Pimavanserin 34 mg at Bedtime for the Treatment of Insomnia in 6 Veterans With Posttraumatic Stress Disorder

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Insomnia is the most common and refractory complaint in Veterans with posttraumatic stress disorder (PTSD).[1–3] Preliminary evidence suggests that pimavanserin, a selective 5-HT_{2A} partial agonist/antagonist approved by the US Food and Drug Administration for treatment of Parkinson's disease psychosis,[4] may improve insomnia without producing daytime somnolence or addictive potential.[5,6] Its relative affinity for 5-HT_{2A} receptors and long half-life (~55 hours) represent novel approaches to insomnia treatment.[7] Like other 5-HT_{2A} antagonists, pimavanserin may enhance "deep" (N3) sleep[7,8]; this sleep stage is deficient in patients with PTSD.[9] Accordingly, this open-label pilot study of pimavanserin describes the experience of 6 adult Veterans with active PTSD and chronic insomnia.

Methods

The study was approved by the Institutional Review Board at Baylor College of Medicine and the Research & Development program of the Michael E. DeBakey VA Medical Center (MEDVAMC) and registered on ClinicalTrials.gov (NCT04188392). See ClinicalTrials.gov for additional eligibility information and feasibility outcomes.[10] Briefly, we recruited non-elderly, medically healthy Veterans with chronic insomnia disorder[11] of at least moderate severity[12] and current PTSD[11,13] from clinics at MEDVAMC between December 19, 2019–March 20, 2020 (pandemic) and June 16, 2021–August 8, 2021. Informed consent was obtained from participants prior to any procedure. After initial screening, subjects completed an at-home actigraphy monitoring week (Actiwatch Spectrum Pro, Philips Respironics); a first polysomnogram (PSG) (Sleepware G3, Philips Respironics) to screen for confounding sleep disorders and mitigate the "first night effect";[14] and a second, baseline PSG. Subjects then received fixed dose pimavanserin 34 mg at bedtime for 6 weeks. Dosing and duration mimicked the pivotal trial of pimavanserin for Parkinson's disease psychosis.[4,5] Its half-life permitted bedtime instead of daily dosing. Evaluations occurred at weeks 3 and 6 in person and otherwise weekly via telephone. Treatment concluded with repeat actigraphy, PSG, and an exit visit. PSGs were performed and scored according to standard criteria.[15] Actigraphy rest intervals were manually edited in conjunction with abbreviated sleep diaries completed by subjects.[16] Subjective[12,13,17,18] and objective measures were compared at the prespecified time points of baseline and week 6 with paired, 2-tailed *t* tests. A *P* value of < .05 was considered significant.

Table 1.

Change in Subjective and Objective Measures Pre- and Posttreatment With Pimavanserin 34 mg at Bedtime for 6 Weeks (n = 6)

	Baseline Mean (SD)	Week 6 Mean (SD)	Posttreatment – Pretreatment			
			Mean (SD)	95% CI	*P*[a]	Hedges *g*
ISI	19.83 (4.75)	10.67 (8.76)	−9.17 (11.72)	[−21.47 to 3.13]	.114	−0.659
PCL-5	46.50 (14.73)	29.67 (19.86)	−16.83 (18.23)	[−35.96 to 2.29]	.073	−0.778
PHQ-9	15.00 (5.87)	11.50 (8.34)	−3.50 (9.59)	[−13.56 to 6.56]	.412	−0.307
PSQI (– meds)	13.33 (1.97)	6.25 (3.68)	−7.08 (3.32)	[−10.57 to −3.60]	**.003**	−1.795
pTSTb (h)	3.89 (2.40)	4.88 (1.03)	0.99 (3.03)	[−2.76 to 4.75]	.503	0.263
pSOLb (min)	70.18 (83.92)	55.20 (23.98)	−14.98 (96.58)	[−134.90 to 104.94]	.746	−0.124
pWASOb (min)	40.24 (23.40)	24.88 (14.18)	−15.36 (24.96)	[−46.35 to 15.63]	.241	−0.492
pN3b (min)	21.00 (35.66)	42.70 (44.15)	21.70 (39.57)	[−27.43 to 70.83]	.287	0.439
aTSTavg (h)	6.82 (1.44)	7.05 (1.55)	0.23 (1.55)	[−1.40 to 1.86]	.736	0.123
aSOLavg (min)	50.50 (29.57)	29.72 (24.42)	−20.78 (15.75)	[−37.30 to −4.25]	**.023**	−1.111
aWASOavg (min)	36.27 (11.10)	41.88 (16.06)	5.60 (15.36)	[−10.52 to 21.72]	.413	0.307

[a]Boldface indicates statistical significance.
[b]n = 5 (missing 1 posttreatment polysomnogram due to pandemic).
Abbreviations: aSOLavg = actigraphy average sleep onset latency, aTSTavg = actigraphy average total sleep time, aWASOavg = actigraphy average wake after sleep onset, CI = confidence interval, ISI = Insomnia Severity Index, PCL-5 = Post-traumatic Stress Disorder Checklist for the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, PHQ-9 = Patient Health Questionnaire, pN3 = polysomnography N3 duration, pSOL = polysomnography sleep onset latency, PSQI (– meds) = Pittsburgh Sleep Quality Index (omitting the question about use of sleep medication), pTST = polysomnography total sleep time, pWASO = polysomnography wake after sleep onset, SD = standard deviation.

Results

The characteristics of the 6 subjects were mean age 35.33 ± 6.35 years; 2 (33.33%) females; and mean education of 14 ± 1.79 years. Two (33.33%) were Black or African American, 3 were White (50%), and 1 was "Other" (16.67%). Two (33.33%) were Hispanic or Latino. Three (50%) were Army, 1 (16.7%) Navy, and 2 (33.3%) Marine

Veterans. Time since active duty ranged from 3.6 to 15.6 years. All index traumas were deployment-related. Four (66.67%) had comorbid depressive disorders. One (16.7%) was taking a selective serotonin reuptake inhibitor.

All subjects reported severe sleep initiation insomnia on a nightly basis per the Insomnia Severity Index[12]; 5 additionally had severe sleep maintenance insomnia. No subjects were treated for sleep disordered breathing. One subject had mild obstructive sleep apnea during the screening PSG.

All subjects completed treatment. Subjective sleep quality significantly improved (see Table 1 and Supplementary Figure 1). PTSD trended toward improvement. Of the objective measures, only actigraphy derived sleep onset latency significantly decreased. The most frequent adverse event was mild sleepiness after the first dose (n = 2). No serious adverse events occurred.

After study completion, all subjects requested to continue the medication. Two subjects received non-formulary approval to resume pimavanserin 34 mg at bedtime due to previously unsuccessful medication trials for insomnia.

Discussion

This preliminary experience suggests pimavanserin may be well-tolerated at bedtime in patients with severe insomnia associated with PTSD. Patients reported subjective improvement in their insomnia symptoms and requested to continue the medication after the study. Randomized controlled trials are needed to test the efficacy and safety of pimavanserin against placebo. Future studies should also examine the mechanisms by which pimavanserin may influence sleep quality.

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Supplementary Material

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Figure 1** Change in Subjective and Objective Measures Pre- and Post-Treatment With Pimavanserin 34 mg at Bedtime for 6 Weeks (n=6)

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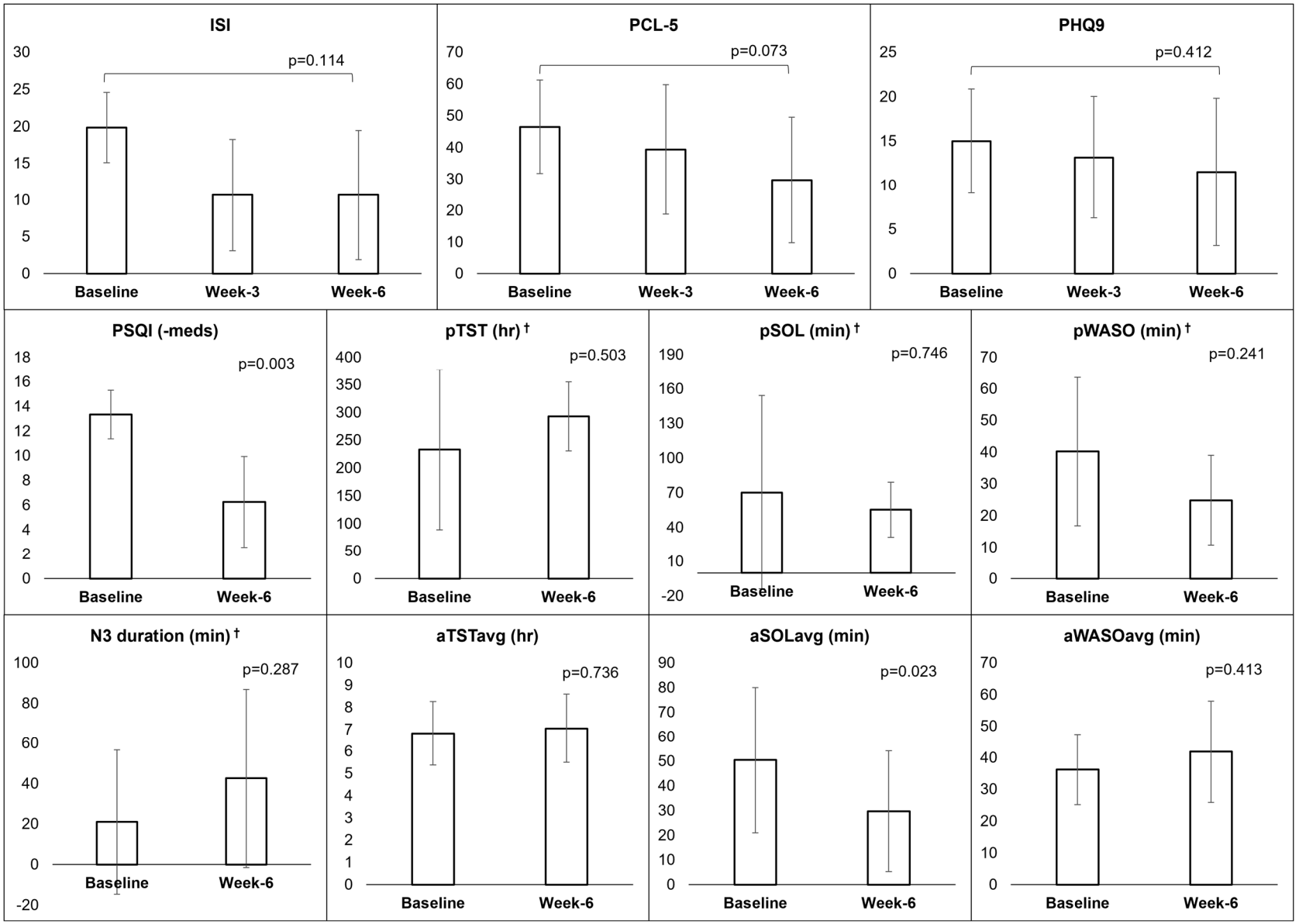

Supplementary Figure 1. Change in subjective and objective measures pre- and post-treatment with pimavanserin 34mg at bedtime for 6 weeks (n=6). Columns and error bars correspond to mean and standard deviations, respectively. ISI=Insomnia Severity Index, PCL-5=Post-traumatic Stress Disorder Checklist for the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, PHQ-9 = Patient Health Questionnaire, PSQI (-meds)=Pittsburgh Sleep Quality Index (– use of medications), pTST=polysomnography total sleep time, hr=hour, pSOL=polysomnography sleep onset latency, pWASO=polysomnography wake after sleep onset, min=minutes, pN3=polysomnography N3 duration, aTSTavg=actigraphy average total sleep time, aSOL=actigraphy sleep onset latency, aWASOavg=actigraphy average wake after sleep onset. †n=5 (missing 1 post-treatment polysomnogram due to pandemic).