Patients With Treatment-Resistant Insomnia Taking Nightly Prescription Medications for Sleep: A Retrospective Assessment of Diagnostic and Treatment Variables

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Background: Some chronic insomnia patients who take nightly prescription medication achieve less than optimal results. The US Food and Drug Administration (FDA) and the American Academy of Sleep Medicine (AASM) recommend reevaluation of this type of patient to assess for potential psychiatric or medical causes to explain this "failure for insomnia to remit."

Method: A retrospective chart review examined a consecutive series of chronic insomnia patients with persistent insomnia complaints despite current nightly use of prescription medication from May 2005 to February 2008. To assess the role of psychiatric influences on insomnia symptoms, our sample (N = 218) was divided into 2 subgroups: a group with a history of psychiatric complaints (psychiatric insomnia, n = 189) and a control group of no psychiatric complaints (insomnia, n = 29).

Results: The average patient reported insomnia for a decade and took prescription medication for sleep for a mean of 4.5 years. Although 100% of the sample used nightly sleep drugs, only 20% believed medication was the best solution for their condition. As evaluated by self-report and polysomnography, these patients exhibited moderately severe insomnia across most measures. Only a few differences were noted between groups. Subjective perception of insomnia severity was worse in the psychiatric insomnia group, which also reported significantly more insomnia-related interference in daily functioning, symptoms of sleep maintenance insomnia, and a trend toward greater daytime fatigue. The mean Apnea-Hypopnea Index score was 19.5 events/hour, yielding an obstructive sleep apnea diagnosis in 75% of patients per conservative AASM nosology (79% in the insomnia group and 74% in the psychiatric insomnia group, $P = .22$).

Conclusions: In this treatment-seeking sample of patients regularly taking sleep medications, residual insomnia was widespread, and patients with psychiatric insomnia may have perceived their condition as more problematic than a control group of insomnia patients without mental health complaints. Both groups exhibited high rates of objectively diagnosed obstructive sleep apnea, a medical condition associated with pervasive sleep fragmentation. These findings support FDA and AASM guidelines to reassess chronic insomnia patients who manifest residual symptoms despite nightly use of prescription medication for sleep.

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Chronic insomnia is a common complaint in the general population as well as in various subpopulations such as the elderly,[1] psychiatric patients,[2,3] and shift workers[4]; however, longitudinal data are lacking on their long-term treatment course. Initially, insomnia patients navigate through 4 common pathways: no discernible treatment, over-the-counter sleep aids,[5,6] substances or alcohol at bedtime,[6,7] and basic sleep hygiene instructions obtained through various media or from primary care providers and educators.[8–10] There is often overlap among these 4 pathways. And, in a progression through these approaches, albeit in no fixed order, some insomnia patients broach the issue with a physician or other provider with whom they regularly interact. This type of health care encounter most frequently involves primary care physicians or mental health providers, including psychiatrists, psychologists, and other therapists. In these environments, insomnia patients may receive exposure to evidenced-based treatments for unwanted sleeplessness,[8,9,11] for example, prescription medications for sleep and cognitive-behavioral therapies (CBTs).

Evidence for CBT as the ideal first-line treatment for insomnia is persuasive and substantial, but the lack of behavioral sleep medicine specialists both at sleep medical centers and in the medical community at large[8] has limited the application of this therapeutic option. In contrast, pharmacotherapy for insomnia is well established throughout all fields of medicine. Traditional standards indicate prescribed medication for acute, transient, or situational insomnia, and the prescribing instructions may recommend nightly use for a few weeks or a few times per week for longer intervals.[12] However, in clinical settings, it is not unusual for various subgroups of patients, for example psychiatric patients, to rely on the regular, long-term use of prescription medications for sleep. Interestingly, these prescription medications may include standard sedatives as well as sedating antidepressants. Indeed,

Clinical Points

- Patients with treatment-resistant insomnia taking hypnotic medication require additional medical and psychiatric evaluations.
- Overnight polysomnography appears to be a useful evaluation tool for patients with treatment-resistant insomnia.
- Sleep-disordered breathing may be common in patients with treatment-resistant insomnia.

for years trazodone[13] was the single most-prescribed medication for sleep, and although there is scant evidence describing the efficacy of antidepressants for insomnia, there can be no doubt that these drugs are often prescribed for the combination of insomnia and depression.[14]

Recently published American Academy of Sleep Medicine (AASM) guidelines provide support for the use of long-term pharmacologic modalities to treat insomnia.[12] However, the guidelines are not a "practice parameter" but rather a "working overview for disease or disorder evaluation and management."[(p490)] In fact, when dealing with duration of pharmacologic treatment, it is clearly stated that "the empirical database for long-term treatment remains small."[12(p501)] Conversely, government regulatory actions from the US Food and Drug Administration (FDA) established indications for long-term use of the hypnotics eszopiclone, zolpidem controlled release, and ramelteon to treat chronic insomnia.[15,16] But, this same agency subsequently posted (March 2007) an important warning about the first 2 medications: "The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated."[17(p3),18(p1)] In a similar vein, the AASM practice parameters, which ordinarily do not recommend polysomnography for insomnia patients, state, "… polysomnography is indicated when initial diagnosis (of insomnia) is uncertain, treatment fails (behavioral or pharmacologic), or precipitous arousals occur with violent or injurious behavior."[12(p487)] Notwithstanding these paradoxical perspectives, newer agents are now routinely advertised in scientific journals, in popular magazines, on television, and through the Internet as nightly long-term solutions to insomnia.

Despite the increase in prescribing patterns for chronic insomnia,[19] scant longitudinal data describe how patients respond to these drugs and whether or not FDA and AASM guidelines are invoked subsequent to the "failure of insomnia to remit." One speculation would comprise a spectrum of patient outcomes, which at one end include responders who continue care with their prescribing physician, whereas those on the opposite end of the spectrum, nonresponders (extreme treatment-resistant cases), might drop out of treatment entirely. In the middle ground, a sizable proportion of partial treatment-resistant insomnia patients manifest mixed results while continuing to use nightly prescription medications.

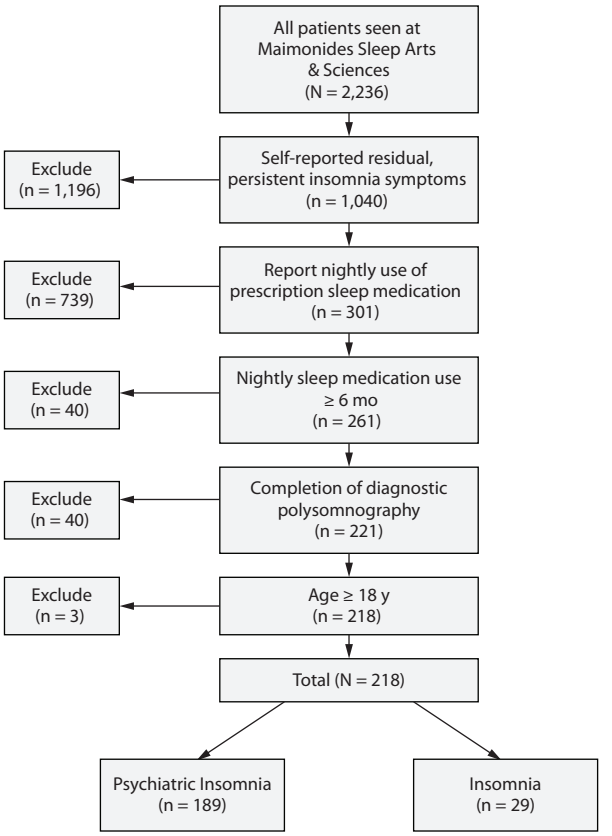
We are interested in this middle group because they commonly present to sleep centers and request further treatment for insomnia despite regularly taking prescription medications. In most cases, these patients align with AASM and FDA guidelines in that further psychiatric evaluations and polysomnography are indicated to assess residual insomnia complaints. For example, prior studies show higher than expected rates of obstructive sleep apnea (OSA) in chronic insomnia patients.[20–24]

In the current study, we gathered data on a consecutive series of chronic insomnia patients who presented to our sleep medical centers with a history of nightly use of prescription medications for sleep and the failure of insomnia to remit. From this pool of consecutive patients, a retrospective chart review was conducted, coinciding with FDA and AASM guidelines, to assess our sample for psychiatric or medical conditions that might be associated with worse insomnia outcomes. For this descriptive study, we developed 2 hypotheses: (1) psychiatric insomnia patients would report or demonstrate worse insomnia outcomes than a nonpsychiatric insomnia group and (2) both psychiatric and nonpsychiatric insomnia groups would show high rates of the medical condition sleep-disordered breathing (SDB) and its resultant sleep fragmentation, which might be associated with residual insomnia symptoms.

METHOD

Per standard protocol at our sleep facilities in Albuquerque and Los Alamos, New Mexico, all patients provide written and verbal consent for their medical information to be used anonymously for research purposes in the context of subsequent chart reviews. This study was a retrospective chart review of existing data on patients treated from May 2005 to February 2008. The study was reviewed and approved by the Los Alamos Medical Center Institutional Review Board, Los Alamos, New Mexico.

Figure 1. Selection Criteria for Patient Inclusion



Sample and Inclusion Criteria for Chart Review

This study contained 4 inclusion criteria: (1) insomnia ranked as the primary reason for seeking treatment despite nightly use of prescription medication for sleep, (2) minimum duration of medication use of 6 months, (3) completion of overnight diagnostic polysomnography or split-night protocol with at least 2 hours of diagnostic sleep data, and (4) at least 18 years of age. Figure 1 (flowchart) shows nearly half the clinic population of 2,236 patients ranked insomnia as their primary problem, but only 301 patients reported both residual insomnia and nightly sleep medication use. Each individual patient's medications were reviewed to determine whether or not their reported nightly agent was in fact being used to treat sleep problems. For example, 3 patients were excluded because the only nighttime medication was lithium, a drug not typically used for insomnia. Additional exclusions were duration of use less than 6 months, no polysomnography testing, or age less than 18 years. And, as anticipated from our introduction, no patients presented to our sleep medical facility with a self-reported optimal response to nightly use of prescription medication for sleep.

Psychiatric Assessment

No formal psychiatric interviewing or instruments were used to evaluate historical complaints of psychiatric conditions; therefore, the information used in this retrospective study relies entirely on subjective reports from the patients' intake questionnaires. However, the intake questionnaire does not ask patients to speculate about their mental health; rather, it specifically asks patients to check those conditions that they believe they suffer from currently or have suffered from in the past. The checklist comprises 4 columns: a list of 8 psychiatric conditions and 2 additional lines for "none" or "other," a list of current medications taken for a condition checked, a list of past medications taken for the condition, and any other therapies used to treat the condition. Two additional questions are asked about a history of traumatic exposure and/or claustrophobia. For trauma, patients are asked if they have suffered a threat to their life, a serious injury, or a serious assault (physical, sexual, etc), which elicited a feeling of fear, helplessness, and/or horror.

Although these data do not corroborate formal psychiatric diagnoses, 87% of the patients in our sample reported a history of at least 1 of the following: depression, anxiety disorder, posttraumatic stress disorder (PTSD), panic disorder, schizophrenia, bipolar disorder, obsessive-compulsive disorder (OCD), traumatic exposure, or claustrophobia. To be clear, however, these data are only describing the association of a putative psychiatric condition with the presence of insomnia; the data do not indicate whether or not the psychiatric condition is a cause or contributor to the patient's insomnia. Therefore, in this article, the term *psychiatric insomnia* is only used to distinguish this group of patients from those with no self-reported psychiatric condition(s).

Sleep Intake, Measurements, and Procedures

All patients seen at both sleep facilities completed an online intake set of questionnaires, including an extensive sleep medicine history[25] on self-reported subjective sleep measures, sleep history, and medication use for sleep. The sleep medicine history also contained 3 questions about patient perceptions on chronic use of sedating medications, and these were scored on a disagree/unsure/agree 3-point scale. These questions dealt with whether medication was perceived as the best solution for their sleep problems, whether they had been seeking help for their sleep problems for an extended period of time, and the level of frustration with past efforts in getting help for their sleep problem(s). Answers to these questions were not considered for inclusion or exclusion in the current study.

The Insomnia Severity Index (ISI)[26] was also completed by all patients. The ISI is the sum of 7 individual questions dealing with the following: (1) difficulty falling asleep, (2) difficulty staying asleep, (3) waking up too early, (4) satisfaction with current sleep pattern, (5) extent of

interference sleep problem has on daily functioning, (6) impairment of quality of life noticeable to others, and (7) level of distress surrounding current sleep problem. Each question is scored on a scale of 0 to 4 based on increasing severity of the symptom, and the total score ranges from 0 to 28 with scores greater than 20 equal to moderately severe to severe insomnia.

Two visual analog scales (VAS) were used to measure daytime sleepiness and tiredness,[27,28] scored on a 0 to 10 metric with scores > 6 indicative of severe symptoms.

Intake questionnaires are reviewed by the sleep specialist (B.K.), and patients are scheduled for polysomnography when criteria are met for apparent risks of physiologic disorders such as SDB. In our clinical experience, we follow FDA and AASM guidelines and recommend diagnostic polysomnography testing in the large majority of these patients[17–18] for failing to achieve a satisfactory or optimal response to pharmacologic treatment of insomnia. However, as noted in Figure 1, 40 patients refused or did not undergo polysomnography testing and were therefore excluded from the study.

Polysomnography Protocol

Overnight sleep studies were performed using standard polysomnography on all Maimonides Sleep Arts & Sciences and Los Alamos Medical Center Sleep Laboratory patients. Technicians prepared patients using the international 10–20 system of electrode placement. The recording had a 14-channel montage: left outer canthus-A_2, right outer canthus-A_1, C_3-A_2, C_4-A_1, O_1-A_2, O_2-A_1, chin, electrocardiogram, left leg-right leg, snore, nasal pressure transducer via nasal canula, chest effort, abdominal effort, pulse oximetry, and position. Polysomnography sleep staging was scored manually by registered technologists using Rechtschaffen and Kales'[29] scoring criteria. Three types of events were scored. An apnea was a > 70% decrease in airflow for at least 10 seconds. Hypopnea was a 30%–70% decrease in airflow coupled with either a 4% oxygen desaturation or an arousal. Flow limitation was a decrease in airflow of ≤ 30% in the form of classic flattening or notching of the airflow limb for at least 2 consecutive breaths, lasting > 10 seconds, ending in an arousal. Minimum oxygen saturation was recorded by pulse oximetry. All patients were tested using their regular bedtime regimen of medications. The Apnea-Hypopnea Index (AHI) was calculated for each patient and per AASM nosology.[30] An AHI score ≥ 5 was used as a diagnostic cut point for the diagnosis of SDB. A total of 18 patients completed split nights, and their data were extrapolated as if they completed a full-night study by using their objective sleep efficiency from the diagnostic portion of the polysomnography testing to estimate relevant objective sleep indices.

Data Analysis

To compare outcomes among those patients with and without self-reported psychiatric conditions, 2 groups were created: insomnia group (no psychiatric complaints, n = 29) and psychiatric insomnia group (self-report of psychiatric complaints, n = 189). One post hoc analysis compared patients with OSA (n = 163) and no OSA (n = 55).

Analysis of variance and χ^2 analyses were performed for continuous and dichotomous variables, respectively. Cohen *d* effect sizes, the standardized mean difference, were calculated from the difference in 2 means, divided by the pooled standard deviation, and used for select comparisons of statistically significant findings only. Statistical significance was .05. Power analysis ($\alpha = .5$, $\beta = .80$) revealed that the 2 unequal samples for the insomnia and psychiatric insomnia groups were slightly underpowered to detect medium-sized effects.

RESULTS

Sample Characteristics

Of the 2 contrasted groups, the psychiatric insomnia group comprised 189 patients who reported the following prevalence of psychiatric conditions: depression (56.4%), traumatic exposure (50.2%), anxiety (42.7%), claustrophobia (41.6%), panic (25.7%), PTSD (17.95%), bipolar illness (9.2%), OCD (2.8%), dissociative disorder (3.2%), and schizophrenia (0.5%).

Table 1 shows that the full sample of unresolved insomnia patients was largely middle-aged and slightly overweight. Distinctions between groups revealed predominantly women in the psychiatric insomnia group and predominantly men in the insomnia group ($P = .004$). Insomnia severity, based on ISI score, was in the moderate to severe range (mean ± SD = 19.16 ± 5.63) with the psychiatric insomnia group having a significantly higher ISI (19.52 ± 5.37) than the insomnia group (16.68 ± 6.75) ($P = .01$, $d = 0.47$). The mean ± SD duration of insomnia was 12.2 ± 13.32 years. Sedating medication use ranged from 6 months to 30 years with a mean of 54.68 months (SD = 69.84) and a median of 25.0 months.

Prescription Medications for Sleep

All patients were using a prescription medication designated by their prescribing physician for the primary purpose of treating a sleep disturbance. Of our total sample, 67% were prescribed sleep medications by their primary care physician, 24% by a psychiatrist, 8% by physicians of various specialties, and 1% by a sleep doctor. However, due to patient inconsistency, we did not collect or report specific dosages used by the patients in this sample. We identified 3 main categories of drugs prescribed (Table 2): benzodiazepines (n = 69), nonbenzodiazepines (n = 75), and mood

Table 1. Sociodemographics, Insomnia Severity and Chronicity, and Daytime Sleepiness and Tiredness Scores of Patients With Insomnia[a]

Characteristic	Insomnia (n = 29)	Psychiatric Insomnia (n = 189)	Total (N = 218)	*P* Value[b]
Age, y	53.62 ± 15.03	50.74 ± 12.41	51.12 ± 12.79	.26
Gender				
Men	19 (65.5)	70 (37.0)	89 (40.8)	
Women	10 (34.5)	119 (63.0)	129 (59.2)	.004
Body mass index, kg/m^2	27.56 ± 4.00	28.15 ± 6.24	28.07 ± 5.99	.63
Marital status				
Married, living with partner	21 (72.4)	121 (64.0)	142 (65.1)	
Single, divorced, or other	8 (27.6)	68 (36.0)	76 (34.9)	.52
Education[c]				
Bachelor's degree or higher	20 (69.0)	109 (59.2)	129 (60.6)	
Some college or lower	9 (31.0)	75 (40.8)	84 (39.4)	.22
Ethnicity				
Hispanic	8 (27.6)	45 (23.8)	53 (24.3)	
White	19 (65.5)	139 (73.5)	158 (72.5)	
Other	2 (6.9)	5 (2.6)	7 (3.3)	.53
Insomnia Severity Index				
Total score	16.68 ± 6.75	19.52 ± 5.37	19.16 ± 5.63	.01
Insomnia chronicity, y	7.25 ± 5.61	12.85 ± 13.92	12.16 ± 13.34	.08
Visual Analog Scale score				
Sleepiness	5.86 ± 2.83	6.12 ± 2.54	6.09 ± 2.57	.61
Tiredness	6.72 ± 2.90	7.53 ± 2.16	7.42 ± 2.28	.08

[a]Dichotomous variables are expressed as n (%) of total, and continuous variables are expressed as mean ± SD.
[b]*P* value determined using χ^2 analysis for dichotomous variables and 1-way analysis of variance for continuous variables.
[c]Five patients did not complete education history information.

Table 2. Patient Medications by Category and Percent of Total Sample (N = 218)[a]

Benzodiazepines (n = 69)	Nonbenzodiazepines (n = 75)	Mood Stabilizers/ Antidepressants (n = 74)
Clonazepam, 17.5	Zolpidem, 23.8	Trazodone, 7.5
Alprazolam, 7.1	Eszopiclone, 10.4	Escitalopram, 5.0
Temazepam, 1.7	Zaleplon, 2.5	Bupropion, 3.8
Diazepam, 1.3		Venlafaxine, 3.3
Lorazepam, 1.3		Sertraline, 2.9
Flurazepam, 0.4		Paroxetine, 2.9
		Fluoxetine, 2.5
		Amitriptyline, 1.7
		Olanzapine, 1.7
		Haloperidol, 0.8

[a]Medications listed are those used for categorization of patients into their respective drug groups.

stabilizers/antidepressants (n = 74). No patients were taking the melatonin agonist ramelteon.

In the psychiatric insomnia group, roughly one-half of the patients were also taking other psychotropic medications that influence sleep,[31,32] although these drugs were not the primary medication prescribed for sleep. No systematic differences were evident between these 3 prescribed groups of medications for any of the variables of interest in this study; therefore, no additional analyses were conducted on the basis of medications.

Patient Perceptions

On the basis of 3 questions about patient perceptions, 74% of the total sample reported that they had been seeking help for their sleep problems for a long time, which is consistent with a mean duration of insomnia of 12 years. Nearly half the sample (47%) reported frustration with previous physicians in their attempts to solve their sleep problems, whereas only 26% reported no frustration and 27% were unsure how to respond. At this point in their care, only 20% of patients believed that the correct medication would solve their sleep problems, whereas 55% were undecided on this question, and 24% believed medications would not solve their problems. There were no statistical differences on these perceptions between the insomnia and psychiatric insomnia groups.

Two individual items on the ISI relating to patient perceptions showed differences between the 2 groups. First, those patients in the psychiatric insomnia group reported more difficulty staying asleep ($P = .05$, $d = 0.36$). Second, the psychiatric insomnia group also perceived that their sleep problems interfered with their daily functioning to a greater degree than the insomnia group ($P = .04$, $d = 0.38$), and these 2 items account for most of the differences between the 2 groups on the total ISI score of self-reported insomnia severity.

Regarding impairment, there were no significant differences among groups for the VAS sleepiness scale (Table 1); however, the VAS for tiredness showed that the psychiatric insomnia group trended toward greater severity than the insomnia group ($P = .08$, $d = 0.32$).

Self-Reported and Objective Sleep Indices

Subjective sleep indices including mean ± SD sleep-onset latency (69.11 ± 65.67 minutes), total

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Table 3. Objective Diagnostic Polysomnography Sleep Data of Patients With Insomnia[a,b]

Characteristic	Insomnia (n = 29)	Psychiatric Insomnia (n = 189)	Total (N = 218)	*P* Value
Sleep onset latency, min	11.90 ± 9.51	20.69 ± 35.11	19.52 ± 32.99	.18
Total sleep time, min[c]	363.06 ± 110.62	364.84 ± 89.07	364.61 ± 91.94	.92
Wake after sleep onset, min[d]	76.54 ± 60.80	74.26 ± 58.40	74.56 ± 58.58	.85
Sleep efficiency, %[e]	75.43 ± 15.38	79.59 ± 15.37	79.04 ± 15.41	.18
Stage 1 ratio, %	18.68 ± 17.29	14.25 ± 11.26	14.84 ± 12.27	.07
Stage 2 ratio, %	59.20 ± 17.87	66.41 ± 13.38	65.45 ± 14.22	.01
Stage 3 ratio, %	5.02 ± 8.77	4.97 ± 7.21	4.98 ± 7.42	.97
Stage 4 ratio, %	3.11 ± 8.19	1.40 ± 4.32	1.63 ± 5.01	.09
REM ratio, %	13.97 ± 9.05	12.96 ± 7.79	13.09 ± 7.95	.53

[a]Data are expressed as mean ± SD. *P* values were determined using 1-way analysis of variance.
[b]Eighteen patients underwent split-night studies. Individual, objective sleep efficiency was used to calculate estimated values for total sleep time, wake after sleep onset, and individual sleep stages for each of the 18 patients.
[c]Duration of rapid eye movement sleep, plus non–rapid eye movement sleep epochs from lights off to lights on.
[d]Number of wake epochs from lights off to lights on.
[e]Total time from persistent sleep onset to the end of the polysomnogram divided by time in bed.

sleep time (6.01 ± 1.93 hours), wake time after sleep onset (100.43 ± 89.72 minutes), and calculated sleep efficiency (73.24 ± 19.98%) consistently showed moderate to severe insomnia. Patients also reported other signs of sleep fragmentation including difficulty maintaining sleep, increased awakenings, and difficulties returning to sleep once awakened. There were no statistical differences between the 2 groups.

For objective sleep indices, the polysomnography testing consisted of 1 night in the sleep laboratory, and the patients used their standard nightly regimen of medications including their primary sleep medication. As expected, consistent signs of moderate to severe insomnia were documented for total sleep time, wake time after sleep onset, and sleep efficiency without significant differences between the 2 groups (Table 3). And, as often seen with first-night effects in sleep laboratory testing of insomnia patients,[33] mean ± SD sleep-onset latency was within normal limits in both groups (insomnia group: 11.90 ± 9.51, psychiatric insomnia group: 20.69 ± 35.11, $P = .18$). When looking at individual sleep stage ratios (Table 3), the psychiatric insomnia group showed a significantly higher ratio (66.41 ± 13.38) of stage 2 non–rapid eye movement (NREM) sleep than the insomnia group (59.20 ± 17.87, $P = .01$) with a medium effect size ($d = 0.46$). The ratio of stage 1 NREM sleep trended lower in the psychiatric insomnia group (14.25 ± 11.26) versus the insomnia group (18.68 ± 17.29, $P = .07$, $d = 0.30$), whereas the ratio of stage 4 NREM sleep in the psychiatric insomnia group trended lower (1.40 ± 4.32) than the insomnia group (3.11 ± 8.19, $P = .09$, $d = 0.26$).

Breathing Event Indices and Sleep-Disordered Breathing Diagnoses

The mean ± SD AHI score was 19.48 ± 23.62 events/hour with no significant differences between the 2 groups (Table 4). Given a significant difference in men versus women between groups (more men in the insomnia group) and the consequent greater severity of OSA (AHI) found in men (men: 29.83 ± 29.76, women: 12.34 ± 14.52, $P = .001$), further analysis showed that the finding of more severe OSA in the insomnia group was primarily due to differences in gender ratios between groups ($F_{2,235} = 8.210$, $P = .0001$).

According to AASM nosology,[30] we found that 163 (75.0%) patients met criteria for OSA based solely on AHI score (≥ 5) (79% of the insomnia group and 74% of the psychiatric insomnia group). For exploratory purposes only and not reported in our tables, we scored flow limitation events 2 ways: (1) according to AASM guidelines,[30] yielding a mean ± SD Respiratory Disturbance Index (RDI) of 37.54 ± 24.83 events/hour, and (2) with so-called "subcortical arousals" using Rapoport's criteria,[31] which would have raised the mean ± SD RDI to 46.53 ± 25.24 events/hour, thereby potentially yielding an even higher proportion of diagnosed cases of OSA. There was no significant difference of mean RDI values between the 2 groups.

Sleep Fragmentation

We assessed sleep fragmentation in the form of awakenings (> 15.0 seconds), arousals (3.0–15.0 seconds), and microarousals (1.5–3.0 seconds) caused by sleep breathing events that might be associated with insomnia outcomes (Table 4). For both groups, SDB events produced a mean of 1 awakening/hour due to apneas (including central apneas) or hypopneas with an additional 1.7 awakenings/hour for flow limitation events (Table 5). The Respiratory Arousal Index showed a mean of 14.21 ± 20.04 arousals/hour for apneas and hypopneas with an increase to 28.60 ± 16.11 arousals/hour when flow limitation events were included. There was a trend toward a higher total of SDB-related arousals in the insomnia group (34.61 ± 26.74) when compared to the psychiatric

Table 4. Objective Diagnostic Polysomnography Respiratory Data of Patients With Insomnia[a]

Characteristic	Insomnia (n = 29)	Psychiatric Insomnia (n = 189)	Total (N = 218)	*P* Value
Sleep breathing events				
Apnea-Hypopnea Index, events/h[b]	25.93 ± 32.66	18.49 ± 21.85	19.48 ± 23.62	.11
Respiratory Disturbance Index, events/h[c]	40.65 ± 31.36	37.06 ± 23.74	37.54 ± 24.83	.13
Central Apnea Index, events/h	0.56 ± 1.49	1.00 ± 5.65	0.95 ± 5.29	.68
Time oxygen saturation < 90%, %	14.65 ± 20.60	17.78 ± 26.18	17.37 ± 25.49	.54
Sleep fragmentation measurements				
Respiratory Awakenings Index, awakenings/h				
Apneas/hypopneas	1.06 ± 1.88	0.99 ± 2.08	1.00 ± 2.05	.87
Flow limitation	1.43 ± 1.43	1.70 ± 1.84	1.66 ± 1.79	.46
Total	2.49 ± 1.64	2.69 ± 1.95	2.66 ± 1.91	.78
Respiratory Arousals Index, arousals/h				
Apneas/hypopneas	22.81 ± 31.79	12.89 ± 17.32	14.21 ± 20.04	.01
Flow limitation	9.80 ± 8.96	15.10 ± 12.52	14.39 ± 12.23	.03
Total	34.61 ± 26.74	28.29 ± 15.02	28.60 ± 16.11	.07
Respiratory Microarousals Index, microarousals/h				
Apneas/hypopneas	1.65 ± 5.26	2.84 ± 10.89	2.68 ± 10.32	.56
Flow limitation	3.91 ± 8.36	3.55 ± 7.13	3.60 ± 7.29	.80
Total	5.56 ± 6.72	6.39 ± 8.88	6.28 ± 8.79	.69

[a]Data are expressed as mean ± SD. *P* values were determined using 1-way analysis of variance.
[b]Number of apneas and hypopneas/hour of sleep time.
[c]Apnea-Hypopnea Index plus flow limitation events ending in a microarousal, arousal, or awakening/hour of sleep time.

insomnia group (28.29 ± 15.02, $P = .07$, $d = 0.29$). And finally, OSA caused 2.68 ± 10.32 microarousals/hour with an increase to 6.28 microarousals/hour when flow limitation events were included. However, none of these awakenings, arousals, and microarousals individually or in combination correlated with ISI severity.

OSA Versus Non-OSA Patients

A final analysis was performed comparing those patients meeting AASM nosology for the diagnosis of OSA (AHI ≥ 5) and those who did not (AHI < 5). Significant or trending differences are found in Table 5. In sum, OSA patients were older and more likely to be men and overweight. Patients with OSA were more likely to report classic breathing symptoms including snoring, history of moving from the bed because of patient's snoring, witnessed apneas, and choking, gasping, or struggling for breath during sleep.

Subjective sleep indices showed the following: OSA patients trended toward shorter sleep-onset latency, longer total sleep time, and more consolidated sleep efficiency. Interestingly, insomnia severity based on mean ± SD total ISI score was worse in the non-OSA group (19.52 ± 5.37) than in the OSA group (16.68 ± 6.75, $P = .004$, $d = 0.47$). Objective measures show expected results of worse values in the OSA group compared to the non-OSA group (Table 5).

Last, we compared all of our subjective sleep data for the 40 individuals who were excluded for not undergoing polysomnography testing with those 218 patients in our study, and we found no significant differences on any variable between the 2 groups.

DISCUSSION

In this retrospective chart review, there were 3 primary findings in this consecutive series of treatment-resistant chronic insomnia patients who averaged reports of insomnia for more than a decade and regular use of prescription medication for sleep for 4 years. First, the findings of moderate to severe residual insomnia clearly indicated a failure to respond adequately to sleep medications. Second, patients reporting psychiatric problems were far more common than insomnia patients without such complaints, but there were only a few differences between these groupings in contrast to what we had predicted. Third, objective polysomnography diagnosed obstructive sleep apnea in three-fourths of this select sample along with the innate sleep fragmentation that invariably accompanies this disorder of sleep respiration. However, despite the potential importance of these findings, no systematic links unequivocally connected psychiatric influences or SDB to the etiology or severity of the residual insomnia reported by this sample.

Regarding psychiatric influences, the only distinctions were that the psychiatric insomnia group believed their sleep maintenance insomnia and daytime impairment were worse than the insomnia group, and the psychiatric insomnia group showed a trend toward worse daytime fatigue. Similarly, there were only a few differences with respect to objective findings on sleep stage comparisons; but these findings might be related to greater use of psychotropic medications in the psychiatric insomnia group.[32,34] The most relevant objective finding was that the psychiatric insomnia group (comprised of more women) showed a greater severity of flow limitation or upper airway resistance

Table 5. Obstructive Sleep Apnea (OSA) Versus No OSA Group Comparisons[a]

Characteristic	OSA (n = 163)	No OSA[b] (n = 55)	Total (N = 218)	*P* Value[c]
Subjective insomnia and sleep indices				
Insomnia Severity Index total score	16.68 ± 6.75	19.52 ± 5.37	19.16 ± 5.63	.004
Sleep onset latency, min[d]	64.24 ± 63.20	83.63 ± 71.20	69.11 ± 65.67	.06
Total sleep time, h	6.15 ± 1.94	5.59 ± 1.85	6.01 ± 1.93	.06
Sleep efficiency, %[e]	75.39 ± 19.77	66.84 ± 19.36	73.24 ± 19.98	.01
Classic symptoms of sleep-disordered breathing				
Breathing problems cause awakenings				
Yes	53 (32.5)	11 (20.0)	64 (29.4)	
No	110 (67.5)	44 (80.0)	154 (70.6)	.05
Snoring				
Yes	125 (76.7)	24 (43.6)	149 (68.3)	
No	38 (23.3)	31 (56.4)	69 (31.7)	.001
Bed partner moved because of snoring				
Yes	58 (35.6)	9 (16.4)	67 (30.7)	
No	105 (64.4)	46 (83.6)	151 (69.3)	.01
Witnessed apneas by bed partner				
Yes	62 (38.0)	7 (12.7)	69 (31.7)	
No	101 (62.0)	48 (87.3)	149 (68.3)	.001
Chokes, gasps, or struggles for breath				
Yes	58 (35.6)	12 (21.8)	70 (32.1)	
No	105 (64.4)	43 (78.2)	148 (67.9)	.04
Objective sleep indices				
Respiratory Disturbance Index, events/h[f]	42.85 ± 25.29	21.82 ± 14.89	37.54 ± 24.83	.001
Stage 4 ratio, %	0.79 ± 2.94	4.11 ± 8.17	1.63 ± 5.01	.001
Respiratory Awakenings Index, awakenings/h apneas/hypopneas	1.28 ± 2.30	0.16 ± 0.33	1.00 ± 2.05	.001
Respiratory Arousals Index, arousals/h apneas/hypopneas	18.61 ± 21.46	1.17 ± 1.16	14.21 ± 20.04	.001
Respiratory Microarousals Index, microarousals/h apneas/hypopneas	3.54 ± 11.82	0.13 ± 0.35	2.68 ± 10.32	.03
Time oxygen saturation < 90%, %	20.23 ± 26.72	8.90 ± 19.24	17.37 ± 25.49	.004

[a]Dichotomous variables are expressed as n (% of total), and continuous variables are expressed as mean ± SD.
[b]Patients in OSA group met American Academy of Sleep Medicine nosologic criteria for diagnosis of OSA (Apnea-Hypopnea Index ≥ 5).
[c]*P* value determined using χ^2 analysis for dichotomous variables and 1-way analysis of variance for continuous variables.
[d]Subjective report of time to fall asleep.
[e] Determined by subjective total sleep time divided by subjective total time in bed.
[f]Apnea-Hypopnea Index plus flow limitation events ending in a microarousal, arousal, or awakening/h of sleep time.

compared to the insomnia group (comprised of more men) that showed greater apneas and hypopneas.

Regarding medical influences on chronic insomnia, the current study revealed that many of these patients suffered from SDB, the most common medical cause of sleep fragmentation,[20] and among the OSA group, 75% reported snoring and one-third of these patients reported various breathing symptoms suggestive of OSA. Yet, it remains unclear to what extent these breathing symptoms had been discussed or evaluated prior to seeking care at our sleep medical center. Our lack of a longitudinal design prevents us from knowing whether use of sleeping pills worsened OSA through respiratory depressant effects[35] or whether these medications ameliorated some of the sleep-fragmenting effects of OSA by raising arousal thresholds.[36] Also, as the study was conducted at 5,200 ft above sea level, altitude may be a contributing factor to increased OSA and central sleep apnea events. We could speculate that therapeutic application of positive airway pressure therapy, the gold standard treatment for SDB, would influence insomnia outcomes or alter medication use or dosage, but there are only a few weakly designed studies[20,37,38] that report improved insomnia outcomes subsequent to the treatment of OSA.

The current findings are consistent with prior research showing higher than anticipated rates of comorbid insomnia and OSA ("complex insomnia")[39] in a sample of patients who would ordinarily not be expected to suffer from a sleep breathing disorder. Of some potential clinical interest, insomnia severity was less in the OSA group compared to those without OSA, and objective measures on polysomnography testing tended to corroborate this finding, which in our view, further highlights the elusive nature of the pathophysiologic relationship between these 2 common sleep disorders.

The many limitations of this design mandate a cautious interpretation of our findings. Most importantly, this sample may prove to be highly select in that they sought treatment because medications were not working for them, and a lack of response to treatment is a well-known motivator to seek additional help or second opinions when the medical condition

is vexing enough to move the patient to action.[40] However, due to the design of this study, we cannot state that psychiatric influences or SDB were the causes of the patients' residual insomnia complaints; we can only state that these influences were present to some degree but are of unknown clinical significance.

Moreover, for psychiatric influences, we only used self-report checklists and did not conduct psychiatric interviews or use psychiatric instruments to make formal diagnoses. As such, our findings on psychiatric influences only suggest information about general distress not about specific diagnostic categories. And, there was no longitudinal data on the interaction between the patients' psychiatric and insomnia treatments, including psychotherapies or medications, so the snapshot design of the protocol limits our understanding of what transpired with these treatment-resistant insomnia patients prior to their arrival at the sleep center.

Along the same lines, 1 night of polysomnography also reflects a snapshot of sleep stages and breathing events. Again, a longitudinal design with more frequent testing and research-oriented polysomnography protocols as well as the utilization of sleep diaries would likely yield more useful clinical data. Regarding our 2 groups, our sample of nonpsychiatric insomnia patients was notably smaller and contained a greater proportion of men with only a few differences between the 2 groups, all of which might have changed with larger more balanced samples.

Last, we gathered no reliable data on specific drug dosages for insomnia used by these patients, which clearly could have influenced outcomes given that many patients do not take their medications consistently as prescribed.[41,42] Moreover, the psychiatric insomnia group consistently and significantly was taking multiple psychotropic drugs compared to the insomnia group. Overall, our findings may not be generalizable to other chronic insomnia patients taking various sleep medications on a long-term basis, particularly in light of the successes that have been described in the research literature for the long-term use of newer sedative medications.

CONCLUSIONS

To our knowledge, this is the first study to examine pertinent outcomes in a sample of chronic insomnia patients maintaining nightly prescription medication for sleep despite clear-cut signs of treatment-resistant insomnia. The scientific literature does not contain much information about such patients perhaps due to a lack of interest or reluctance to look at treatment outcomes in this difficult patient population.[43] Nonetheless, our study demonstrated the value in both the AASM and FDA guidelines,[12,17,18] because our findings suggest psychiatric and medical factors may be associated with patients who are not responding optimally to therapy. In particular, the sleep fragmentation effects of both psychiatric and medical conditions, such as those described in this study, may prove to be important influences in these cases. Although it is tempting to imagine that additional assessment and treatments for either sleep breathing or psychiatric conditions would lead to greater improvement in insomnia severity among this select sample of patients, only randomized controlled trials with evidence-based therapies can address such speculations.

Drug names: alprazolam (Niravam, Xanax, and others), bupropion (Aplenzin, Wellbutrin, and others), clonazepam (Klonopin and others), diazepam (Diastat, Valium, and others), escitalopram (Lexapro and others), eszopiclone (Lunesta), fluoxetine (Prozac and others), flurazepam (Dalmane and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), paroxetine (Pexeva, Paxil, and others), ramelteon (Rozerem), sertraline (Zoloft and others), temazepam (Restoril and others), venlafaxine (Effexor and others), zaleplon (Sonata and others), zolpidem (Ambien, Zolpimist, and others).

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Potential conflicts of interest: Dr Krakow owns and operates 3 Web sites that provide education and offer products and services for patients with sleep disorders (http://www.nightmaretreatment.com, http://www.sleeptreatment.com, and http:www.sleepdynamictherapy.com); markets and sells 3 books for patients with sleep disorders (*Insomnia Cures, Turning Nightmares Into Dreams,* and *Sound Sleep, Sound Mind*); owns and operates Maimonides Sleep Arts & Sciences, Ltd; and serves as president of a nonprofit sleep research center, the Sleep & Human Health Institute, which occasionally provides consultation services. Messrs Ulibarri and Romero report no financial or other affiliations relevant to the subject of this article.

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