

Trazodone improves the results of cognitive behaviour therapy of primary insomnia in non-depressed patients

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Abstract

OBJECTIVES: Cognitive behaviour therapy (CBT) of primary insomnia is frequently combined with various pharmacological treatments, including sedative antidepressants. The present study was undertaken to evaluate the clinical efficacy of CBT, singly and combined with trazodone pharmacotherapy, for primary insomnia.

DESIGN AND SETTING: Randomised, comparative clinical trial, at a single academic medical centre.

METHODS: Twenty outpatients (15 women, 5 men) with chronic primary insomnia were randomly assigned to CBT or CBT +100mg trazodone and treated for 8 weeks. The treatment outcome was estimated by mean changes from baseline in self-reported clinical scales, sleep continuity data and sleep architecture parameters.

RESULTS: All patients perceived significant subjective sleep improvements. Sleep latency significantly shortened ($p=0.03$), sleep efficiency increased ($p=0.004$) and the total sleep time was significantly prolonged ($p=0.006$) after the CBT treatment in both groups. Sleep architecture showed that the combined approach (CBT + trazodone) resulted in a significant increase in slow wave sleep duration compared to treatment by CBT only ($p=0.04$).

CONCLUSIONS: CBT, singly and combined with the sedative antidepressant trazodone, is effective for the short-term management of chronic primary insomnia. Trazodone combined with CBT significantly increases slow wave sleep duration and this influence seems to be unrelated to its antidepressant effect.

Abbreviations:

CBT	– cognitive behaviour therapy
PSG	– polysomnography
EEG	– electroencephalogram/electroencephalography
REM	– rapid eye movement sleep
NREM	– non-rapid eye movement sleep
SWS	– slow wave sleep (the deeper stages of NREM, i.e., stages 3 and 4)
TST	– total sleep time
SL	– sleep-onset latency
SE	– sleep efficiency (ratio of total sleep time to the time spent in bed multiplied by 100)
WASO	– wake time after sleep-onset
ISI	– insomnia severity index
ESS	– Epworth sleepiness scale
BDI-SF	– Beck depression inventory, short form
BAI	– Beck anxiety inventory
HAM-A	– Hamilton anxiety rating scale

INTRODUCTION

While cognitive behaviour therapy (CBT) has been shown to be substantially effective and is generally considered the first line treatment for primary insomnia (Edinger *et al.* 2001; Morin *et al.* 1999a; 2006), the treatment is not curative; instead it produces an approximately 30–50% reduction in illness severity during acute treatment (Perlis *et al.* 2001). The lack of “cure” has prompted several investigators to assess whether combined treatment (CBT + a medical intervention) might produce larger and/or more persistent clinical effects. To date, there have been two kinds of “augmentation” studies including CBT + benzodiazepines/benzodiazepine receptor agonists (Jacobs *et al.* 2004; Morin *et al.* 1999b; Sivertsen *et al.* 2006) and CBT + modafinil (Perlis *et al.* 2004). The findings from these studies suggest, by and large, that combination treatment does not produce greater sleep continuity effects or more persistent clinical outcomes. To date no investigators have reported the effects of combined therapy on sleep architecture, although two studies have noted that CBT alone produces a 27–38% increase in slow wave sleep (SWS) (Cervena *et al.* 2004; Sivertsen *et al.* 2006). A third possible strategy for augmentation, which to our knowledge has not been sufficiently explored, is the combination of CBT with sedating antidepressants. The therapeutic spectrum of antidepressants is broader than the depression itself, as suggested by the report on improved sleep in patients with organic brain disorder (Palomäki *et al.* 2003) or anticataleptic effects in narcolepsy (Sonka *et al.* 2006), and their off-label use in lieu of hypnotics for the symptomatic treatment of insomnia has considerably increased (Walsh & Schweitzer, 1999). Trazodone was chosen for this study based on its feasibility for long-term use, low abuse potential, positive effects on sleep architecture and negligible daytime residual effects. Despite a paucity of data regarding its efficacy, trazodone is currently the second most commonly prescribed agent for the treatment of insomnia (Mendelson, 2005). Although the precise mechanisms of action are not fully understood, trazodone is thought

to be a weak but specific inhibitor of synaptosomal reuptake of serotonin (5-HT). It also has antagonistic action at the 5-HT_{1A}, 5-HT_{1C}, 5-HT₂ receptors and α 1-adrenoceptors (Haria *et al.* 1994). As demonstrated in several studies, its antidepressive effect combines with sedation and better patient-rated sleep quality (Blacker *et al.* 1988; Mashiko *et al.* 1999; Nierenberg *et al.* 1994). After administration of trazodone, a significant change in sleep architecture was observed in both patients and healthy volunteers. This consisted mostly of an increase in SWS (non-REM stages 3 and 4) and a decrease in superficial sleep stages 1 and 2 (Mouret *et al.* 1988; Parrino *et al.* 1994; Saletu & Saletu-Zyhlarz, 2002; Saletu-Zyhlarz *et al.* 2001; Saletu-Zyhlarz *et al.* 2002). Congruently, normalization of the sleep architecture in patients receiving trazodone has been observed in clinical studies (Hertzberg *et al.* 1996; Saletu-Zyhlarz *et al.* 2001; Warner *et al.* 2001).

Despite these favourable effects, the application of trazodone without any other type of treatment seems to be a disputable method in treatment of chronic primary insomnia. The reason is that pharmacotherapy cannot change the psychopathological basis of primary insomnia and, therefore, guarantee a durable effect. On the other hand, it is plausible to suppose that trazodone may be helpful during CBT. A temporary drug effect can thus be combined with long-lasting re-education and adjustment of the patient's lifestyle.

The hypothesis for the present study was that combined therapy (CBT + trazodone) for chronic primary insomnia would result in a significant improvement of treatment outcome than that achieved by CBT alone. Hence, we have undertaken an evaluation of both subjective change in sleep quality and the modifications of sleep parameters after eight weeks of CBT +/- trazodone treatment.

MATERIAL AND METHODS

Subjects

The study was based on twenty consecutive outpatients meeting DSM-IV criteria for primary insomnia (American Psychiatric Association, 1994) by history for at least three months. Basic data on the patients can be found in Table 1. Exclusion criteria were psychotic disorder, depression, personality disorders, chronic alcoholism, dementia or other organic brain disorder and a chronic administration of hypnotics or other psychotropic drugs. All the patients were in good physical health. According to the PSG examination carried out as part of the study, no signs of sleep-disordered breathing or other sleep disorders except primary insomnia were found in any of the patients. The local ethics committee reviewed and approved this study and written informed consent to participate in the research was obtained from all subjects. The study was carried out in accordance with the latest version of the Declaration of Helsinki.

Clinical examination

The clinical examination consisted of a psychiatric interview and a somatic examination supplemented with a study of sleep quality. All patients kept sleep logs, starting two weeks before the first PSG. A physician board-certified in psychiatry and sleep medicine conducted the sleep interviews and the medical examination. To characterise the insomnia and sleepiness more precisely and to assess the therapy outcome, the self-reported Insomnia Severity Index (ISI) (Bastien *et al.* 2001; Morin, 1993) and the Epworth Sleepiness Scale (ESS) (Johns, 1991) were completed prior to and following CBT. Further, to assess the depressive and anxiety symptomatology, the following inventories were also applied before the start of treatment: BDI-SF (Beck & Beck, 1972), BAI (Beck *et al.* 1988) and HAM-A (Hamilton, 1959).

Design of the study

Following clinical examination, the study began with a two-week observation period when the patients were asked to fill in their sleep logs. Afterwards, a PSG examination ("adaptive") was performed. On the following day, the self-reported sleep scales and psychometric inventories were recorded and another PSG examination ("pre-treatment") was performed. The patients were then randomised into two groups, each with ten subjects. Group A was treated by CBT monotherapy and group B received CBT combined with trazodone (Trittico® AC 150 mg, controlled-release tablets). The dosage was 100mg per night, administered in a single dose in the evening, about 30 minutes before going to bed. The length of the treatment was eight weeks in both groups. The day after the completion of treatment, self-reported sleep scales were recorded and a third PSG examination ("post-treatment") was performed.

Cognitive behaviour therapy

CBT for chronic insomnia (Morin, 1993; Jacobs *et al.* 1996) consisted of eight 60-minute therapy sessions conducted weekly in small groups of five individuals. The purpose of this treatment was to help the patients to identify and modify their dysfunctional insomnia-related thoughts, beliefs and behaviour, and to break the recurring cycle of anticipatory anxiety. The major components of CBT were: (1) sleep education and cognitive restructuring concerning sleep (i.e., recognising and changing distorted attitudes and beliefs about sleep requirements, attributions, effects of sleep loss etc.), (2) sleep restriction and stimulus control (Spielman *et al.* 1987; Bootzin & Nicassio, 1978) (i.e., employing a regular rising time, limiting time in bed to 1.5 hours beyond the average sleep length, using the bedroom for sleep or relaxing activities only, going to bed only when drowsy, and, if not asleep within 20 to 30 minutes, opening eyes and engaging in relaxing activity until drowsy again, with repetition as necessary), (3) review of sleep hygiene principles related to the effects of diet,

exercise, caffeine, alcohol, and environmental factors, (4) cognitive work with autonomic negative thoughts, behaviour, emotion and physical reaction, and cognitive restructuring to change the distorted negative appraisals concerning daily stressors, and (5) progressive relaxation (a set of integrated physiological changes that are consistent with reductions in sympathetic nervous system activity – muscular relaxation and breath focusing, while passively ignoring distracting thoughts).

Sessions were supplemented with educational and directive reading materials.

Polysomnography

The recording montage consisted of EEG, electrocardiogram, two electrooculograms, a bipolar mentalis electromyogram, nasal/oral airflow, thoracic respiratory movements, oxygen saturation and two bipolar tibial electromyograms. The EEG was derived from ten electrodes and recomputed to nine bipolar derivations (F3-T3, T3-T5, T5-O1, F8-T4, T4-T6, T6-O2, Fz-Cz, T3-Cz, and Cz-T4). Bedtime in the sleep laboratory was within one hour of the subjects' typical sleep schedule. Sleep stages, respiratory disturbances, and limb movements were scored according to standard criteria (Rechtschaffen & Kales, 1968) by an experienced somnologist who was blind to the subjects' condition. The scores were registered, serving as a basis for a whole-night hypnogram. The main outcome measures included (1) sleep continuity variables (total sleep time, TST; sleep-onset latency, SL; wake time after sleep onset, WASO; and sleep efficiency, SE) and (2) sleep architecture variables (the amount of time spent in sleep stages 1, 2, SWS and REM sleep).

Statistical analysis

The Independent-Samples T tests were used to compare the demographic measures and baseline level of sleep complaint of the two groups. Within-group changes (pre-treatment to post-treatment) were assessed with Paired-Samples T tests. For data with non-normal statistical distribution (determined by Shapiro-Wilk test), nonparametric statistical tests were used to perform within-group (Wilcoxon signed-rank test) and between-group (Mann-Whitney U test) analyses. Additionally, a 2 × 2 (Time × Intervention) ANOVA analysis with repeated measurement was used in order to investigate whether there were any differences between the two interventions in terms of treatment outcome. In the case of variables with significant pre-treatment differences between groups, an analysis of covariance (ANCOVA), based on a linear relationship between the pre-treatment scores (covariate) and post-treatment scores (variate), was applied. All procedures were performed with statistical software SPSS, version 12.0.1.

Table 1. Pre-treatment characteristics of all subjects included in the study (N=20) and comparison of both subgroups (N=10).

Characteristic	Total (n=20)	CBT (n=10)	CBT + trazodone (n=10)	p value
Demographic variables				
Age, years	47.4 (12.6)	48.6 (13.7)	46.10 (12.0)	0.67 ^a
Sex, women/men	15/5	2/8	3/7	0.50 ^b
Education, years	14.4 (4.1)	15.3 (4.2)	13.5 (4.0)	0.34 ^a
Insomnia duration, years	10.6 (7.0)	10.1 (7.5)	11.2 (6.9)	0.74 ^a
Psychometric variables				
ISI	16.4 (4.5)	16.3 (3.8)	16.4 (5.2)	0.96 ^a
ESS	11.2 (4.3)	10.9 (2.2)	11.4 (5.8)	0.53 ^c
BDI-SF	5.5 (3.7)	5.2 (3.3)	5.7 (4.2)	0.77 ^a
BAI	6.2 (4.5)	5.8 (4.1)	6.5 (5.1)	0.74 ^a
HAM-A	5.4 (4.0)	5.5 (4.0)	5.3 (4.3)	0.85 ^c
PSG variables				
Sleep continuity				
TST, minutes	314.5 (70.6)	323.5 (67.6)	305.6 (76.1)	0.59 ^a
SL, minutes	50.8 (68.6)	36.2 (34.0)	65.4 (91.1)	0.63 ^c
WASO, minutes	102.9 (52.5)	97.3 (41.9)	108.6 (63.2)	0.97 ^c
SE, %	68.0 (16.9)	70.7 (13.7)	65.3 (20.0)	0.49 ^a
Sleep architecture				
Sleep stage 1, minutes	35.4 (19.0)	37.3 (19.0)	33.4 (19.9)	0.44 ^c
Sleep stage 2, minutes	164.8 (53.8)	179.0 (42.0)	150.7 (62.4)	0.25 ^a
SWS, minutes	58.9 (28.3)	42.8 (21.3)	75.0 (25.7)	0.01 ^a
REM, minutes	55.5 (20.8)	64.4 (21.3)	46.6 (19.9)	0.07 ^c

Data are presented as mean with standard deviation in parentheses.

Abbreviations: **CBT** – cognitive behaviour therapy; **ISI** – Insomnia severity index; **ESS** – Epworth sleepiness scale; **BDI-SF** – Beck depression inventory-short form; **BAI** – Beck anxiety inventory; **HAM-A** – Hamilton anxiety rating scale; **TST** – Total sleep time; **SL** – Sleep latency; **WASO** – Wake time after sleep onset; **SE** – Sleep efficiency; **SWS** – Slow wave sleep; **REM** – Rapid eye movement sleep

^a – Independent-Samples T Test; ^b – Fischer Exact Test; ^c – Mann-Whitney U Test;

RESULTS

All twenty patients (15 women and 5 men) completed the treatment protocol. There was no significant baseline difference between the two treatment groups for age, sex, education, insomnia severity and duration, daytime sleepiness, depressive symptomatology and anxiety level (Table 1). Baseline sleep continuity data indicated severe impairment of sleep in all subjects, mainly a prolonged SL with an average duration of 50.8 minutes (normally less than 30 minutes) and substantially reduced SE of 68% on average (normally at least 85%). As can be seen in Table 1, the groups did not differ in the baseline PSG measures for any of the sleep-continuity variables. By contrast, there was a clear difference in the pre-treatment sleep architecture data, where we found a significantly longer duration of SWS ($p < 0.01$) in the CBT + trazodone group, despite the randomisation process.

Clinical outcome ratings

Across both groups we found improvement in the severity of self-reported insomnia and daytime sleepiness evaluated by ISI and ESS, shown by the significant Time effect in repeated-measures ANOVAs ($p < 0.001$ and $p = 0.002$, respectively). There were no significant differences in terms of Intervention effect from pre- to post-treatment between the two interventions, CBT vs. CBT + trazodone (Table 2).

Sleep continuity

Repeated-measures ANOVAs of sleep continuity data yielded significant Time effects for all four variables ($p \leq 0.03$) but no significant effects of Intervention or Time \times Intervention interaction. The results suggest that TST, SL, WASO and SE significantly improved after treatment in both groups, but there was no significant difference in these changes in terms of treatment conditions

Table 2. Comparison of self-reported scales, sleep continuity and sleep architecture parameters across groups of insomniac subjects before and after CBT.

	CBT (N=10)			CBT + trazodone (N=10)			2 × 2 ANOVA (p value)*	
	Pre-treatment	Post-treatment	p value	Pre-treatment	Post-treatment	p value	Intervention	Time
Self-reported sleep scales								
ISI	16.3 (3.8)	10.1 (4.1)	0.008 ^a	16.4 (5.2)	11.0 (4.5)	0.02 ^a	0.78	<0.001
ESS	10.9 (2.2)	9.2 (2.2)	0.006 ^a	11.4 (5.8)	8.1 (5.9)	0.02 ^a	0.87	0.002
Polysomnography (PSG)								
Sleep continuity								
TST, minutes	323.5 (67.6)	359.1 (56.7)	0.02 ^a	305.6 (76.1)	361.9 (47.0)	0.07 ^a	0.75	0.006
SL, minutes	36.2 (34.0)	12.4 (13.3)	0.007 ^b	65.4 (91.1)	14.1 (17.4)	0.05 ^b	0.33	0.03
WASO, minutes	97.3 (41.9)	75.0 (33.2)	0.08 ^a	108.6 (63.2)	74.8 (56.7)	0.13 ^b	0.59	0.02
SE, %	70.7 (13.7)	80.9 (8.0)	0.04 ^a	65.3 (20.0)	80.8 (11.5)	0.04 ^a	0.78	0.004
Sleep architecture								
Sleep stage 1, minutes	37.3 (19.0)	38.5 (21.0)	0.68 ^b	33.4 (19.9)	28.5 (11.1)	0.47 ^a	0.34	0.62
Sleep stage 2, minutes	179.0 (42.0)	197.4 (20.9)	0.12 ^a	150.7 (62.4)	148.2 (60.5)	0.92 ^a	0.06	0.56
SWS, minutes	42.8 (21.3)	40.2 (24.9)	0.96 ^b	75.0 (25.7)	120.3 (61.9)	0.007 ^b	0.04 ^c	N.A.
REM, minutes	64.4 (21.3)	83.0 (47.9)	0.22 ^b	46.6 (19.9)	65.0 (26.8)	0.03 ^a	0.13	0.06

Data are presented as mean with standard deviation in parentheses. Characters in bold indicate significance ($p < 0.05$).

Abbreviations: **CBT** – cognitive behaviour therapy; **ISI** – Insomnia severity index; **ESS** – Epworth sleepiness scale; **TST** – Total sleep time; **SL** – Sleep latency; **WASO** – Wake time after sleep onset; **SE** – Sleep efficiency; **SWS** – Slow wave sleep; **REM** – Rapid eye movement sleep; **ANOVA** – Analysis of variance; **N.A.** – non applicable.

^a - P value is based on Paired-Samples T tests to examine time effects within each treatment condition compared with pre-treatment.

^b - P value is based on Wilcoxon signed-rank tests to examine time effects within each treatment condition compared with pre-treatment.

^c - P value is based on ANCOVA statistic (with pre-treatment values as a covariate) due to significant difference of pre-treatment values.

* - P values refer to (2[intervention]×2[time]) interactions using repeated measurement ANOVAs with Bonferroni-corrected post hoc comparisons.

(Table 2). Within-groups analyses showed significant pre-treatment to post-treatment changes in SL and SE ($p \leq 0.05$), a significant increase in TST duration in the CBT group ($p = 0.02$) and a trend toward significance of TST duration in the CBT + trazodone group ($p = 0.07$).

Sleep architecture

Statistical analyses were performed on the amount of time spent in sleep stages 1, 2, SWS (sum of the minutes spent in sleep stage 3 and 4) and REM sleep. Based on the length of stage 1 and 2, none of the groups exhibited significant pre-treatment to post-treatment change (Table 2). Regarding the duration of REM sleep, a significant post-treatment increase was observed only within the CBT + trazodone treated group ($p = 0.03$), but there was no significant Intervention effect in repeated-measures ANOVAs, thus suggesting that the two groups did not significantly differ in REM duration changes in terms of treatment conditions. The statistical analysis of SWS (based on ANCOVA due to significant difference of pre-treatment values between groups) showed that only the combined treatment (CBT + trazodone) produced a significant increase compared to CBT alone ($p = 0.04$).

DISCUSSION

The present study was designed to evaluate whether combining a sedative antidepressant with CBT positively affects treatment outcome of patients with primary insomnia. Trazodone was chosen as a representative due to its feasibility for long-term use, low abuse potential and positive influence on increase in SWS duration and reduction of NREM stages 1 and 2 in healthy controls (Yamadera *et al.* 1998).

The present findings indicate that CBT, both alone and in combination with trazodone, is effective in the short-term management of chronic primary insomnia. The two treatment groups demonstrated significant sleep improvements and a decrease in daytime sleepiness according to the self-reported ISI and ESS scales. In accordance with previous studies (Cervena *et al.* 2004; Edinger *et al.* 2001; Morin *et al.* 1999b; Perlis *et al.* 2001), CBT produced the largest effect on sleep fragmentation parameters and consequently on TST. For the whole group, SL and WASO were significantly decreased by 74% and 27% respectively. This significant decrease in sleep fragmentation was responsible for the 19% increase in SE and the 15% increase in TST.

The results of our study partially confirmed our hypothesis that a combined approach (CBT + trazodone) would result in a significant improvement of treatment outcome compared to that achieved by CBT only. Based on the self-reported inventories and sleep continuity measures (TST, SL, WASO, SE) the combined treatment was not more effective than CBT alone. However, a combined approach produced considerable changes in sleep architecture (i.e. the duration of individual sleep stages) with a significantly prolonged duration of SWS. This effect was not observed in the group of patients treated by CBT only.

SWS is thought to be the most "restorative." There is indeed evidence that SWS plays a role in waking neurobehavioural function (Bonnet, 1986), particularly in memory consolidation (Marshall *et al.* 2006; Stickgold, 2005), but it is also important for peripheral physiological function (e.g. maintenance of normal glucose homeostasis) and its reduction may increase the risk of type 2 diabetes (Tasali *et al.* 2008).

According to observations in patients with depression, trazodone increases SE, TST and both SWS and REM (Saletu & Saletu-Zyhlarz, 2002; Saletu-Zyhlarz *et al.* 2001). Nevertheless, the baseline data of patients participating in our study showed an average BDI-SF of 5.5 (\pm 3.7), an average BAI of 6.2 (\pm 4.5) and an average HAM-A of 5.4 (\pm 4.0) suggesting that they were not in the clinically significant range for depression or anxiety disorders. Although these average scores could represent some subclinical levels of symptoms, the presence or absence of depression or anxiety does not seem to be substantial enough to explain the favourable effect of trazodone in patients with sleep disturbances.

A possible objection is that trazodone treatment could be used alone and that combination with CBT is unnecessary. In fact, our study does not address this issue. The main argument against chronic drug intake is that it does not affect the pathological mechanisms that are responsible for maintaining chronic insomnia in the patients.

Several factors may limit the generalisability of the findings. First, the effect of trazodone was not compared with a placebo. However, the aim of the study was not to verify the efficacy of an antidepressant, which is already known, but to compare the effects of CBT with and without this additional therapy. It may also be questioned whether or not objective indicators sufficiently reflect an improvement in subjective feelings. This is a common problem in clinical sleep studies showing that patients are not able to correctly estimate sleep quality and sleep continuity (Matousek *et al.* 2004). Therefore, our argumentation is mostly based on the objective indicators obtained by PSG in this study.

Objections may also arise concerning the limited size of the treated groups. The limiting factor was, of course, the difficulty in finding patients with primary insomnia who were drug-free, and not taking hypnotics or other psychotropic drugs. The sizes of the subgroups

made direct comparison impossible because it would make the conventional statistical treatment inadequate. Therefore, a rather complicated way of evaluating the data with repeated-measures analyses of variance was used. Regardless of the size of the subgroups, a significant result can be taken as support for the hypothesis. Moreover, the differences might be more pronounced, and cover more sleep variables, with an increased number of observations. These are certainly issues that should be addressed in future studies.

Given these limitations, the results may not be fully generalisable to patients with chronic primary insomnia and the study did not produce clear suggestions about which patients should be selected for additional treatment with trazodone. Another important question is whether or not the effect is sustained and, therefore, additional follow-up studies are needed to determine the essential therapeutic components of this intervention.

CONCLUSIONS

Our data demonstrated that both CBT monotherapy and its combination with trazodone are effective in the treatment of chronic primary insomnia. However, trazodone combined with CBT restores SWS more effectively than CBT monotherapy and this influence seems to be unrelated to its antidepressant effect.

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