Sleep and Sleep Disorders in Chronic Users of Zopiclone and Drug-Free Insomniacs

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Study Objectives: To examine polysomnographic parameters and sleep diary data, as well as the prevalence of sleep apnea and periodic limb movement disorder (PLMD) in older chronic users of zopiclone compared with aged-matched drug-free patients with insomnia and good sleepers.

Methods: Polysomnographic data were collected at a university-based outpatient clinic for adults and elderly. Seventeen patients using zopiclone on a daily basis for at least 1 year were compared with 64 drug-free patients with insomnia and 26 good sleepers. Mean (SD) age was 63.8 (7.0) years. Outcome measures were polysomnographic sleep parameters, sleep diary data, and psychological symptoms, as well as prevalence estimates of sleep apnea and PLMD.

Results: The zopiclone users spent more time awake, had longer sleep latencies, and reduced sleep efficiency compared with the good sleepers. The amount of slow-wave sleep was also significantly lower in the zopiclone group compared with the good sleepers. There were no differences between the zopiclone and insomnia group on any of the polysomography parameters. A similar pattern was found for data based on sleep diaries. The frequency of sleep apnea (apnea-hypopnea index > 10) were 41% to 42% in both the zopiclone and insomnia groups, compared with 12% in the good sleepers group, whereas there were no significant group differences in the frequency of PLMD. The zopiclone group reported higher levels of anxiety and depression compared with the other groups.

Conclusions: This study suggests that the sleep of chronic users of zopiclone is no better than that of drug-free patients with insomnia. It is disturbing that 41% of the patients treated pharmacologically for insomnia also had sleep apnea. We suggest careful sleep assessment as a prerequisite for long-term prescription of sleep medications.

Keywords: Sleep disorders, sleep medications, sleep apnea, periodic limb movement disorder, PLMD

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(PLMD).\textsuperscript{20} Only a small portion of these sleep disorders are properly diagnosed, which often relates to insufficient awareness of sleep disorders among physicians and the public at large.\textsuperscript{21} One important reason for this may be that symptoms of both sleep apnea and PLMD are rarely experienced by the patients themselves. Rather, symptoms are attributed to more general sleep problems, including insomnia, which also increases significantly with advancing age.\textsuperscript{22-26}

Based on the above considerations, the aims of the present study were (1) to explore objective (polysomnographic) and subjective (sleep diary) sleep parameters in individuals with chronic use of zopiclone and to compare these parameters with those of age-matched drug-free patients with chronic insomnia and good sleepers, (2) to examine subjective data on daytime functioning and psychological symptoms in these 3 groups, and (3) to estimate the frequency of sleep apnea and PLMD.

\section*{METHODS}

\subsection*{Participants}

\textbf{GROUP 1—CHRONIC ZOPICLONE USERS}

Participants were recruited through newspaper advertisements. Inclusion criteria were 55 years of age or older and daily usage (5-7 days per week) of sleep medications for at least 1 year. Of a total of 51 respondents, 32 were excluded due to too infrequent use of sleep medications, unwillingness to undergo polysomnographic recordings, or serious psychopathology (severe depression) or physical handicap precluding transport to the university clinic. In all, 19 persons fulfilled the criteria, of which 17 persons used zopiclone. The most common daily dosage was 7.5 mg (range = 3.75-22.5 mg). The 2 remaining persons used zolpidem and nitrazepam, but these were omitted for purposes of the present study. In total, the sample comprised 10 women and 7 men with a mean age of 64.0 years (SD = 6.5).\textsuperscript{27} Patients’ adherence to the sleep medications were estimated by 2 weeks of sleep diaries.

\textbf{GROUP 2—DRUG-FREE PATIENTS WITH CHRONIC INSOMNIA}

Participants in this group were recruited through newspaper advertisements for a treatment study of chronic insomnia.\textsuperscript{13,28} Inclusion criteria were (1) age 55 years or older; (2) fulfilment of the DSM-IV criteria for insomnia, including difficulties initiating sleep, maintaining sleep, and/or early morning awakenings with no ability of return to sleep; (3) insomnia duration of at least 3 months; and (4) complaints of impaired daytime functioning. The following exclusion criteria were used: (1) use of sleep medication the last 4 weeks before the polysomnographic assessment, (2) use of antidepressant or antipsychotic medications, (3) signs of dementia or other serious cognitive impairment defined by a score below 23 on the Mini-Mental State Examination,\textsuperscript{29} (4) presence of a major depressive disorder or other severe mental disorder as identified by a clinical assessment based on The Structured Clinical Interview for DSM-IV,\textsuperscript{30} or (5) having a physical handicap precluding transport to the university clinic. A total of 64 patients (29 women and 35 men) were included for the purpose of the present study (mean age 61.8 years, SD = 6.0).

\textbf{GROUP 3—GOOD SLEEPERS}

Twenty-six healthy participants (19 women and 7 men) aged 55 years or older with self-reported good sleep were recruited through newspaper advertisements. The participants underwent a short screening to ensure that they did not fulfill the diagnostic criteria for insomnia. Mean age was 68.2 years (SD = 7.2).

\section*{Polysomnography}

Participants in all 3 groups were assessed using ambulatory clinical polysomnography for 2 consecutive nights. Data from the first night were not used to control for the first-night effect\textsuperscript{31}; hence, the design allowed for patient adaptation to the polysomnography recording and equipment. Data collected during the polysomnography recordings included electroencephalogram, electromyogram, and electrooculogram. The 4 electroencephalographic derivations used for recording were C4-A1, C3-A2, O1-A2, and O2-A1. Respiratory flow was recorded by both a nasal pressure cannula and a thermistor. Respiratory effort was assessed by means of a piezo thorax and abdominal belt. Limb movements were recorded from anterior tibialis. In addition, measures of pulse and heart function (electrocardiogram), body position, and snoring were included. Sleep stages in all 3 groups were scored according to Rechtschaffen and Kales criteria\textsuperscript{32} in 30-second epochs, employing the Somnologica\textsuperscript{5.1} software package (Flaga-Medcare Somnologica\textsuperscript{5.1}, Reykjavik, Iceland). The criteria for sleep apnea were defined as more than 50\% reduction of air flow at the nose and mouth associated with fall in oxygen saturation of at least 3\%. The duration of the apnea or hypopnea must be a minimum 10 seconds. Sleep apnea was defined as an apnea-hypopnea index (AHI) of greater than 10, which has been suggested as a more appropriate cut-off in this age cohort.\textsuperscript{33,34} Periodic limb movements of sleep were defined according to standard criteria;\textsuperscript{15} leg movements were scored only if they were part of a series of 4 or more successive movements lasting at least 0.5 seconds, separated by intervals between 4 to 90 seconds. PLMD was defined as a periodic limb movement index greater than 15.

\section*{Subjective Data}

All participants completed sleep diaries\textsuperscript{36} every morning for 2 weeks. The sleep diary provided self-reported information about the same sleep parameters as collected from the polysomnography recordings. To increase the reliability, data-analysis were based on the average scores of the 2-week period.

The Beck Depression Inventory\textsuperscript{37} is a 21-item questionnaire measuring depressive symptoms along a 4-point scale (range = 0-3). A score of 10 or above is considered to be an indication of mild depressive symptoms.\textsuperscript{38}

The State-Trait Anxiety Inventory\textsuperscript{39} is a self-report instrument. It includes 20 items measuring state anxiety (State-Trait Anxiety Inventory-state) and 20 items measuring trait anxiety (State-Trait Anxiety Inventory-trait). Each item is rated on a 4-point scale (range = 1-4). On the trait measure, 39 is recommended as a clinical cutoff value.\textsuperscript{39}
significant differences in reported bedtimes among the 3 groups. There were no drug-free insomniacs, whereas both groups scored worse on all sleep parameters compared with the group of good sleepers (see Table 1 for details).

sleepers had also significantly less SWS (55.0 minutes) compared with the good sleepers (44.3 minutes, 7.7 minutes, and 90.0%, respectively; all p < 0.05). The chronic zopiclone users had significantly more wake time during the night (114.5 minutes), had a longer sleep latency (37.9 minutes), and consequently had a lower sleep efficiency (76.9%).

Statistics

SPSS for Windows version 17 (SPSS, Inc., Chicago, Ill) was used in the statistical analysis. One-way analysis of variance with posthoc tests and Pearson χ² test were used to test for differences between the 3 groups. The level of significance was set at less than 0.05.

RESULTS

Sleep Parameters

Based on polysomnography, the group comprising the chronic zopiclone users had significantly more wake time during the night (114.5 minutes), had a longer sleep latency (37.9 minutes), and consequently had a lower sleep efficiency (76.9%), compared with the good sleepers (44.3 minutes, 7.7 minutes, and 90.0%, respectively; all p < 0.05). The chronic zopiclone users had also significantly less SWS (55.0 minutes) compared with the good sleepers (120.0 minutes, p < 0.001). The drug-free patients with insomnia did not differ from the chronic zopiclone users on any of the polysomnographic parameters but scored significantly worse on most sleep measures compared with the group of good sleepers (see Table 1 for details).

Similar to polysomnography, the sleep diaries revealed few differences on the sleep parameters between the zopiclone users and drug-free insomniacs, whereas both groups scored worse on all sleep parameters compared with the good sleepers. There were no significant differences in reported bedtimes among the 3 groups.

DISCUSSION

In the present study, we found that older patients treated with daily use of zopiclone for more than 1 year had significantly impaired sleep, compared with a sample of age-matched good sleepers, as indicated by both polysomnographic and subjective

Table 1—Sleep, Sleep Disorders, and Psychological Functioning in Chronic Zopiclone Users, Drug-Free Patients with Insomnia, and Good Sleepers

<table>
<thead>
<tr>
<th>Data type</th>
<th>Chronic zopiclone users (n = 17)</th>
<th>Drug-free patients with insomnia (n = 64)</th>
<th>Good sleepers (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysomnographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST, min</td>
<td>372.6 ± 64.8</td>
<td></td>
<td>366.4 ± 64.0</td>
</tr>
<tr>
<td>WASO, min</td>
<td>114.5 ± 57.4</td>
<td></td>
<td>93.0 ± 58.0</td>
</tr>
<tr>
<td>SOL, min</td>
<td>37.9 ± 54.9</td>
<td></td>
<td>28.2 ± 41.3</td>
</tr>
<tr>
<td>SE, %</td>
<td>76.9 ± 9.3</td>
<td></td>
<td>80.3 ± 10.5</td>
</tr>
<tr>
<td>Sleep stage, min (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>58.6 ± 32.7 (15.7)</td>
<td>50.2 ± 36.3 (13.7)</td>
<td>48.0 ± 23.6</td>
</tr>
<tr>
<td>2</td>
<td>194.3 ± 54.5 (52.2)</td>
<td>188.5 ± 50.2 (51.4)</td>
<td>155.8 ± 49.7</td>
</tr>
<tr>
<td>3/4</td>
<td>55.0 ± 31.2 (14.8)</td>
<td>65.5 ± 27.8 (17.9)</td>
<td>120.0 ± 53.3</td>
</tr>
<tr>
<td>REM</td>
<td>64.7 ± 26.5 (17.4)</td>
<td>64.2 ± 30.3 (17.5)</td>
<td>71.9 ± 26.2</td>
</tr>
<tr>
<td>AHI &gt; 10, %</td>
<td>41.2</td>
<td>42.2</td>
<td>11.5</td>
</tr>
<tr>
<td>PLMD, %</td>
<td>35.3</td>
<td>39.1</td>
<td>38.5</td>
</tr>
<tr>
<td>Subjective data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST, min</td>
<td>348.9 ± 72.4</td>
<td>313.6 ± 60.9</td>
<td>424.1 ± 43.9</td>
</tr>
<tr>
<td>WASO, min</td>
<td>113.3 ± 62.8</td>
<td>121.7 ± 64.5</td>
<td>10.5 ± 9.5</td>
</tr>
<tr>
<td>SOL</td>
<td>38.1 ± 27.1</td>
<td>35.4 ± 28.3</td>
<td>11.5 ± 9.7</td>
</tr>
<tr>
<td>SE, %</td>
<td>68.6 ± 13.0</td>
<td>66.1 ± 12.0</td>
<td>86.8 ± 6.4</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>3.0 ± 0.8</td>
<td>2.8 ± 0.7</td>
<td>4.2 ± 0.8</td>
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<tr>
<td>Psychological functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression (BDI)</td>
<td>10.5 ± 5.8</td>
<td>7.1 ± 5.1</td>
<td>2.5 ± 3.1</td>
</tr>
<tr>
<td>Anxiety (STAI-T)</td>
<td>44.5 ± 9.1</td>
<td>38.7 ± 8.8</td>
<td>26.6 ± 5.1</td>
</tr>
<tr>
<td>Anxiety (STAI-S)</td>
<td>40.1 ± 6.0</td>
<td>35.3 ± 8.7</td>
<td>26.2 ± 5.8</td>
</tr>
</tbody>
</table>

Data are provided as mean ± SD (%), mean ± SD, or percentage. TST refers to total sleep time; WASO, wake time after sleep onset; SOL, sleep-onset latency; SE, sleep efficiency; REM, rapid eye movement sleep; AHI, apnea-hypopnea index; PLMD, periodic limb movement disorder (15 or more periodic limb movements per hour of sleep without arousal); BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; a, b, c = different letters within the same line signify significant (p < 0.05) differences between the groups.
data. Sleep parameters did not differ significantly from those of drug-free patients with insomnia. We also found high a frequency of sleep apnea in the 2 clinical groups, compared with the sample of good sleepers.

In addition to increased wake time and sleep-onset latency, as well as decreased sleep efficiency, found among the chronic zopiclone users, perhaps the most noteworthy finding was the reduced amount of SWS in this group. A few studies have investigated the polysomnographic effects of zopiclone in patients with chronic insomnia, with the majority of studies showing that the amount of SWS remains unchanged or increases following 2 to 3 weeks of drug administration. However, the findings are mixed, and SWS has also been found to decrease following short-term use of zopiclone. Although a recent trial showed sustained effects of eszopiclone on self-reported measures after 6 months, no studies have, to our knowledge, examined the effects of long-term use of zopiclone on objective sleep measures. As such, the present study thus provides the first evidence that using zopiclone on a daily basis for more than 1 year is associated with reduced duration of SWS.

Also, the subjective sleep data and increased daytime sleepiness underscore the patients’ sleep problems in the zopiclone group. There were few differences between the zopiclone users and drug-free insomniacs on either the objective or subjective measures, indicating that the zopiclone users were still dissatisfied with their sleep after prolonged use of zopiclone.

However, an alternative explanation for the poor sleep found among the chronic zopiclone users may be that these patients had worse sleep quality to begin with. Also, our finding that the zopiclone users reported higher levels of anxiety and depression than did the other 2 groups may suggest that the group differences in psychopathology or health in general and, consequently, may indicate a possible group-selection bias. However, the cross-sectional nature of the current study and, hence, the lack of baseline data do not permit us to examine possible differences concerning initial insomnia severity nor to determine the direction of causality—whether the symptoms of anxiety or depression serve as consequences of poor sleep or as prodromal symptoms preceding the sleep problems.

Still, our findings support the general scientific opinion that nonpharmacologic treatments should be considered as an alternative to chronic use of hypnotics. Today, cognitive behavior therapy is the most widely used nonpharmacologic intervention for insomnia, and several meta-analyses have concluded that most people with insomnia will benefit from such interventions. Although most randomized controlled trials have focused on younger and middle-aged adults, there is now also evidence that older adults will significantly benefit from cognitive behavior therapy, in both the short- and long-term management of insomnia.

In the present study, we also found high frequency rates of sleep apnea in both clinical samples, compared with the sample of good sleepers. However, although high, the rates are in fact comparable with what other studies in this age cohort previously have found. As for insomnia, untreated sleep apnea represents a significant burden for both the affected individual, as well as for society as a whole. For example, sleep apnea has been shown to be a risk factor for a range of medical conditions, including glucose intolerance, impotence, hypertension, myocardial infarction, stroke, and mortality. Untreated sleep apnea also increases the risk of automobile crashes, leads to poor quality of life, and has been linked with several neurocognitive consequences. Also, symptoms of sleep apnea have recently been found to predict both long-term sick leave and permanent work disability. Given these consequences of untreated sleep apnea, we consider it disturbing that as many as 41% of the chronic zopiclone users fulfilled the diagnostic criteria for sleep apnea. The findings emphasize the need to inform healthcare professionals in primary care settings about the relatively high prevalence rates of sleep disorders in this age cohort, as well as appropriate treatment options for the specific disorders. Failure to do so may result in patients receiving inappropriate treatment for their condition. This is particularly a concern regarding hypnotics, which may actually exacerbate the sleep apnea.

There are several limitations in the present study. First, the sample sizes were small, limiting the generalizability of the results and, thus, preventing us from determining exact frequency rates in the population. Second, the sample sizes in the 3 groups were not identical, resulting in different statistical power when comparing the groups. Third, the age and sex distribution across the 3 groups were not identical, which may have influenced some of the findings. For example, the low frequency of sleep apnea in the sample of good sleepers may be related to an overrepresentation of women in this group. Fourth, no attempts were undertaken to standardize the patients’ nightly dose of zopiclone. Moreover, the different recruiting procedures may have resulted in biased samples, excluding patients not willing or unable to submit to the burden of completing 2 nights of polysomnographic assessments. On one hand, this may result in inclusion of healthier subjects, which again may lead to an underestimation of possible pathology. Alternatively, this may also have led to the inclusion of participants who were seeking help for their sleep problems. Unfortunately, the current design did not allow us to assess the severity of the sleep problems of the chronic users before they started taking hypnotics. Also, we did not measure the body mass index of all participants and were, thus, unable to examine potential group differences in obesity. And, because the sleep structure of patients with sleep apnea is characterized by several electroencephalographic alterations, including reductions in SWS, we cannot disregard the possibility that potential group differences in obesity may have influenced the study results. Finally, the polysomnographic data in the 3 groups were collected and scored on different time points, and scorers were consequently not blinded for purposes of the present study.

In conclusion, the current study shows that the sleep of chronic users of zopiclone is no better than that of drug-free patients with insomnia. We also find it disturbing that more than 40% of the patients treated pharmacologically for insomnia also suffer from sleep apnea. Consequently, we suggest careful sleep assessment as a prerequisite for long-term prescription of sleep medications.

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DISCLOSURE STATEMENT

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REFERENCES


