Effects of trazodone on insomnia and anxiety in depressed patients: a clinical and sleep EEG study

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Clinical and sleep EEG effects of trazodone in major depression were investigated using a 5-week single-blind study design. Nine patients with DSM-IV major depression were selected. Trazodone (50–250 mg) was given following a 2-week placebo run-in period. Both sleep and psychiatric evaluations were performed at different time points. Early and persistent sleep-inducing effects were detected, including the improvement of objective insomnia features and increased amounts of slow wave sleep. However, no significant changes of REM sleep measures were found. The sleep EEG changes seem to be related to the clinical improvement of both anxiety and insomnia, but there is no apparent relationship with the antidepressant action, which occurs at a later stage of the treatment. Trazodone may be useful in depressed patients, either as a hypnotic-like agent or as an effective antidepressant drug with beneficial effects on sleep. (*Int J Psych Clin Pract* 1997; 1: 281–286)

Keywords
anxiety *major depression*
sleep *trazodone*

INTRODUCTION

The great majority of depressed patients have insomnia, which is commonly reported as a long-lasting disturbance.[1,2] Furthermore, among tricyclic agents and selective serotonin re-uptake inhibitors (SSRIs), several antidepressants may cause insomnia or exacerbate pre-existing insomnia.[3–5]

Trazodone is a triazolopyridine derivative widely used as an antidepressant agent.[6] Along with its antidepressant efficacy, trazodone seems to possess hypnotic-like properties; several clinical and polysomnographic studies suggest its beneficial effects on sleep in a variety of clinical conditions, including 'poor sleepers',[7] depression[8–10] and antidepressant-induced insomnia.[11] More recently, the antidepressant nefazodone has been shown to improve sleep in depressed patients.[12] Taken together, these data suggest that these compounds may be useful in the management of depression, especially when anxiety and insomnia are prominent complaints.

The use of sedative tricyclic antidepressants as hypnotic agents is a controversial issue.[13] In addition to the well-known undesirable side-effects of tricyclics, polysomnographic studies have demonstrated that these drugs tend to disrupt the sleep macrostructure, with potentially deleterious consequences for day-time well-being and performance.[4,5] Therefore it is important to determine whether trazodone has clear advantages in this respect.

In spite of some discrepancies, probably due to methodological differences (in relation to baseline conditions and treatment schedules), the polysomnographic data indicate that trazodone has potentially therapeutic sleep-inducing properties. Beneficial effects on sleep duration and continuity have consistently been reported in patients with complaints of insomnia;[7–10] a clear increase in slow wave sleep (SWS) was found in at least two studies conducted in depressed patients;[9,10] and increased sleep stages 2 and 3 with no changes in stage 4,[8] and a trend toward SWS increase,[14] have been found in other studies. In normal subjects, trazodone significantly increases stage 4 sleep.[15] With a single exception,[14] relatively modest effects on rapid eye movement (REM) sleep have been reported,[8–10] apparently confined to an increase in latency with no changes of REM sleep percentage. On the contrary, it is well established that most classic antidepressants and SSRIs—including sedative compounds—have mixed effects on SWS and a powerful effect in suppressing REM sleep.[3,4,16]

Trazodone is a potent 5-HT_2 receptor antagonist.[17] It has been demonstrated that this action is involved in sleep-inducing effects and selective increases of SWS.[18] Trazodone is able to produce this type of effect, with no significant disruption of sleep architecture. New studies are needed to clarify the effects of nefazodone on sleep, but its strongest pharmacological action is 5-HT_2 blockade.[17] The 'restorative effects' of SWS have been hypothesized[19] and the promotion of SWS is currently considered a desirable effect as far as the 'quality' of sleep is concerned. However, it is unclear whether the increase of SWS is relevant in counteracting depression. It has been hypothesized that SWS disturbances play a pathogenic role in depression,[20,21] but other theories have assumed that REM sleep dysfunctions play a primary role.[22,23] Moreover, data on the effects of antidepressant treatments on SWS make a possible link between the increase of SWS and antidepressant efficacy unlikely.[4] Alternatively, it has been suggested that an increase in SWS contributes to the improvement of anxiety and insomnia, and therefore constitutes a valuable therapeutic approach whenever those symptoms are a major concern.[24,25]

There is limited information regarding the sleep EEG effects of trazodone, and new data are needed in order to confirm its reported advantages for quality of sleep. Also, the therapeutic contribution of changes in sleep patterns remains obscure. Our main objective was to evaluate the effects of trazodone on sleep EEG in depressed patients, and to determine the relationships between those effects and depressive and anxiety symptoms.

METHODS

Nine patients with a diagnosis of major depression without melancholic features, according to DSM-IV[26] criteria, were selected. They were recruited from a population of outpatients attending the psychiatric clinic of a university hospital in Lisbon. An initial score of at least 18 on the Hamilton Depression Rating Scale (HAM-D; 17 items)[27] was required, and, for the item 'suicide', an initial score not exceeding 1. All subjects were women, aged between 32 and 55 years (mean 43.33; sd = 7.37); the duration of their illnesses ranged between 3 and 15 years (mean 8.78; sd = 4.21). Patients gave their informed consent after explanation of procedures and possible side-effects; approval for the study was given by the Ethics Committee of the Faculty of Medicine, University of Lisbon.

The following exclusion criteria were used:

1 Patients suffering from concomitant mental illness other than the target indication;
2 A diagnosis of organic or neurological disorders;
3 Patients receiving any medication that could not be discontinued (with the exception of oral contraceptives);
4 Alcohol abuse and addiction to other drugs;
5 Shift workers;
6 Pregnancy or lactation and—in the case of women of child-bearing potential—absence of contraceptive measures.

All patients started the study with a 2-week placebo run-in period (single-blind) at day −13. After this, patients were eliminated from the study if their total score on the HAM-D dropped below 15 (day 0). The remaining patients then received (single-blind) active medication with trazodone for 5 weeks.

The following medication schedule was used: trazodone 50 mg during the first 2 days; 100 mg at days 3 and 4; 150 mg at days 5 and 6; 250 mg from day 7 on (once a day; evening dosages).

Psychiatric evaluations were performed on days −13, 0, 8, 21 and 35; day −1 was an adaptation night for the patients to become accustomed to recording discomfort; at day 0 the last tablets of the run-in placebo phase were administered (sleep was monitored between 11 p.m. and 7 a.m. to check for baseline data); between days 1 and 35 active treatment (trazodone) was taken daily; days 7 and 34 were adaptation nights (as day 0); sleep recordings took place at days 8 and 35 (as day 0); day 35 was the last day of medication intake. Body weight, blood pressure (at the end of the interview, with the patient seated) and pulse rate were measured at days −13, 0, 8, 21 and 35.

Sleep recordings were performed in a sleep laboratory. Electrodes were placed according to a standard and internationally accepted configuration. Polysomnography included the use of six EEG electrodes, according to the 10–20 system (F4, FZ, C4, CZ, C3, O2), electro-oculogram (EOG) with two electrodes at the outer corner of the eyes, and submental electromyogram (EMG). Between 'lights-out' at 11 p.m. and awakening the following morning with 'lights-on' at 7 a.m., recordings were carried out continuously during the whole 8-hour period. Sleep records were scored according to the criteria of Rechtschaffen and Kales[28] by an experienced electroencephalographer unaware of the diagnosis and treatment conditions.

At each night on which sleep recording took place (days 0, 8 and 35), self-assessments of the subjective quality of sleep and the subjective state at waking were made using Oswald's visual analogue scales[29] and the HAM-D insomnia items.

Psychiatric measurements were carried out by the Hamilton scales for anxiety (HARS)[30] and depression (HAM-D; 17 items)[27] and the Beck Depression Inventory (BDI).[31]

ANOVA-repeated measures were used for statistical comparisons between observations; post-hoc comparisons were made by the Scheffé test.[32]

RESULTS

The results are summarized in Tables 1–4. For each variable, the average and standard deviation are indicated, together with the F-values (ANOVA–repeated measures); statistically significant differences ($P < 0.05$) among observations according to post-hoc comparisons by the Scheffé test are also indicated.

Table 1
Anxiety and depression scores (mean ± sd)

	Day 0	Day 8	Day 21	Day 35	ANOVA F-value	ANOVA P
HARS						
Psychic anxiety	12 ± 3.04	7.67 ± 2.5[a]	6 ± 3[a]	4.56 ± 3.81[a,b]	53.57	< 0.001
Somatic anxiety	11.89 ± 4.4	8.33 ± 4.18[a]	6.22 ± 4.99[a]	5.56 ± 4.45[a]	12.49	< 0.001
Total	23.89 ± 7.11	16 ± 6.28[a]	11.56 ± 6.95[a]	10.11 ± 7.78[a,b]	29.83	< 0.001
HAM-D (total)	24 ± 3.67	19.78 ± 4.15	14.56 ± 6.62[a]	13.33 ± 6.89[a,b]	15.02	< 0.001
BDI (total)	28.89 ± 8.22	27.22 ± 12.67	13.44 ± 7.28[a,b]	14.67 ± 10.82[a,b]	19.33	< 0.001

Post-hoc comparisons by the Scheffé test: $P < 0.05$; [a]vs day 0; [b]vs day 8.

Table 2
Subjective quality of sleep and morning vigilance (mean ± sd)

	Day 0	Day 8	Day 35	ANOVA F-value	ANOVA P
Sleep quality	67.67 ± 17.34	40.22 ± 17.09[a]	40.67 ± 23.49[a]	5.16	< 0.05
Morning vigilance	63.11 ± 16.38	40.89 ± 10.23[a]	33.78 ± 8.93[a]	17.18	< 0.001

Post-hoc comparisons by the Scheffé test: $P < 0.05$; [a]vs day 0.

Table 3
HAM-D insomnia items (mean ± sd)

	Day 0	Day 8	Day 35	ANOVA F-value	ANOVA P
Early insomnia	2 ± 0	0.67 ± 0.71[a]	0.44 ± 0.53[a]	25.96	< 0.001
Middle insomnia	1.67 ± 0.5	0.56 ± 0.53[a]	0.56 ± 0.53[a]	15.09	< 0.001
Late insomnia	1 ± 0.87	0.11 ± 0.33	0.33 ± 0.71	3.78	< 0.05

Post-hoc comparisons by the Scheffé test: $P < 0.05$; [a]vs day 0.

Data from psychiatric rating scales (HARS, HAM-D and BDI) are shown in Table 1. Statistically significant differences were found for all measures, when all observations were compared. Post-hoc comparisons show significant reductions of anxiety scores at days 8, 21 and 35 as compared to day 0; furthermore, HARS 'psychic anxiety' and total scores are significantly reduced at day 35 as compared to day 8. With regard to depression measures, significant reductions of both HAM-D and BDI total scores, as compared to day 0, are detected at days 21 and 35; in the same direction, as compared to day 8, statistical differences are observed at days 21 and 35 for the BDI score and at day 35 for the HAM-D score. No significant differences were found between days 21 and 35. Treatment with trazodone was well tolerated and no patient dropped out from the study.

Data from clinical sleep evaluations are presented in Tables 2 and 3. As compared to day 0, significant improvements of sleep complaints were detected at days 8 and 35 for all measures, with the exception of 'late insomnia' (HAM-D). No differences were observed between days 8 and 35.

Concerning sleep EEG variables (Table 4), statistically significant differences were detected at day 8 as compared to day 0, in total sleep time, sleep latency, wake percentage, stage 2, stage 4 and stages 3+4. These all indicate objective improvements in sleep duration and quality. Significant changes were also observed at day 35 (as compared to day 0) in sleep efficiency, total sleep time, sleep latency, wake percentage and stage 2 sleep. No significant differences were detected between days 8 and 35.

Table 4
Sleep EEG variables (mean ± sd)

	Day 0	Day 8	Day 35	ANOVA F-value	ANOVA P
Sleep efficiency	78.65 ± 18.37	88.52 ± 8.64	90.34 ± 9.43[a]	4.4	< 0.05
Total sleep time, min	302.06 ± 72.13	393.69 ± 29.37[a]	416.64 ± 33.59[a]	16.65	< 0.001
Sleep latency	50.39 ± 14.22	23.86 ± 18.15[a]	27.03 ± 14.13[a]	6.51	< 0.01
Morning wake time	130.58 ± 79.88	89.22 ± 52.08	83.72 ± 64.04	1.81	NS
Wake, %	17.02 ± 6.14	10.37 ± 7.37[a]	10.23 ± 4.16[a]	5.02	< 0.05
Stage 1, %	11.51 ± 4.12	15.03 ± 7.19	14.02 ± 3.89	1.5	NS
Stage 2, %	60.81 ± 4.78	45.62 ± 9.96[a]	50.42 ± 9.48[a]	8.52	< 0.01
Stage 3, %	6.24 ± 2.99	9.93 ± 3.9	8.65 ± 6.06	1.32	NS
Stage 4, %	3.13 ± 2.78	8.08 ± 3.9[a]	7.09 ± 5.21	3.98	< 0.05
Stages 3+4, %	9.36 ± 4.42	19.24 ± 5.86[a]	16.85 ± 8.13	6.27	< 0.01
REM sleep, %	19.22 ± 4.44	20.9 ± 5.63	17.63 ± 5.32	1.02	NS
REM latency, min	70.56 ± 19.64	90 ± 42.44	82.19 ± 40.48	1.29	NS
REM efficiency	67.93 ± 14.48	74.33 ± 13.6	69.8 ± 18.2	1.09	NS

Post-hoc comparisons by the Scheffé test: $P < 0.05$; [a]vs day 0; NS, not significant

DISCUSSION

The results show a significant improvement in anxiety symptoms and clinical and EEG sleep disturbances at day 8. The objective effects on sleep include a reduction in sleep latency, an increase in sleep duration, and improvement of sleep continuity, as well as an increase of SWS percentages (along with % reductions in stage 2), in the absence of any change of REM sleep features. These objective effects tended to persist during the period of the study, since no significant changes were observed between days 8 and 35. However, as compared to baseline, no increase in SWS percentages (stages 4 and 3+4) was detected at day 35. A statistically significant antidepressant effect was identified only at day 21 and remained unchanged at day 35.

We were unable to detect any significant changes of REM sleep features, although an increase in REM sleep latency (with no changes in REM sleep percentage) had been observed in previous polysomnographic studies.[9,10] This may be due to different doses and treatment schedules. The available data suggest that trazodone—as well as some new antidepressant agents[33,34]—does not induce the full REM sleep-suppressing effect typically associated with antidepressant action. The dosage used in this study may explain the absence of effects on REM sleep, as well as the fact that the antidepressant effect was relatively modest. We detected a statistically significant reduction of depression scores following 3 weeks of treatment, but these changes are less dramatic than those observed with higher doses of trazodone, or reported with most antidepressants.[6]

It has been hypothesized by Vogel[22,23] that REM sleep suppression is the mechanism by which classic antidepressants produce their therapeutic effect. Polysomnographic data in depressed patients treated with trazodone seem to argue against that possibility, suggesting that REM sleep suppression is not required for antidepressant efficacy. However, Vogel's hypothesis addresses 'endogenous' depression, and it is not clear whether this type of depression can be effectively treated with new antidepressant agents which do not induce REM sleep suppression, or at least with doses and/or treatment schedules not associated with this sleep effect. According to our results, antidepressant efficacy does not require changes in REM sleep cyclicity in non-melancholic depressed patients, but this conclusion cannot be generalized to all types of depression. But perhaps many different mechanisms of action, yet to be fully established, may contribute to distinctive therapeutic profiles.

Our results confirm previous observations that trazodone improves sleep and increases SWS, in normal subjects,[15] 'poor sleepers'[7] and in depressed patients.[9,10,14] This effect is identical to that observed with other 5-HT_2 antagonists and is probably explained by this biochemical action. SWS and REM sleep features are not modified by nefazodone, but early improvement of anxiety and insomnia also occur with this compound; 5-HT_2 receptor blockade is probably responsible for the beneficial effects on sleep, but nefazodone has also some activity as a serotonin re-uptake inhibitior.[12,17] Furthermore, the early objective effects on sleep are associated with the onset of improvement in both anxiety and insomnia, but have no apparent relationship with the antidepressant action. Indeed, significant antidepressant activity occurred after 3 weeks of treatment, and persisted until the end of the treatment.

In line with other psychopharmacological data, our observations do not support the hypothesis that 5-HT_2 receptor blockade contributes to antidepressant activity. Antidepressants produce a variety of effects on sleep, and some 5-HT_2 receptor antagonists increase SWS but do not possess antidepressant properties. In previous studies, we have

observed that the increase of SWS induced by ritanserin, a potent and selective 5-HT_2 receptor antagonist, was related to a global clinical improvement of patients with mild and mainly 'neurotic' forms of depression.[24,25] Therefore it is conceivable that the increase in SWS may be useful for the treatment of anxiety, insomnia and emotional disturbances, but this action should be differentiated from the antidepressant effect.

Since trazodone has these effects on sleep, it may be useful in treating the symptom of insomnia in depressed patients. The beneficial effect on sleep, along with the improvement of associated symptoms of anxiety, is rapidly obtained with low doses of trazodone, and persists when doses are increased to reach the threshold for antidepressant efficacy. Along with data from other studies, our observations provide a rationale for the use of trazodone in depressed patients, either as a hypnotic-like agent (low doses being effective for this purpose) or as an effective antidepressant drug with beneficial effects on sleep.

KEY POINTS

- Most antidepressant drugs suppress REM sleep, and many have untoward effects or slow wave sleep
- Treatment with trazodone increased sleep duration, improved sleep continuity, and increased the proportion of slow wave sleep
- Drugs with 5-HT_2 receptor antagonist properties may be useful for the treatment of anxiety and insomnia, as well as depression

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