Preliminary communication

Excessive daytime sleepiness and fatigue in depressed patients and therapeutic response of a sedating antidepressant

Jianhua Shen a,⁎, Naheed Hossain a, David L. Streiner b, Aruu V. Ravindran c, Xuehua Wang a, Prativa Deb a, Xin Huang a, Frank Sun a, Colin M. Shapiro a,d

a Sleep Research Laboratory, Department of Psychiatry, University Health Network, University of Toronto, Canada
b Kunin-Lunenfeld Applied Research Unit, Baycrest Centre and University of Toronto, Canada
c Center for Addiction & Mental Health, University of Toronto, Canada
d Youthdale Child and Adolescent Sleep Clinic, Toronto, Canada

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ABSTRACT

Background: Although sleepiness and fatigue are common symptoms in depressed patients, the relationships among sleepiness, fatigue and treatment of depression have not been fully elucidated. The main objective of this study was to investigate the therapeutic effects of a sedating antidepressant on sleepiness and fatigue in patients with depression.

Methods: Forty-two depressed patients, who met DSM-IV diagnostic criteria, and 32 matched healthy controls participated in the baseline measurements. Sixteen of the depressed patients were treated with mirtazapine. At baseline, daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) and Stanford Sleepiness Scale (SSS), and fatigue was assessed using the Fatigue Severity Scale (FSS) and Fatigue Impact Scale (FIS). During treatment, Multiple Sleep Latency Test (MSLT), ESS and SSS were used to measure daytime sleepiness, and the FIS, FACES Checklist-Fatigue subscale (FAF) and Fatigue Assessment Instrument (FAI) were used to measure fatigue.

Results: At baseline, there were significant group differences between the depressed and healthy controls on the ESS (P=0.001), SSS (P<0.001), FSS (P<0.001) and FIS (P<0.001). Significant improvement of sleepiness and fatigue measures was seen after treatment with mirtazapine on the MSLT (P=0.011), ESS (P=0.021), SSS (P=0.001), FIS (P=0.002) and FAF (P=0.004).

Limitations: Open-label treatment and relatively small sample size.

Conclusion: Daytime sleepiness and fatigue are significant symptoms in depressed patients. Slightly paradoxically, a sedating antidepressant may alleviate these symptoms.

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1. Introduction

Sleepiness and fatigue are common complaints in both clinical and non-clinical populations (Hickie et al., 2002; Shen et al., 2006a). Excessive daytime sleepiness is frequently seen in the depressed population. A study found that most (57.1%) depressive disorder patients scored high on the Epworth Sleepiness Scale (ESS) — a measure of daytime sleepiness (Chellappa and Araujo, 2006). Some suggest that depression may be even more relevant than sleep apnea as the most common risk factor for excessive daytime sleepiness (Bixler et al., 2005).

Fatigue is a frequent and often a dominant symptom of depressive disorders (Gaudiano et al., 2008). Co-occurring fatigue and depressed moods are often associated with a variety of neurological and psychiatric disorders (Chellappa and Araujo, 2006; Williamson et al., 2005). For example, in patients with multiple sclerosis, fatigue and depressed moods are frequent complaints. In a study conducted by Chwastiak et al. (2005), 76% of significantly fatigued multiple sclerosis
patients scored 16 or higher on the Center for Epidemiologic Studies Depression Scale (CES-D), indicating that they had many symptoms of depression. In contrast, in the multiple sclerosis patients without significant fatigue, only 31% had clear symptoms of depression (Chwastiak et al., 2005).

Sleepiness and fatigue are often considered as residual symptoms among depressed patients who have partially recovered following treatment with antidepressants (Baldwin and Papakostas, 2006). Such residual symptoms are thought to predict poor outcome and high risk of relapse (Fava, 2004). While the relationship between depressed mood and fatigue are complex, there is a significant overlap of the latter with daytime drowsiness.

Despite the great importance of sleepiness and fatigue in depression, few published studies have specifically attempted to evaluate the relationship between these symptoms and sleep function, and the effect of antidepressants on these specific complaints (Baldwin and Papakostas, 2006).

The objectives of this study was to investigate the severity of daytime sleepiness and fatigue in depressed patients (compared to normal controls) and to observe therapeutic effects of a sedating antidepressant, mirtazapine, on these parameters. It was hypothesized that daytime sleepiness and fatigue would be more frequent and severe in depressed patients compared to normal controls and mirtazapine treatment would significantly alleviate these symptoms in patients with depression.

2. Methods

2.1. Procedure

The protocol was approved by the institutional Research Ethics Board. The study was conducted in the Sleep and Alertness Clinic, Toronto Western Hospital – a tertiary university teaching center.

On admission to the study, potential subjects signed informed consent. The depressed subjects fulfilled the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) for depression (American Psychiatric Association, 1994). The age of the study population was 18 or older. The subjects were free of psychotropic medications in the two weeks prior to entry into the study (four weeks if previously on fluoxetine). Patients with Axis I or II co-morbidity (including substance abuse and dependence) and significant physical illness were excluded.

At baseline, all the patients (N = 42) completed the CES-D (Radloff, 1977) and the Beck Depression Inventory, version II (BDI-II; Beck et al., 1997). To further observe therapeutic effects of mirtazapine treatment in sleepiness and fatigue, 16 patients received mirtazapine treatment. In addition to the CES-D and BDI-II, these 16 patients completed an assessment with the 17-item Hamilton Rating Scale for Depression (HRDS-17; Hamilton, 1967). The scores of the mood measurement tools were 17 or higher on the HRDS-17, 16 or higher on the CES-D and/or 15 or higher on the BDI-II. At baseline, in addition to providing mood state information, all the subjects, including 42 depressed patients and 32 normal controls, completed four questionnaires: the ESS, Stanford Sleepiness Scale (SSS), Fatigue Severity Scale (FSS) and Fatigue Impact Scale (FIS).

The ESS and SSS were used to measure sleepiness, and the FSS and FIS were used to measure fatigue.

Inclusion criteria of the subjects in the control group were the same as those in patient group, except that they were not depressed. Subjects in the control group included normal people from various populations, such as factory workers and university students. Subjects in the control group were only assessed at baseline.

The 16 patients who received mirtazapine treatment completed a 58-day therapeutic regimen. They took mirtazapine (30 mg daily) 30 min prior to bedtime, while the rest (N = 26) received treatments other than mirtazapine; they were not included in the treatment limb of the data analysis and report in this study.

At baseline and on Days 2, 9, 16, 30 and 58, mirtazapine treated patients performed the multiple sleep latency test (MSLT) after a standard polysomnographic recording and completed a battery of questionnaires. The questionnaires measuring sleepiness and fatigue included the ESS, SSS, FIS, FACES Checklist-Fatigue subscale (FAT; Shapiro et al., 2002) and Fatigue Assessment Instrument (FAI; Schwartz et al., 1993). Mood state of those patients in the treatment group was monitored using the HRDS-17 and BDI-II at baseline and on Days 9, 16, 30 and 58 (i.e. not on Day 2).

2.2. Measurements

As noted above, several tests and instruments were used to evaluate mood, sleepiness and fatigue during the study.

Mood state was measured using the HRDS-17, CES-D and BDI-II. The HRDS-17 is a commonly used instrument to measure the severity of depression. The score range of the HRDS-17 is between 0 and 54. The CES-D is a well-established depression measurement instrument. This 20-item scale measures the presence and severity of depressive symptoms during the last week. Each item of the scale ranges from 0 (rarely or none of the time) to 3 (most or all of the time). The CES-D has excellent internal consistency and sensitivity for depression (Beekman et al., 1997; Paddison et al., 2006). The BDI-II is a 21-item self-report questionnaire measuring severity of depression. Items in the BDI-II are scored on a four-point scale (0–3); the sum of the scores is between 0 and 63 (Beck et al., 1997; Hamilton, 1967).

In this study, there are both objective and subjective measurements available for evaluating sleepiness. Considering a weak or moderate correlation between the multiple sleep latency test (MSLT) and those subjective sleepiness measurements (Johnson et al., 1990; Johns, 1994; Punjabi et al., 2003; Shen et al., 2006a) we used the MSLT and two subjective measurements (ESS and SSS) to measure sleepiness, trying to avoid any potential bias induced by a single sleepiness measurement.

The MSLT is a widely accepted objective assessment; it is considered the “gold standard” for evaluating sleepiness. The test consists of 4–5 nap opportunities during the day. While being recorded, subjects reclined in bed in a quiet darkened room are instructed to close their eyes and try to fall asleep. The mean sleep onset latency is used to judge the level of daytime sleepiness (Bailes et al., 2006; Shapiro et al., 2006; Thorpy et al., 1992). Various authors view a mean score below 5 or 6 min as indicative of severe sleepiness and a score below...
10 or 11 min as indicative of moderate sleepiness. The ESS is a reliable subjective instrument measuring sleepiness. It retrospectively questions the behavioral aspects of sleepiness. Participants rate the potential of dozing off or falling asleep in eight different situations. Each item is scored with a four-point scale (0 = never doze, 3 = high chance of dozing). The total scores are between 0 and 24 (Johns, 1991; Johns, 1992; Johns, 1994). The SSS consists of a seven-point Guttman scaled item. It ranges from 1 (Feeling active and vital; alert; wide awake) to 7 (Almost in reverie; sleep onset soon; lost struggle to remain awake). Respondents select the most suitable option (Hoddes et al., 1973).

Currently, no reliable objective measurement is available to evaluate fatigue. Therefore, fatigue was measured using only subjective measurement tools. Because each such measurement tool has its own measurement range and distinct features, we used the FSS, FIS, FAF and FAI to concurrently measure fatigue. In this way, these instruments would compensate each other’s limitation and would show a relatively full picture of fatigue in the subjects.

The FSS was developed by Krupp et al. (1989). As described by its title, it is mainly used to measure the severity of fatigue. This nine-item scale has good internal consistency. It has been successfully used in clinical research involving patients with systemic lupus erythematosus, multiple sclerosis and insomnia to differentiate patients and controls (Krupp et al., 1989; Lichstein et al., 1994). The FIS is a 40-item self-report instrument to assess the impact of fatigue on cognitive, physical and psychosocial functions. The score range of the FIS is between 0 and 160 (Fisk et al., 1994). The FAF is the Fatigue Assessment Inventory (FAI; Schwartz et al., 1993). This 29-item scale was effectively used to measure the quantitative and qualitative components of fatigue in patients and healthy controls (Schwartz et al., 1993).

Of all above measurements, higher scores on any of the subjective measurements (HRSD-17, CES-D, FSS, FIS, ESS, SSS, FAF and FAI) indicate greater severity or higher impact of depressed mood, sleepiness or fatigue. The MSLT is the only one where lower values to indicate higher severity of sleepiness.

2.3. Statistical analyses

Student’s t-tests were used to compare age and the scores of the ESS, SSS, FSS, and FIS between the patient group and the control group at baseline. Repeated measures analysis of variance (rMANOVA) was used to evaluate the possible linear trend of each measure during the research procedure. The Huynh–Feldt correction was applied for the factors that did not meet the sphericity assumption. The data were analyzed with Statistical Package for the Social Sciences (SPSS) software, version 15.0, for Windows (SPSS Inc., 2007). Significance cut point was set at 0.05.

3. Results

3.1. Participants

At baseline, subjects included patient group (N = 42; M = 8; F = 34) and control group (N = 32; M = 14; F = 18). There was no significant difference (t = 1.39; df = 72; P = 0.17) between the mean ages of the patients (43.9) and that of the normal controls (39.7). The mean scores of the CES-D were 27.4 (standard deviation [SD] 9.2) for the patient group and 6.2 (SD 4.3) for the control group, and those of the BDI were 23.9 (SD 12.5) for the patient group and 4.6 (SD 3.5) for the control group.

3.2. Sleepiness and fatigue at baseline

The mean scores of the ESS, SSS, FSS and FIS in the patient group were significantly higher than those in the control group (Fig. 1). These results indicated that the severity of daytime sleepiness and fatigue in depression patients were significantly higher than that reported by the normal controls.

3.3. Treatment effects of mirtazapine

Fig. 2 shows the effects of mirtazapine on sleepiness in the depressed treated group. After taking the medication for 2 days, the mean sleep latency, as measured by the MSLT, of the patients was shortened from 7.8 (SD 5.0) min to 5.5 (SD 3.2) min. On Day 9, the mean sleep latency was 6.9 (SD 3.9) min, which was close to that at baseline. Subsequently, the mean sleep latency increased continuously. On Day 58, it was 9.7 (SD 5.8) min, 1.9 min longer than that at baseline. The effects of mirtazapine on the scores of the ESS and SSS are similar to each other. The mean score of the ESS increased from 8.3 (SD 4.8) at baseline to 9.9 (SD 5.3) on Day 2, and that of the SSS increased from 4.5 (SD 1.6) to 4.8 (SD 1.8). On Day 9, the mean scores of the ESS and SSS were lower than those at baseline. Then, the scores of both the ESS and SSS decreased continuously. On Day 58, the mean score of the ESS was 6.2 (SD 4.5), 33.9% lower than that at baseline, and the mean score of the SSS was 3.5 (SD 1.3), 28.6% lower than that at baseline.
depression than that in normal controls, as shown by the results of rMANOVA from the data at 6 time points (baseline and Days 2, 9, 16, 30 and 58) showed that 5 (MSLT, ESS, SSS, FIS and FAF) of the 6 sleepiness and fatigue measurements showed a statistically significant change. For the data following Day 2, the trend was linear and significant for all 6 measurements (Table 1). This indicates that a "long-term" (58 days) administration of mirtazapine effectively reduced the severity and impact of both daytime sleepiness and fatigue in patients with depression.

4. Discussion

In this study, we found that the severity of daytime sleepiness and fatigue is significantly higher in patients with depression than that in normal controls, as shown by the greater mean scores on the ESS, SSS, FSS and FIS. This finding is consistent with those of previous studies (Baldwin and Papakostas, 2006; Zifko, 2004), confirming that both excessive daytime sleepiness and fatigue are common in depression (Martin and Menza, 2005). Posternak and Zimmerman (2002) found that 36.2% of their patients (N = 130) with atypical MDD had excessive daytime sleepiness. An epidemiological investigation (Tylee et al., 1999) of depressed patients has further confirmed high frequency of fatigue with 73% of those being surveyed having significant fatigue. This symptom frequency is only second to depressed mood (76%). Other research suggests that the presence of fatigue may be a vulnerability factor that predicts the later onset of major depression (Addington et al., 2001).

The mechanism underlying the relationship between depression, daytime sleepiness and fatigue has not been fully elucidated. A correlation between sleep disorder and depression and the associations of depressed mood with increased daytime sleepiness and fatigue suggest that sleep symptoms, especially insomnia, and depressed mood may be key features in the daytime sleepiness and fatigue in patients with depression (Samborski et al., 2004; Shen et al., 2005; Shen et al., 2006b). It has been proposed that increased serotonin activity in certain brain areas may contribute to fatigue and daytime sleepiness (Martin and Menza, 2005). This proposition is certainly worthy of further study to clarify the possible underlying mechanisms. Current established theory and clinical evidence indicate that depressed patients have a decrease, rather than an increase, in serotonin level and activity (Baldwin and Papakostas, 2006).

The most important findings of this study are that the effect of mirtazapine on sleepiness and fatigue has two phases. After taking the medication for 2 days, the patients seemed to feel sleepier and more fatigued than they were prior to taking the medication at baseline. However, after the patients took mirtazapine for 9 to 16 days, their sleepiness and fatigue returned to close baseline level. Subsequently, the level of sleepiness and fatigue decreased progressively. Scores on five instruments at 6 time points showed significant linear time effects. This indicates that during an 8-week treatment with mirtazapine, a decrease in severity of both daytime sleepiness and fatigue occurs. These findings have important clinical implications. For example, at the onset of using a sedating antidepressant, patients should be advised to avoid potentially dangerous activities, such as driving a car or operating machinery.

The reported treatment effects of mirtazapine on sleepiness and fatigue are not consistent. In short-term (≤1 week) and/or non-quantitative studies (Bremener, 1995), sleepiness and fatigue are usually regarded as side effects of mirtazapine (Baldwin and Papakostas, 2006). However, in Samborski’s study, after taking mirtazapine 15–30 mg daily for 6 weeks, both depression and fatigue symptoms of the 26 patients with fibromyalgia syndrome were significantly improved. These results are similar to ours, although the subjects in the study were fibromyalgia sufferers, rather than depressed patients (Samborski et al., 2004).

Mirtazapine is a clinically established antidepressant. Via the blockade of adrenergic alpha-2 receptors, it enhances central noradrenergic and serotoninergic neurotransmission. As well, mirtazapine blockades postsynaptic 5-HT₂ and 5-HT₃ receptors. In addition, it has a high affinity to histamine H₁ receptors (Lee et al., 2009; Rawlings et al., 2010). This may
account for the reduction in sleepiness and fatigue. The effects may be detected only short-term, as benefits from antidepressants may be not sustained, as demonstrated by Bockting et al. (2008).

The major limitation of this study is its open-label treatment, leading to a lack of comparison. To compensate for this limitation, we applied the MSLT to objectively measure sleepiness. It has been reported in previous studies that polysomnographic measurements, including MSLT, are not significantly affected by a placebo response (Aslan et al., 2002; Dorsey et al., 1996). However, because no reliable objective measurements of fatigue are available, it is possible that the results of those related variables are negatively affected on their explanation. Another limitation is that the study sample size is relatively small.

In conclusion, sleepiness and fatigue are more common in depressed patients than in normal individuals. The effects of mirtazapine on sleepiness and fatigue appear to have two phases. There is a short-term (less than 1 week) tendency of increasing sleepiness and fatigue, but subsequently a decrease in the severity of sleepiness and fatigue in depressed patients. Alerting patients to this pattern will improve both compliance with treatment (“riding through” a sleepy first week) and safety (avoiding driving or operating dangerous machinery in the first week of treatment).

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Conflict of interest
All authors declare that they have no conflicts of interest.

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References
Punjabi, N.M., Bandeen-Roche, K., Young, T., 2003. Predictors of objective sleep tendency in the general population. Sleep 26, 678–683.


