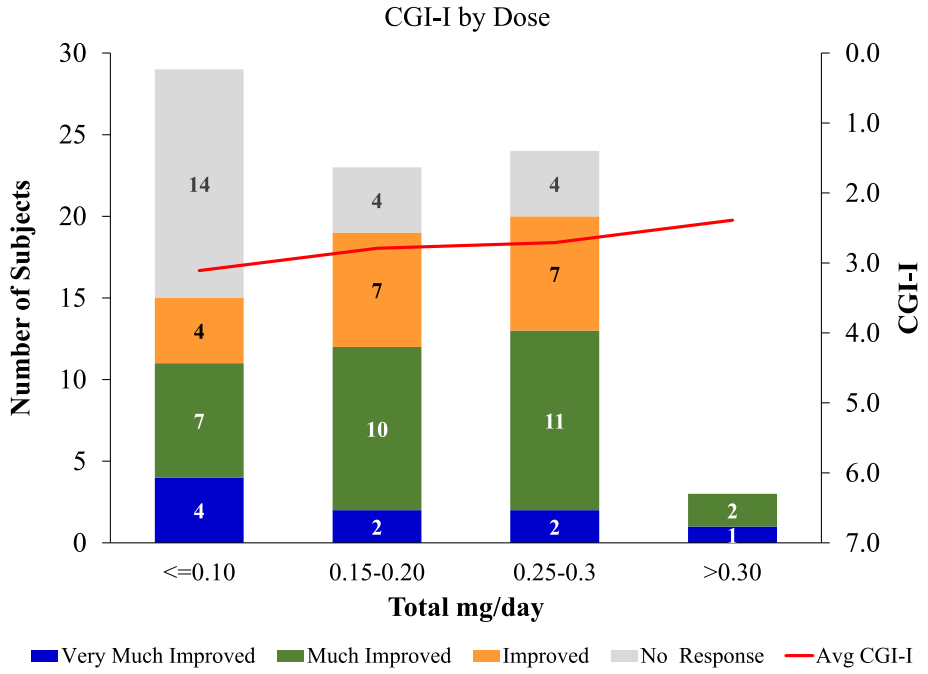

Fig. 1. CGI-I scores by clonidine dosage. Number of subjects in each CGI-I score by clonidine dose range and mean CGI-I score by clonidine dose range (p value = 0.12). P value was determined by ANOVA.

Table 2
CGI score comparisons between groups based on current diagnoses or prescriptions. CGI-S scores were obtained prior to clonidine prescribing; CGI-I scores were obtained following clonidine use. IBS = irritable bowel syndrome; GERD = gastroesophageal reflux disease; ADHD = attention deficit hyperactivity disorder; SNRI = serotonin-norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitor. Prazosin (historical) represents subject switched from prazosin to clonidine.

	CGI-S					CGI-I				
	Diagnosed		Not Diagnosed			Diagnosed		Not Diagnosed		
Diagnoses	CGI-S	N	CGI-S	N	P value	CGI-I	N	CGI-I	N	P value
Traumatic Brain Injury[a]	**5.2**[c]	10	4.8	69	**.04**	3.1	10	2.8	69	.30
Pain[b]	4.9	55	4.7	24	.33	2.9	55	2.8	24	.65
IBS[b]	**5.3**[c]	11	4.8	68	**.002**	3.0	11	2.8	68	.56
GERD[b]	4.9	24	4.8	55	.86	2.8	24	2.9	55	.75
Diabetes[b]	4.5	15	**4.9**[c]	64	**.01**	2.9	15	2.8	64	.85
Obesity[a]	4.9	22	4.8	57	.70	2.9	22	2.9	57	.94
Hypertension[b]	4.7	33	4.9	46	.10	2.9	33	2.8	46	.50
Hyperlipidemia[b]	4.7	30	4.9	49	.33	2.7	30	3.0	49	.17
Erectile Dysfunction[b]	4.8	21	4.8	58	.95	3.2	21	2.7	58	.06
Vitamin D Deficiency[b]	4.7	12	4.8	67	.27	2.9	12	2.9	67	.66
Alcohol Use Disorder[b]	5.0	29	4.8	50	.08	3.1	29	**2.7**[c]	50	**.04**
Cannabis Use Disorder[b]	5.1	7	4.8	72	.05	3.2	7	2.8	72	.22
Opioid Use Disorder[a]	5.0	5	4.8	74	.55	3.8	5	**2.8**[c]	74	**.01**
Cocaine Use Disorder[a]	5.2	5	4.8	74	.15	3.8	5	**2.8**[c]	74	**.01**
Tobacco Use[a]	5.0	17	4.8	62	.25	3.1	17	2.8	62	.25
Insomnia[b]	4.9	23	4.8	56	.23	2.8	23	2.9	56	.69
Depression[b]	**4.9**[c]	39	4.7	40	**.04**	3.0	39	2.7	40	.13
Anxiety[b]	4.6	7	4.9	72	.26	**2.3**[c]	7	2.9	72	**.05**
ADHD[a]	4.7	9	4.9	70	.35	2.7	9	2.9	70	.67
	Prescribed		**Not Prescribed**			**Prescribed**		**Not Prescribed**		
Medications	**CGI-S**	**N**	**CGI-S**	**N**	**P value**	**CGI-I**	**N**	**CGI-I**	**N**	**P value**
ACE inhibitors/ARB[b]	4.8	23	4.9	56	.43	3.0	23	2.8	56	.21
Antipsychotics[a]	4.9	9	4.8	70	.71	3.1	9	2.8	70	.36
Benzodiazepines[a]	4.7	12	4.8	67	.48	2.7	12	2.9	62	.60
Beta blockers[b]	4.6	7	4.9	72	.30	2.8	7	2.9	72	.85
Buprenorphine[b]	5.3	2	4.8	77	.15	3.9	2	2.8	77	.11
Bupropion[a]	5.0	14	4.8	65	.30	3.0	14	2.8	65	.45
Buspirone[a]	5.1	6	4.8	73	.18	2.6	6	2.9	73	.61
Cyproheptadine[a]	5.3	4	4.8	75	.06	3.4	4	2.8	75	.17
Sedative-hypnotics[b]	4.8	14	4.8	65	.92	2.8	14	2.9	65	.65
Melatonin[a]	**5.6**[c]	6	4.8	73	**<.001**	3.2	6	2.8	73	.29
Mirtazapine[a]	4.8	8	4.8	71	.85	3.0	8	2.8	71	.79
Opioids[a]	4.7	11	4.9	68	.35	3.3	11	**2.8**[c]	68	**.04**
Prazosin (historical)[a]	4.8	13	4.8	66	.69	3.3	13	**2.8**[c]	66	**.03**
Stimulants[a]	4.6	4	4.8	75	.36	2.3	4	2.9	75	.26
SNRI[a]	5.1	9	4.8	70	.15	3.0	9	2.8	70	.79
SSRI[a]	4.8	25	4.8	54	.90	**2.6**[c]	25	3.0	54	**.04**
Tramadol[b]	4.9	9	4.8	70	.89	3.0	9	2.8	70	.69
Trazodone[a]	4.9	14	4.8	65	.68	2.8	14	2.9	65	.88

[a] Spearman's correlation coefficient.
[b] Mann-Whitney *U* Test.
[c] Statistically significant.

variables (e.g., comorbid diagnoses, concurrent medications, substance use).

Whereas previous studies relied on the treating clinicians' notes specifying improvement (e.g., note of "frequency of nightmares decreased"), this study measured outcomes based on overall PTSD symptoms and additional global clinical data. Consistent with smaller studies indicating at least partial improvements in nighttime symptoms for 50–60% of the veteran PTSD population on clonidine (Detweiler et al., 2016; Wendell and Maxwell, 2015), 49% of subjects showed "much improvement" or more while on clonidine.

Subpopulation analyses suggested that other clinical variables, such as substance use, potentially influenced outcomes. This is consistent with the reduced efficacy of clonidine with concurrent alcohol dependence (Petrakis et al., 2016). Our analysis indicated reduced reported efficacy (significantly worse average CGI-I score) with comorbid alcohol, opioid, or cocaine use disorders. Interestingly, subjects diagnosed with comorbid anxiety disorder had greater improvements on clonidine. This may be due to similarities between anxiety symptoms and PTSD hyperarousal symptoms, and/or these symptoms could potentially be a function of elevated norepinephrine levels. Additionally, results suggest reduced efficacy in patients who were previously on prazosin. Given that both drugs are anti-adrenergics, it is possible that subjects had some symptom improvement from prazosin, which blunted the potential response to clonidine.

Clonidine has several possible advantages over other medications used for the treatment of PTSD. Unlike paroxetine, sertraline and other SSRIs used for PTSD, clonidine can be effective quickly, not requiring weeks for medication response. Use of clonidine also avoids potential adverse events related to SSRI use, such as sexual dysfunction, drowsiness, and weight gain, as well as any subsequent discontinuation effects (Cascade et al., 2009). Moreover, this study showed significantly more improvement of PTSD symptoms when the patient was prescribed both clonidine and an SSRI. Although the mechanism is unknown, this may be due to synergistic effects of decreased norepinephrine and increased serotonin levels, or perhaps improvement in sleep quality made the SSRI more effective, consistent with previous studies (Arnedt et al., 2016). Compared to other adrenergic agents which antagonize α- or β-adrenergic receptors, clonidine is an α2-adrenergic agonist which reduces the

release of norepinephrine and adrenaline. Mechanistically this should result in reduced cerebrospinal fluid norepinephrine levels.

Importantly, this study identified a low rate of adverse effects, which were categorically consistent with previous studies on clonidine and prazosin in this population (Raskind et al., 2018; Wendell and Maxwell, 2015). Although fewer adverse effects were reported here than previous analyses, the retrospective methodology of this study precluded the ability to directly query patients on common events, potentially resulting in underreporting. Despite 22.8% of subjects reporting minor side effects, only half (11.4%) discontinued clonidine.

One of the main clinical apprehensions with using clonidine has been the concern for rebound hypertension if discontinued abruptly. In this study, clonidine was being used for the treatment of PTSD and not hypertension. Furthermore, even when clonidine has been used to treat hypertension, rebound hypertension has been shown to be a return of blood pressure toward pretreatment levels, as is common with abrupt discontinuation of most antihypertensive medications (Hoobler and Kashima, 1977; Weber, 1980). A rise in blood pressure in excess of pretreatment levels known as "overshoot" hypertension is very rare (Weber, 1980). Rebound hypertension and symptoms of sympathetic overactivity (anxiety, tremulousness, tachycardia, headache, insomnia) were shown to be absent or minimal at dosages of 1.2 mg/day or below (Hoobler and Kashima, 1977; Weber, 1980). In contrast, this study used dosages at or below the threshold of 0.5 mg/day, and therefore subjects were not at risk for rebound hypertension. Another clinical concern is starting clonidine while the patient is on other antihypertensive medications. In this study, 28 subjects were on antihypertensives. Only one subject (on ACE inhibitor only) discontinued due to orthostatic hypotension. Also, clonidine is available in extended-release formulations which may further reduce concern for side effects or rebound hypertension. Future studies should compare immediate-release and extended-release clonidine formulations.

Although these data suggest that open-label clonidine use is correlated with improved PTSD symptoms, the results are limited by study design. Data were collected retrospectively from patient records; therefore, data and CGI scoring were influenced by the records completeness and accuracy. Data were further limited by the relatively small population size of patients with PTSD prescribed clonidine, which resulted in some expected over/underrepresentation of patient groups. For example, although Wisconsin's veteran population was projected to be 91% male and 91% White (State Summaries Wisconsin, 2017), the patient population in this study was 100% male and 71% White. Further, clonidine was provided open-label and without programmed controls, and dosing was not consistent between subjects. These results offer opportunities for future studies using prospective methodologies with control subjects and standardized dosing and titration regimens.

Another limitation is the use of the CGI. Although validated, these are subjective scores influenced by rater experience. Nevertheless, subjectivity was controlled for by utilizing independent raters. Another potential issue is that the CGI accounts for all PTSD-relevant symptoms and does not rate specific PTSD symptoms. As a result, the direct correlation between clonidine and sleep disruption was not directly assessed. Future studies should assess the direct effects of clonidine on sleep disruption and other PTSD symptoms.

5. Conclusion

This is the largest retrospective study assessing clonidine use for PTSD to-date. Low-dose clonidine may be an effective treatment for PTSD and was well tolerated by most subjects with few reported side effects. This study provides valuable evidence for the efficacy and safety of low-dose clonidine in the treatment of PTSD and points to clinical variables that may influence treatment outcomes. Results can inform future studies of clonidine effectiveness using randomized, controlled methods.

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Author statement

Gregory Burek: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project administration.

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Declaration of competing interest

The authors declare no conflict of interest.

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