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The sleep effects of tiagabine on the first night of treatment predict post-traumatic stress disorder response at three weeks

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Abstract

Introduction: We sought to test the hypothesis that improvements in sleep might mediate treatment-related improvements in daytime symptoms of post-traumatic stress disorder (PTSD). We evaluated whether changes in sleep occurring on the first night of tiagabine (a gamma-amino butyric acid (GABA) reuptake inhibitor) administration predicted subsequent PTSD response.

Methods: This was an open-label three-week polysomnographic (PSG) study of nightly treatment with tiagabine dosing from 2–12 mg including 20 adults with PTSD with ≥ 30 min of self-reported and PSG wake time after sleep onset (WASO).

Results: A treatment night 1 decrease in self-reported and PSG WASO and an increase in slow-wave sleep (SWS) accounted for 94% of the variance in week 3 Short PTSD Rating Interview (SPRINT) score, the primary outcome measure ($p < 0.001$). Increased night 1 SWS also accounted for 91% of the variance in Work/School Impairment and 45% of the variance in Social Life Impairment as measured with the Sheehan Disability Scale ($p < 0.001$). These relationships were much stronger correlates of three-week outcome than three-week sleep effects.

Conclusions: The initial sleep response to tiagabine may mediate or be an indicator of the subsequent PTSD response. The findings highlight the importance of sleep maintenance and SWS in the treatment of PTSD and also suggest a potential relationship between SWS and daytime function.

Keywords

Sleep, tiagabine, post-traumatic stress disorder

Introduction

Post-traumatic stress disorder (PTSD) is defined by the development of a constellation of symptoms following a traumatic event including: persistent and intrusive recollections of the trauma, avoidance of associated stimuli, emotional numbing, and hyperarousal (American Psychiatric Association, 1997). Problems related to sleep are considered core aspects of the disorder and are among the most common difficulties reported by affected individuals (Germain et al., 2008; Maher et al., 2006). In fact, 70–90% of individuals with PTSD report difficulties falling or staying asleep while nightmares related to the traumatic event, a form of intrusive re-experiencing, are also frequently reported (Maher et al., 2006). As has long been noted in patients with insomnia, polysomnographic (PSG) evidence of sleep disturbance is inconsistent in patients with PTSD (Breslau et al., 2004; Carskadon et al., 1976; Klein et al., 2002; Kobayashi et al., 2007).

Among studies reporting PSG alterations in sleep in PTSD, several have reported evidence of sleep disturbance including a decrease in sleep efficiency (sleep time divided by time in bed) and/or an increase in wake time after sleep onset (WASO) (Dow et al., 1996; Mellman et al., 1995a, 1995b, 1997). In one study, patients with PTSD who had disturbing trauma-related dreams had elevated WASO compared with PTSD patients without such dreams (Woodward et al., 2000). There have also been a number of reports of an increase in rapid eye movement (REM) density (the total number of eye-movements in REM divided by the total REM time) or lessened slow-wave sleep (Dow et al., 1996; Mellman et al., 1995b, 1997; Woodward et al., 1996). A recent

meta-analysis of the PSG findings in PTSD concluded that there was evidence for an increase in stage 1 sleep and REM density, and a decrease in slow wave sleep in those with this condition compared with normals (Kobayashi et al., 2007).

In addition, there is evidence that sleep disturbance may be an independent contributor to impairment and may, at least in part, mediate the symptoms of PTSD (Germain et al., 2008). In an uncontrolled study of a non-medication treatment for sleep disturbance in 59 PTSD patients, the subjects experienced improvement not only in sleep but also in daytime symptoms of PTSD (Krakow et al., 2002). The same type of improvement in both sleep and daytime PTSD symptoms was noted in a recent pilot study of seven subjects where a different behavioral intervention for PTSD-related nightmares and sleep disturbance was administered (Germain et al., 2007).

This point of view represents a reversal of the traditional view of the relationship of sleep disturbance and associated conditions,

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wherein the sleep disturbance has long been viewed as a symptom of underlying medical and psychiatric disorders. However, the findings in PTSD find resonance with recent studies of the treatment of major depressive disorder (MDD) and generalized anxiety disorder (GAD), where targeting treatment to insomnia with a hypnotic agent (eszopiclone) in addition to a selective serotonin reuptake inhibitor (SSRI) led not only to improvements in sleep but also led to significant improvement in non-sleep symptoms of MDD and GAD compared with treatment with the SSRI and placebo (Fava, 2006; Krystal et al., 2007; Pollack et al., 2008).

Based on these studies and the evidence from studies of behavioral sleep therapy that sleep might mediate some degree of the symptoms of PTSD, we tested the hypothesis that changes in sleep occurring with the pharmacologic treatment of PTSD might mediate therapeutic effects on daytime symptoms of the disorder. We tested this hypothesis on data from an open-label pilot study in which we evaluated the effects of the gamma-amino butyric acid (GABA) reuptake inhibitor, tiagabine, on both self-reported and PSG measures of sleep in addition to scales of PTSD symptoms in a group of PTSD patients with sleep difficulty (Fink-Jensen et al., 1992). The increase in slow-wave sleep with tiagabine has been noted in other studies with this agent (Walsh et al., 2006a, 2006b) and is of particular interest given the evidence for a decrease in slow-wave sleep in PTSD patients (Kobayashi et al., 2007). In this report, we present results of an analysis of the relationship of the change in polysomnographic sleep indices occurring on the first night of treatment with tiagabine and subsequent improvement in daytime symptoms of PTSD in order to determine if improvements in these PTSD symptoms might be mediated by earlier changes in sleep.

Methods

Design

This was a three-week open-label study of tiagabine treatment. All subjects provided written informed consent prior to completing any study procedures and the trial was approved by the Duke University Medical Center Institutional Review Board.

All subjects meeting initial screening criteria (see below) underwent PSG screening to rule out sleep apnea and periodic movements of sleep and to allow adaptation to the sleep laboratory. A second PSG screening was subsequently carried out following dosing with placebo to determine eligibility in terms of PSG entry criteria and to establish baseline sleep indices (see below). Qualifying subjects were entered into the three-week treatment phase which began the next night at which time they received the initial 2 mg dose of study drug (dosage over the three-week period was titrated based on clinical judgment (see below)) and underwent PSG testing. The difference between PSG indices on this night and the baseline night were used in analysis to determine the relationship with subsequent outcome. PSG tests were also performed after one week of treatment and at the end of the study. Subjects received \$100 for each of the five PSG tests they completed to compensate them for their time and travel.

Subjects

Subjects were recruited through advertisement and clinical referral. Inclusion criteria were as follows: (a) age between 18–75

years; (b) current diagnosis of PTSD, according to DSM-IV, as assessed by the MINI International Neurodiagnostic Interview (MINI; Sheehan et al., 1998) and the Short PTSD Rating Interview (SPRINT; Connor and Davidson, 2001); (c) a score ≥ 8 on items 1–4 of the SPRINT; (d) usual morning rising time between 05:00–09:00; (e) usual bedtime between 21:00–01:00; (f) Clinical Global Impression-Severity (CGI-S; Guy, 1976) score of at least four (i.e. moderate severity) for sleep disturbance at baseline; (g) nocturnal awakenings lasting >30 min for more than three nights per week in the last three months; (h) DSM-IV criterion for insomnia due to a psychiatric disorder; and (i) at least 30 min of WASO on their baseline PSG test.

The exclusion criteria consisted of the following: (a) history of bipolar disorder, schizophrenia or other psychotic disorder; (b) history of treatment with electroconvulsive therapy (ECT); (c) taking medications including zolpidem, zaleplon, benzodiazepines, antidepressants, sedating antihistamines, phenobarbital, primidone, phenytoin, carbamazepine, valproate, gabapentin, topiramate, lamotrigine, or any other antiepileptic drugs; (d) clinically significant medical conditions; (e) clinically significant laboratory abnormalities; (f) having been in an investigational study within the past month; (g) having donated one pint or more of blood within one month of study start date; (h) alcohol or drug abuse/dependence within the past year; (i) smoking more than 15 cigarettes daily and/or getting up at night to smoke; (j) drinking more than eight caffeine containing beverages daily; (k) sleep apnea defined as more than 10 apneas/hypopneas per hour of sleep; or (l) periodic leg movements of sleep defined as more than 10 leg movement related arousals per hour of sleep.

Tiagabine dosing

Subjects received three weeks of open-label treatment with tiagabine. The drug was initiated at 2 mg twice daily for one week, after which it was adjusted based on clinical judgment in 2 mg increments every three days, to a maximum daily dose of 12 mg. After three weeks, subjects were tapered off of study drug by decreasing the dosage by 2 mg every three days. The mean dosage at the end of the three-week treatment period of the study was 6.3 mg/day with the range being 2–12 mg. The dosage at the final visit was evenly distributed among the subjects: 2 mg ($n=4$), 4 mg ($n=4$), 6 mg ($n=4$), 8 mg ($n=4$), 10–12 mg ($n=4$).

Polysomnographic procedures and outcomes

All PSG studies were conducted in the Duke sleep laboratory using Grass-Telefactor Aurora™ Dextlue PSG Recording and Review systems equipped with Twin™ Software. The screening PSG consisted of four electroencephalogram (EEG) channels (C3-A2, C4-A1, O2-A1, O1-A2), one chin electromyogram (EMG) channel, two channels of electrooculogram (EOG) (left eye-A2, right eye-A1), one channel of airflow (nasal-oral thermistor), two channels of respiratory effort (thoracic and abdominal impedance), one channel of pulse oximetry (taken from the index finger), two channels of anterior tibialis EMG (right and left legs) and one channel of body position monitoring. The montage for the four other PSG studies included only EEG, EOG, and submental EMG since they were not used for apnea or leg movement detection. All PSG studies were eight hours duration and started at the usual bedtime for each subject. All PSG records other than the

Table 1. Effects of open-label tiagabine treatment on polysomnographic changes in post-traumatic stress disorder.

Outcome measure	Baseline day 0 ^a	First night day 1 ^a	Week 1 day 8 ^a	Last night day 21 ^a	F value	p value	Baseline to day 21 effect-size ^d
WASO (min)	46.2 (46)	52.4 (47)	36.5 (33)	29.0 (24)	5.5	0.033	0.49
TST (min)	425.4 (64)	403.6 (60)	428.1 (48)	444.2 (55)	0.09	NS	0.33
Latency to persistent sleep (min) ^b	25.1 (29)	30.0 (22)	30.8 (37)	21.0 (21)	0.00	NS	0.16
NAW ^c	9.1 (5.7)	7.9 (5.7)	7.7 (5.4)	6.6 (4.7)	7.7	0.014	0.48
SWS time (min)	81.2 (43)	91.4 (49)	98.9 (38)	104.4 (59)	8.8	0.01	0.45
SWS%	18.5 (10)	22.5 (11)	23.2 (10)	23.5 (13)	7.8	0.014	0.43
REM time (min)	98.2 (27)	88.9 (26)	91.2 (28)	99.0 (26)	1.0	NS	0.02
REM%	22.8 (4.5)	22.0 (5.7)	21.1 (5.5)	22.3 (5.5)	0.4	NS	0.1
Stage 2 time (min)	207.3 (44)	189.3 (37)	209.3 (43)	210.7 (53)	1.1	NS	0.07
Stage 2%	48.8 (8.5)	46.9 (6.9)	49.0 (9.4)	47.4 (10)	0.2	NS	0.16
Stage 1 time (min)	38.6 (23)	34.1 (15)	28.9 (20)	30.1 (18)	9.3	0.009	0.43
Stage 1%	9.9 (8.4)	8.5 (3.6)	6.6 (4.3)	6.8 (4.1)	9.0	0.006	0.51

NAW: number of awakenings; NS: not statistically significant; REM: rapid eye movement; SWS: slow wave sleep; TST: total sleep time; WASO: wake time after sleep onset;

^aResults are given as mean (standard deviation (SD)).

^bTime until 10 min of contiguous sleep.

^cNumber of periods of 1 min or longer occurring out of sleep that are staged as waking.

^dCohen's *D* was calculated as estimate of effect-size (Cohen, 1988).

first one were scored blinded to the time point at which they were recorded by ADK, who is board certified in sleep medicine. Studies were scored using standard criteria (Iber et al., 2007). The stages assigned during scoring were used to generate the PSG indices used in outcome assessment including: WASO, total sleep time (TST); sleep onset latency (SOL); number of awakenings (NAW); minutes of slow wave sleep (SWS); minutes of REM; minutes of stage 1 sleep; minutes of stage 2 sleep; SWS%; REM%; stage 1%; stage 2%; and REM latency.

Outcome measures

PTSD outcome measures included changes from baseline to week 3 (or final evaluation visit) in SPRINT total score (Connor and Davidson, 2001), the Davidson Trauma Scale (DTS; Davidson et al., 2002) and Sheehan Disability Scale (SDS; Sheehan et al., 1996). The SDS consists of three items each of which is a 10-point visual-analog scale evaluating impairment in: (a) work/school function; (b) social function; and (c) family life (Sheehan et al., 1996). These three items were analyzed as separate measures. The a priori primary outcome measure for the study was the SPRINT total score.

We considered using the Clinician-Administered PTSD Scale (CAPS) for DSM-IV as the primary outcome measure as it is the most widely used observer measure of PTSD. However, we choice to use the SPRINT because of evidence that it performs comparably to the CAPS in the assessment of PTSD symptom clusters and total scores, yet it takes significantly less time to complete (Vaishnavi et al., 2006). This was a consideration for our study because we assessed outcome repeatedly throughout the study. Further, the SPRINT has been well validated and has good psychometric properties and includes some items that are clinically relevant (to PTSD) that are not present in the DSM-driven CAPS, such as somatization and stress-tolerance (a proxy for resilience).

In addition to PSG measures, sleep was assessed using self-reported indices of sleep derived from sleep logs which were completed daily, each morning of the study.

Statistical analyses

Analyses included all subjects who completed at least one post-baseline visit and who comprised the intent-to-treat sample, and the last-observation-carried-forward analysis was performed. Analyses for therapeutic effects on PTSD clinical outcome measures and self-reported and PSG sleep variables consisted of repeated measures analyses of variance (see Tables 1–3).

For analysis of the relationship of sleep variables with clinical outcome variables we first carried out exploratory correlation analyses of the change in the PTSD outcome measures (baseline value minus value at end of three-week treatment phase) and the change in PSG indices of sleep from baseline to night 1 (baseline night minus night 1). We then carried out multiple regression analyses in which the change in the PTSD outcome measures (baseline value minus value at end of three-week treatment phase) served as the dependent variables and the change in PSG indices of sleep from baseline to night 1 (baseline night minus night 1) were the independent predictor variables. We employed this analysis of change scores rather than carrying out growth curve or time series analyses because of the small sample size. This analysis was carried out with step-wise inclusion of variables so that only PSG indices that accounted for a significant percentage of variance in the PTSD outcome measures were retained in the models.

In order to control for the increased likelihood of type I errors due to carrying out five multiple regression analyses, the Bonferroni correction was carried out for these multiple regression analyses. A significance level of 0.01 was employed to correct for the fact that five separate regression analyses were carried out, one for each of the five PTSD outcome measures. We only employed Bonferroni correction for the multiple regression analyses as these analyses were the apriori primary outcome analyses for our study.

Results

Forty-nine subjects were screened for this study and 20 of these met the entry criteria and were enrolled. These subjects comprised

Table 2. Effects of open-label tiagabine treatment on self-rated daily sleep diaries in post-traumatic stress disorder.

Outcome measure	Baseline week ^a	Week 1 ^a	Final week ^a	<i>F</i> value	<i>p</i> value	Baseline to final week effect-size ^b
WASO (min)	38.7 (37)	35.9 (40)	26.3 (36)	7.0	0.006	0.34
SOL (min)	45.0 (23)	30.2 (19)	28.7 (28)	16.2	0.001	0.64
NAW	2.75 (0.76)	2.29 (0.45)	2.03 (0.51)	12.5	0.001	1.13
Sleep quality	40.0 (20)	51.6 (21)	54.1 (23)	10.1	0.001	0.64

NAW: number of awakenings; SOL: sleep onset latency; WASO: wake time after sleep onset.

^aResults are given as mean (standard deviation (SD)).

^bCohen's *D* was calculated as estimate of effect-size (Cohen, 1988).

Table 3. Clinical effects of open-label tiagabine treatment on post-traumatic stress disorder.

Outcome measure scores	Baseline ^a (<i>n</i> =20) ^b	Week 3 ^a (<i>n</i> =20) ^b	<i>F</i> value	<i>P</i> value	Baseline to week 3 effect-size ^c
PTSD					
SPRINT total	20.1 (5.5)	13.0 (8.4)	28.3	0.001	1.02
DTS total	70.5 (20.1)	44.6 (32.7)	16.3	0.001	0.98
Resilience					
CD-RISC total score	62.0 (19.8)	70.4 (22.2)	14.4	0.001	0.4
Sleep and nightmares					
PSQI total score	34.5 (5.2)	30.1 (5.6)	9.7	0.006	0.81
PSQI item 5b (woke up at night or early morning)	3.8 (0.5)	3.4 (0.6)	7.7	0.014	0.8
PSQI item 5h (bad dreams)	3.3 (0.8)	2.9 (1.0)	8.3	0.008	0.44
DTS item 2 (distressing dreams) frequency	1.8 (1.2)	1.3 (1.3)	6.0	0.03	0.42
DTS item 2 (distressing dreams) severity	1.5 (1.1)	1.3 (1.2)	3.0	0.11	0.18
DTS item 12 (falling/staying asleep) frequency	3.2 (1.1)	1.6 (1.5)	19.97	0.001	1.23
DTS item 12 (falling/staying asleep) severity	3.6 (0.8)	1.9 (1.5)	27.2	0.001	2.3
SPRINT items (unwanted memories, nightmares)	2.3 (1.0)	1.5 (1.2)	5.5	0.05	0.73
Disability					
SDS total	15.6 (7.3)	10.5 (7.6)	7.5	0.01	0.68
Global severity					
CGI-S	4.8 (0.8)	3.2 (1.4)	30.2	0.001	1.45

CD-RISC: Connor Davidson Resilience Scale; CGI-S: Clinical Global Impression, Severity Scale; DTS: Davidson Trauma Scale; PSQI: Pittsburgh Sleep Quality Index; SDS: Sheehan Disability Scale; SPRINT: Short PTSD Rating Interview.

^aResults are given as mean (standard deviation (SD)).

^bIntent-to-treat (ITT) sample, last observation carried forward (LOCF).

^cCohen's *D* was calculated as estimate of effect-size (Cohen, 1988).

the intention to treat (ITT) sample. Subjects failed to qualify for enrollment because of: not meeting diagnostic criteria for PTSD (*n*=4), active substance abuse (*n*=4), exclusionary psychiatric comorbidity (*n*=10), medical condition or medications (*i*=4), sleep disorder (*n*=1), not meeting insomnia criteria (*n*=2), other (*n*=4). Seventeen subjects completed the study with three terminating early due to side-effects (headache, limited symptom panic attack, tinnitus, and sedation). The data from these three subjects were included in analyses using a 'last-observation-carried-forward' approach.

The intent-to-treat sample was predominantly female (*n*=16; 80%), Caucasian (*n*=11; 55%), single, divorced, or widowed (*n*=15; 75%) and had at least some college education (*n*=11; 55%). The mean age ($\pm$ standard deviation (SD)) was 42.2 (12.9) years. The worst traumatic experiences reported as associated with PTSD were as follows: sexual trauma (*n*=6), sudden death of a loved one or a close friend (*n*=5), physical

assault (*n*=4), domestic violence (*n*=2), accident (*n*=1), and other (*n*=2). At baseline, subjects reported moderate-to-marked PTSD on SPRINT with a mean of 20.1 ($\pm$ 5.5) and associated sleep disruption on CGI-S for sleep with the mean being 4.8 ($\pm$ 0.8).

Dosing and tolerability. The average dose of tiagabine was 6.3 mg at the end of the study. Tiagabine was generally well-tolerated, and the most frequently reported adverse events were dizziness (*n*=4), unsteadiness (*n*=4), nausea (*n*=4), and drowsiness (*n*=3). Two of the subjects noted forgetfulness, headaches, palpitations, swelling, thirst, and uncomfortable urge to move about.

Effects of treatment on PTSD outcomes. In the intent-to-treat sample, repeated measures analyses of variance indicated that

significant improvements were observed on the primary clinical outcome measures including the SPRINT total score, the CGI-S, as well as secondary outcome measures including DTS, Connor Davidson Resilience Scale (CD-RISC) and SDS scores (Table 3).

The overall PTSD remission rate (defined a priori as a CGI-S < 3) was 35%. The remission rate in terms of the SPRINT total score (score of < 9) was 41%, whereas 24% of the subjects met the DTS remission criterion (score < 19).

Effects of treatment on sleep outcomes

Changes in sleep maintenance. Repeated measures analyses of variance indicated that tiagabine treatment was associated with statistically significant improvement in PSG WASO, the primary sleep outcome variable for this study, as well as an additional PSG measure of sleep maintenance, NAW (Table 1). Complementing these effects, with treatment there was significant improvement in self-reported WASO and NAW obtained from daily sleep diaries based on repeated measures analyses of variance (Table 2). There was also significant improvement in the Pittsburgh Sleep Quality Index (PSQI) item 5b, which assesses middle-of-the-night and early morning awakening ($p=0.014$) (Table 3).

Changes in nightmares. Significant improvements in nightmares were observed on the PSQI item 5h (bad dreams), DTS item 2 (distressing dreams) frequency, and SPRINT item 1 (unwanted memories and nightmares (Table 3) were also identified with repeated measures analyses of variance.

Changes in other sleep parameters. Similar to reports in other studies (Roth et al., 2006; Walsh et al., 2006c), tiagabine was associated with an increase in both total amount and percentage of SWS during the night (Table 1). This appeared to occur in conjunction with the decreased WASO noted above, but also at the expense of stage 1 sleep, which decreased significantly over the three weeks of tiagabine treatment (Table 1). Significant improvements in additional self-report indices of sleep included the SOL and sleep quality items on the daily sleep diary (Table 2), frequency and severity of the sleep problems item on DTS (Table 3).

Relationship of changes in sleep indices with treatment and PTSD outcomes. Changes in sleep indices from baseline to the first night of tiagabine treatment were significantly correlated with the change from baseline to the end of the treatment period for a number of the measures of PTSD symptomatology studied (see Table 4) based on exploratory correlation analysis. For the primary outcome measure of the study, the total SPRINT score, which improved significantly with treatment (baseline mean: 20.1, SD=5.5, week 3 mean: 13.0, SD=8.4; $p<0.0001$) significant correlations were found with PSG WASO ($r=0.91$, $p<0.001$), SWS time (-0.81 , $p<0.001$), Stage 1 sleep time ($r=0.94$, $p<0.001$), Number of PSG awakenings ($r=0.78$, $p<0.001$), and self-reported WASO ($r=0.45$, $p<0.01$). These relationships were such that a greater decrease in WASO, Stage 1 sleep time, and awakenings and a greater increase in SWS time were associated with greater reduction in PTSD severity as indicated by the SPRINT score. Greater improvement in PSG WASO ($r=0.6$, $p<0.01$) and self-reported WASO ($r=0.82$, $p<0.001$) was also significantly correlated with the Total DTS score.

A number of significant relationships were also found between day 1 sleep changes and with the change in SDS scores at week 3. Greater improvement in Work Function with treatment was significantly associated with a relative decrease in PSG WASO (0.80, $p<0.001$), Stage 1 sleep time ($r=0.55$, $p<0.01$), and PSG awakenings ($r=0.6$, $p<0.01$) and a relative increase in SWS time ($r=-0.84$, $p<0.001$) on the first night of treatment with tiagabine. Greater improvement in Social Function was significantly associated with a relative decrease in PSG WASO ($r=0.65$, $p<0.01$) and PSG awakenings ($r=0.57$, $p<0.01$) and a relative increase in SWS time ($r=-0.60$, $p<0.01$) on the first night of treatment compared with from baseline. The only significant relationship with the Family Life Function score of the SDS was with self-reported WASO ($r=0.63$, $p<0.01$).

Multiple regression analyses were carried out for the five PTSD outcome measures (see Table 5). Of the sleep measures added stepwise to a model of SPRINT total score, PSG WASO (partial $R^2=0.73$, $p<0.001$), self-reported WASO (partial $R^2=0.14$, $p<0.001$), and SWS (partial $R^2=0.07$, $p<0.01$) were significant contributors to the final model (Total $R^2=0.94$). For the model of the DTS total score, PSG WASO (partial $R^2=0.58$, $p<0.001$) was the only significant predictor variable (total $R^2=0.58$). Greater SWS time was the only variable in the final model of SDS Work/School Impairment (partial $R^2=0.91$, $p<0.001$) and SDS Social Life Impairment (partial $R^2=0.45$, $p<0.01$). None of the predictor variables met the significance criterion for the SDS Family Life Function score model.

These multiple regression analyses were repeated controlling for baseline values in the sleep parameters to determine whether the observed effects might not have been specific to changes occurring with sleep on the first night of treatment but instead reflected relationships between baseline degree of sleep disturbance and clinical outcomes. These repeated analyses indicated that this was generally not the case. For the model of SPRINT total score, a first night decrease in PSG WASO (partial $R^2=0.55$, $p<0.001$) and self-reported WASO (partial $R^2=0.26$, $p<0.001$) continued to be significant predictors after controlling for baseline values, though SWS no longer accounted for a significant amount of variance in SPRINT total score. The model of DTS total score was unchanged by inclusion of baseline PSG WASO such that a greater decrease in PSG WASO (partial $R^2=0.58$, $p<0.001$) continued to predict the pre-to-post change in DTS total score. After controlling for baseline SWS time, a greater first-night increase in SWS time continued to be a significant predictor of SDS Work/School Impairment (partial $R^2=0.64$, $p<0.001$) and SDS Social Life Impairment (partial $R^2=0.24$, $p<0.03$).

In order to further evaluate the nature of the observed significant relationships, exploratory post-hoc analyses were carried out to determine whether the PTSD response to tiagabine is predictable only by the initial sleep response to treatment or whether the sleep response at the end of treatment (three weeks later) was an equal or stronger correlate of the change in PTSD indices (see Table 6). While the effects of tiagabine on the first night of treatment accounted for 94% of the variance in the change in SPRINT total score over the three weeks of treatment, the effects of tiagabine on sleep at the end of the three-week period were not significantly related to the change in SPRINT total score. Some significant relationships were observed with other outcome measures but these were fewer and tended to be weaker associations than were noted with first night sleep effects. There was a

Table 4. Spearman correlations and effect-sizes of change in post-traumatic stress disorder (PTSD) outcome measures from baseline to end of treatment with change in sleep parameters from baseline to first night of treatment.

	Polysomnographic (PSG) sleep measures								Self-reported sleep measures				
	WASO	SWS	Stg1	Stg2	REM	NAW	TST	LPS	SOL	WASO	NAW	TST	Quality
SPRINT total	0.91 ^a /4.9	-0.81 ^a /1.9	0.94 ^a /7.6	-	-	0.78 ^a /1.55	-	-	0.45 ^b	-	-	-	-
DTS total	0.60 ^b /0.56	-	-	-	-	-	-	-	-	0.82 ^a /2.0	-	-	-
SDS Work	0.80 ^a /1.8	-0.84 ^a /2.4	0.55 ^b /0.43	-	-	0.60 ^b /0.56	-	-	-	-	-	-	-
SDS Social	0.65 ^b /0.73	-0.60 ^b /0.56	-	-	-	0.57 ^b /0.47	-	-	-	-	-	-	-
SDS Family	-	-	-	-	-	-	-	-	-	0.63 ^a /0.66	-	-	-

LPS: latency to persistent sleep onset (time until achieving 10 contiguous min of sleep); NAW: number of awakenings; REM: total min of rapid eye movement (REM); SOL: sleep onset latency (time from lights out until sleep onset); Stg1: total min of stage 1 sleep; Stg2: total min of stage 2 sleep; SWS: total min of slow-wave sleep; TST: total sleep time; WASO: wake time after sleep onset.

^a $p < 0.001$; ^b $p < 0.01$; Note the data presented for each variable consist of the Spearman correlation coefficient/effect-size (Cohen, 1988).

Table 5. Results of step-wise multiple regression analyses: Predicting change in post-traumatic stress disorder (PTSD) outcome measures from baseline to end of treatment with change in polysomnographic (PSG) indices from baseline to first night of treatment.

PTSD outcome measure	Total R ² / effect-size	R ² / effect-size PSG WASO	R ² / effect-size SWS	R ² / effect-size Self-reported WASO
SPRINT total	0.94/15.7	0.73^a/2.7	0.07^b0.08	0.14^b0.16
DTS total	0.58/1.38	0.58^a/1.38	-	-
SDS Work	0.91/10.1	-	0.91^a/10.1	-
SDS Social	0.45/0.82	-	0.45^b0.82	-
SDS Family	-	-	-	-

DTS: Davidson Trauma Scale; SDS: Sheehan Disability Scale; SPRINT: Short PTSD Rating Interview; SWS: total min of slow-wave sleep; TST: total sleep time; WASO: wake time after sleep onset.

^a $p < 0.001$; ^b $p < 0.01$; Note: effect-size is $R^2/(1-R^2)$ (Cohen, 1988).

significant correlation between the change in self-reported WASO at three weeks and the DTS total score ($r=0.55$, $p<0.01$). The change in SDS Social Function was correlated with the change in the number of PSG awakenings ($r=0.64$, $p<0.01$), while the change in the SDS Family Life Function measure was significantly correlated with the change in self-reported WASO ($r=0.74$, $p<0.001$). No significant correlates of the SDS Social Function measure were found.

Additional post-hoc analysis was carried out to better delineate the nature of the relationship between changes in sleep on the first night of treatment and subsequent PTSD treatment outcomes. We pursued this because the data presented in Table 1 indicate that the mean values on PSG WASO, one of the key predictors of subsequent PTSD response, indicated worsening of sleep on night 1. We sought to determine whether it was greater improvement in PSG WASO on night 1 or less worsening of PSG WASO on night 1 that was predictive of better PTSD outcome. We addressed this by carrying out exploratory analyses of variance comparing key PTSD outcomes at week 3 in those subjects who had improvement in PSG WASO on night 1 of treatment ($n=8$) vs those who had worsening of PSG WASO on night 1 of treatment ($n=12$)

compared to baseline. We found that those manifesting improvement in PSG WASO had significantly greater improvement three weeks later in SPRINT total score ($F=12.4$; $p<0.003$), DTS total score ($F=6.2$; $p<0.03$), SDS Social Function ($F=11.3$; $p<0.004$), and SDS Work Function ($F=16.8$; $p<0.007$) than those where PSG WASO worsened on night 1.

Discussion

The results of this open-label study provide evidence that the effects of tiagabine on sleep occurring with the first night of treatment are predictive of the subsequent degree of improvement in overall PTSD response as well as the associated improvement in daytime function. With respect to the effects of tiagabine on PTSD symptoms, it is important to note that there has been a negative placebo-controlled trial of tiagabine in PTSD patients (Davidson et al., 2007).

The findings of our study are consistent with the hypothesis, based on studies where behavioral sleep treatment led to improvement not only in sleep but also daytime PTSD symptoms, that improvements in sleep might mediate improvements in PTSD

Table 6. Spearman correlations of change in post-traumatic stress disorder (PTSD) outcome measures from baseline to end of treatment with change in sleep parameters from baseline to end of treatment.

	Polysomnographic (PSG) sleep measures								Self-reported sleep measures				
	WASO	SWS	Stg1	Stg2	REM	NAW	TST	LPS	SOL	WASO	NAW	TST	Quality
SPRINT total	–	–	–	–	–	–	–	–	–	–	–	–	–
DTS total	–	–	–	–	–	–	–	–	–	0.55 ^a /0.43	–	–	–
SDS Work	–	–	–	–	–	–	–	–	–	–	–	–	–
SDS Social	–	–	–	–	–	0.64 ^a /0.68	–	–	–	–	–	–	–
SDS Family	–	–	–	–	–	–	–	–	–	0.74 ^b /1.2	–	–	–

DTS: Davidson Trauma Scale; SPRINT: Short PTSD Rating Interview; LPS: latency to persistent sleep onset (time until achieving 10 contiguous min of sleep); NAW: number of awakenings; REM: total min of rapid eye movement (REM); SDS: Sheehan Disability Scale; SOL: sleep onset latency (time from lights out until sleep onset); SPRINT: Short PTSD Rating Interview; Stg1: total min of stage 1 sleep; Stg2: total min of stage 2 sleep; SWS: total min of slow-wave sleep; TST: total sleep time; WASO: wake time after sleep onset.

^a $p < 0.01$; ^b $p < 0.001$. Note the data presented for each variable consist of the Spearman correlation coefficient/effect-size (Cohen, 1988).

symptoms and daytime function (Germain et al., 2008; Krakow et al., 2002). Another possibility that cannot be ruled out is that the changes in sleep occurring on night 1 of treatment do not, in themselves, mediate the therapeutic PTSD response to tiagabine but are indicators that the key therapeutic process is occurring. A related possibility is that the initial sleep response to 2 mg of tiagabine is an indicator of the potential of an individual to respond to treatment with this agent. As such, the first night could be viewed as a 'tiagabine challenge test' for the physiological potential for a therapeutic PTSD response. The data from this study do not allow a resolution of this uncertainty.

It is particularly notable that the first night sleep effects were much stronger correlates of three-week outcome than three-week sleep effects. This is somewhat unexpected considering that an increase in tiagabine dosage occurred in 80% of the subjects over the three-week period after the first night of treatment. It is important to note that this is not a reflection of a loss of improvement in sleep occurring over the treatment course. In fact, as a group, sleep indices steadily improved over the three weeks of treatment. The reasons for the observed time course of the relationship between changes in sleep and PTSD outcome are unknown.

One possible explanation for this observation is that the increases in dosage which occurred following the first night did not have an impact on therapeutic response. If this model is correct, it would be expected that the same therapeutic response at three weeks would have been observed if everyone had received 2 mg of tiagabine and it would suggest that dosages above this level were superfluous. Based on this logic, a placebo-controlled study of 2 mg of tiagabine for the treatment of PTSD would be of high interest.

There is another possibility for why the first night effects of tiagabine correlate better with three-week outcome than do the three-week sleep effects. It could be that the changes in sleep are, in themselves, therapeutic with respect to PTSD but their PTSD effects do not become manifest for several weeks. According to this hypothesis, increases in dosage occurring over the three-week treatment period would have had effects on sleep that would not have had time to manifest in a therapeutic PTSD effect, thereby leading to a decreased correlation between three-week sleep

indices and PTSD outcome measures. In order to address this question, it will be necessary to carry out studies of a longer duration than the current trial.

Lastly, considering that one large placebo-controlled tiagabine trial of was negative in PTSD patients it must be borne in mind that, in the absence of a placebo control, we have no sure way of ascribing the findings to the drug (Davidson et al., 2007). Placebo-controlled trials will be needed to determine the extent to which non-specific factors including the tendency for subjects to improve over time in this open-label study might have contributed to the findings. There are several factors that motivate carrying out such studies. One is the magnitude of this effect. The effects of tiagabine on sleep on the first night of therapy accounted for 94% of the variance in the SPRINT total score, the primary outcome measure of the study, while the effects on sleep noted after 3 weeks of therapy were not significantly correlated with this measure. Another motivation is to determine whether sleep effects of some treatments are early markers that will predict the likely response to therapies. Further, if the sleep effects, in themselves, turn out to mediate the therapeutic response, this could have a profound impact on clinical practice and would indicate the need to focus efforts on therapies which target sleep in PTSD patients.

The particular aspects of sleep which were predictive of the PTSD response are worthy of note. The strongest relationships with the outcome measures occurred with both self-reported and PSG WASO. This may in part be due to the fact that subjects were required to have a significant degree of self-reported and PSG WASO in order to qualify to participate in this study. At the same time, tiagabine's effect on sleep maintenance on night one was a very consistent correlate of outcome that was noted with both PSG and self-reported WASO as well as number of PSG awakenings.

The relationship between the increase in SWS and outcome is noteworthy and would not have been expected on the basis of subject selection. While SWS was predictive of global PTSD outcome in terms of the SPRINT total score, it was the strongest of all sleep variables in its association with daytime functional outcome. In fact, the change in SWS on night 1 of tiagabine accounted for 91% of the variance in Work Function with treatment and 45%

of the variance in Social Function. A role of SWS and sleep restoration has long been hypothesized. This model derives from evidence that slow-wave activity during sleep is increased following sleep deprivation and following nights of disrupted sleep and is reduced by prior napping (Bonnet, 1987; Dijk et al., 1990; Werth et al., 1996).

While an increase in SWS has been consistently observed with tiagabine (Walsh et al., 2006a, 2006b, 2006c), an association of this effect with daytime functional improvement occurring with treatment of individuals with sleep disturbance has not previously been reported. However, a study of interest in this regard was carried out in 38 normal sleepers who received either tiagabine or placebo during four nights where their sleep was curtailed to five hours per night (Walsh et al., 2006b). Subjects receiving tiagabine during this period of sleep restriction had better daytime performance on the Psychomotor Vigilance Test, and the Wisconsin Card Sorting Task and also reported that they felt more restored by their sleep. The authors hypothesized that these beneficial effects were a consequence of the increase in SWS that occurred with tiagabine treatment (Walsh et al., 2006b). Thus, the results of the current study support further studies of the role of tiagabine and increasing SWS on daytime function and on the process of restoration that occurs with sleep.

The SWS findings of this study also reinforce the importance of SWS in PTSD patients that was noted in a recent meta-analysis indicating that individuals with PTSD are characterized by a decrease in SWS compared with normals (Kobayashi et al., 2007). They suggest the potential benefit of evaluating other treatments that might increase SWS in this population. The recent meta-analysis also observed that PTSD patients tend to have a relative increase in stage 1 sleep and REM density (Kobayashi et al., 2007). Consistent with this observation, there was a significant relationship between the decrease in stage 1 sleep and the therapeutic response to tiagabine. This occurred with the SPRINT Total Score and Work Function. In contrast, while REM density was not specifically measured in this study, no effects of the amount of REM sleep were noted. It will be of interest to determine whether there is a relationship between REM density and outcome in PTSD patients in future research. One consideration in this regard is that tiagabine did not have a significant effect on REM sleep, and as a result, there is a low likelihood of a significant relationship between changes in REM and outcome.

In summary, the effects of tiagabine on sleep on the first night of treatment were significant predictors of PTSD response at three weeks of therapy as well as associated daytime functional changes with treatment. The association of sleep and PTSD outcome was substantially greater with first night sleep effects than with the effects of treatment on sleep noted at three weeks. The effect of tiagabine on sleep maintenance was the strongest predictor of PTSD outcome, while the effects on SWS had a striking association with subsequent daytime functional outcome. Further work will be needed to determine whether these findings reflect that improvements in sleep: (a) mediate the therapeutic response to PTSD treatment; (b) are indicators of the potential to respond to treatment; or (c) signal that key therapeutic processes are occurring but do not, themselves, mediate those effects. It will be important to carry out further work to determine the role of increasing SWS and improving sleep maintenance on PTSD outcome in general, as well as to determine whether the relationships noted in this study occur with treatments other than tiagabine. The results of this study

also support the need to further evaluate the role of increasing SWS on daytime function and sleep restoration. Overall, this study underscores the importance of sleep in PTSD and the salience of improving sleep for the treatment this condition.

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Conflict of interest

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KM Connor is an employee of Merck and Co. Inc.

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