ORIGINAL RESEARCH

Retrospective, nonrandomized controlled study on autoadjusting, dual-pressure positive airway pressure therapy for a consecutive series of complex insomnia disorder patients

Barry Krakow[1–3]
Natalia D McIver[1,2]
Victor A Ulibarri[1,2]
Michael R Nadorff[4,5]

[1]Sleep & Human Health Institute, [2]Maimonides Sleep Arts & Sciences, Ltd, Albuquerque, [3]Los Alamos Medical Center, Los Alamos, NM, [4]Department of Psychology, Mississippi State University, Mississippi, MS, [5]Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA

Video abstract

Correspondence: Barry Krakow
Sleep & Human Health Institute, 6739 Academy Rd NE, Ste 380, Albuquerque, NM 87109, USA
Tel +1 505 998 7204
Fax +1 505 998 7220
Email bkrakow@sleeptreatment.com

Purpose: Emerging evidence shows that positive airway pressure (PAP) treatment of obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS) in chronic insomnia patients (proposed "complex insomnia" disorder) leads to substantial decreases in insomnia severity. Although continuous PAP (CPAP) is the pressure mode most widely researched, intolerance to fixed pressurized air is rarely investigated or described in comorbidity patients. This retrospective study examined dual pressure, autoadjusting PAP modes in chronic, complex insomnia disorder patients.

Patients and methods: Chronic insomnia disorder patients (mean [SD] insomnia severity index [ISI] =19.11 [3.34]) objectively diagnosed with OSA or UARS and using either autobilevel PAP device or adaptive servoventilation (ASV) device after failing CPAP therapy (frequently due to intolerance to pressurized air, poor outcomes, or emergence of CSA) were divided into PAP users (≥20 h/wk) and partial users (<20 h/wk) for comparison. Subjective and objective baseline and follow-up measures were analyzed.

Results: Of the 302 complex insomnia patients, PAP users (n=246) averaged 6.10 (1.78) nightly hours and 42.71 (12.48) weekly hours and partial users (n=56) averaged 1.67 (0.76) nightly hours and 11.70 (5.31) weekly hours. For mean (SD) decreases in total ISI scores, a significant (group × time) interaction was observed (F[1,300]=13.566; $P<0.0001$) with PAP users (–7.59 [5.92]; d=1.63) showing superior results to partial users (–4.34 [6.13]; d=0.81). Anecdotally, patients reported better tolerability with advanced PAP compared to previous experience with CPAP. Both adaptive servoventilation and autobilevel PAP showed similar ISI score improvement without statistical differences between devices. Total weekly hours of PAP use correlated inversely with change in insomnia symptoms (r=–0.256, $P<0.01$).

Conclusion: Insomnia severity significantly decreased in patients using autoadjusting PAP devices, but the study design restricts interpretation to an association. Future research must elucidate the interaction between insomnia and OSA/UARS as well as the adverse influence of pressure intolerance on PAP adaptation in complex insomnia patients. Randomized controlled studies must determine whether advanced PAP modes provide benefits over standard CPAP modes in these comorbidity patients.

Keywords: insomnia, obstructive sleep apnea, upper airway resistance syndrome, CPAP failure, autobilevel, adaptive servoventilation

Introduction

Chronic insomnia is noted to be the "most prevalent sleep disorder worldwide".[1] Extensive research has evaluated the etiology and assessment of insomnia,[2–7] economic impact,[1,5,8,9] and evidence-based pharmacological and nonpharmacological

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treatments.[1,5,6,9–11] Yet, according to Edinger et al[12] "[t]he optimal insomnia nosology has yet to be determined." In a recent prospective, validation study, the constructs of "insomnia due to [various conditions] and *obstructive sleep apnea* were well supported".[12] Surprisingly, only a small corpus of research has investigated the relationships between obstructive sleep apnea (OSA) or upper airway resistance syndrome (UARS) and insomnia.[13–17] In the earliest works, Guilleminault et al[18,19] showed a link between central sleep apnea and insomnia. More than 20 years later, Lichstein et al[20] demonstrated an OSA rate of 43% in older insomnia patients; and in 2001, we proposed the term "complex insomnia" to categorize the comorbidity between chronic insomnia and OSA or UARS, after the unexpected discovery of a 90% rate of objectively diagnosed sleep breathing disorders in a consecutive series of crime victims seeking treatment for insomnia and nightmares.[21]

From other clinical perspectives, several research groups have demonstrated that 30–60% of OSA patients present with clinically meaningful comorbid insomnia symptoms.[17,22–25] In a recent study among a large sample of chronic insomnia disorder patients regularly using yet failing prescription or over-the-counter sleep aids, 91% were objectively diagnosed with OSA or UARS.[26] Nasal cannula pressure transducer technology appears to yield the most accurate rates of complex insomnia in the samples studied.[27]

Much as these findings are thought-provoking; a series of commentaries on causal relationships between insomnia and sleep-disordered breathing have been especially provocative by raising questions about a potential bidirectional relationship between insomnia and sleep breathing disorders.[28–31] And, each of these published viewpoints noted a likely requirement for multimodal, evidence-based treatments to address this unusual comorbidity, that is, treatment of insomnia symptoms may require cognitive behavioral therapy for insomnia (CBT-I) or sedatives as well as positive airway pressure (PAP) therapy.[28,29,31]

Nine studies conducted since 2000 evaluated the effects of sleep-disordered breathing treatments on chronic insomnia (Table 1).[32–40] All studies, despite weaknesses of retrospective designs in the majority, systematically demonstrated clear-cut improvements following the use of PAP, upper airway surgery, bariatric surgery, or nasal dilator strips.[32–40] One of the 9 studies looked at PAP therapy sequentially applied after CBT-I.[37] In another study, a small sample of insomnia patients (n=56) who previously failed and then ceased the use of standard forms of continuous PAP (CPAP) therapy were subsequently titrated with adaptive servoventilation (ASV), after which 75% of them reinitiated PAP with this advanced technology.[39] Among the 39 ASV users, large decreases in

the insomnia severity index (ISI)[2] were noted (16.8 vs 9.7; P=0.001; d=1.40) after an average of 1.3 years of ASV use.[39]

A distinctive observation in this ASV study pinpointed the ubiquitous inability of chronic insomnia disorder patients with comorbid OSA/UARS to adapt to standard PAP devices, such as continuous positive airway pressure (CPAP), continuous positive airway pressure with expiratory pressure relief (CFLEX), automatic continuous positive airway pressure (APAP), and Bilevel positive airway pressure (BPAP) due to self-reported discomfort and intolerance triggered by the vaguely defined phenomenon of expiratory pressure intolerance (EPI)[41,42] even among those using PAP devices with basic expiratory pressure relief (EPR) systems.[39] These adverse effects resolved with ASV use,[43] and in our clinical experience, many insomnia patients also adapt well to autobilevel PAP (ABPAP) devices.[43,44] Anecdotally, manually titrated, auto-adjusting algorithms embedded in these devices create a smoother airflow delivery system, which in turn diminishes insomnia patients' anxious responses to pressurized air.[43,44] These findings are consistent with prior research showing the inadequacy of exclusive reliance on autotitrating algorithms in these devices,[45] despite their known ambulatory rescue capabilities.[46,47]

To examine the effects of manually titrated, dual-pressure, autoadjusting technologies on insomnia outcomes, we conducted a retrospective chart review on a nonrandomized controlled cohort of chronic insomnia patients who presented with moderate-to-severe symptoms and comorbid OSA/UARS. All patients were currently using advanced PAP technology. We hypothesized:

1. Regular users of advanced PAP devices would demonstrate greater decreases in insomnia severity compared to a control group of partial users;
2. Increased hours of use of advanced PAP technology would correlate inversely with change in insomnia severity.

Patients and methods
Study criteria and consent
Adult patients who met the following criteria were included: 1) ISI ≥15; 2) subjective report of multiple indicators of psychophysiological insomnia, poor sleep hygiene or psychiatric comorbidity as the most likely causes of insomnia; 3) objectively diagnosed OSA (apnea–hypopnea index [AHI] ≥5) or UARS (AHI <5 and respiratory disturbance index ≥15); 4) failed standard forms of PAP therapy (see "Procedure for CPAP failure determination" section for detailed explanation) at Maimonides Sleep Arts & Sciences (MSAS)

Table 1 Prior research investigations on the impact of sleep-disordered breathing treatments on chronic insomnia severity[a]

Author(s), study type	Level of evidence[b]	Treatment sample (n)	Treatment type(s)	Control group (Y/N), type of control	Insomnia measure[c]	Time to follow-up	Notes on insomnia data
Krakow et al,[36] prospective study	1b	14	PAP	(Y), no SDB treatment	SSQ	20.6 mo	Thirteen of the 14 patients (92.9%) in treatment group subjectively reported better sleep quality after treatment compared to 3 of 9 (33.3%) in control group (Fisher statistic =8.69; P=0.005)
Guilleminault et al,[22,34] comparative controlled study	1b	62	ENT, PAP	(Y), no SDB	SOL	6 mo	Limited quantitative data published but authors reported improvements in objective SOL and WASO in UARS patients treated with radiofrequency ablation or PAP therapy
Krakow et al,[37] retrospective chart review (part 1)	4	19	PAP	(N)	SOL		Significant decrease in objective SOL (P=0.04; d=0.49) with the use of PAP
Krakow et al,[37] prospective cross-over study (part 2)	1b	17	CBT, PAP	(Y), patients served as own CBT vs PAP control	ISI	3 mo	Large improvement for ISI from baseline to CBT follow-up (F[1,16]=17.58, P=0.001, d=1.53) and highly significant effects from CBT follow-up to PAP follow-up at the end of study (F[1,16]=12.09, P=0.003, d=1.11)
Krakow et al,[38] randomized controlled trial	1b	42	NDS	(Y), nontreatment	ISI, SOL, TST, WAKE	4 wk	Significant improvement in ISI (P=0.0001; d=1.20), subjective TST (P=0.02), and subjective number of awakenings (P=0.05) in nasal dilator strip users vs controls
Guilleminault et al,[35] prospective crossover study	1b	25	Surgery	(Y), CBT-I only	TST, WASO	3 mo	TST increased from 6.24 h/night at baseline to 6.75 h/night after SDB treatment (P=0.0001). WASO decreased from 45.4 min at baseline to 8.4 min after SDB treatment (P=0.0001)
Nguyen et al,[40] prospective and observational study	2b	80	APAP	(Y), PAP discontinuers	ISI	2 years	Mean ISI [SD] decreased significantly (13.7 [5.7] vs 8.2 [6.3]; P=0.0001) from baseline to 2 years follow-up. Of the 39 patients with ISI >15 at baseline, 20 (51%) had an ISI decrease of ≥9 at the 2-year follow-up
Krakow et al,[39] retrospective chart review	4	56	ASV	(N)	SE, WASO, WAKE, ARSL, ISI	1.3 years	Significant improvement in objective SE (P<0.001; d=0.71), WASO (P<0.05; d=0.40), total awakenings index (P<0.01; d=0.49), and total arousals index (P<0.05; d=0.44) when using ASV vs traditional PAP. Outcomes data available for 39 of the 56 patients showed a significant improvement in ISI score (16.8 vs 9.7; P=0.001; d=1.40).
Bjornsdottir et al,[32] longitudinal cohort study	2b	473	PAP	(N)	BNSQ	2 years	Symptoms of sleep maintenance insomnia were most common at baseline and improved significantly (P<0.001) among patients using PAP

(*Continued*)

Table 1 (*Continued*)

Author(s), study type	Level of evidence[b]	Treatment sample (n)	Treatment type(s)	Control group (Y/N), type of control	Insomnia measure[c]	Time to follow-up (days)	Notes on insomnia data
Glidewell et al,[33] retrospective chart review	4	53	PAP	(N)	ISI	43	Twenty-four of the 53 (45%) patients with moderate-to-severe insomnia at baseline reported no/mild insomnia symptoms after PAP therapy. The remaining 55% had persistent moderate-to-severe insomnia but had significantly higher pretreatment ISI scores ($P<0.001$), lower RDI ($P=0.01$), and lower PAP use ($P=0.04$)

Notes: [a]Change in outcomes reported as direct result of PAP use. [b]Level of evidence based on Sackett's criteria. [c]Measurements included in each outcomes category: ↓ objective sleepiness, MSLT; ↓ subjective sleepiness, ESS, FOSQ-10, and FOSQ.
Abbreviations: APAP, automatic continuous PAP; ARSL, total objective arousals; ASV, adaptive servoventilation; BNSQ, Basic Nordic Sleep Questionnaire; CBT, cognitive behavioral therapy; CBT-I, CBT for insomnia; ENT, ear nose and throat doctor; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; FOSQ-10, Functional Outcomes of Sleep Questionnaire Short Form; ISI, insomnia severity index; MSLT, Multiple Sleep Latency Test; N, no; NDS, nasal dilator strip; PAP, positive airway pressure; RDI, respiratory disturbance index; SDB, sleep disordered breathing; SE, sleep efficiency; SOL, objective sleep onset latency; SSQ, subjective sleep quality; TST, total sleep time; UARS, upper airway resistance syndrome; WAKE, objective total awakenings; WASO, objective wake after sleep onset; Y, yes.

or at a previous sleep facility; 5) completed one or more in-lab manual titrations with autoadjusting technology; 6) filled a prescription, initiated and maintained the use of ABPAP or ASV, and returned for follow-up; and 7) provided subjective and objective follow-up measures at clinic appointments. As per standard protocol at MSAS, all patients provided verbal and written consents for their medical information to be used anonymously for research and educational purposes in the context of chart and data reviews. This study was approved by Los Alamos Medical Center's Institutional Review Board.

Chart review and extracted sample

This retrospective chart review commenced with all patients seen at MSAS between March 2011 and August 2014 (n=1,967). Adult patients were included who presented with intake ISI scores ≥15, diagnosed with OSA or UARS, and underwent a titration polysomnography (PSG). Of the 590 eligible patients, 438 patients filled prescriptions for ABPAP or ASV, of whom 302 patients provided follow-up outcome measures (ISI and Epworth Sleepiness Scale [ESS]) and objective data downloads (ODD) on average 6.9 months from the initiation of therapy (Figure 1).

Procedure for CPAP failure determination

In our clinical experience in working with predominantly psychiatric patients with sleep disorders, we observed frequent problems with EPI triggered by fixed pressurized airflow devices,[39,43,44] and this phenomenon often heralds "claustrophobic tendencies" in relationship to or irrespective of mask issues.[4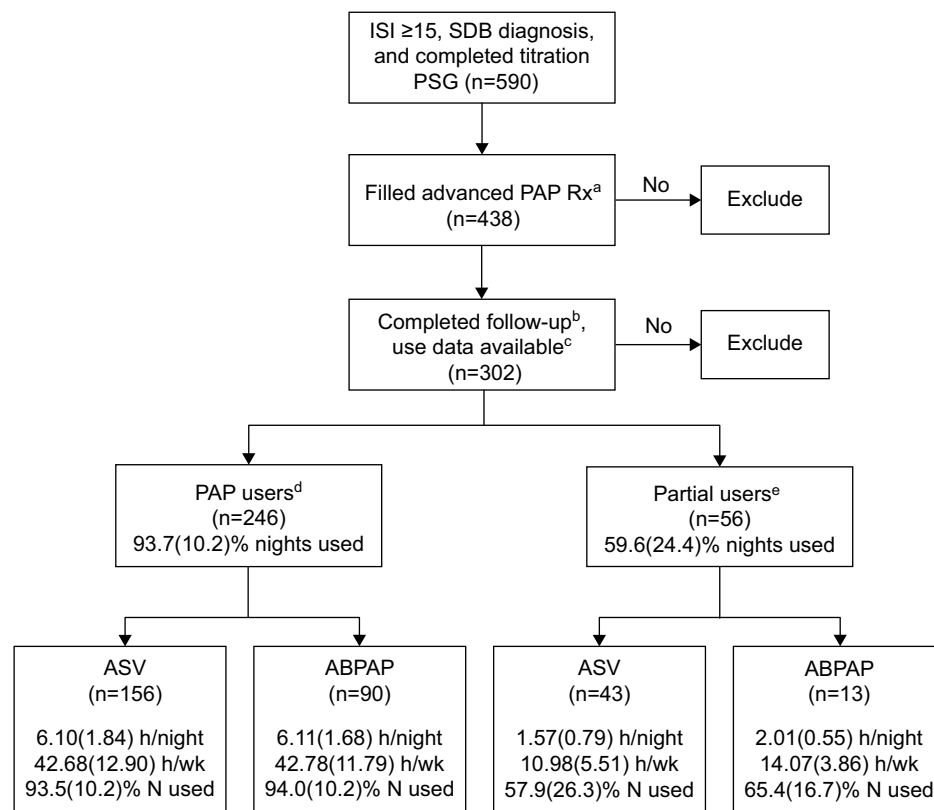8–50] Since 2005, our policies and procedures focused on preventing or eliminating EPI and related claustrophobic tendencies in vulnerable patients with co-occurring insomnia and psychiatric conditions (Supplementary materials).[39,44,51–55] As noted in Figure 2, 3 main pathways ultimately led to CPAP failure in this study cohort, and subjective and objective EPI were the most common problems, necessitating a switch to advanced PAP devices. Overall, taking into account patients' efforts to attempt multiple modes of PAP, the average patient experienced multiple (~5 per patient) reasons for failure.

Of the 89 patients prescribed PAP devices to use at home, failure was mainly due to poor outcomes (persistently elevated ISI, fatigue, or daytime symptoms despite PAP therapy use), subjective EPI, and aborted use (Figure 2A). For 205 patients during their prestudy PAP desensitization, subjective expiratory intolerance was the main reason for traditional PAP mode failures (Figure 2B). For 268 patients undergoing a sleep technologist conducted titration, PAP failure was largely due to objectively observed EPI, emergent central-like pause(s), complex sleep apnea (CompSA), and residual sleep breathing events persisting despite pressure increases (Figure 2C). A total of 1,625 specific indications of failure manifested with various PAP modes for these 302 patients, which eventually led to insurance coverage for the use of autoadjusting PAP technology.

PSG and titration practice model for autoadjusting technology

PSG was conducted and scored with American Academy of Sleep Medicine (AASM) guidelines[56] to diagnose OSA/UARS.[56] For titrations, our policies and procedures align with AASM guidelines[41] and other research[57] to normalize the airflow curve by eliminating all breathing events including

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                    ┌─────────────────────────┐
                    │  ISI ≥15, SDB diagnosis, │
                    │  and completed titration │
                    │      PSG (n=590)         │
                    └─────────────────────────┘
                                 │
                                 ▼
              ┌─────────────────────┐   No   ┌──────────┐
              │ Filled advanced PAP Rxᵃ│─────▶│ Exclude  │
              │      (n=438)        │        └──────────┘
              └─────────────────────┘
                                 │
                                 ▼
              ┌─────────────────────┐   No   ┌──────────┐
              │ Completed follow-upᵇ,│─────▶│ Exclude  │
              │ use data availableᶜ  │        └──────────┘
              │      (n=302)        │
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	PAP usersᵈ (n=246) 93.7(10.2)% nights used	Partial usersᵉ (n=56) 59.6(24.4)% nights used

ASV (n=156)	ABPAP (n=90)	ASV (n=43)	ABPAP (n=13)
6.10(1.84) h/night	6.11(1.68) h/night	1.57(0.79) h/night	2.01(0.55) h/night
42.68(12.90) h/wk	42.78(11.79) h/wk	10.98(5.51) h/wk	14.07(3.86) h/wk
93.5(10.2)% N used	94.0(10.2)% N used	57.9(26.3)% N used	65.4(16.7)% N used

Figure 1 Flowchart of inclusion criteria and group definition.
Notes: Data presented as mean (SD). ᵃPrescription given after a full night ASV or ABPAP titration PSG or split-therapy PSG where traditional PAP was failed early in the study allowing for subsequent titration with advanced PAP device. ᵇFollow-up included appointments during which patients completed outcome questionnaires: ISI and ESS. ᶜCurrent PAP use defined by Objective Data Download or Subjective report. ᵈPAP users: PAP use ≥20 h/wk. ᵉPartial users: PAP use <20 h/wk.
Abbreviations: ABPAP, autobilevel positive airway pressure; ASV, adaptive servoventilation; ESS, Epworth Sleepiness Scale; h, hours; ISI, insomnia severity index; N, nights; PAP, positive airway pressure; PSG, polysomnography; Rx, prescription; SDB, sleep disordered breathing; wk, week.

respiratory effort-related arousals (RERAs).[41,57] We also follow 2006 AASM practice parameters for BPAP indications "[…]where high pressure is needed and the patient experiences difficulty exhaling against a fixed pressure[….]" This adverse EPI effect (described earlier for CPAP failure) occurs while increasing the pressure to resolve RERAs, especially for patients on fixed CPAP. Subjective or objective EPI manifests in patients with anxiety symptoms (an omnipresent insomnia finding). When manually titrating advanced technology in the sleep laboratory, a fine-tuning process permits minute increases in inspiratory pressures to treat RERAs while simultaneously providing concomitant pressure relief through fastidious titration of expiratory pressures. Thus, the synergistic goals of normalized airflow and patient comfort are achieved.[39,47]

A sequential changing of pressure delivery modes follows an algorithm that begins with CPAP, which then moves to either CPAP or APAP with an EPR setting or to BPAP, followed by ABPAP and finally ASV when CompSA or in some cases subthreshold CompSA develops. To eliminate RERAs without aggravating EPI, pressures are titrated by 0.2–0.4 cm/H_2O increments.[39,47]

Advanced PAP technology prescription practices

Using the above algorithm in the manual titration of autoadjusting dual-pressure devices has resulted in the vast majority of complex insomnia patients ultimately receiving a prescription for either an ABPAP device or an ASV device at our center, which specializes in the treatment of complex patients suffering psychiatric comorbidities. Thus, a minority of patients used standard CPAP devices at home. Some used APAP or BPAP devices for varying periods of time before returning to the sleep center with the complaint of poor to mediocre results, at which point a repeat titration was conducted, and ABPAP or ASV was prescribed as qualified by insurance criteria.[47]

Subjective and objective determinations of hours of PAP use

Hours of PAP use and percentage of nights used (nights with PAP use divided by total number of nights) were determined by ODD. Rarely (<10% of sample), ODDs were not available due to computer or software malfunction. In these instances, subjective report for hours of PAP use was determined by patient report on bed time, wake time, time of mask removal,
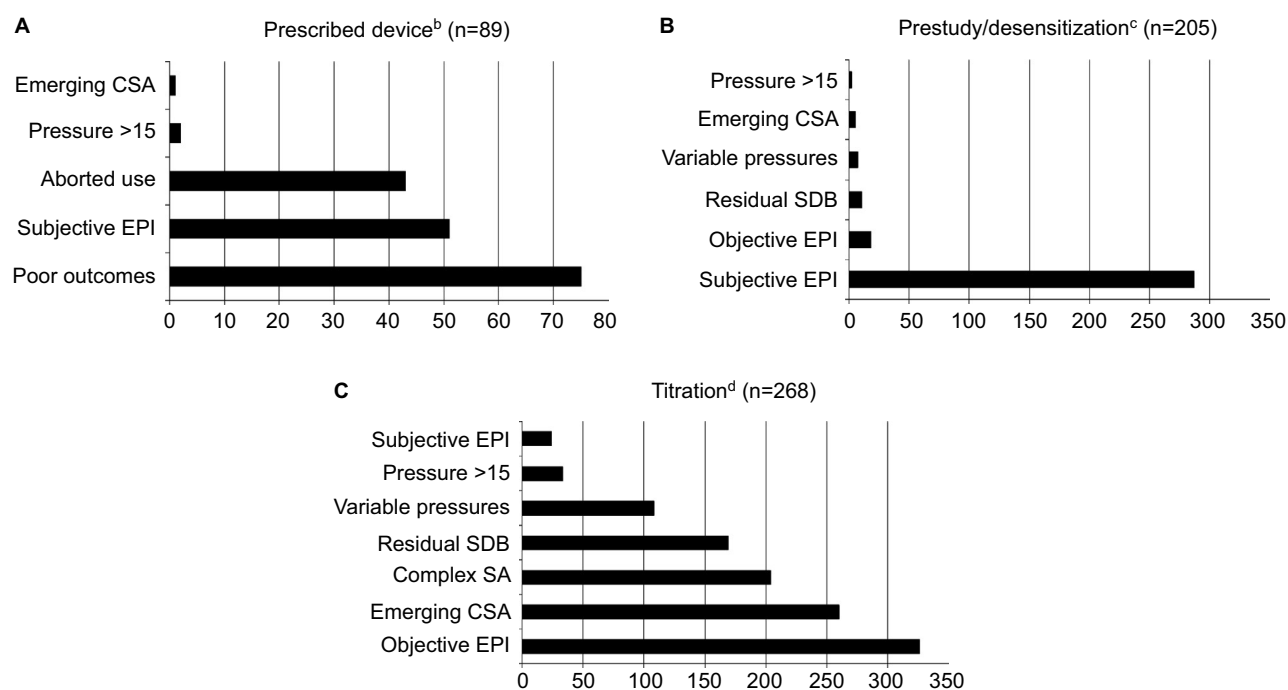
Figure 2 Timing of subjective and objective PAP mode failure.[a]

Notes: (**A**) Reasons for PAP failure following prescription from MSAS or other sleep laboratories. (**B**) Reasons for PAP failure during PSG desensitization. (**C**) Reasons for PAP failure during technologist-attended titration PSG. Total number of reasons for failure at each time point exceeds sample size (n) due to multiple reasons for failure. Single-item reasons for failure in graphs (**B**) and (**C**) exceed sample size (n) due to failure on multiple modes of PAP (CPAP, BPAP, and ABPAP). [a]Subjective and objective reasons for PAP failure: emerging CSA: objective central-like pauses on airflow curve; pressure >15: optimal pressures >15 cmH$_2$O; aborted use: very limited or no use at home; subjective EPI: subjective intolerance to pressurized air (difficulty exhaling against PAP pressure); poor outcomes: persistently elevated ISI, fatigue, or daytime symptoms despite PAP therapy use; variable pressures: technologist observed need for variable pressures due to body position or sleep stage; residual SDB: persistent CSA, OSA, or UARS evident on data download or despite increases in PAP pressure; objective EPI: objective EPI on airflow waveform; and complex SA: presence of ≥5.0 central events/h (CAI) comprising >50% of AHI events. [b]Prescribed device: patients who were prescribed a device and demonstrated subjective and objective PAP failure at home. [c]Presleep/desensitization: PAP failure occurred either during a prestudy pressure desensitization the night of a titration or during daytime nap study used to gradually introduce PAP therapy to apprehensive patients (PAP-NAP). [d]Titration: PAP failure occurred during a technologist-attended titration PSG in the sleep laboratory.

Abbreviations: ABPAP, autobilevel positive airway pressure; AHI, apnea–hypopnea index; BPAP, Bilevel PAP; CAI, Central Apnea Index; CPAP, continuous positive airway pressure; CSA, central sleep apnea; EPI, expiratory pressure intolerance; MSAS, Maimonides Sleep Arts & Sciences; OSA, obstructive sleep apnea; PAP, positive airway pressure; PSG, polysomnography; SA, sleep apnea; SDB, sleep disordered breathing; UARS, upper airway resistance syndrome.

estimated nightly PAP use, and corroboration with bed partner. ODD was available for 275 patients (ASV =177; ABPAP =98), and personal estimates of nightly use were obtained in 27 patients (ASV =22; ABPAP =5).

Nonrandom assignment divided patients into the following 2 groups: PAP users (n=246; ≥20 h/wk, averaging 6.10 [1.78] h/night and 42.71 [12.48] h/wk) and partial users (n=56; <20 h/wk, averaging 1.67 [0.76] h/night and 11.70 [5.31] h/wk). The cutoff value of 20 h/wk was calculated based on CMS compliance standards of 70% of nights with ≥4 h per night use (ie, 4.9 nights ≥4 h =19.6 h/wk).

Additional metrics

Intake and follow-up scores for ISI questions # 1–3 were analyzed individually to examine changes in the type of insomnia: sleep onset insomnia (SOI), sleep maintenance insomnia (SMI), and early morning awakening (EMA). To further identify insomnia severity, subjective sleep indices (time in bed, total sleep time, sleep onset latency, and wake after sleep onset) were reported at intake; sleep efficiency was calculated from these

responses. As an additional measure of change in insomnia, frequency of sleep aid use was gathered at intake and clarified at follow-up. Psychiatric history (including trauma history and claustrophobia) was obtained at intake to identify comorbid disorders. To evaluate the presence of comorbid sleep disorders, patients treating periodic limb movement disorder or restless leg syndrome were identified at the time of most recent follow-up.

Data analyses

Descriptive statistics provided baseline characteristics, including sociodemographics and standard self-report sleep metrics and hours of objective use of PAP therapy. Analysis of variance (ANOVA) compared use means among groups. PAP user and partial user groups, as well as ASV and ABPAP groups, were compared for changes in insomnia severity with repeated measures ANOVA, including within- and between-subjects analyses while controlling for subjective psychiatric comorbidities. Pearson product-moment correlations were conducted on hours of use by change in insomnia symptom severity. Cohen's *d* measured within-subjects effect sizes,

and Hedge's *g* measured between-subjects effect sizes due to unequal sample sizes. Statistical significance was 0.05. All continuous variables were expressed as mean (SD).

Results
Baseline characteristics

Our study sample was predominantly overweight (body mass index =31.59 [8.00]), Caucasian (61.9%) or Hispanic (28.1%), married or living with partner (67.2%), males (55.6%) with a bachelor's degree or higher (48.0%), and age 53.44 (14.21) years. OSA was diagnosed in 274 and UARS in 28 patients. ESS total score was 10.89 (6.02), just above the most conservative cutoff for clinically meaningful daytime sleepiness (Table 2). For 246 PAP users, 156 used ASV and 90 used ABPAP, and for 56 partial users, 43 used ASV and 13 used ABPAP (Figure 1).

Subjective intake data were consistent with chronic insomnia in the moderate-to-severe range (ISI score =19.11 [3.34]) with an insomnia chronicity of 10.28 (7.33) years.

Figure 3 identifies indicators of psychophysiological conditioning and poor sleep hygiene, which patients directly attributed to their insomnia, such as learning to be a poor sleeper, losing sleep over losing sleep, and time monitoring behavior. Patients endorsed an average of 9.48 (3.68) of a possible 18 indicators for maladaptive sleep behaviors. Medical co-morbidities were reported in 96.7% of all patients (Table 2, see Supplementary Results for details of system categories). Three-quarters (75.2%) of all patients reported at least one psychiatric condition or disorder (Table 2).

Hours of use by objective data or subjective report by PAP mode

Nightly and weekly hours of use were nearly identical for ASV users (6.10 [1.84], 42.68 [12.90]) and ABPAP users (6.11 [1.68], 42.78 [11.79]). Nightly hours for ASV and ABPAP partial users (1.57 [0.79] vs 2.01 [0.55]; P=0.067, g=0.58) and weekly hours (10.98 [5.51] vs 14.07 [3.86]; P=0.065,

Table 2 Sociodemographics, psychiatric history, and baseline subjective sleep and objective respiratory indices for PAP users vs partial users[a]

| Variable	Total sample (n=302)	PAP users (n=246)	Partial users (n=56)	PAP users vs partial users (P-value; Hedge's g[b])
Sociodemographics				
Sex				
Male	168 (55.6%)	137 (55.7%)	31 (55.4%)	0.54
Female	134 (44.4%)	109 (44.3%)	25 (44.6%)	0.54
Ethnicity				
Caucasian	187 (61.9%)	158 (64.2%)	29 (51.8%)	0.09
Hispanic	85 (28.1%)	65 (26.4%)	20 (35.7%)	0.19
Other[c]	30 (9.9%)	23 (9.34%)	7 (12.5%)	0.46
Marital status				
Married/living with partner	203 (67.2%)	168 (68.3%)	35 (62.5%)	0.25
Single/divorced	99 (32.8%)	78 (31.7%)	21 (37.5%)	0.25
Education level completed				
Bachelor's degree or higher	145 (48.0%)	116 (47.2%)	29 (51.8%)	0.32
Some college or less	157 (52.0%)	130 (52.8%)	27 (48.2%)	0.32
Age, years	53.44 (14.21)	53.34 (14.07)	53.84 (14.94)	0.81; 0.04
BMI (kg/m²)	31.59 (8.00)	31.92 (7.87)	30.17 (8.50)	0.14; 0.22
Insomnia chronicity, years[d]	10.28 (7.33)	10.35 (7.26)	9.94 (7.73)	0.71; 0.06
ISI score	19.11 (3.34)	19.02 (3.23)	19.52 (3.79)	0.31; 0.15
ESS score	10.89 (6.02)	10.84 (6.06)	11.11 (5.90)	0.76; 0.04
Prescription sleep aid use	127 (42.1%)	100 (40.7%)	27 (48.2%)	0.19
OTC sleep aid use	85 (28.1%)	72 (29.3%)	13 (23.2%)	0.23
Psychiatric history				
Anxiety	99 (32.8%)	78 (31.7%)	21 (37.5%)	0.25
Depression	149 (49.3%)	120 (48.8%)	29 (51.8%)	0.39
PTSD	37 (12.3%)	32 (13.0%)	5 (8.9%)	0.28
Panic attacks	61 (20.2%)	46 (18.7%)	15 (26.8%)	0.12
Bipolar disorder	15 (5.0%)	14 (5.7%)	1 (1.8%)	0.20
OCD	20 (6.6%)	15 (6.1%)	5 (8.9%)	0.30
Other[e]	13 (4.3%)	9 (3.7%)	4 (7.1%)	0.21
Trauma history	92 (30.5%)	76 (30.9%)	16 (28.6%)	0.43
Claustrophobia	84 (27.8%)	68 (27.6%)	16 (28.6%)	0.50
None	75 (24.8%)	65 (26.4%)	10 (17.9%)	0.12

(*Continued*)

Table 2 (*Continued*)

	Total sample (n=302)	PAP users (n=246)	Partial users (n=56)	PAP users vs partial users (*P*-value; Hedge's g[b])
Medical history[f]				
Arthritis/pain	116 (38.4%)	95 (38.6%)	21 (37.5%)	1.0
Cardiac	48 (15.9%)	38 (15.4%)	10 (17.9%)	0.67
Drug/alcohol abuse	21 (7.0%)	14 (5.7%)	7 (12.5%)	0.08
Endocrine	162 (53.6%)	132 (53.7%)	30 (53.6%)	1.0
Hypertension	133 (37.4%)	106 (43.1%)	27 (48.2%)	0.55
Kidney	63 (20.9%)	52 (21.1%)	11 (19.6%)	1.0
Neurologic	74 (24.5%)	60 (24.4%)	14 (25.0%)	1.0
Pulmonary	249 (82.5%)	202 (82.1%)	47 (83.9%)	0.85
Reflux	115 (38.1%)	89 (36.2%)	26 (46.4%)	0.17
Subjective sleep indices				
TIB, h	7.98 (1.60)	8.08 (1.51)	7.54 (1.88)	0.020; 0.34
TST, h	5.91 (1.71)	6.02 (1.69)	5.41 (1.70)	0.015; 0.36
SE, %	75.14 (19.25)	75.68 (19.28)	72.76 (19.13)	0.31; 0.15
SOL, min	64.56 (63.08)	62.10 (60.19)	75.34 (74.15)	0.16; 0.21
WASO, min	110.56 (97.08)	109.21 (95.67)	116.52 (103.73)	0.61; 0.08
Objective respiratory indices				
AHI[g], events/h	32.02 (28.17)	31.16 (27.93)	35.64 (29.17)	0.28; 0.16
RDI[h], events/h	60.26 (29.66)	60.27 (28.70)	60.24 (33.69)	1.00; 0.00
Diagnosis[i]				
OSA	274 (90.7%)	220 (89.4%)	54 (96.4%)	0.047
UARS	28 (9.8%)	26 (10.6%)	2 (3.6%)	0.076

Notes: [a]PAP users: ≥20 h/wk; partial users: <20 h/wk. [b]Hedge's g used to determine effect size between unequal samples sizes for continuous variables. [c]Other: unspecified, n=10; Asian American, n=7; African American, n=5; Hispanic/Caucasian, n=3; Native American, n=3; Indian, n=1; Middle Eastern, n=1. [d]Fifteen patients did not report duration for their insomnia, average was calculated using 287. [e]Other: ADD/ADHD, n=5; addiction, n=5; memory loss, n=2; agoraphobic, n=1. [f]Medical history: number of patients identifying at least one comorbidity per category. Of the 302 patients, 292 patients reported at least one medical comorbidity with an average of >5 comorbidities per patient. Medical co-morbidities were organized into specific categories. [g]AHI available for 292 of the 302 patients, 236/246 PAP users and 56/56 partial users. [h]RDI available for 265 of the 302 patients, 214/246 PAP users and 51/56 partial users. [i]AHI was unavailable for 10 patients previously diagnosed with OSA with no obtainable records or no reported AHI; RDI was unavailable for 37 patients previously diagnosed with OSA with no obtainable records or no reported RDI.
Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; ISI, insomnia severity index; OCD, obsessive compulsive disorder; OSA, obstructive sleep apnea; OTC, over the counter; PAP, positive airway pressure; PTSD, post-traumatic stress disorder; RDI, respiratory disturbance index; SE, sleep efficiency; SOL, sleep onset latency; TIB, time in bed; TST, total sleep time; UARS, upper airway resistance syndrome; WASO, wake after sleep onset.
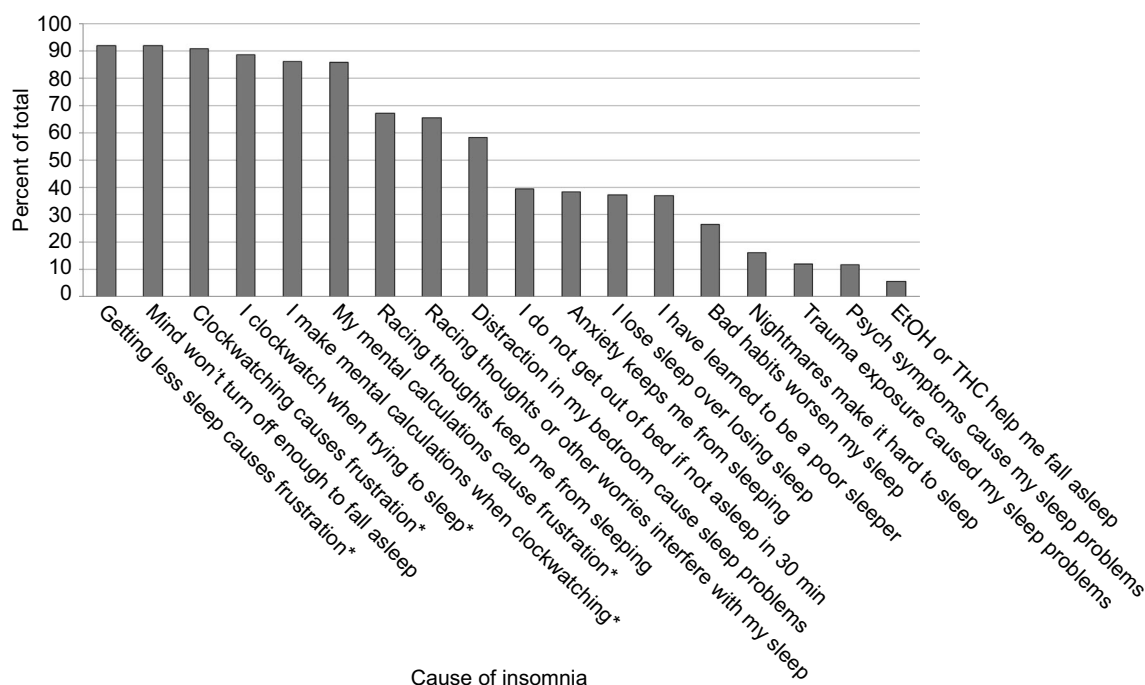
Figure 3 Subjective symptoms for psychophysiological conditions and poor sleep hygiene reported at intake.[a]
Notes: [a]Items extracted from Intake Questionnaires. *Data from TMB-10, a questionnaire assessing time-monitoring behavior as it pertains to an individual's insomnia.
Abbreviations: EtOH, alcohol; THC, marijuana TMB-10, Time Monitoring Behavior questionnaire.

g=0.59) were not significantly different, albeit the effect sizes indicated that ABPAP use was moderately greater than ASV use. There was a significant difference in the percentage of nights used between PAP users and partial users (93.7 [10.2] vs 59.6 [24.4]; P=0.001, g=2.44); no difference was found between modes among PAP users (93.5 [10.2] vs 94.0 [10.2]; P=0.7, g=0.05) or partial users (57.9 [26.3] vs 65.4 [16.7]; P=0.3, g=0.27) for ASV vs ABPAP respectively (Figure 1).

Changes in insomnia severity

For decreases in total ISI scores, a significant (group × time) interaction was observed ($F[1,288]=13.895$; $P<0.0001$) with PAP users (−7.59 [5.92]; d=1.63) showing superior results compared to partial users (−4.34 [6.13]; d=0.81). Clinical severity decreased markedly in the PAP user group to below the currently applied clinical cutoff of 15, equivalent to less than a moderate level of insomnia (11.43 [5.73]), whereas partial users remained above the moderate level of severity (15.18 [6.60]) (Figure 4A).

Within PAP users, ISI scores significantly decreased for both the ASV (n=156; −7.32 [5.98]; d=1.55; Figure 4B), and

ABPAP groups (n=90; −8.02 [5.83]; d=1.78; Figure 4C) without significant differences between PAP modes (P=0.59).

In partial users, ISI scores significantly decreased for the ASV group (n=43; −5.00 [6.19]; d=0.97; Figure 4B), but ISI decrease among ABPAP users was not significant (n=13; −2.15 [5.63]; P=0.33; d=0.39; Figure 4C), albeit without differences between groups (P=0.24; g=0.46).

To provide a more clinically relevant view of the changes in insomnia severity, we measured the following 2 ISI clinical cutoffs: subclinical insomnia (<11) and nonclinical insomnia (<8). There was a significant difference in PAP users vs partial users attaining subclinical ISI scores (112 [45.5%] vs 15 [26.8%], P=0.01). Nonclinical ISI scores were attained in 59 (24.0%) PAP users and 9(16.1%) partial users, with no significant difference between the groups, P=0.20.

Examining individual insomnia subtype scores (SOI, SMI, and EMA) at intake revealed no significant differences between PAP users and partial users. Follow-up scores for each of the 3 insomnia subtypes showed significant
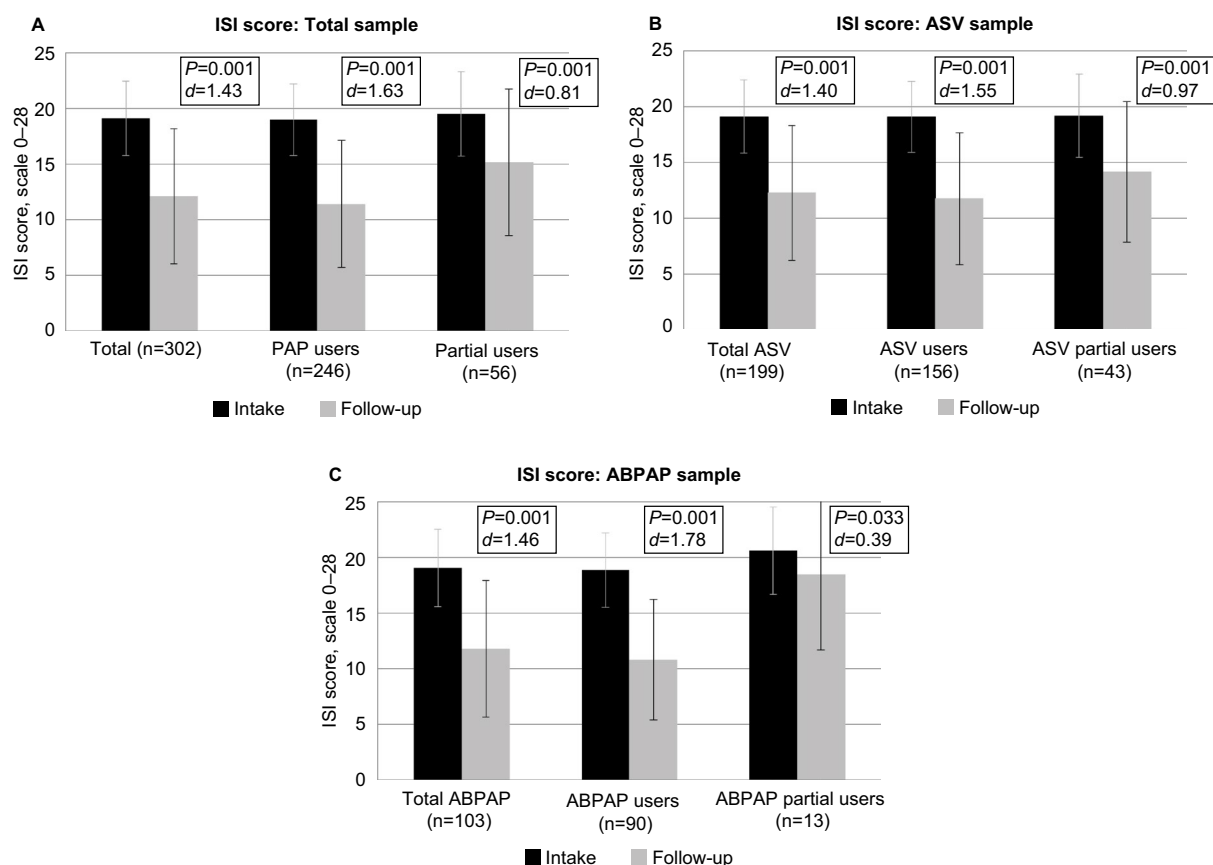
Figure 4 Within-group comparison of mean (SD) intake vs follow-up ISI values for (**A**) Total sample (n=302), (**B**) ASV sample (n=199), and (**C**) ABPAP sample (n=103).
Abbreviations: ABPAP, autobilevel positive airway pressure; ASV, adaptive servoventilation; ISI, insomnia severity index; PAP, positive airway pressure.

improvement in the PAP users (n=243) with large effect sizes, whereas partial users' (n=56) improvements were non-significant with small-to-medium effect sizes (Figure 5A). Mean improvements were as follows in the PAP user group: SOI (−0.76 [1.14]; d=0.70), SMI (−0.86 [1.19]; d=0.87), and EMA (−0.74 [1.43]; d=0.65).

Within ASV subjects, users' (n=154) ISI subtype scores significantly decreased as follows: SOI (−0.64 [1.14]; d=0.58), SMI (−0.83 [1.20]; d=0.86), and EMA (−0.67 [1.33]; d=0.58) (Figure 5B). And, within ABPAP subjects, users' (n=89) insomnia subtype scores significantly decreased as follows: SOI (−0.96 [1.13]; d=0.94), SMI (−0.90 [1.17]; d=0.90), and EMA (−0.88 [1.58]; d=0.74) (Figure 5C).

Of the 302 total patients, 135 reported taking prescription or over-the-counter medications for insomnia at intake (108 PAP users [ASV 74 and ABPAP 34] and 28 partial users [ASV 20 and ABPAP 8]) (Table S1 for the list of medications). At follow-up, 80 of the 135 sleep aid users reported no change in insomnia medication, whereas 40 reported a decrease in medication, including 33 PAP users (ASV 23

and ABPAP 10) and 7 partial users (ASV 3 and ABPAP 4). An additional 3 patients reported an increase in medication (ASV users 3).

Numerous significant changes also occurred with daytime sleepiness outcomes (ESS), but effects were small (Supplementary materials). There was a significantly greater proportion of PAP users treating leg jerks compared to partial users. However, when comparing change in ISI score for PAP users vs partial users treating leg jerks, no significant difference was found (Supplementary materials). Controlling for psychiatric history also did not affect results.

Correlations between hours of use and change in insomnia severity

When analyzing all 302 patients, total weekly hours of PAP use correlated inversely with change in insomnia symptoms (r=−0.256, P<0.01). Looking at each mode individually, insomnia symptoms decreased with total weekly hours of PAP use for all ASV patients (n=199, P=0.001, r=−0.235) and for all ABPAP patients (n=103, P=0.002, r=−0.299),
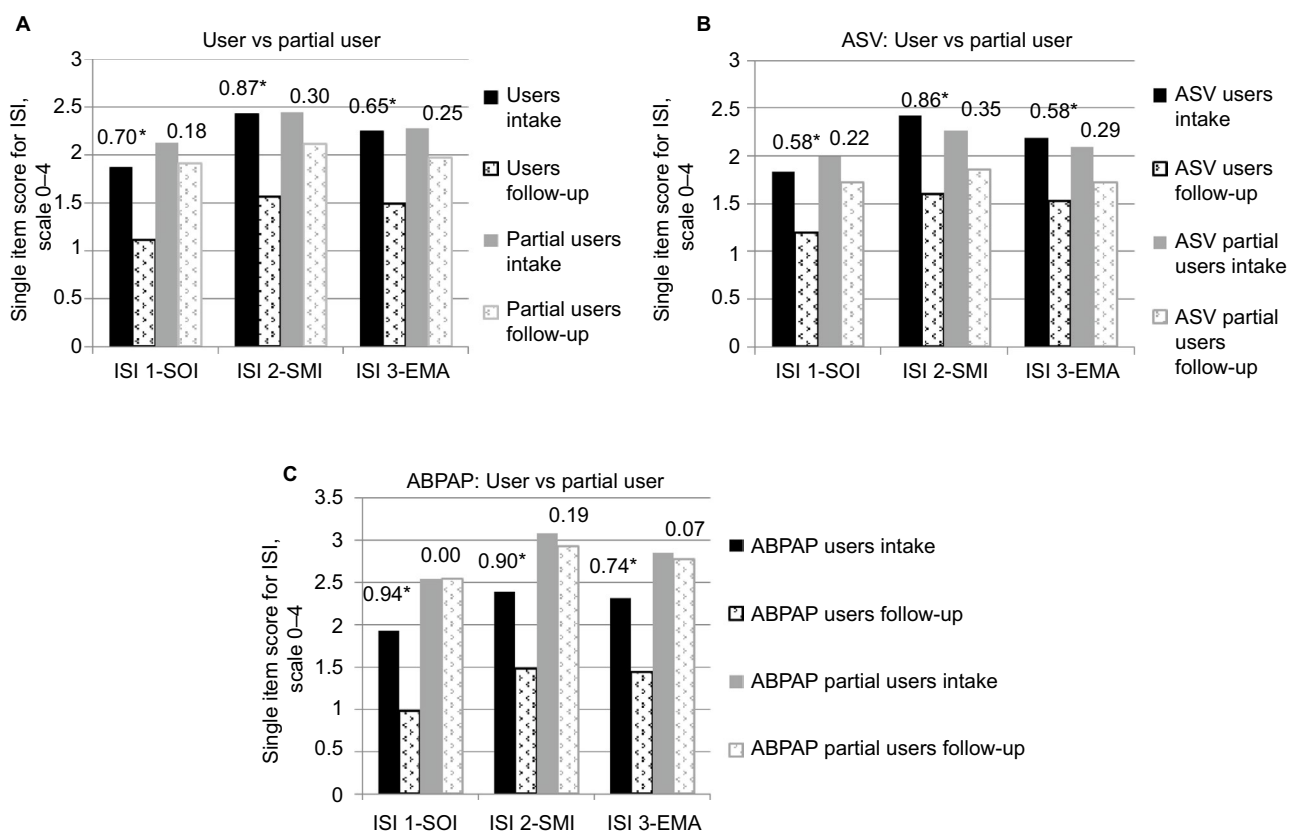
Figure 5 Within-group comparison of mean intake vs follow-up values[a] for 299[b] patients on the following 3 ISI questions: SOI, SMI, and EMA.
Notes: (**A**) PAP users (n=243) vs partial users (n=56). (**B**) ASV users (n=154) vs ASV partial users (n=43). (**C**) ABPAP users (n=89) vs ABPAP partial users (n=13). [a]Cohen's d reported above each follow-up average. [b]Individual ISI responses were unavailable for 3 subjects. *P=0.001.
Abbreviations: ABPAP, autobilevel positive airway pressure; ASV, adaptive servoventilation; EMA, early morning awakenings; ISI, insomnia severity index; PAP, positive airway pressure; SMI, sleep maintenance insomnia; SOI, sleep onset insomnia.

suggesting potential efficacy in both groups. The difference between the 2 correlations was not significant (z=0.56, P=0.58).

Discussion

In a medium-size clinical sample of OSA/UARS patients diagnosed with comorbid, moderate-to-severe insomnia symptoms (the proposed complex insomnia designation),[21] large improvements manifested in association with the use of manually titrated, autoadjusting PAP technology. Correlations between hours of use with either ASV or ABPAP and improvements in insomnia were highly significant. Taken together, the findings appear to support the emerging theory on OSA/UARS as a causative factor in insomnia pathophysiology, albeit in the absence of a randomized controlled prospective trial, the results of this case series of clinical patients can only be described as an association between sleep-disordered breathing and insomnia symptoms. However, from an anecdotal perspective, it seemed clear that these advanced devices proved especially well-suited for relieving the problem of EPI among vulnerable insomnia patients suffering from generalized distress or specific anxiety about using PAP therapy.

Future studies must use more rigorous protocols to evaluate the relationships between these 2 most common sleep disorders. Although a small number of studies have already been conducted (Table 1), new protocols are needed with various evidence-based forms of therapy for OSA/UARS, including different PAP therapy modes, oral appliances, upper airway surgery, and even weight loss treatments. Based on this study and that of past research, newer studies must quantify more precisely the extent to which the treatment of sleep breathing problems improves insomnia symptoms as well as the extent of residual insomnia symptoms. Programs with combination therapies including PAP and CBT-I or PAP and sedatives are likely to provide the most clinical relevance and generalizability, given the high proportion of insomnia disorder patients who would benefit optimally from both treatments instead of just one. Urgent research is warranted to examine PAP vs CBT-I, PAP vs PAP/CBT-I, and finally PAP/CBT-I vs CBT-I, because of the growing demand for nonpharmacological treatment of insomnia[11,28,58] as well as the rising need to increase access for evidence-based insomnia interventions through on-line therapies.[58,59] Results should attempt to rapidly clarify how best to implement these treatment regimens in clinical and non-clinical settings.

To assist in the development of this new therapeutic framework, we initiated a randomized single-blind, controlled study on the benefits of ASV vs CPAP therapy in chronic insomnia disorder patients (clinical trials # NCT02365064). Also, other clinical and research groups have begun development to treat complex insomnia patients with multimodal therapies,[58,60–62] and early results suggest the importance of these approaches.

The study has several limitations due to the nonrandomized, retrospective case series design with a medium-sized sample. Selection bias may have occurred as not all insomnia patients presenting to our center underwent PSG testing or filled their PAP prescriptions. Thus, by focusing only on users of PAP devices, our results provide no information on cost-effectiveness. The cohort reported a wide range of psychiatric comorbidity that may limit generalizability of our findings. Information regarding other factors such as medication changes, other insomnia treatments, and education on sleep hygiene was unavailable for this review. Regardless of the potential therapeutic impact, speculatively PAP may have acted as a relaxation placebo for some patients. Also, this cohort may have been more motivated to pursue treatment, and the results may not translate to insomniacs who did not move forward with diagnostic or treatment steps. Our sleep center focuses on an experiential model of patient education via greater use of hands-on coaching and titrations[47] as well as encouraging struggling patients to reach out rapidly to problem solve. These 2 patient-centric features of our sleep medical center may lead to greater interactions between the patients and our sleep staff and, therefore, might limit the generalizability of our findings for centers that might spend less time with their patients. In addition, ineffective treatment or nontreatment of comorbid sleep disorders could have had an effect on PAP use and, in some cases, insomnia severity. Our data represent an association between advanced PAP technology and observed decreases in insomnia; a prospective, randomized controlled protocol with monitoring of longitudinal progress is needed to confirm or reject these findings in a sample of chronic insomnia patients. In particular, it will prove highly relevant to determine whether or not more advanced PAP technology devices are more suitable for complex insomnia patients.

Conclusion

Improvements in insomnia severity were greater in regular users of autoadjusting PAP devices compared to a nonrandom control group of partial users, and the former group demonstrated average decreases in insomnia below the

clinical ISI cutoff for moderate insomnia. Increased hours of autoadjusting PAP use correlated inversely with change in insomnia severity. Autoadjusting PAP devices seemed especially salient for complex insomnia patients, who were prone to anxious tendencies that may have increased vulnerability to EPI and claustrophobic feelings. Speculatively, advanced PAP technology may provide an adaptation advantage for those who might otherwise struggle with traditional PAP therapy devices.[39,43,44,47]

Acknowledgments

Disclosure

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Supplementary materials
Methods

Although research and conventional wisdom often allude to a very narrow window (eg, 3–4 d) in which patients may accept or reject positive airway pressure (PAP) therapy,[1–3] there does not seem to be a formal policy or protocol on how to act on this information to improve patient compliance. Patients are commonly sent home on continuous PAP (CPAP) with the notion that they will learn to get used to it, notwithstanding their progress by day 4.

In our sleep laboratory, we proactively attempt to troubleshoot issues that may interfere early in the patient's adaptation experience.[4–8] Our desensitization protocol on the night of the titration seeks extensive patient feedback regarding comfort with both pressurized air and the mask. Instead of presuming that the patient will tolerate pressurized airflow over time, we make the assumption that more discomfort indicates a lesser likelihood for adaptation. Thus, when a patient reports discomfort with mask or pressurized air, we seek to remedy the discomfort during the desensitization or the actual titration. Although, in some cases, the discomfort may be minor and easily fixed by changing a mask size or style, we often encounter more serious complaints with pressurized air that are best defined as claustrophobic tendencies or frank claustrophobic responses.[4–8]

Our objective is to increase physiological and psychological comforts during the desensitization and titration instead of waiting for discomfort to abort the patient's effort when using PAP at home. In practical terms, every patient will try CPAP, but in vulnerable insomnia and psychiatric patients, there is usually an immediate, negative response to this mode due to difficulties breathing out against fixed pressurized air. Most patients rapidly report the elimination of this discomfort, accompanied by a new sense of comfort, after switching to a dual-pressure device. Later, while asleep during the titration, we seek to eliminate all respiratory effort-related arousals (RERAs) without provoking further episodes of subjective or objective expiratory pressure intolerance (EPI), and we have found manually titrating patients on autoadjusting dual-pressure devices (adaptive servoventilation [ASV] and autobilevel PAP [ABPAP]) to be well-suited to achieve these results.[4,7,8]

Last, in applying our protocol to eliminate RERAs as well as EPI, we have also noticed a set of objective markers that tend to correlate with a normalized airflow signal – normal on both inspiration and expiration. Specifically, a normalized airflow signal appears linked to fewer arousals, awakenings, and sleep stage shifts,[7,9] as well as a greater degree of sleep efficiency, rapid eye movement (REM) sleep rebound,[10] and possibly REM sleep consolidation (uninterrupted periods of REM sleep) as described by Riemann et al.[11]

Results

Medical comorbidities are reported in Table 2. Of the 302 patients, 292 patients reported at least one medical comorbidity with an average of >5 comorbidities per patient. Comorbidities were classified into categories and were defined as: arthritis/pain – arthritis (96), chronic fatigue syndrome (23), chronic pain (85), fibromyalgia (23); cardiac – heart disease (9), myocardial infarction (8), heart failure (2), premature ventricular contractions (8), atrial fibrillation (10), bradycardia (5), tachycardia (13), heart surgery (16), and other heart conditions (17); drug/alcohol abuse – drug addiction (13) and alcoholism (14); endocrine – diabetes (44), menopausal symptoms (51), obesity (111), thyroid problems (59); hypertension (133); kidney – bladder problems (55) and kidney problems (9); neurologic – epilepsy/seizure (10), head injury with concussion (50), head injury without concussion (29), and stroke (6); pulmonary – allergies (177), asthma (54), deviated septum (61), emphysema (3), nasal trauma (16), sinus problems (113), current smoker (18), former smoker (68), and tonsillectomy (69); and reflux (115).

Epworth Sleepiness Scale (ESS) scores for the entire sample decreased by 2.47 (5.14) from 10.89 (6.02) to 8.42 (5.44) ($P=0.001$; $d=0.43$). The PAP user group (n=246) showed a significant decrease in ESS scores (mean [SD] =2.60 [5.35]; $P=0.001$; $d=0.46$). Among ASV users (n=156), ESS scores significantly decreased (2.93 [5.34]; $P=0.001$; $d=0.50$), and among ABPAP users, ESS scores significantly decreased (2.03 [5.35]; $P=0.01$; $d=0.38$) without significant differences between PAP pressure modes ($P=0.20$; $g=0.17$).

ESS scores did not significantly decrease for the 56 partial users (mean [SD] change =1.91 [4.12]; $P=0.10$; $d=0.31$), the 43 ASV partial users (2.05 [4.30]; $P=0.13$; $d=0.33$), or the 13 ABPAP partial users (1.46 [3.57]; $P=0.55$; $d=0.23$) without significant difference between PAP pressure modes ($P=0.66$; $g=0.14$). There was no significant difference between changes in ESS scores among PAP modes ($P=0.21$; $g=0.15$), although the changes within each mode were significant: ASV (2.74 [5.13]; $P=0.001$; $d=0.46$) and ABPAP (1.96 [5.15]; $P=0.01$; $d=0.36$).

There was a significant difference in the proportion of patients treating leg jerks between users and partial users (84/246 [34.1%] vs 10/56 [17.9%]; $P=0.017$). Similar findings existed within ASV user and partial user groups (58/156 [37.2%] vs 9/43 [20.9%]; $P=0.047$); among ABPAP patients,

Table S1 Categorized medications used for insomnia at intake

Benzodiazepines	Nonbenzodiazepines	Mood stabilizers/antidepressants	Over the counter
Lorazepam, 5.6%	Zolpidem, 33.1%	Trazodone, 18.5%	Antihistamines, 42.7%
Temazepam, 5.6%	Eszopiclone, 8.9%	Amitriptyline, 4.0%	Melatonin, 41.3%
Alprazolam, 4.0%		Mirtazapine, 2.4%	Herbal, 16.0%
Clonazepam, 4.0%		Quetiapine, 1.6%	
Diazepam, 2.4%		Carbamazepine, 0.8%	
Triazolam, 0.8%		Clomipramine, 0.8%	
		Doxepin, 0.8%	
		Nortriptyline, 0.8%	

Notes: Percentage of total prescription medications and percentage of total over the counter medications are reported. Prescription medication used for sleep that did not fit into the above categories included hydroxyzine (1.6%), opiates (1.6%), hydroxybutanoic acid (0.8%), pregabalin (0.8%), and ramelteon (0.8%). One patient reported the use of recreational marijuana for insomnia.

there were too few partial user subjects to allow statistical analysis. Among ASV and ABPAP users, there were no significant differences in the proportions of patients treating leg jerks (67/199 [33.7%] vs 27/103 [26.2%]; P=0.19). Change in insomnia severity index score from intake to follow-up for users (19.29 [3.33]–12.06 [5.98]) and partial users (19.40 [3.27]–12.80 [5.31]) treating leg jerks compared to users (18.88 [3.18]–11.10 [5.59]) and partial users (19.54 [3.93]–15.70 [6.79]) not treating leg jerks was not significant (P=0.14).

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