# A Novel Therapy for Chronic Sleep-Onset Insomnia:

A Retrospective, Nonrandomized Controlled Study of Auto-Adjusting, Dual-Level, Positive Airway Pressure Technology

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#### ABSTRACT

*Objective:* Evidence indicates that behavioral or drug therapy may not target underlying pathophysiologic mechanisms for chronic insomnia, possibly due to previously unrecognized high rates (30%–90%) of sleep apnea in chronic insomnia patients. Although treatment studies with positive airway pressure (PAP) demonstrate decreased severity of chronic sleep maintenance insomnia in patients with cooccurring sleep apnea, sleep-onset insomnia has not shown similar results. We hypothesized advanced PAP technology would be associated with decreased sleep-onset insomnia severity in a sample of predominantly psychiatric patients with comorbid sleep apnea.

Methods: We reviewed charts of 74 severe sleeponset insomnia patients seen from March 2011 to August 2015, all meeting American Academy of Sleep Medicine Work Group criteria for a chronic insomnia disorder and all affirming behavioral and psychological origins for insomnia (averaging 10 of 18 indicators/patient), as well as averaging 2 or more psychiatric symptoms or conditions: depression (65.2%), anxiety (41.9%), traumatic exposure (35.1%), claustrophobia (29.7%), panic attacks (28.4%), and posttraumatic stress disorder (20.3%). All patients failed continuous or bilevel PAP and were manually titrated with auto-adjusting PAP modes (auto-bilevel and adaptive-servo ventilation). At 1-year follow-up, patients were compared through nonrandom assignment on the basis of a PAP compliance metric of > 20 h/wk (56 PAP users) versus < 20 h/wk (18 partial PAP users).

**Results:** PAP users showed significantly greater decreases in global insomnia severity (Hedges' g = 1.72) and sleep-onset insomnia (g = 2.07) compared to partial users (g = 1.04 and 0.91, respectively). Both global and sleep-onset insomnia severity decreased below moderate levels in PAP users compared to partial users whose outcomes persisted at moderately severe levels.

*Conclusions:* In a nonrandomized controlled retrospective study, advanced PAP technology (both auto-bilevel and adaptive servo-ventilation) were associated with large decreases in insomnia

hronic insomnia is extremely prevalent in primary care and psychiatric patients.<sup>1–4</sup> Pharmacotherapy is commonly prescribed to address this vexing condition,<sup>5,6</sup> and many individuals rely on over-the-counter sleep aids<sup>7,8</sup> or substances.<sup>9,10</sup> Despite widespread use of anti-insomnia drugs, therapeutic effects vary<sup>6,10</sup>; in contrast, many sleep medicine specialists and psychologists advocate cognitive-behavioral therapy for insomnia (CBT-I), a gold-standard psychological treatment.<sup>11</sup> In primary care practice, 2 opposing arguments emerge regarding practical treatment considerations: (1) CBT-I is potent, yet largely inaccessible<sup>12</sup> and (2) drug therapy is readily available, vet yields unsatisfactory results in many patients.<sup>13,14</sup>

behavioral Much drug and as therapies effective for some are commentaries<sup>17–19</sup> patients, 11, 15, 16 and reviews<sup>20-25</sup> raise questions as to whether these paradigms attend to all underlying mechanisms of chronic insomnia. Research on the pathophysiology of chronic insomnia mostly investigates psychophysiologic factors influencing learned sleeplessness<sup>11</sup> or sleep-regulating central nervous system receptors.<sup>26</sup>

Since 2001, we theorized another pathophysiologic mechanism for insomnia related to sleep-disordered breathing,<sup>27,28</sup> which requires treatment distinct from CBT-I or sedatives. This mechanism is supported by mounting evidence on the high prevalence of comorbid obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS) in chronic insomnia patients<sup>23</sup> at rates from 30% to 90% in diverse cohorts, including chronic hypnotic users,<sup>29–31</sup> trauma survivors with posttraumatic stress disorder,<sup>27</sup> elderly individuals,<sup>32</sup> postmenopausal women,<sup>33</sup> and community samples of treatmentseeking insomniacs.<sup>34,35</sup> Consequently, sleep breathing treatment for comorbid severity for sleep-onset insomnia patients who strongly believed psychological factors caused their sleeplessness. PAP treatment of sleep-onset insomnia merits further investigation.

Prim Care Companion CNS Disord 2016;18(5):doi:10.4088/PCC.16m01980 © Copyright 2016 Physicians Postgraduate Press, Inc.

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\**Corresponding author:* Barry Krakow, MD, Sleep & Human Health Institute, 6739 Academy NE, Ste 380, Albuquerque, NM 87109 (bkrakow@sleeptreatment.com). insomnia and OSA/UARS appears to be a novel intervention in which positive airway pressure (PAP) therapy and additional modalities have all demonstrated medium to large effects on insomnia outcomes,<sup>36–40</sup> measured on the Insomnia Severity Index (ISI).<sup>41</sup>

These therapeutic observations align with current theory on how sleep breathing events cause sleep maintenance insomnia, the most common sleep complaint in psychiatric patients.<sup>42</sup> Difficulty staying asleep (the phrase used by patients with sleep maintenance insomnia), previously attributed solely to central nervous system hyperarousal or psychiatric distress,<sup>15,16</sup> has also been related to the disruptive sleep fragmentation effects of OSA/UARS in 1 small study.<sup>43</sup> In 20 classic insomnia patients with no clinical breathing symptoms and who reported psychological factors as the main cause of sleeplessness,<sup>43</sup> 19 cases of covert OSA (n = 11) and UARS (n = 8) were diagnosed,

and 90% of the sample's awakenings in the sleep laboratory (mean = 25 per patient) were preceded and provoked by sleep breathing events (ie, apneas, hypopneas, flow limitation). Reversal of sleep breathing events lessens sleep fragmentation and improves middle of the night insomnia,<sup>36,44</sup> thus sleep maintenance insomnia may prove to be a clinically relevant target for sleep breathing treatments.

Sleep breathing treatments for sleep-onset insomnia (SOI), in contrast, have not yielded similar results to those observed in sleep maintenance insomnia patients with sleep-disordered breathing. Only 1 study<sup>37</sup> on insomnia patients with OSA/UARS treated with PAP showed significant improvement in subjective and objective sleep-onset latency; whereas, 3 studies<sup>44-46</sup> showed no change in sleep-onset latency. As SOI operates via well-described mechanisms<sup>11,47,48</sup> related to psychophysiologic conditioning, poor sleep hygiene, or psychiatric distress,<sup>11,15,16</sup> sleep breathing treatments would not be expected to resolve sleep-onset complaints.<sup>19</sup>

Moreover, scant research explicates how sleep breathing problems might cause SOI other than the obvious finding of breathing events at sleep onset, leading to arousals or awakenings.<sup>49</sup> One theory was elaborated indirectly from a small study of untreated OSA patients, wherein Broström et al<sup>50</sup> indicated "fear of dying" was commonly reported; Luyster et al<sup>23</sup> cited this work in speculating how waking fear leads to psychophysiologic conditioning. Another theory (Respiratory Threat Matrix Model of Chronic Insomnia) hypothesizes racing thoughts—the omnipresent complaint linked to sleep-onset difficulties—emerge into consciousness at bedtime and thwart sleep initiation, thereby preventing both sleep and ensuing breathing events.<sup>51</sup> Speculatively, abnormal breathing (eg, apneas, hypopneas, or flow limitation), given the life-sustaining nature of breathing itself, may transform sleep into an aversive stimulus in susceptible individuals.<sup>51</sup>

Although standard PAP has proven efficacious in sleep maintenance insomnia treatment,<sup>36–40,44–46,52</sup> we often observe greater severity of continuous PAP (CPAP)–induced "claustrophobic tendencies"<sup>53–55</sup>



in SOI patients, which culminates in CPAP failure or rejection. Anecdotally, we observe а reduction in claustrophobic tendencies in patients undergoing PAP trials with advanced technology: auto-adjusting dualpressure devices, auto-bilevel (ABPAP) or adaptive servoventilation (ASV-PAP), the latter diagnosis mode for the of apnea.<sup>39</sup> complex sleep We speculate these technologies provide better results at sleep initiation, because they effectively eradicate the common problem of expiratory pressure intolerance (EPI)—the unpleasant, uncomfortable sensation provoked by attempting to exhale against the inward force of positive airway pressure.<sup>56</sup> This distressing sensation may trigger claustrophobic tendencies<sup>53–55</sup> in susceptible individuals, such as psychiatric patients.<sup>39</sup> Pressure

# Positive airway pressure (PAP) may provide combined therapeutic effects for patients with comorbid insomnia and sleep-disordered breathing.

- Patients treated for this comorbidity (proposed "complex insomnia" diagnosis) may fail or reject standard continuous PAP due to the anxiety triggered by expiratory pressure intolerance.
- The results of this study suggest future investigations should test whether advanced PAP devices using dual pressures are more efficacious in the treatment of global insomnia and sleep-onset insomnia in complex insomnia patients.

intolerance is common with CPAP, the standard fixed-pressure mode, which in past studies<sup>44–46</sup> theoretically caused discomfort at sleep onset and negated potential therapeutic effects of PAP.<sup>39</sup> Speculatively, CPAP-induced pressure intolerance may remind individuals of the potential underlying threat to respiration from OSA/UARS.<sup>51</sup>

Clinical Points

In our experience, ABPAP or ASV function as a rescue strategy to promote expedient adaptation instead of requiring patients to endure repeated unpleasant exposure to standard CPAP for weeks or months. Even with extended CPAP use, adherence is not guaranteed.<sup>57</sup> To the contrary, the experiences of repeated failed CPAP attempts can produce adverse psychophysiologic responses to any subsequent efforts to try PAP,<sup>58</sup> and, in some cases, acute phobic responses are elicited.<sup>59</sup>

Some insomnia patients never tolerate CPAP, as recently described in a case series of 273 former CPAP failure patients (all abandoned treatment) of whom 72% subsequently reinitiated a device after completing an overnight titration with ABPAP or ASV; this advanced PAP technology was associated with elimination or prevention of claustrophobic tendencies (B.K., unpublished data, 2016). To examine manually titrated auto-adjusting PAP technology in the treatment of SOI, the current report gathered retrospective data on consecutive OSA/UARS patients who presented with a predominant pattern of severe SOI. All patients failed CPAP or BPAP at various stages and subsequently qualified for and were currently using ABPAP or ASV. We hypothesized regular PAP users would show significantly greater decreases in global or total insomnia severity and SOI compared to partial users.

## **METHODS**

## **Study Subjects and Design**

We reviewed charts of a consecutive series of treatment-seeking chronic insomnia patients at Maimonides Sleep Arts & Sciences, Ltd (March 2011 to August 2015), a private, community-based sleep medical center that specializes in the treatment of mental health patients with sleep disorders.<sup>29,60,61</sup> All patients completed online intake surveys to measure degree of insomnia and related findings of

psychophysiologic conditioning (see Supplementary Appendix 1), poor sleep hygiene, and psychiatric distress. The online intake also elicits subjective estimates of sleep-onset latency, total sleep time, total time in bed, and time awake after first sleep onset. All patients met the following inclusion criteria (Figure 1): (1) insomnia lasting longer than 6 months (chronic) with a subjective emphasis (chief insomnia complaint) of prolonged sleep-onset latency (> 60 minutes) and severe SOI symptoms; (2) severe to very severe rating on the ISI single-item SOI score; (3) selfreported daytime impairment qualifying patients for a research diagnosis of chronic insomnia disorder<sup>62</sup>; (4) self-reported multiple indicators of psychophysiologic insomnia, poor sleep hygiene, or psychiatric symptoms as presumptive causes of SOI; (5) objective diagnosis of OSA or UARS; (6) failed CPAP therapy (see Procedures for explanation of CPAP failure); (7) manual in-laboratory titration of auto-adjusting PAP technology and initiated use of ABPAP or ASV; and (8) returned for follow-up. The Los Alamos Medical Center Institutional Review Board exempted this study from medical ethical approval, as testing and therapy were routine and data were deidentified.

# Figure 1. Flowchart of Inclusion Criteria and Group Definition<sup>a</sup>





<sup>a</sup>Continuous variables expressed as mean (SD).

<sup>b</sup>Medical director (B.K.) reviewed intake questionnaires showing subjective sleep complaints warranting diagnostic PSG testing.

- <sup>c</sup>Adult patients diagnosed with SDB following a PSG and completed a technologist-attended titration.
- <sup>d</sup>Prescription given after a full night of ASV or ABPAP titration PSG or split-therapy PSG wherein traditional PAP was failed early in the study, allowing for subsequent titration with advanced PAP device.
- <sup>e</sup>Follow-up included daytime appointments or repeat titration PSGs during which the patient completed outcome questionnaires: ISI.

<sup>f</sup>Current PAP use based on multiple factors discussed in the methods section: users = PAP use ≥ 20 h/wk, partial users = PAP use < 20 h/wk.

Abbreviations: ABPAP = auto-bilevel positive airway pressure therapy, ASV = adaptive servo-ventilation, ISI = Insomnia Severity Index, PAP = positive airway pressure PSG = polysomnography, SDB = sleep-disordered breathing, SOI = sleep-onset insomnia, SOL = sleep-onset latency.

> Additional information collected from the online intake included subjective report of past psychological disorder diagnoses and treatment; however, no formal psychiatric interviewing or instruments were used to evaluate historical complaints of psychiatric conditions. The information used in this retrospective study relies entirely on subjective reports from the patients' intake questionnaires. As part of the intake procedures, individuals were asked to report past psychiatric conditions, use of psychotropic medications, and psychotherapy experience. Individuals were also asked to provide information concerning history of trauma and claustrophobia.

## Procedures

All patients underwent diagnostic polysomnography and were scored per standards from the American Academy of Sleep Medicine (AASM).<sup>63</sup> An OSA diagnosis required an Apnea Hypopnea Index  $\geq$  5 events/h, and a diagnosis of UARS

required an Apnea Hypopnea Index < 5 and Respiratory Disturbance Index  $\ge 15.^{63}$ Titration protocols followed AASM guidelines<sup>56</sup> up to a point in which ABPAP or ASV was instituted, and then the algorithm for manual titration of auto-adjusting technology was applied as described previously in chronic insomnia patients.<sup>39</sup> Patients completed ISI at baseline and follow-up, approximately 1.2 years after PAP initiation, at which time objective data downloads determined hours of use.

Failure with PAP therapy occurred in all patients for multiple reasons, most conspicuously due to experiences associated with claustrophobic tendencies or due to poor results with a device (Figure 2). In brief, 24 patients prescribed PAP failed due to poor outcomes, noncompliance, and subjective EPI (Figure 2A). Another 48 failed PAP during presleep desensitization in the sleep laboratory before a titration. Desensitization failure was caused by subjective EPI, at which point patients verbalized discomfort, choking, or suffocating feelings; requested a temporary halt to the procedure; and then received the option to try a different pressure delivery mode. Some patients described the EPI experience as traumatic or verging on a panic attack (Figure 2B). Nearly every patient (n = 69) also failed at least 1 traditional PAP mode (CPAP, APAP, BPAP) during a technologist-attended titration in which objective expiratory pressure intolerance eventually worsened their breathing, resulting in central apneas or other residual breathing events (persisting despite increased pressures) (Figure 2C). Among all 74 patients, 403 specific indicators (> 5 per patient) of failure or rejection manifested with various PAP modes, which ultimately led to prescriptions for ResMed ABPAP (n = 24) or ResMed ASV (n = 50) (ResMed, San Diego, California), and both types of devices received insurance coverage.

Figure 2. Subjective and Objective Reasons for PAP Mode Failure at 3 Time Points: (A) PAP Failure Following Prescription, (B) PAP Failure During Desensitization at Polysomnography, and (C) PAP Failure During Technologist-Attended Titration Polysomnography<sup>a,b</sup>



A. Prescribed Device<sup>c</sup> (n = 24)

Objective EDI



<sup>a</sup>Subjective and objective reasons for PAP failure: pressure > 15: optimal pressures > 15 cmH<sub>2</sub>O; complex SA: presence of ≥ 5.0 central events/h (Central Apnea Index) and comprising > 50% of Apnea Hypopnea Index events; noncomplaint: PAP use < 4 h/night and/or < 70% of nights/wk; subjective EPI: subjective intolerance to pressurized air (difficulty exhaling against PAP pressure); poor outcomes: persistently elevated Insomnia Severity Index, fatigue, or daytime symptoms despite PAP therapy use; emerging CSA: objective central-like pauses on airflow curve; objective EPI: objective EPI on airflow waveform; variable pressures: technologist observed need for variable pressures due to body position or sleep stage; residual SDB: persistent CSA, obstructive sleep apnea, or flow limitation evident during titration (residual breathing events may also have been observed on objective data downloads but are not criteria for PAP failure).

- <sup>b</sup>Total number of reasons exceeds sample size (N) at each time point due to failure on multiple PAP modes (continuous, bilevel, auto-bilevel) and multiple reasons per failure mode.
- <sup>c</sup>Prescribed Device: patients who were prescribed a device and demonstrated subjective and objective PAP failure indicators at home.
- <sup>d</sup>Presleep/Desensitization: PAP failure indicators occurred during a prestudy pressure desensitization the night of a titration or during a daytime nap study used to gradually introduce PAP therapy to apprehensive patients (PAP-NAP).
- <sup>e</sup>Titration: PAP failure indicators occurred during a technologist-attended titration polysomnography in the sleep laboratory.

### Data Analysis

Descriptive statistics characterized sociodemographic data, standard self-report sleep metrics, relevant medication use, psychiatric history, patterns of psychophysiologic conditioning, poor sleep hygiene, and proportions of CPAP failure indicators. Objective data downloads provided hours of PAP use to divide the sample into 2 groups on the basis of the general clinical practice guideline that deems compliance as  $\geq 20$  hours/wk and noncompliance as < 20 hours/wk. The compliant patient group was termed *PAP users* and the noncompliant group *partial users*. Changes in global insomnia severity and SOI severity were tested with repeated-measures analysis of variance for within- and between-subjects analyses. Continuous variables were expressed as mean (SD) and dichotomous variables as percentages. Hedges' g was calculated to assess effect sizes for unequal or small samples. Statistical significance was .05. Data were analyzed using SPSS version 23.0.

## RESULTS

### **Baseline Characteristics**

All 74 patients diagnosed with OSA/UARS included PAP users (n = 56) and partial users (n = 18). Sociodemographic data indicate a sample of predominantly male, white, mildly obese, married or living with a partner, middle-aged adults (Table 1); initial outcome analyses demonstrated no significant findings for these sociodemographics. Despite prior attempts at CPAP or BPAP therapies, intake total mean (SD) ISI scores were 21.74 (3.68), at the cutoff for severe insomnia (ISI = 22), even as the majority of patients presented using prescription (68%) or over-the-counter (51%) sleep aids. Baseline difficulty falling asleep (SOI) as reported on the ISI averaged between severe and very severe categories (3.43 [0.50]) on the 0 to 4 scale. Subjective baseline sleep indices showed patients reported more than 2 hours to fall asleep and averaged less than 5 hours total sleep. There were no significant differences between PAP users and partial users except for the latter group's lower use of over-the-counter sleep aids and shorter time in bed.

Table 1. Baseline Sociodemographics and Subjective Sleep and Objective Respiratory Indices	
for Compliant Positive Airway Pressure Users Versus Noncompliant Partial Users	

	Total Sample	PAP Users	Partial Users	PAP vs Partial
Variable	(N=74)	(n=56)	(n=18)	<i>P</i> Value; Hedges' <i>g</i> <sup>a</sup>
Sociodemographics				
Sex, n (%)				
Male	41 (55.41)	30 (53.57)	11 (61.11)	
Female	33 (44.59)	26 (46.43)	7 (38.89)	.39
Ethnicity, n (%)				
White	33 (44.59)	27 (48.21)	6 (33.33)	
Hispanic	29 (39.19)	19 (33.93)	10 (55.56)	
Other	12 (16.22)	10 (17.86)	2 (11.11)	.26
Marital status, n (%)				
Married, living with partner	50 (67.57)	39 (69.64)	11 (61.11)	
Single, divorced	24 (32.43)	17 (30.36)	7 (38.89)	.35
Education level completed, n (%)				
Bachelor's degree or higher	28 (37.84)	20 (35.71)	8 (44.44)	
Some college or less	46 (62.16)	36 (64.29)	10 (55.56)	.35
Age, mean (SD), y	49.20 (15.81)	51.21 (15.33)	44.97 (16.40)	.17; 0.43
Body mass index, mean (SD)	31.30 (8.07)	31.09 (7.72)	31.95 (9.29)	.70; 0.10
Insomnia chronicity, mean (SD), y	8.63 (7.48)	8.67 (7.51)	8.51 (7.59)	.94; 0.02
Prescription sleep aid use, % using	67.57	67.86	66.67	.57
Over-the-counter sleep aid use, % using	51.35	60.71	22.22	.005
Subjective sleep indices, mean (SD)				
Total time in bed, h	8.18 (1.74)	8.45 (1.41)	7.35 (2.38)	.02; 0.64
Total sleep time, h	4.83 (1.75)	4.83 (1.71)	4.82 (1.93)	.98; 0.01
Sleep efficiency, %	60.74 (21.86)	58.63 (21.64)	67.31 (21.82)	.14; 0.40
Sleep onset latency, min	129.82 (71.36)	128.89 (65.52)	132.72 (89.26)	.85; 0.05
Wake after sleep onset, min	169.45 (128.42)	176.30 (128.31)	148.11 (130.05)	.42; 0.22
Objective respiratory indices, mean (SD)				
Apnea Hypopnea Index, events/h	30.44 (27.52)	29.02 (27.85)	34.69 (26.81)	.45; 0.20
Respiratory Disturbance Index, events/h	57.74 (28.23)	57.94 (28.99)	57.19 (26.80)	.93; 0.03
Diagnosis, n (%)				
Obstructive sleep apnea	66 (89.19)	49 (87.50)	17 (94.44)	
Upper airway resistance syndrome	8 (10.81)	7 (12.50)	1 (5.56)	.37
<sup>a</sup> Hedges' g effect size was calculated for all	continuous variab	oles.		

Figure 3 illustrates pervasive indicators of psychophysiologic conditioning and poor sleep hygiene, which patients directly attributed to insomnia in general or SOI in particular, such as learning to be a poor sleeper, losing sleep over losing sleep, and time monitoring behavior. Patients endorsed a mean (SD) of 9.49 (3.68) of a possible 18 indicators for maladaptive behaviors. Patients completed 3 distinct queries for bedtime ruminations, each of which was consistently endorsed by 71% to 82% of the sample as the most prevalent etiologic factor in SOI. As another presumptive explanation for their SOI, patients averaged by self-report more than 2 psychiatric disorders, symptoms, or conditions: depression (65.2%), anxiety (41.9%), traumatic stress disorder (20.3%), obsessive-compulsive disorder (9.5%), and bipolar disorder (5.4%), albeit no formal psychiatric evaluations were conducted in these patients.

Figure 3. Subjective Symptoms Reported at Intake Showing Psychophysiologic Conditioning and Poor Sleep Hygiene for the Total Sample (N = 74)<sup>a</sup>



<sup>a</sup>Items extracted from online intake.

<sup>b</sup>Answers obtained from Time-Monitoring Behavior–10 questionnaire<sup>64</sup>: 10 questions (5 related to sleep onset, 5 related to sleep maintenance) scored on a 0 to 3 Likert scale (range, 0–30) assessing time monitoring, mental calculations, and resultant frustration due to this behavior.

#### Adherence to PAP Therapy

PAP users (n = 56) averaged a mean (SD) of 6.13 (1.92) h/night and 42.89 (13.45) h/wk, and partial users (n = 18) 1.67 (0.71) h/night and 11.70 (4.95) h/wk. There were no significant differences on the basis of ABPAP or ASV modes.

#### **Changes in Insomnia Severity**

For changes in total ISI scores (Figure 4A), a significant group × time interaction was observed ( $F_{1,72} = 4.472$ ; P = .04), with PAP users showing greater improvement from intake to follow-up (21.8 to 13.0, g = 1.72) compared to partial users (21.6 to 16.3, g = 1.04). Clinical insomnia severity decreased in the PAP user group to a mean outcome ISI of 13.0, which is below the currently applied ISI cutoff score of 15, equivalent to less than a moderate level of insomnia, whereas partial users remained above 15, with a mean outcome ISI of 16.3, indicative of moderate insomnia levels.

# Figure 4. Positive Airway Pressure (PAP) Users (n = 56) and Partial Users (n = 18) Within-Group Comparisons of Mean (SD) Intake Versus Outcome Values





**B. ISI-SOI Score** 





Measured by more stringent ISI clinical cutoffs, we calculated subclinical insomnia (< 11) and nonclinical insomnia (< 8). Among PAP users, 22 (39.3%) were subclinical and 10 (17.9%) were nonclinical at follow-up, whereas in the partial users, only 4 (22.2%) were subclinical and 2 (11.1%) were nonclinical.

For changes in the single-item SOI score (Figure 4B), a significant (group  $\times$ 

time) interaction was observed ( $F_{1,72} = 9.597$ ; P = .03), with PAP users showing superior results compared to partial users (g = 2.07 vs g = 0.91, respectively). For changes in clinical severity, PAP users decreased from an intake range of severe to very severe SOI to a score < 2, equivalent to less than a moderate level of difficulty falling asleep, whereas partial users showed improvement but remained at the moderately severe level.

Using an experimental ISI single-item SOI score of < 2 as the cutoff for clinical SOI, we noted 20 PAP users (35.7%) and 4 partial users (22.2%) attained an outcome SOI score < 2.

#### **Supplemental Analyses**

The use of ABPAP or ASV manifested equally large effects, with no statistical differences for mode type in either regular or irregular users. Controlling for over-the-counter sleep aids did not change results. However, at the clinical level, 51 of 74 patients were taking prescription or over-the-counter medication (Supplementary eFigure 1) for insomnia at intake, including 40 users (ASV = 27, ABPAP = 13) and 11 partial users (ASV = 6, ABPAP = 5). At follow-up, 32 of the 51 sleep aid users reported no change in insomnia medication at follow-up, whereas 16 reported a decrease in medication, including 11 users (ASV = 7, ABPAP = 4) and 5 partial users (ASV = 2, ABPAP = 3). An additional 3 patients reported an increase in medication (users = 3, ASV = 3). Proportions of change were no different between groups or types of modes, but the sample sizes were too small to detect differences.

Last, the time-in-bed analysis was confounded by the fact that more time spent in bed most likely equated to more time using PAP therapy. Thus, a patient spending more or less time in bed would appear to have a greater chance for more or less PAP use, respectively. When controlling for the time in bed variable, the analyses still manifest differences between the 2 groups.

### DISCUSSION

Marked clinical changes in global insomnia severity as well as sharp decreases in SOI occurred in association with use of advanced auto-adjusting PAP technology in a predominant sample of psychiatric patients with chronic SOI of which 68% were currently using prescription sleeping pills and 51% were using over-the-counter sleep aids. Clinical improvements in the regular PAP users were consistently greater than in the nonrandomized control group of partial users. Whether these findings are a result of the use of advanced PAP technology that ameliorated patients' difficulties with EPI and potential claustrophobic tendencies can only be determined with prospective randomized controlled studies.

It is noteworthy these patients strongly attributed their sleep-onset difficulties to numerous psychological factors, which may explain their reliance on medications; yet, despite the use of sleep aids, they presented with severe residual insomnia, which appeared to respond well to the physiologic intervention of PAP therapy. Notwithstanding, it has already been proven that other nontechnological-based treatments could yield similar benefits.<sup>11,15,16</sup>

Therefore, a question is raised as to whether combined physiologic, psychological, and pharmacologic interventions could produce additive benefits if each therapy were proven to further decrease symptoms not relieved by any individual treatment.<sup>51</sup> Regardless, in our sample of patients, insomnia was not cured, only reduced in severity, and, therefore, further insomnia interventions such as CBT-I or sedatives would most likely yield further gains in the treatment of their residual insomnia.<sup>11,46,48,65,66</sup>

Some patients indicated racing thoughts dissipated with PAP, but these anecdotal statements were not intended for measurement due to the retrospective design. Nonetheless, these assertions are congruent with the aforementioned Respiratory Threat Matrix Model of Chronic Insomnia.<sup>51</sup> Researching this theory is difficult given

the subtlety of the mental functions described in the model. Nevertheless, prospective randomized controlled studies with larger sample sizes could assess whether cognitive activation at bedtime increases or decreases with PAP, regardless of underlying pathophysiologic mechanisms. The potential relationship between racing thoughts and claustrophobic tendencies in these types of patients also merits investigation, including how various PAP delivery modes affect these complaints. Finally, complementary studies could examine recently reported observations that sleep apnea patients with SOI are less likely to attain adherence with PAP therapy.<sup>44</sup>

### Limitations

To our knowledge, although this study is the first to demonstrate a marked association between PAP use and improvement in SOI symptoms, the research suffers from several weaknesses in its retrospective, nonrandomized controlled design in a medium-sized sample of patients. Selection bias occurred for several reasons, as we focused only on patients using PAP therapy; therefore, sleep-onset insomniacs who presented to our center and chose other pathways such as psychological treatments or other medications were excluded, and some patients refused sleep testing or dropped out of care. Some patients completed all steps that could have included them in the study, but with no follow-up measures, we could not determine PAP therapy use. Another possible confound is the use of only the most recent follow-up. While we make the assumption that treatment-seeking patients attend clinic appointments much of the time to solve a problem, it is also true that such patients are sticking with PAP therapy and therefore are probably receiving some benefit; the former issue of problem-solving might underestimate the benefits of PAP, whereas, the latter issue of maintaining treatment might overestimate the benefits of PAP.

Our sample of patients also did not complete formal psychiatric evaluations to confirm and clarify their psychiatric distress and its potential impact on sleep, and, during the time period covered by the retrospective design, we did not track changes in their psychiatric diagnoses or treatments, both of which could have affected their insomnia outcomes. Moreover, use of sleep diaries to track progress would have yielded more precise information about patient responses. Most importantly, without a prospective, randomized controlled protocol and without intercurrent information on the longitudinal progression for each patient-for example, any other medications or treatments that might have favorably influenced insomnia—we can only note the association between advanced PAP technology and observed decreases in SOI. Patients may have initiated or adjusted medications for insomnia during this time period, but our data only include their baseline and final follow-up drugs, whereas no longitudinal tracking of medications occurred. Conceivably, patients also may have accessed salient information to gain knowledge about psychological therapies for insomnia, including educational material at our sleep center. Last, speculatively, PAP may provide relaxation benefits as a placebo, irrespective of its evidence-based, therapeutic effects.

In sum, emerging research on comorbid OSA/UARS and insomnia (proposed "complex insomnia" designation)<sup>27</sup> is opening new therapeutic pathways via physiologic interventions for a vexing health condition, commonly explicated through psychological theories<sup>11,47</sup> and conventionally treated with medications.<sup>5–8,67</sup> The current study, while at a lower level of evidence, suggests the need for research with larger samples to determine the full impact or lack thereof regarding sleep breathing treatments on 3 cardinal complaints of chronic insomnia disorder patients: difficulty falling asleep, difficulty staying asleep, and early morning awakenings. This research must include formal psychiatric evaluations to clarify the impact of mental health symptoms and disorders on insomnia outcomes. Prospective studies that examine multimodal therapies such as the combination of PAP therapy and CBT-I or sedatives will most likely prove the most illuminating and clinically relevant.<sup>65,66</sup>

Potential conflicts of interest: Dr Krakow owns and operates www.nightmaretreatment.com, www.ptsdsleepclinic.com, www.sleeptreatment.com,

www.sleepdynamictherapy.com, www.soundsleepsoundmind.com, and www.nocturiacures.com; is the medical director of a national durable medical equipment company Classic Sleep Care for which his sole functions are consultation and quality assurance (he has no patient encounters and does not benefit from the sale of any durable medical equipment); and markets and sells 3 books for sleep disorder patients: *Insomnia Cures, Turning Nightmares into Dreams*, and *Sound Sleep, Sound Mind: 7 Keys to Sleeping Through the Night.* He owns and operates one commercial sleep center, Maimonides Sleep Arts & Sciences, Ltd, and conducts continuing medical education/continuing education unit educational programs for medical and mental health providers to learn about sleep disorders. Sometimes, these programs involve the attendee paying a fee directly to his center. Other times, he conducts the workshops at other locations, which may be paid for by vendors such as Respironics and ResMed, or other institutions such as the US Army Medical Department Center and School, VA Medical Center, and regional sleep center conferences. He is president of a nonprofit sleep research center, the Sleep & Human Health Institute (www.shhi.org), that occasionally provides consultation services or receives grants for pilot studies, the most recent of which were ResMed ~\$400,000 January 2015 (funding for randomized controlled trial of treatment in insomnia patients) and Respironics \$50,000 January 2009 (study on prevalence of sleep disordered breathing in insomnia patients). **Dr Nadorff, Mr Ulibarri**, and **Ms McIver** report no conflicts of interest related to the subject of this article.

#### *Funding/support:* None.

Acknowledgments: The authors are grateful to the Los Alamos Medical Center and the Los Alamos Medical Center Sleep Laboratory for administrative and clinical assistance in the completion of this research project.

Supplementary material: See accompanying pages.

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