# The effects of nefazodone on women with seasonal affective disorder: clinical and polysomnographic analyses

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**Objective:** To outline the clinical and polysomnographic changes induced by nefazodone in patients with seasonal affective disorder. **Methods:** Twelve patients were enrolled, and 9 of them studied, in an open-label trial with objective and subjective measurements. The mean age of the studied patients was 45 (range 35–58) years. They met *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), criteria for major depressive disorder and current major depressive episode with seasonal patterns. The patients' mean baseline score on the Seasonal Patterns Assessment Questionnaire (SPAQ) was 15.7 (standard deviation [SD] 5.3). The total nefazodone treatment period was 8 weeks, and the daily dosages were 100 mg in week 1, 200 mg in week 2, 300 mg in week 3, and up to 400 mg in weeks 4–8. Each patient received the 29-item version of the Hamilton Rating Scale for Depression (HAM-D), the Hamilton Rating Scale for Anxiety (HAM-A) and 2-night polysomnographic assessments on 3 occasions: before treatment (baseline, W0), at the end of week 4 (W4) and at the end of week 8 (W8). **Results:** There were statistically significant improvements in depression, anxiety, sleep latency and sleep efficiency during the 8-week treatment protocol. Repeated-measures analysis of variance results indicated that nefazodone has a time-dependent effect on both HAM-D and HAM-A scores. After 8 weeks of nefazodone therapy, HAM-D scores decreased from 33.4 (SD 8.1) to 11.6 (SD 5.6) ($F_{2,14} = 13.68$, $p = 0.001$) and HAM-A decreased from 26.6 (SD 7.0) to 11.5 (SD 11.1) ($F_{2,14} = 13.46$, $p = 0.001$). The results of paired *t* tests show that, compared with baseline, HAM-D and HAM-A scores decreased at both W4 ($p = 0.004$ and $p = 0.002$, respectively) and W8 ($p = 0.002$ and $p = 0.005$, respectively). The time-dependent effects on stage 1 sleep ($F_{2,16} = 6.06$, $p = 0.011$) and periodic leg movement index ($F_{2,16} = 4.31$, $p = 0.035$) were also significant. The mean sleep latency of these patients decreased from 39.9 (SD 32.7) minutes at W0 to 16.6 (SD 15.3) minutes at W8 ($p < 0.05$). Sleep efficiency increased from 78.8% (SD 14.6%) at W0 to 91.5% (SD 5.5%) at W8 ($p < 0.05$). Stage 1 sleep decreased from 4.9% (SD 1.9%) at W0 to 3.4% (SD 2.6%) at W8 ($p < 0.05$). **Conclusions:** The results of this preliminary study indicate that nefazodone not only has favourable antidepressant and anxiolytic effects but also enhances sleep efficiency and sleep latency.

**Objectif :** Décrire les changements cliniques et polysomnographiques produits par la néfazodone chez des patients atteints du trouble affectif saisonnier. **Méthodes :** On a inscrit douze patients et étudié neuf d'entre eux au cours d'un essai ouvert comportant des mesures objectives et subjectives. Les patients étudiés avaient en moyenne 45 ans (de 35 à 58 ans). Ils satisfaisaient aux critères du *Diagnostic and Statistical Manual of Mental Disorders*, (DSM-IV), aux critères du trouble dépressif majeur et de l'épisode dépressif majeur courant à tendances saisonnières. Le score de référence moyen des patients sur l'échelle du questionnaire SPAQ (Seasonal Pattern Assessment Questionnaire) était de 15,7 (écart-type [ET] 5,3). La période de traitement à la néfazodone a duré au total 8 semaines et les doses quotidiennes se sont établies à 100 mg au cours de la semaine 1, 200 mg au cours de la semaine 2 et 300 mg au cours de la semaine 3, et ont atteint jusqu'à 400 mg au cours des semaines 4 à 8. Chaque patient a fait l'objet d'évaluations de la version à 29 points de la

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Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A) et polysomnographique sur deux nuits à trois occasions : avant le traitement (référence, semaine 0 [S0]), à la fin de la semaine 4 (S4) et à la fin de la semaine 8 (S8). **Résultats :** On a constaté des améliorations statistiquement significatives de la dépression, de l'anxiété, de la latence du sommeil et de l'efficience du sommeil au cours du protocole de traitement d'une durée de huit semaines. Une analyse de mesures répétitives des résultats de la variance a indiqué que la néfazodone a un effet lié au temps à la fois sur les résultats HAM-D et HAM-A. Après huit semaines de thérapie à la néfazodone, les résultats HAM-D sont passés de 33,4 (ET 8,1) à 11,6 (ET 5,6) ($F_{2,14} = 13,68$, $p = 0,001$) et les résultats HAM-A, de 26,6 (ET 7,0) à 11,5 (ET 11,1) ($F_{2,14} = 13,46$, $p = 0,001$). Les résultats de tests $t$ jumelés montrent que comparativement au niveau de référence, les résultats HAM-D et HAM-A ont diminué à la fois à la S4 ($p = 0,004$ et $p = 0,002$ respectivement) et à la S8 ($p = 0,002$ et $p = 0,005$, respectivement). Les effets liés au temps du sommeil du stade 1 ($F_{2,16} = 6,06$, $p = 0,011$) et l'indice de mouvement périodique des jambes ($F_{2,16} = 4,31$, $p = 0,035$) ont été significatifs aussi. La latence moyenne du sommeil chez ces patients est tombée de 39,9 (ET 32,7) minutes à la S0 à 16,6 (ET 15,3) minutes à la S8 ($p < 0,05$). L'efficience du sommeil est passée de 78,8 % (ET 14,6 %) à la S0 à 91,5 % (ET 5,5 %) à la S8 ($p < 0,05$). Le sommeil du stade 1 est passé de 4,9 % (ET 1,9 %) à la S0 à 3,4 % (ET 2,6 %) à la S8 ($p < 0,05$). **Conclusions :** Les résultats de ces études préliminaires indiquent que la néfazodone n'a pas seulement des effets antidépresseurs et anxiolytiques favorables : elle améliore aussi l'efficience et la latence du sommeil.

## Introduction

Seasonal affective disorder (SAD) is a clinical subtype of mood disorder consisting of recurrent episodes of major depression that have a seasonal pattern. Depressed mood, sleep disorder, fatigue and anxiety are important symptoms of SAD.[1-4] Recent evidence suggests that sleep disruptions commonly occur with or without the typically reported hypersomnia[5] and that these seemingly contradictory sleep disorders are not mutually exclusive.

Many SAD treatment studies have focused on treatment by exposure to bright artificial light. Light-therapy studies suggest that although light is an effective treatment for many patients with SAD, a significant minority do not respond.[2,6-8] Furthermore, many patients experience side effects, such as eyestrain and headaches, whereas others cannot use light because of the time commitment involved.[2,7,9-12] Thus, alternative strategies based on pharmacotherapy have become increasingly necessary.

Among the selective serotonin reuptake inhibitors, fluoxetine in particular has been evaluated as a treatment for SAD. Although fluoxetine is superior to placebo in the clinical response rate in patients with SAD, it may induce sleep disturbance.[13-15] Antidepressants that promote favourable sleep profiles, such as the serotonin receptor and reuptake inhibitor nefazodone, may prove to be a valuable treatment option for patients with SAD.[15,16]

Another rationale for nefazodone is its mechanism of action on the serotonin system. A large body of work points to marked seasonality in measures of serotonin function such as tryptophan availability and, indeed, to serotonergic disturbance in SAD,[17-19] including studies that suggest that there is a disturbance of serotonergic regulation in SAD.[20] Compared with other neurotransmitters of interest in depression, serotonin is the only one with a clear seasonal pattern of metabolism. In healthy subjects, measures of central serotonin function are highest in summer and autumn and lowest in winter and spring.[21] Nefazodone is an antidepressant that primarily blocks postsynaptic serotonin type 2 (5-HT$_2$) receptors, in addition to inhibiting the reuptake of serotonin and norepinephrine.[16,22-24] It has low affinity for muscarinic, cholinergic, α-adrenergic, dopaminergic and histaminergic receptors.[25]

The objective of our study was to characterize the effect of nefazodone on sleep and the combined symptoms of SAD.

## Methods

All patients gave written informed consent before data collection began. Subjects were aged 18 years or more and met the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV),[26] criteria for major depressive disorder with seasonal pattern based on the Structured Clinical Interview for DSM-IV axis I disorder (SCID).[27] These patients were medically stable, not pregnant and free of psychiatric medication in the 4 weeks before the study. Patients who were dependent on alcohol or drugs in the preceding 12 months, acutely suicidal, or had sleep apnea or periodic leg movements in sleep (PLMS) sufficient to meet the diagnostic criteria of PLMS were excluded from the study.

A 29-item Hamilton Rating Scale for Depression (HAM-D) was used to assess the severity of symptoms. This version of the HAM-D includes an 8-item addendum to assess atypical symptoms of depression, such as increased eating behaviour and fatigue.[28] It was chosen because of the high rates of atypical symptoms reported in populations with SAD.[2,4,11,21,29,30] The total score on the first 17 items of the HAM-D was required to be 17 or higher. The Hamilton Rating Scale for Anxiety (HAM-A) is a 14-item semi-quantitative scale with a score range between 0 and 56. It was designed to determine the intensity of anxiety. The Seasonal Patterns Assessment Questionnaire (SPAQ) is a self-report questionnaire. A score of 11 or higher on the SPAQ suggests a seasonal feature of depression.

Subjects were treated with nefazodone for 8 weeks under open-label conditions, and the daily dosages were 100 mg in week 1, 200 mg in week 2, 300 mg in week 3 and up to 400 mg in weeks 4–8. The increments were fixed in weeks 1–3 but were flexible in weeks 4–8. The doses of nefazodone were not maximal. The HAM-D and the HAM-A were administered at baseline and after 4 and 8 weeks of treatment.

Each subject also completed baseline polysomnographic

measurements before administration of nefazodone and after 4 and 8 weeks of treatment. Polysomnographic recordings were carried out in the Sleep and Alertness Clinic, Toronto Western Hospital, Toronto. Each sleep assessment consisted of 2 consecutive overnight studies, the first night being an adaptation night in the sleep laboratory to eliminate the well-documented first-night effects.[31] Only the recordings of the second night were analyzed. The methodology for the laboratory sleep studies is described elsewhere.[32]

A repeated-measures analysis of variance (ANOVA) was used to assess the changes in HAM-D and HAM-A and the sleep measurements. Paired $t$ tests were used to compare the baseline clinical and sleep data with those of week 4 and week 8. Data from week 4 were compared with those of week 8 as well. Significance was set at $p < 0.05$.

## Results

A total of 12 patients, 11 female and 1 male, met the inclusion criteria. Two female subjects withdrew before taking the medication. The male subject withdrew after taking nefazodone for 1 week, because there was a conflict between his working and the treatment schedules. The remaining 9 female subjects, whose mean age was 45 (range 35–58) years, completed the polysomnographic measures over 8 weeks. Complete clinical data were collected for 8 subjects. At baseline, the patients' mean HAM-D score was 33.4 (standard deviation [SD] 8.1), the mean HAM-A score was 26.6 (SD 7.0) and the patients' mean value on the SPAQ was 15.7 (SD 5.3).

There were statistically significant reductions in mean values on HAM-D and HAM-A over time (Table 1). Four of the 8 patients for whom complete clinical data were collected met predefined criteria for remission (score of the 29-item HAM-D ≤ 10). A fifth patient was considered to be a responder as evidenced by a reduction of greater than 50% in the HAM-D score (final score 14).

The results of paired $t$ tests indicate that, compared with baseline, HAM-D scores were significantly decreased at week 4 ($t = 3.26$, $p = 0.004$) and week 8 ($t = 4.86$, $p = 0.002$). Similarly, HAM-A scores decreased at week 4 ($t = 5.020$, $p = 0.002$) and week 8 ($t = 4.010$, $p = 0.005$). The differences in HAM-D and HAM-A scores between week 4 and week 8 were not statistically significant.

Of the 9 patients, 4 had insomnia. One of them had initiating insomnia, with a sleep latency, or time before sleep ensues, of 67 minutes. Three patients had both initiating and

maintenance insomnia. The sleep latencies of these 3 patients were 63.5, 69.5 and 92.5 minutes, respectively, and the sleep efficiencies, that is, the ratio of total sleep time to total time in bed, were 48.3%, 65.4% and 75.2%, respectively. The mean sleep latency was 39.9 minutes, which was beyond the normal range, and the mean sleep efficiency was 78.8%, which was slightly lower than the normal cut point of 80%.

The results of the repeated-measures ANOVA suggested that the time effects of stage 1 sleep (stage 1 sleep is the lightest sleep; stage 2 sleep is consolidated sleep; stage 3 and stage 4 sleep are deep sleep. Stages 1-4 sleep are non–rapid eye movement [non-REM] sleep) ($F_{2,16} = 6.06$, $p = 0.011$) and the periodic leg movement index ($F_{2,16} = 4.31$, $p = 0.035$) were significant.

The means and standard deviations of all polysomnographic measures by treatment condition are presented in Table 2. Several sleep parameters showed significant changes with nefazodone treatment. Nefazodone significantly decreased sleep latency ($t = 2.74$, $p = 0.025$) and significantly increased sleep efficiency ($t = -2.57$, $p = 0.033$) by the end of week 8. It significantly decreased stage 1 sleep by the end of week 4 ($t = 3.32$, $p = 0.011$) and week 8 ($t = 3.90$, $p = 0.005$). The differences in the sleep variables between week 4 and week 8 were not statistically significant. Nefazodone generally increased sleep quality.

A self-report adverse event questionnaire was filled out by the patients at baseline, week 4 and week 8. After taking nefazodone for 4 weeks, the most frequent adverse events experienced were headache, difficulty concentrating, dry mouth and increased thirst. Interestingly, all these symptoms had disappeared by the end of week 8, although the average dosage of nefazodone had been increased.

## Discussion

To our knowledge, only 1 published study has used nefazodone to treat SAD.[33] We found that there were significant reductions in mean values on the HAM-D and HAM-A scales over time. Compared with baseline, HAM-D and HAM-A scores decreased significantly at week 4 and week 8. It seems clear that nefazodone has beneficial antidepressant and anxiolytic effects in this small population of patients who met the criteria for MDD with a seasonal pattern. These findings are similar to those being seen in patients with MDD who were treated with nefazodone. Placebo-controlled studies show that nefazodone is effective for treating patients with MDD and is as effective as imipramine, amitriptyline, paroxetine,

**Table 1: Depression and anxiety scores for study subjects ($n = 8$)**

| Score | Mean (and standard deviation) | | | ANOVA | | |
|---|---|---|---|---|---|---|
| | Baseline | Week 4 | Week 8 | $F$ | $df$ | $p$ |
| HAM-D | 33.4 (8.1) | 17.9* (7.2) | 11.6*  (5.6) | 13.68 | 2,14 | 0.001 |
| HAM-A | 26.6 (7.0) | 14.6* (6.6) | 11.5* (11.1) | 13.46 | 2,14 | 0.001 |

Note: ANOVA = repeated-measures analysis of variance; df = degrees of freedom; HAM-A = 14-item Hamilton Rating Scale for Anxiety; HAM-D = 29-item Hamilton Rating Scale for Depression.
*Paired $t$ test, compared with baseline, $p < 0.05$.

fluoxetine and sertraline.[34–37] Nefazodone was found to reduce comorbid anxiety symptoms in patients with MDD.[36–38]

The antidepressant and anxiolytic mechanism of action of nefazodone most probably relates to both its presynaptic and postsynaptic actions. Presynaptically, nefazodone inhibits 5-HT reuptake, which increases 5-HT levels within the synapse, prevents 5-HT metabolism and results in an increased availability of 5-HT to interact with $5\text{-HT}_{1A}$ receptors. These receptors may play a pivotal role in mood homeostasis. Nefazodone also inhibits norepinephrine uptake presynaptically. Postsynaptically, nefazodone blocks $5\text{-HT}_2$ receptors in depressed patients. Although results from postmortem and positron emission tomography neuroimaging studies are inconsistent, decreased $5\text{-HT}_2$ receptor activity may occur in depression, and it might reflect a secondary compensatory response of the brain to the state of depression.[39,40] Blockade of the $5\text{-HT}_2$ receptor by nefazodone ultimately results in facilitation of $5\text{-HT}_{1A}$-receptor-mediated neurotransmission, which may be beneficial in the reduction of both depression and depression-related anxiety symptoms.[41,42]

This report also highlights the beneficial effects of nefazodone on sleep as ascertained from repeated polysomnographic recordings. At baseline, 4 of the patients had disturbed sleep. The mean value of sleep latency was increased and that of sleep efficiency was slightly decreased, even though 5 of the patients in this group had relatively normal or better-than-average sleeping patterns.

Previous reports on the sleep of patients with SAD are inconclusive.[5] Brunner et al[43] reported that patients with SAD had better sleep than controls. Those patients had higher sleep efficiency, longer total sleep time and more stage 2 sleep during the entire sleep episode. They also were less wakeful during the first 4 hours of sleep.[43] However, other reports have indicated that patients with SAD display features of poor sleep quality, including decreased sleep efficiency and decreased slow-wave sleep (deep sleep), although they probably have a long sleep time.[5,44]

One of the important findings in this study is that nefazodone increased quality of sleep among patients with SAD. Nefazodone decreased both sleep latency and stage 1 sleep and increased sleep efficiency. Our results support previous studies in depressed patients suggesting that nefazodone has clinically meaningful sleep benefits including increased sleep efficiency[39,45–48] and REM sleep.[49] Nefazodone also decreased sleep latency,[47] night-time awakenings[39,46] and percentage of awake and movement time.[15,45,50] Interestingly, nefazodone has little effect on sleep architecture in healthy volunteers[51] or in patients with post-traumatic stress disorder.[52]

The relation between 5-HT neurotransmission and sleep is complicated.[53] Data suggest a role for the $5\text{-HT}_2$ receptor in sleep physiology.[39] Nefazodone-mediated blockade of $5\text{-HT}_2$ receptors may directly relieve insomnia associated with depression.[54] This is supported by reports that ritanserin, a potent $5\text{-HT}_2$ postsynaptic receptor antagonist, increased slow-wave sleep.[55] Likewise, trazodone and mirtazapine, antidepressants that also have $5\text{-HT}_2$ blocking properties, are also sleep promoters.[56–59]

The limitations of this study are its open design and small sample. Notwithstanding, this study provides clinically relevant data on the sleep profiles of patients with SAD and offers preliminary support for the antidepressant, anxiolytic and sleep promotion effects of nefazodone in a small sample of patients with SAD. A larger patient sample and a placebo-control design are required to further evaluate the effects of nefazodone on clinical and sleep parameters.

**Table 2: Polysomnographic variables for study subjects ($n$ = 9)**

| Variable | Time of data collection; mean (and standard deviation) | | |
|---|---|---|---|
| | Baseline | Week 4 | Week 8 |
| Total sleep time, min | 365.0 (72.8) | 390.7 (110.0) | 397.9 (42.4) |
| Sleep latency, min | 39.9 (32.7) | 23.9 (38.0) | 16.6* (15.3) |
| REM latency, min | 98.9 (86.6) | 85.7 (59.3) | 48.1 (23.2) |
| Sleep efficiency, % | 78.8 (14.6) | 85.3 (17.2) | 91.5* (5.5) |
| Time awake, % | 13.1 (13.2) | 10.2 (13.2) | 5.5 (5.3) |
| Stage of sleep, % | | | |
| 1 | 4.9 (1.9) | 3.4* (2.2) | 3.4* (2.6) |
| 2 | 49.2 (11.2) | 52.4 (13.4) | 50.9 (5.3) |
| 3 | 8.7 (3.5) | 8.4 (5.1) | 9.1 (6.0) |
| 4 | 4.1 (4.1) | 4.3 (4.9) | 6.0 (5.1) |
| Slow-wave (deep) sleep, % | 12.9 (5.9) | 12.6 (9.2) | 15.1 (9.2) |
| REM sleep, % | 18.8 (5.6) | 19.5 (4.3) | 23.6 (6.1) |
| Periodic leg movement index | 6.1 (5.9) | 2.6 (3.6) | 2.2 (1.4) |
| Arousal index | 8.2 (3.6) | 11.2 (6.6) | 12.2 (7.1) |

Note: REM = rapid eye movement.
*Paired $t$ test, compared with baseline, $p < 0.05$.

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