

TREATMENT OF INSOMNIA WITH HYPNOTICS RESULTING IN IMPROVED SEXUAL FUNCTIONING IN POST-MENOPAUSAL WOMEN

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SUMMARY

Background: This study sought to determine whether trazodone used in hypnotic doses, compared to the hypnotic agent zopiclone, had any specific positive effect on sexual function in non-depressive post-menopausal women with insomnia.

Subjects and methods: Fifty (50) subjects participated in the study. Insomnia and sexual performance were evaluated before and after 4 weeks of hypnotic treatment.

Results: At week four, both treatments improved sleep quality to a similar degree. Sexual function also improved significantly with both treatments, with no significant difference between the groups.

Conclusions: In post-menopausal women, sexual problems and sleep problems may be related and solving sleep problems may help sexual functioning, independently of depression.

Key words: trazodone – zopiclone - sexual function – insomnia - menopause

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INTRODUCTION

Sexual function and sleep are two important areas for women during the menopausal transition. During the normal menopausal transition, a dramatic decline in sexual functioning is reported (Dennerstein et al. 2003). Diminished libido at this period is one of the most common problems in sexual function (Dennerstein et al. 2001, Goldstat et al. 2003). In one recent study, diminished libido, defined as diminished frequency and level of desire, was present in 64% of women in the late peri-menopausal transition and early post-menopause (Reed et al. 2007). The menopausal transition is also marked with affective symptoms, which are in part a result of vasomotor symptoms such as night sweats and hot flushes, accompanied by discomfort caused by palpitations, fatigue and insomnia (Bosworth et al. 2001). The women who are most troubled by vasomotor symptoms, difficulty in getting to sleep, early morning awakening, and awakening during the night report significantly lower sexual desire (Woods et al. 2010). One study reported that poor sleep was significantly associated with diminished libido in the later peri-menopausal or post-menopausal group (Reed et al. 2007). Whether the vasomotor and sleep problems experienced by perimenopausal and post-menopausal women actually cause depression in this group remains controversial (Öztürk et al. 2006). However, there is no doubt that sexual dysfunction and sleep problems in non-depressed post-menopausal women are two related areas which should be addressed.

Trazodone is a well-known heterocyclic antidepressant which, because of its highly sedating properties, is often used to treat patients with insomnia. A 3% incidence of priapism in men is a well-known side effect of trazodone which tends to lead to the discontinuation of treatment with this anti-depressant (Russell 1996). Clitoral priapism has also been reported with this agent (Medina 2002). Although not justified by placebo controlled studies (Enzlin et al. 2000), the use of trazodone in erectile dysfunction (ED) is common. Trazodone has a moderate to high degree of affinity for alpha1- and alpha2-adrenoceptors, respectively, which may contribute to its reported beneficial effects in treating erectile dysfunction (Krege et al. 2000, Fink et al. 2003). Reports also suggest a considerable increase in libido with trazodone in both males and females (Gartrell 1986, Woods & Sullivan 1987, Sullivan 1988, Michael & O'Donnell 2000).

Zopiclone is a hypnotic drug which is thought to act on the GABA-A receptor complex at a certain subunit distinct from, but closely related to, the benzodiazepine binding site (Waldworth & McTavish 1993). Zopiclone causes minimal impairment to psycho-motor performance and mental alertness in the morning after night-time administration. The drug is generally well tolerated by patients of all ages; the most frequently reported adverse effects being a bitter taste and dry mouth, while no sexual side-effects are reported (Drover 2004). Studies show that eszopiclone, the stereoisomer of zopiclone, provides significant improvements in sleep during peri-menopause and early post-menopause (Soares et al. 2006).

The aim of this naturalistic study was to determine whether trazodone has any positive effect on sexual function in non-depressive post-menopausal women in comparison to the hypnotic agent zopiclone, when both are used as hypnotics to treat insomnia.

SUBJECTS AND METHODS

This study was carried out in a menopause unit of a general health center and was ethically approved by its authorities as required by the regulations at the time of the study. A written consent was obtained from the participants. The unit follows up more than 2500 registered women with a team of gynecologists and staff trained in internal medicine and psychiatry. This study adheres to the Declaration of Helsinki.

Eighty-three (83) women who were diagnosed as having insomnia according to the ICD-10 Classification of Diseases and Related Health Problems and who were not receiving hormone replacement therapy were evaluated as participants in the study. According to the ICD-10 criteria, the sleep disturbance occurred at least three times a week, but the duration of sleep disturbance varied. Women with estrogen levels lower than 25 IU/l and follicle stimulating hormone levels higher than 40 IU/l were considered as post-menopausal. We excluded women using a psychotropic medication or any medication that is known to cause sleep problems at the time of the study (including over the counter medication), and women who were previously diagnosed with any mental or physical disorder that could be sleep disorders. A psychiatric evaluation with SCID-I was carried out after consent for the study participation and 17 were excluded due to being diagnosed as clinically depressive, since their insomnia could have been depression-related. 9 of the 66 women refused to use any hypnotic drugs and 57 women were randomized to receive open-label treatment with either zopiclone or trazodone. Seven women did not complete 4 weeks of hypnotic treatment because of such side effects as dizziness, daytime sedation, a bitter sweet taste in the mouth and hypersomnia. Of the 50 women who went on with the treatment, 28 women received 50 to 100 mg trazodone and 22 women received 3.75-7.5 mg zopiclone per day. Insomnia was evaluated by the total score (0 min, 6 max) of sleep items in the Hamilton Depression Scale (HAM-D) (Williams 1988). Sexual

performance was evaluated by the Turkish version of Arizona Sexual Experiences Scale (ASEX) (Soykan 2004). Both scales were applied twice, once before and once after 4 weeks of hypnotic treatment.

Statistical analysis

The Kolmogorov-Smirnov test of normality was applied to evaluate the distribution of samples. An independent samples t test between the trazodone and zopiclone groups was carried out to compare age, duration of the post-menopausal period, HAM-D total and sleep items score before treatment where normal distribution was secured. A paired samples t test was used to determine the significance of differences between the pre- and post-treatment HAM-D sleep items scores and the ASEX score. Repeated measures ANOVA between subject comparisons was used to estimate whether the effects of both drugs on sexual performance and sleep quality differed from each other. Pearson's r was used to estimate the correlations between the duration of the post-menopausal period, sexual performance before hypnotic treatment, sleep and depression. The significance criterion was determined as $p < 0.05$.

RESULTS

50 women were enrolled on the study. 28 of them received 50-100 mg trazodone (mean: 78.57 ± 25.39 mg) and 22 of them received 3.75-7.5 mg (mean: 5.45 ± 1.91 mg) zopiclone. The mean age of the trazodone group was 51.28 ± 3.35 , while it was 51.27 ± 3.23 for the zopiclone group ($t = 0.11$, $p = 0.99$). Mean duration of the post-menopausal period was 4.46 ± 1.48 years for the trazodone group and 4.27 ± 1.28 years for the zopiclone group and there was no significant difference between the two groups ($t = 0.23$, $p = 0.81$). Both of the groups were normally distributed and there was no significant difference according to the HAM-D total score ($t = -1.53$, $p = 0.13$) and the ASEX score ($t = 1.32$, $p = 0.19$) before hypnotic treatment. The zopiclone group had significantly worse sleep quality at the beginning of treatment than had the trazodone group ($t = -2.32$, $p = 0.02$). Table 1 shows a comparison of the trazodone and the zopiclone groups according to age, duration of the post-menopausal period and ASEX and HAM-D sleep items scores before hypnotic treatment.

Table 1. The comparison of trazodone and zopiclone groups according to age, duration of post-menopausal period, ASEX, total HAM-D and HAM-D sleep items score before hypnotic treatment

	Mean scores of Zopiclone group, S.D (n=22)	Mean scores of Trazodone group, S.D (n=28)	t	p
Age	51.27	51.28	0.11	0.99
Duration of post-menopausal period (years)	4.27	4.46	0.23	0.81
HAM-D sleep items score before treatment	5.27	4.67	-2.32	0.02*
ASEX score before treatment	19.43	20.53	1.32	0.19
Total HAM-D score before treatment	7.68	6.82	-1.53	0.13

* $p < 0.05$ (Independent samples t test); ASEX: Arizona Sexual Experiences Scale; HAM-D: Hamilton Depression Rating Scale

Table 2. The significance of mean differences between the HAM-D sleep items score and ASEX score before and after hypnotic treatment

	Mean (S.D)	<i>t</i>	<i>p</i>
Differences between pre- and post- treatment HAM-D sleep items scores	3.68(1.68)	15.45	0.00**
Differences between pre- and post- treatment ASEX score	1.9(2.39)	5.61	0.00**

***p*<0.01 (Paired samples *t* test); ASEX: Arizona Sexual Experiences Scale; HAM-D: Hamilton Depression Rating Scale

Table 3. The comparison of trazodone and zopiclone groups according to the changes made in the ASEX score and HAM-D sleep items score after 4 weeks of treatment

	Trazodone Group		Zopiclone Group		<i>F</i>	<i>p</i>
	Pre-treatment (S.D.)	Post-treatment (S.D.)	Pre-treatment (S.D.)	Post-treatment (S.D.)		
ASEX score	20.53 (3.16)	18.78 (3.75)	19.40 (2.75)	17.31 (3.44)	2.16	0.148
HAM-D sleep items score	4.67 (0.98)	1.46 (1.50)	5.27 (0.76)	1 (1.27)	0.07	0.790

ASEX: Arizona Sexual Experiences Scale; HAM-D: Hamilton Depression Rating Scale

There was a significant decrease in the ASEX score after 4 weeks of hypnotic treatment, indicating an improvement in sexual performance with both drugs ($t=5.61$, $p<0.01$). The HAM-D sleep items score also significantly decreased after 4 weeks of treatment with both drugs ($t=15.45$, $p<0.01$). Table 2 shows the significance of the mean differences between the HAM-D sleep items score and the ASEX score before and after hypnotic treatment.

Table 3 shows a comparison of trazodone and zopiclone groups according to the changes in the ASEX scores and HAM-D sleep items scores after 4 weeks of treatment. The effects of trazodone and zopiclone on sexual performance ($F=2.16$, $p=0.148$) and sleep quality ($F=0.07$, $p=0.79$) did not differ from each other.

Correlation analysis revealed no significant relationship between the duration of the post-menopausal period, sexual performance before hypnotic treatment, sleep and depression scores, but a positive correlation ($p=0.06$) was found between the duration of the post-menopausal period and the ASEX score before treatment, which needs to be clarified in a larger sample.

DISCUSSION

In a woman's life cycle, there are vulnerable periods such as the menopausal transition in which the risk of insomnia may be increased (Soares 2005). Sexual dysfunction also affects women in this period (Dennerstein et al. 2003). Pharmacological interventions to treat sexual disorders within this period may not be successful unless appropriate psychological support is included, because, due to a complex interplay of sociocultural factors, past experiences, relationships and hormones, a woman's experience at menopause and beyond is highly individual (Reddish 2002).

In our study, both zopiclone and trazodone were shown to have decreased the ASEX score significantly after 4 weeks of treatment, indicating an improvement

in sexual functioning. Notwithstanding some clinical studies and anecdotal reports about increased libido with trazodone (Gartrell 1986, Woods & Sullivan 1987, Sullivan 1988, Michael & O'Donnell 2000), in our study 50-100 mg trazodone daily had no superiority to zopiclone in improving sexual performance. As our aim was to treat insomnia in non-depressive post-menopausal women and the suggested hypnotic dose of trazodone is 50-100 mg (Schwartz et al. 2004), we did not use higher doses. Although zopiclone has no known physiological or psychopharmacological effect on sexual functioning, a placebo controlled study to test the sexual effects of zopiclone in post-menopausal women would be of benefit to verify this result.

Of the 66 women who were offered to participate in the study, 9 refused to participate, and 7 were unable to finish the study, due to side affects. It is possible that the group that did not accept to be included in the study was somehow clinically different and these factors could have influenced their sleep and sexual activity. This is a possible limitation of the study. The small sample size and the fact that other factors like consumption of coffee and cigarettes during the day, exercise habits, stressful events and the correlations of hormone levels and the severity of the problems were not controlled are other limitations of the study.

At the beginning of the study, the sleep quality of the zopiclone group was significantly worse than that of the trazodone group. After 4 weeks of hypnotic treatment, the HAM-D sleep items score decreased significantly, with both agents indicating that hypnotic treatment was successful; however, no significant difference between trazodone and zopiclone in improving sleep quality was found. These data show that trazodone 50-100 mg daily may be a drug of choice in post-menopausal women with insomnia in whom clinicians want to avoid Z-group hypnotic agents because of the risk of dependence.

There are limited data on whether sleep disturbances are independently associated with diminished libido in

the menopausal transition and peri-menopause. In one cross sectional study, poor sleep was reported to be associated with diminished libido in peri- and post-menopausal women. In the present study, poor sleep quality was correlated with both vasomotor symptoms and depression (Kaynak et al. 2004). Depression is a risk factor for both sexual dysfunction and sleep problems. At the same time, our study found that sexual function was improved by both trazodone and zopiclone, suggesting that reduced sleep quality may have a negative effect on the sexual functioning of this group. Thus, agents which improve sleep quality, together with agents targeting vasomotor symptoms in the post-menopausal period may also be helpful in improving sexual performance.

Although statistically not significant ($p=0.06$), the duration of the post-menopausal period had a considerable positive correlation with the ASEX score before treatment, indicating poorer sexual functioning when the duration of post-menopausal period is longer. These data need to be confirmed by studies with larger samples. No significant correlation between the duration of the post-menopausal period, sexual functioning before hypnotic treatment, sleep and depression scores was found. In addition, the ASEX score before hypnotic treatment was not related to the HAM-D score before treatment, indicating that the sexual problems of our study group can not be explained by depression. This study is important because it shows that, even in post-menopausal women, sleep problems are associated with sexual dysfunction, and improving sleep helps with sexual function, independently of depressive symptoms.

CONCLUSION

Both trazodone and zopiclone have improved sexual dysfunction probably via improving sleep quality, but trazodone 50-100 mg daily has no specific superiority in improving sexual dysfunction when it is used as a hypnotic in the post-menopausal period.

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