

# Reversal of PAP Failure With the REPAP Protocol

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**BACKGROUND:** Re-titrations, an atypical approach to reverse PAP failure, was investigated retrospectively. **METHODS:** Application of our re-titration of PAP (REPAP) protocol in subjects with previous PAP failure assessed original technology (masks, modes, and pressures) in 273 subjects, of which 70% reported co-occurring psychiatric conditions. The REPAP protocol emphasized changes in pressure modes and settings to address expiratory pressure intolerance and residual breathing events; mask changes were facilitated. Objective sleep and breathing metrics and subjective post-titration ratings were analyzed in subsequent PAP users and non-users. **RESULTS:** Following REPAP protocol (average follow-up = 2 y), 196 of 273 subjects with previous PAP failure were PAP users, and 77 were non-users. Previous PAP failure was attributed to technology factors, including pressure intolerance, mask discomfort, adaptation difficulties, and no benefits. At second opinion re-titration, mask changes resolved discomfort, mouth breathing, or leak (91.2% of sample); pressure mode changes resolved expiratory pressure intolerance (83.5%); and pressure setting changes decreased residual breathing events and improved air flow (96.7%), all of which were associated with renewed PAP use. PAP users showed objective sleep improvements on re-titrations and reported better sleep quality than non-users. Multiple logistic regressions showed 2 subjective, re-initiation predictors: (1) post-re-titration ratings of better sleep quality and (2) less anticipated difficulty in using PAP after initial or multiple re-titrations. User rates were significantly higher for subjects completing multiple ( $n = 158$ ) versus one ( $n = 115$ ) re-titration (80% vs 61%,  $P = .001$ ). In multiple re-titration subjects, PAP users showed significance or a trend for lower apnea-hypopnea index ( $P = .02$ ,  $g = 0.48$ ) and respiratory disturbance index ( $P = .07$ ,  $g = 0.36$ ) compared with non-users. Available user downloads averaged  $>5$  h/night. **CONCLUSIONS:** Technology-related problems due to mask discomfort/leak, pressure intolerance, and residual breathing events were associated with PAP failure in subjects seeking second opinions. Technological solutions (changes in masks, modes, and pressures) were addressed during REPAP protocol, after which 72% of subjects re-initiated PAP use. These technological interventions were associated with improved objective and subjective sleep variables and reversal of PAP failure. *Key words:* PAP failure; obstructive sleep apnea; upper airway resistance; respiratory effort-related arousals; expiratory pressure intolerance; bi-level; auto-bi-level; adaptive servo-ventilation. [Respir Care 0;0(0):1–. © 0 Daedalus Enterprises]

## Introduction

Positive airway pressure (PAP) technology is the accepted standard treatment for obstructive sleep apnea

(OSA)<sup>1</sup> and is typically initiated after a patient completes a single titration experience (full or split night).<sup>1</sup> However, one study<sup>2</sup> suggests that issues of discomfort may play an important role in patients' lack of acclimatization during their first titration. Scant sleep literature reports on the value of repeat titrations, and even less research comments on a role for re-titrations in rescuing PAP failure

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## REPAP PROTOCOL FOLLOWING PAP FAILURE

cases.<sup>3-10</sup> In PAP failure (defined as cessation or rejection of PAP use), there is no evidence to suggest that such patients are routinely offered re-titrations in the sleep laboratory to restart therapy. Rather, in the current health-care climate for sleep medicine, sleep professionals are trending toward home testing, auto-adjusting PAP devices, and objective data downloads.<sup>11</sup> Straightforward sleep apnea patients appear to respond to the objective data download paradigm, whereas complicated OSA patients with psychiatric comorbidities<sup>12-14</sup> or specific vulnerabilities<sup>15-17</sup> may require a hands-on, experiential approach involving re-titrations.<sup>9,18,19</sup>

Remarkably, no high-level evidence confirms that a first and only titration method in OSA patients establishes definitive pressure settings as defined by the American Academy of Sleep Medicine (AASM) grading system<sup>1</sup>; in fact, a small body of research shows opposite effects in which re-titrations highlight the need for substantive changes in pressure settings after only a few months of PAP use.<sup>20,21</sup> Netzer et al<sup>21</sup> studied 905 subjects invited for re-titrations a few months after initial testing, and 58.2% required pressure changes. Konermann et al<sup>20</sup> studied 106 subjects at 7.5 months after initial titrations, of which 55% needed large PAP pressure increases ( $>5$  cm H<sub>2</sub>O) due to residual symptoms in most subjects. Along the same lines, Mulgrew et al<sup>22</sup> showed frequent residual breathing events (eg, 25% with apnea-hypopnea index [AHI]  $>10$ ) in subjects re-titrated 3 months after initiating PAP. In the most salient re-titration research, which also addressed PAP failure, Ballard et al<sup>18</sup> prospectively studied “hard-core non-compliers” in 2 phases, the second phase examining 104 subjects in a randomized double-blind controlled re-titration study in which an alternate mode (bi-level positive airway pressure [BPAP]) yielded significantly greater compliance than PAP (49% vs 28%,  $P = .03$ ). Thus, in this one study, both re-titrations and changes in PAP mode were successful in rescuing PAP failure cases.<sup>18</sup>

Compared with the objective data download model, a repeat titration approach to improve pressure settings, change PAP modes, or overcome PAP failure would be viewed as cost-prohibitive.<sup>11,23</sup> Nevertheless, a study analyzing hypothetical models of adherence for Medicare patients predicted higher rates of use through re-titrations and follow-up appointments compared with a control group

**QUICK LOOK****Current knowledge**

Regarding OSA/upper-airway resistance syndrome treatment, sleep medicine is trending toward a more hands-off system of patient care with the advent of home sleep studies and auto-titrating devices. However, for vulnerable individuals, such as psychiatric patients, who may seek second opinions following PAP failure, there is no clear-cut policy or consensus on how to facilitate PAP rescue. Limited research suggests a potentially valuable role for technology changes in reversing PAP failure in select patients.

**What this paper contributes to our knowledge**

This study describes the utility of a re-titration of PAP (REPAP) protocol involving technological solutions that emphasized changes in masks, pressure delivery modes, and pressure settings. The REPAP protocol was associated with PAP re-initiation in 72% (196 of 273) of predominantly psychiatric subjects who had previously abandoned PAP, albeit comorbid depression was associated with lower rates of re-initiation. Technology innovations also appeared to improve objective sleep variables and subjective impressions of sleep quality and PAP adaptability, all of which were associated with achieving PAP user status.

exposed to a conventional practice using follow-up appointments only.<sup>24</sup> Although probably more costly in the short term, the authors alluded to the cost savings that might occur with greater adherence.<sup>24</sup> Surprisingly or not, Centers for Medicare and Medicaid Services (CMS) adopted both objective data download and re-titration models by means of data review and mandated, repeat polysomnography (PSG) as part of follow-up for nonadherence or PAP failure.<sup>24</sup>

Although we regularly apply the objective data download model in our clinic, this approach has proven of limited value among patients presenting months or years after having ceased treatment. In contrast, we observe greater rates of re-initiation in previously failing patients (including home-tested patients) after they complete a re-titration protocol with new PAP modes and settings in the sleep laboratory.<sup>25,26</sup> These re-titrations generate greater periods of normalized air flow and consolidated sleep for 2 reasons. First, we aggressively attempt to eliminate respiratory effort-related arousals, as mandated by AASM,<sup>1</sup> and second, concurrently, we prevent or resolve subjective and objective expiratory pressure intolerance, the iatrogenic adverse effect triggered in susceptible individuals when exhaling against incoming pressurized air flow.<sup>1,2,27,28</sup> In our experience, these 2 therapeutic goals diminish claus-

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## REPAP PROTOCOL FOLLOWING PAP FAILURE

trophobic tendencies observed among many PAP attempters,<sup>15-17</sup> particularly those with psychiatric comorbidities.<sup>26</sup> Successful management of respiratory effort-related arousals and expiratory pressure intolerance has been associated with renewed use of PAP therapy and more satisfied patients.<sup>29-32</sup> Likewise, objective findings on repeat titrations, including greater sleep efficiency, rapid eye movement (REM) sleep, and total sleep as well as more positive ratings of morning-after subjective experiences, were also associated with greater PAP use at our center,<sup>26</sup> the latter findings also described in other research.<sup>33,34</sup>

Since 2005, our experience with re-titration studies gave rise to a REPAP (repeat, rescue, retitration) protocol to facilitate renewal of therapy in PAP failure patients. Our model aligns with the need to resolve pressure-related side effects in vulnerable patients (see the 2006 AASM review<sup>35</sup>) that occur soon after PAP initiation, especially among patients unable to tolerate optimal settings (pressures that would otherwise eliminate all breathing events) due to iatrogenic, unresolved expiratory pressure intolerance. These adverse effects lead to worse sleep and decreased adherence.<sup>5</sup> The REPAP protocol addresses these adverse effects<sup>35</sup> by the *manual* titration of auto-adjusting PAP technology in the sleep laboratory.<sup>26</sup>

To research the REPAP protocol in subjects with PAP failure, we reviewed records on second-opinion patients and included only those reporting extreme forms of PAP failure (device rejection) after having attempted PAP at another sleep center. This method permitted us to consider each subject as an historical control so as to compare data among those who persistently failed PAP therapy with data from those who eventually achieved PAP user status. We hypothesized that: (1) self-reported PAP therapy failure occurring at the original sleep center would be associated with technology-related factors; (2) during re-titrations, subjects would require technology changes (masks [type or style], pressure delivery mode, and pressure settings) to resolve problems with leak, mouth breathing, expiratory pressure intolerance, and residual breathing events; (3) re-titration technology changes would yield improvements in objective sleep, self-reported sleep quality, and capacity to use the device, all associated with renewed PAP use; and (4) completion of more than one re-titration would be associated with higher use rates than a single re-titration.

## Methods

### Sample Study Criteria and Consent

Subjects in the study included adults  $\geq 18$  y old who (1) were diagnosed with OSA at another sleep facility (original opinion), (2) completed one original titration indicating an attempt at PAP, (3) rejected or ceased PAP use

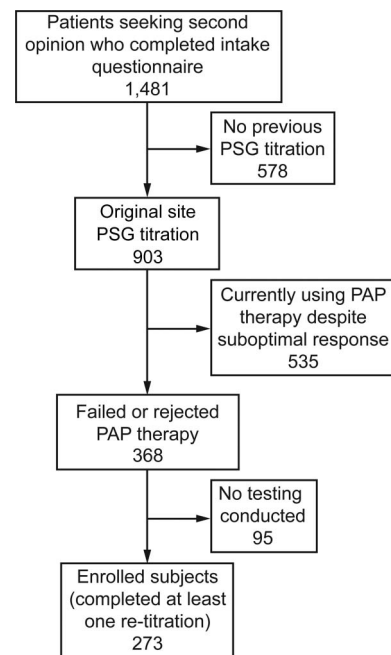


Fig. 1. Flow chart. PAP = positive airway pressure, PSG = polysomnography.

thereafter, and (4) underwent at least one second-opinion re-titration at our center. Current partial users of PAP seeking second opinions were excluded (Fig. 1). The second opinion occurred in Albuquerque, New Mexico, at Maimonides Sleep Arts and Sciences, a private, community-based sleep center specializing in treatment of sleep disorders in mental health patients or other patients with self-reported psychiatric symptoms or conditions. Per standard protocol at Maimonides Sleep Arts and Sciences, all patients provide verbal and written consent for medical information, including original sleep medical records, to be used anonymously for research and educational purposes in the context of chart and data reviews. This project was reviewed and approved by the Los Alamos Medical Center institutional review board.

### Chart Review, Polysomnography, Breathing Event Metrics

This chart review covered 2006–2013. Maimonides Sleep Arts and Sciences patients complete a web-based intake centered on sleep medicine nosology, mirroring a sleep medicine interview, including 2 additional scales (insomnia severity index<sup>36</sup> and Epworth sleepiness scale<sup>37</sup>). After exclusion criteria were evaluated on 1,481 second-opinion patients, 273 subjects remained (see Fig. 1). PSG was conducted and scored using AASM guidelines<sup>38</sup> (see the supplementary materials at <http://www.rcjournal.com>); apnea index = obstructive + central apneas/h of sleep;

## REPAP PROTOCOL FOLLOWING PAP FAILURE

central apnea index = central apneas/h of sleep; apnea hypopnea index (AHI) = apneas + hypopneas/h of sleep; and respiratory disturbance index (RDI) = AHI + respiratory effort-related arousal index.<sup>27,38</sup>

### REPAP: Repeat, Rescue, Re-Titration Practice Model

Our policies and procedures for re-titrations align with AASM practice parameters for PAP therapy indications for BPAP "... where high pressure is needed and the patient experiences difficulty exhaling against a fixed pressure ..."<sup>27</sup>; Other researchers describe this phenomenon as intolerance to higher pressures on exhalation,<sup>28,39-41</sup> that is, subjective or objective expiratory pressure intolerance, the latter manifesting as subtle irregularities on the expiratory limb of the air-flow curve.<sup>26</sup> As described above, raising pressures to titrate out respiratory effort-related arousals may induce expiratory pressure intolerance in susceptible individuals (eg, anxiety or other mental health patients). In our work, failing to attend to respiratory effort-related arousals and expiratory pressure intolerance adversely influences PAP adherence in these types of patients.<sup>26</sup>

Before admittance into the REPAP protocol, a patient who originates at our center must have attempted all standard steps for PAP management as dictated by AASM guidelines and conventional wisdom, including: vigorous attempts to solve all mask issues (extensive mask fittings, chin strap use, accessible loaner mask program, leak evaluation via objective data download, on-site mask fit evaluation, and collaboration with durable medical equipment companies), evaluation of outcome data, or subjective report of progress. REPAP protocol candidates will have also experienced multiple encounters (in person or via telephone /e-mail) with the sleep physician, sleep technologists, or coordinating staff. In addition to any earlier exposure to mask fittings through our center or durable medical equipment companies, the REPAP protocol always includes mask fitting and desensitization at the first and all subsequent re-titrations. Physical (eg, nasal congestion, nasal anatomy) and psychological (eg, claustrophobia, anxiety) factors influence mask type (nasal pillow, nasal, or full-face). Optimizing mask fit is crucial to long-term use and may include chin straps as well,<sup>4</sup> albeit mask and related technology only indirectly facilitate resolution of respiratory effort-related arousals and elimination of expiratory pressure intolerance. PAP pressure desensitization begins with CPAP for every patient.

For the patient population included in this current study, all of whom were seeking a second opinion after failing a previous attempt of PAP therapy at another center, the majority were forced to return their PAP devices to the durable medical equipment company before presenting to our facility; thus, mask fit opportunities were not always

feasible and applicable at initial presentation. Although it was not uncommon for subjects in our study to complete one or more daytime encounters before their first REPAP re-titration, some were directly scheduled in the sleep laboratory due to patient preference. Thus, this cohort of subjects seeking second opinions was exposed to all aspects of the REPAP protocol, but the order of steps was dictated by subject circumstances.

Our previously published re-titration protocol<sup>26</sup> follows the AASM mandate to eliminate all breathing events (apneas, hypopneas, respiratory effort-related arousals)<sup>1</sup> while addressing expiratory pressure intolerance.<sup>26</sup> Our most consistently successful efforts occur with the *manual*, attended titration of auto-adjusting, dual pressure devices (bi-level): auto-bi-level (ABPAP) (VPAP Auto 25 and S9 VPAP auto-BPAP devices, ResMed, San Diego, California) or adaptive servo-ventilation (ASV) (ASV Enhanced and S9 VPAP ASV-Auto devices, ResMed), the latter to treat diagnosed or subthreshold complex sleep apnea. In contrast to other research where ABPAP has been tested strictly in the auto mode,<sup>42-44</sup> in our sleep laboratory, the auto-adjusting device is set to auto<sup>26,31</sup> mode and then manually titrated by raising minimum expiratory settings in the face of end-expiratory collapsibility or lowering pressures in the face of expiratory pressure intolerance; raising inspiratory settings also occurs when subtle collapsibility manifests as respiratory effort-related arousals. These increases or decreases may be as minute as 0.2–0.4 cm H<sub>2</sub>O<sup>26</sup>; nevertheless, the changes are required as the auto mode fails to maintain the overarching goal to "round the air flow" curve to normal. Rounding of the air flow signal on inspiration and expiration aligns with the study by Condos et al<sup>45</sup> describing how aggressive treatment of flow limitation provides further daytime improvements.

Last, with nearly universal use of CPAP in patients presenting for second opinions, this chart review could not compare all pressure settings between original opinion and new PAP devices other than to identify original fixed PAP pressure and new expiratory positive airway pressure settings on the dual-pressure devices.

### Determination of PAP User Versus Non-User Status

Among the final sample ( $n = 273$ ), current users were distinguished from non-users based on the presence of any of these recent factors: (1) prescription renewal for PAP supplies<sup>46</sup>; (2) clinic appointment regarding continued PAP use; (3) re-titration and confirmation of use; (4) contact with office staff, discussing continued PAP use. Among subjects with objective data downloads, average nightly hours were calculated separately for all nights and for nights with PAP use only.

## REPAP PROTOCOL FOLLOWING PAP FAILURE

**Data Analyses**

Descriptive statistics provided baseline characteristics; proportions of PAP failure factors from original centers; and changes in proportions of mask, modes, and pressures prescribed at our center. Objective and subjective data from user and non-user groups were contrasted using analysis of variance for continuous variables; Hedges'  $g$  was calculated for effects from unequal sample sizes. Chi-square analyses examined dichotomous variables. The McNemar chi-square test was performed on repeated measures of dichotomous variables. Comparisons of those undergoing a single re-titration versus those completing multiple re-titrations were also analyzed.

To find the most parsimonious predictors of PAP use, a 2-step process was used for single re-titration and multiple re-titrations. First, factor analysis identified re-titration-related predictors of PAP use that could be combined into composite factors (see supplementary Table S1). Second, factor scores for each participant were computed, and then this reduced set of predictors was tested using multiple logistic regression (see supplementary Table S1), controlling for non-re-titration-related predictors of PAP use (marital status, ethnicity, depression, BMI, and insomnia severity index). Statistical significance was .05.

**Results**

The following analyses report on statistically significant findings regarding the total sample based on user versus non-user status in the context of completing single or multiple re-titrations. Where no significant findings manifested, data are reported for the entire sample.

**Socio-Demographics, Subjective Sleep Characteristics, and Psychiatric History**

The 273 subjects were predominantly obese (mean  $\pm$  SD body mass index  $33.3 \pm 8.8$  kg/m<sup>2</sup>), white (61.2%) or Hispanic (23.8%), married (72.9%), male (60.4%), and with less than a bachelor's degree (50.5%). Intake data showed subjective mean  $\pm$  SD sleep onset latency of  $59.3 \pm 118.8$  min, total sleep time of  $6.1 \pm 1.5$  h, sleep efficiency of  $80.2 \pm 18.3\%$ , and subjective wake after sleep onset of  $88.3 \pm 89.80$  min, indicative of co-occurring insomnia symptoms in the average patient while not using PAP. Mean  $\pm$  SD total insomnia severity index score was  $16.0 \pm 5.8$ , just above the most conservative cutoff for clinically moderate insomnia; subjective insomnia duration was  $11.4 \pm 8.5$  y. Mean  $\pm$  SD Epworth sleepiness scale total score was  $10.9 \pm 6.2$ , just above a frequently used cutoff for clinically meaningful daytime sleepiness.

Of 273 subjects, 190 (69.6%) suffered one or more psychiatric illnesses or symptoms: depression (45.1%), trauma

exposure (36.6%), claustrophobia (31.5%), anxiety (22.7%), posttraumatic stress disorder (15.0%), panic attacks (14.0%), bipolar illness (3.7%), and obsessive compulsive disorder (3.0%). Both history of depression and being single demonstrated significant findings for predicting lower PAP use and are described below in final analyses using multiple regressions.

**PAP Failure History**

Most subjects received first opinions at sleep centers in New Mexico, comprising: private, free-standing (49.1%), community hospital-based (33.0%), or academic (4.8%). The remaining 13.2% comprised subjects treated at out-of-state centers. All subjects were diagnosed with OSA, but no facilities recorded the diagnosis of upper-airway resistance syndrome. Of the 273 subjects, 39 refused to initiate PAP, and 234 (85.7%) attempted PAP therapy at home (range in use of 4 d to  $\geq 5$  y; mean  $\pm$  SD duration of use  $18.4 \pm 28.8$  months) before abandoning PAP, thus meeting conventional criteria for PAP failure. The mean  $\pm$  SD duration of time between original diagnostic PSG to initial second-opinion re-titration was  $5.37 \pm 8.01$  y.

The vast majority of our sample (88.6%) was originally prescribed CPAP compared with other modes (auto-CPAP 5.1%, BPAP 4.2%, ABPAP 0.8%, ASV 0.8%, intelligent volume-assured pressure support [iVAPS] 0.4%). Reasons for PAP therapy cessation were numerous, including pressure intolerance (24.5%), mask discomfort (20.1%), inability to adapt to PAP (10.6%), no appreciable benefits (10.6%), or no specific reason (8.8%). Another 25.4% reported adverse effects from PAP use, other treatment options, or financial reasons. As such, it would appear that clinical standards and guidelines for care were not followed per AASM practice parameters at the original institutions in a large majority (73.9%) who verbally indicated that the above factors were not addressed before terminating PAP.

**Establishing User Versus Non-User Groups and Their Frequency of Re-titrations**

As seen in Figure 2, after the 273 subjects with PAP failure underwent their initial re-titration at our center, 210 (76.9%) became users, and 63 remained non-users (including 7 complex sleep apnea cases scheduled for ASV titration). Of 273 total subjects, 158 completed more than one re-titration (mean  $\pm$  SD total re-titrations =  $3.15 \pm 1.33$ ; median = 2 re-titrations). Additional re-titrations were recommended for various reasons (Fig. 3): 113 subjects had 2 issues necessitating another re-titration, and 45 had 3 or more factors. The mean  $\pm$  SD time between re-titrations was  $9.28 \pm 9.40$  months. The mean  $\pm$  SD time was  $7.35 \pm 10.50$  months between the first and second re-titra-

## REPAP PROTOCOL FOLLOWING PAP FAILURE

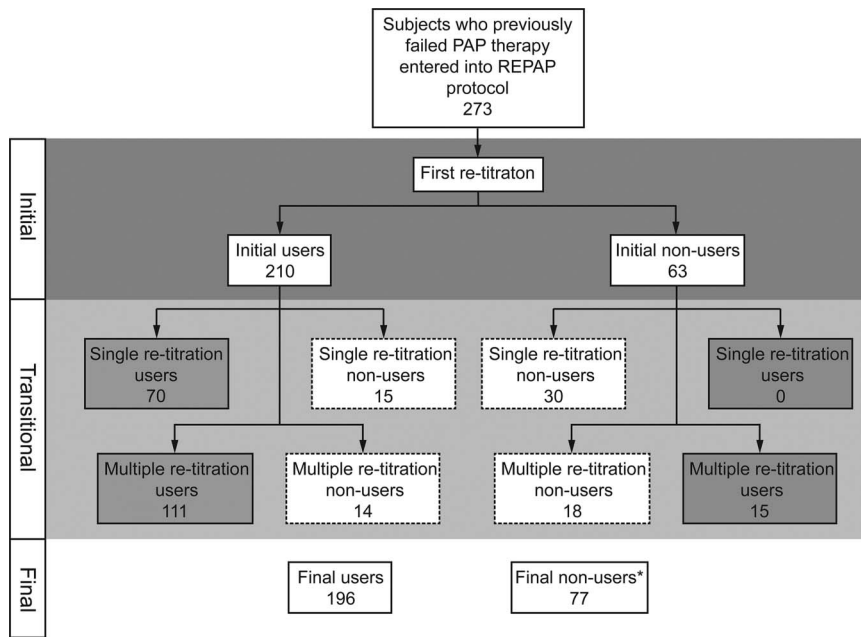


Fig. 2. Flow chart showing positive airway pressure (PAP) therapy use during three distinct time periods. Initial = period immediately after the first or only re-titration; Transitional = period where subjects either used PAP but had no further re-titrations, used PAP and had one or more additional re-titrations, or were not using PAP but completed one or more additional re-titrations; Final = user status as of chart review end date. Final users (sum of all dark gray boxes) and Final non-users (sum of all dashed line boxes). \*Of the 77 final non-users, 58 re-initiated PAP therapy either after initial or repeat re-titration studies but once again failed for various reasons (mask issues: 9, pressure intolerance: 9, lost to follow-up: 9, general adaptation problems: 7, money/insurance: 6, nasal congestion/allergy exacerbation: 4, no appreciable benefit: 4, claustrophobia: 3, physical side effects: 2, believed PAP was no longer needed: 2, focus on other health issues: 1). The remaining 19 subjects never re-initiated PAP. Of all 77 final PAP non-users, 21 pursued oral appliance therapy, and 9 elected to have surgery.

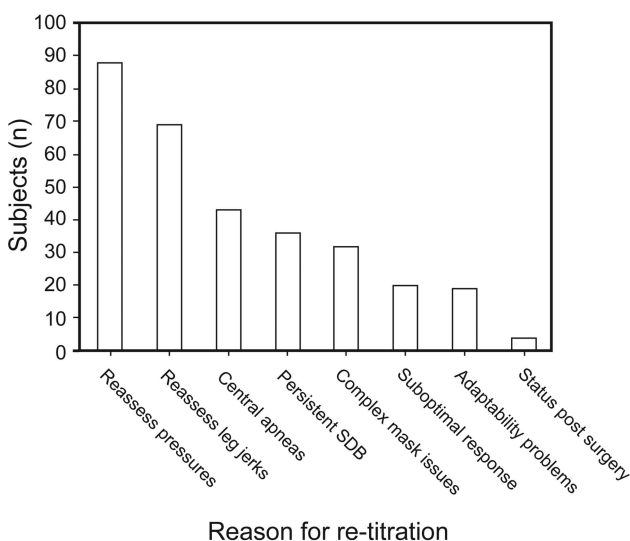


Fig. 3. Indications for recommended  $\geq 2$  re-titrations in subjects completing multiple re-titrations ( $n = 158$ ). SDB = sleep-disordered breathing.

tions,  $10.99 \pm 10.53$  months between second and third, and finally  $11.07 \pm 6.64$  months between third and fourth.

After accounting for subjects undergoing multiple re-titrations, final net follow-up yielded a total of 196 users

and 77 non-users, and the multiple-re-titration group (126 of 158 [79.7%]) demonstrated a significantly ( $P = .001$ ) higher proportion of use than the single-re-titration group (70 of 115 [60.9%]). The Fig. 2 legend details factors that influenced 44 transitional subjects who changed from user to non-user status or vice versa. Overall, the average time of PAP use was  $24.44 \pm 21.51$  months from device re-initiation to most recent sleep center follow-up.

### REPAP Protocol: Mask Changes

The mask type for subjects at time of PAP failure included: nasal (45.8%), full face (37.4%), and nasal pillows (16.8%). Pre-sleep mask fitting at our center led to changes in type for 53.1% of the sample with 89 of 145 subjects switching from nasal to either full face ( $n = 55$ ) or nasal pillows ( $n = 34$ ) due to mouth breathing or discomfort. Among 128 subjects who remained with the original mask types, 104 changed mask styles (new vendor models). After initial re-titration, mask prescriptions reflected 154 (57.9%) full face masks, 72 (27.1%) nasal pillows, and 40 (14.7%) nasal masks, a significant increase in the former two and decrease in the latter ( $P = .001$ ). Among users, similar proportions of mask type were associated with current use, nasal pillows (60 of 72 [83.3%]), full face masks

## REPAP PROTOCOL FOLLOWING PAP FAILURE

(121 of 154 [78.6%]), and nasal masks (28 of 40 [70.0%]), without significant differences.

This inclination toward full face masks and away from nasal masks continued among those pursuing multiple titrations: full face (110 [69.6%]), nasal pillows (27 [17.1%]), and nasal (21 [13.3%]). Again, use rates by mask type showed similar proportions with full face (84 of 103 [81.6%]), nasal pillows (22 of 27 [81.5%]), and nasal (16 of 21 [76.2%]) without significant difference for those undergoing multiple titrations. Although all mask types were associated with nearly similar proportions of users, subjects gravitated over time toward full face and nasal pillows and away from nasal masks.

Of clinical import, 92 of 273 subjects (33.7%) in our sample were prescribed and regularly using a chin strap at various points during their REPAP protocol experience, of which 71 of 92 (77.2%) were current PAP users. Mask types used by subjects with chin straps included: direct nasal pillow ( $n = 32$ ), standard nasal ( $n = 21$ ), and full face masks ( $n = 39$ ).

### REPAP Protocol: PAP Mode Changes

At the first re-titration, 227 of 273 subjects manifested subjective or objective expiratory pressure intolerance during pressure desensitization or during the re-titration, necessitating an eventual switch to auto-adjusting technology. Another 45 subjects switched because they failed PAP despite years of use and either qualified for a new device or manifested residual breathing events. Only one subject remained on the originally prescribed mode (auto-CPAP), and seven were not prescribed a device after their first re-titration. In total, 97.1% of subjects received a prescription for a new PAP mode, including: ABPAP (130 [48.9%]), ASV (82 [30.8%]), and fixed BPAP (53 [19.9%]). The proportion of users by mode included: BPAP (35 of 53 [66.0%]), ASV (65 of 82 [79.3%]), and ABPAP (109 of 130 [83.8%]).

Of the 158 subjects undergoing multiple re-titrations, 60 were prescribed a new PAP mode after using another mode for an average of  $9.28 \pm 9.40$  months; they averaged  $1.62 \pm 0.71$  re-titrations before changing modes.

Updated PAP modes included: ASV (104 [65.8%]), ABPAP (42 [26.6%]), BPAP (7 [4.4%]), and iVAPS (5 [3.2%]). The proportion of users by mode included: ABPAP (39 of 42 [92.9%]), BPAP (6 of 7 [85.7%]), ASV (78 of 98 [77.6%]), and iVAPS (3 of 5 [60.0%]). The predominant pattern of prescriptions tended toward ABPAP after first re-titration, but then among subjects undergoing multiple re-titrations, ASV prescriptions were more common. Of note, there were 7 subjects who completed an initial re-titration but were not prescribed a device until a subsequent re-titration using ASV could be completed (average was 1.65 mo between these titrations).

### REPAP Protocol: Pressure Setting Changes

At the point of PAP failure, the average pressure setting was  $10.0 \pm 3.21$  cm H<sub>2</sub>O. Among all subjects, new or residual breathing events as well as objective expiratory pressure intolerance manifested during re-titrations, necessitating changes in expiratory or inspiratory settings in all 273 subjects to attempt to normalize the air-flow curve. Changes in originally prescribed expiratory positive airway pressure settings, following the initial re-titration study, were necessary for 94.1% ( $n = 257$ ) of our sample: 177 (64.8%) decreased pressure (mean  $\pm$  SD =  $-3.48 \pm 2.61$  cm H<sub>2</sub>O) due to expiratory pressure intolerance, and 80 (29.3%) increased pressure ( $+3.24 \pm 2.52$  cm H<sub>2</sub>O) due to residual breathing events. Only nine required no change in expiratory positive airway pressure, albeit inspiratory pressures changed. In the subset completing multiple re-titrations, expiratory positive airway pressure increased for 83 subjects ( $+3.16 \pm 2.53$  cm H<sub>2</sub>O), decreased for 40 subjects ( $-3.40 \pm 2.31$  cm H<sub>2</sub>O), and remained unchanged for 35 subjects, albeit this latter subgroup required a second change in PAP mode (15 switched from ABPAP to ASV, 6 from BPAP to ASV, and 5 from BPAP to ABPAP) or change in inspiratory pressure (9 subjects had IPAP or pressure support increased). Average final pressure settings by device mode are reported in supplemental Figure S1. In sum, pressure changes were pervasive for inspiratory and expiratory settings to attempt to normalize the air-flow curve, according to the AASM mandate to eliminate all breathing events.<sup>1</sup>

### Factors Associated With PAP Therapy Use

In Table 1, objective data from the initial re-titration showed users with significant, small to medium improvements for sleep efficiency, sleep onset latency, and ratios of REM and stage 1 non-REM sleep during total sleep time compared with non-users. Subjectively, among those with morning-after ratings of better sleep versus those reporting no change/worse sleep, use rates were 82.2% versus 66.1% ( $P = .01$ ). Among those anticipating no difficulty using PAP versus those anticipating difficulty or uncertainty, use rates were 90.8% versus 50.0% ( $P = .001$ ).

From the most recent re-titrations of the 158 multiple-re-titration subjects, comparison of objective sleep indices (Table 2) again revealed that users had significant improvements in total sleep time, sleep efficiency percentage, sleep onset latency, wake after sleep onset, stage 1 percentage non-REM, REM time, and AHI with a trend toward lower RDI, with small to large effects compared with non-users. Subjectively, among those with morning-after ratings of better sleep versus those reporting no change/worse sleep, use rates were 87.3% versus 65.8% ( $P = .01$ ). Among those anticipating no difficulty using PAP versus those anticipating difficulty or uncer-

## REPAP PROTOCOL FOLLOWING PAP FAILURE

Table 1. Comparison of Objective Sleep Indices, Breathing Indices, and Subjective Post-Sleep Questionnaire Data From Initial Re-Titration for Users Versus Non-Users

Characteristic	Total (N = 273)	Users (n = 210)	Non-Users (n = 63)	P*	g†
Sleep indices, mean ± SD					
Total sleep time, h	5.37 ± 1.08	5.41 ± 1.02	5.23 ± 1.31	.25	0.16
Sleep efficiency, %	80.09 ± 12.88	80.86 ± 12.10	77.17 ± 15.27	.050	0.29
Sleep onset latency, min	10.88 ± 11.86	9.91 ± 10.65	14.62 ± 15.27	.01	0.40
Total awakenings/night	26.18 ± 12.93	26.13 ± 12.84	26.36 ± 13.42	.91	0.01
Wake after sleep onset, min	70.57 ± 46.56	69.92 ± 48.12	73.09 ± 40.30	.64	0.07
Stage 1, %	10.93 ± 9.89	10.31 ± 8.50	13.35 ± 13.91	.043	0.29
Stage 2, %	59.55 ± 12.03	59.69 ± 12.11	58.99 ± 11.79	.69	0.06
Stage 3, %	9.94 ± 10.10	10.07 ± 10.01	9.45 ± 10.50	.67	0.06
REM, %	19.07 ± 8.00	19.75 ± 8.04	16.43 ± 7.33	.001	0.42
Breathing indices, mean ± SD					
AHI, events/h	5.21 ± 7.21	5.26 ± 6.81	5.05 ± 8.47	.84	0.03
RDI, events/h	20.42 ± 16.68	21.17 ± 17.19	17.93 ± 14.68	.18	0.19
Post-sleep questionnaire data‡					
Sleep quality rating, mean ± SD	4.29 ± 1.32	4.41 ± 1.29	3.85 ± 1.37	.01	0.43
Anticipates trouble adapting, n (%)§					
Yes	116 (42.5)	79 (39.7)	37 (66.1)		
No	139 (50.9)	120 (60.3)	19 (33.9)	.01	NA

User status was based on positive airway pressure use evidence following first re-titration only.

\* Determined using one-way analysis of variance for continuous variables.

† Used to determine effect size for unequal sample sizes.

‡ Questionnaire given to all subjects the morning following titration polysomnography containing 2 questions: (1) rank quality of sleep during the titration relative to a normal night's sleep at home on a 7-point Likert scale (0 = much worse and 6 = much better) and (2) anticipated trouble adapting to positive airway pressure at home (yes, no, or unsure).

§ Eighteen subjects did not answer this question on the post-sleep questionnaire.

REM = rapid eye movement

AHI = apnea-hypopnea index

RDI = respiratory disturbance index

NA = not applicable

tainty, use rates were significantly different, 90.9 and 48.6%, respectively ( $P = .001$ ).

Last, a trend was noted for non-users reporting a higher proportion of psychiatric conditions at intake (77.9%) compared with users (66.3%) ( $\chi^2 = 3.51$ ,  $P = .060$ ).

### Predictors of PAP Use: Factor Analysis and Multiple Logistic Regression Analysis

Following single re-titration, factor analysis showed 3 factors, termed macro-sleep (sleep efficiency and sleep onset latency), stage (percentage stage 1 and percentage REM), and subjective (sleep quality and anticipated problems with PAP) (see supplementary Table S1). After controlling for RDI, marital status, ethnicity, body mass index, RDI, insomnia severity index, and depression variables, the stage and subjective factors significantly predicted PAP use after initial re-titration (ORs = 1.80 and 2.11, respectively). Being married or living with a partner was significantly associated with an increased likelihood of PAP use (OR = 2.29), whereas a history of depression was significantly associated with lower likelihood of PAP use (OR = .30) (Table 3).

Following multiple re-titrations, factor analysis showed 2 factors, termed objective (total sleep time, sleep onset

latency, wake after sleep onset, and REM time) and quality (stage 1 percentage non-REM, sleep quality, anticipated problems with PAP) (see supplementary Table S1). After controlling for RDI, marital status, ethnicity, BMI, RDI, insomnia severity index, and depression variables, the quality factor significantly predicted PAP after multiple titrations (OR = 10.30). Being married or living with a partner was significantly associated with increased likelihood of PAP use (OR = 9.55), and history of depression was significantly associated with lower likelihood of PAP use (OR = 0.08) (Table 3). For analyses demonstrating no impact of leg movement symptoms on study findings, see the supplementary materials.

### Adherence Data

Objective data downloads available for 126 users showed mean ± SD use of  $5.34 \pm 2.34$  h/night, median  $6.00 \pm 2.12$  h/night, and  $6.48 \pm 2.83$  h/night for nights used (range 1.5–10 h/night), on average, well above adherence guidelines. Overall, average actual use was  $37.24 \pm 17.41$  h/week. The mean ± SD objective data download AHI was  $3.20 \pm 3.92$  events/h, apnea index was  $0.59 \pm 1.17$  events/h, and hypopnea index was  $2.59 \pm 3.47$

## REPAP PROTOCOL FOLLOWING PAP FAILURE

Table 2. Multiple Retitration Sub-Sample ( $n = 158$ ): Comparison of User vs Non-User Objective Sleep and Breathing Indices, and Post-Sleep Subjective Questionnaires

Characteristic	Total ( $n = 158$ )	Users ( $n = 126$ )	Non-Users ( $n = 32$ )	$P^*$	$g^\dagger$
Sleep indices, mean $\pm$ SD					
Total sleep time, h	5.30 $\pm$ 1.39	5.51 $\pm$ 1.27	4.47 $\pm$ 1.56	.001	0.78
Sleep efficiency, %	78.40 $\pm$ 12.88	80.46 $\pm$ 14.00	70.29 $\pm$ 20.42	.001	0.65
Sleep onset latency, min	10.92 $\pm$ 10.97	10.05 $\pm$ 9.81	14.32 $\pm$ 14.36	.049	0.39
Total awakenings/night	24.60 $\pm$ 12.20	24.62 $\pm$ 11.93	24.53 $\pm$ 13.41	.97	0.01
Wake after sleep onset, min	70.57 $\pm$ 46.56	69.80 $\pm$ 49.47	93.63 $\pm$ 60.72	.02	0.46
Stage 1, %	10.84 $\pm$ 11.63	9.76 $\pm$ 9.22	15.10 $\pm$ 17.83	.02	0.46
Stage 2, %	57.35 $\pm$ 14.99	57.67 $\pm$ 14.78	56.09 $\pm$ 15.96	.60	0.10
Stage 3, %	9.94 $\pm$ 10.10	10.07 $\pm$ 10.01	9.45 $\pm$ 10.50	.46	0.06
REM, %	17.98 $\pm$ 10.19	18.53 $\pm$ 10.46	15.86 $\pm$ 8.91	.19	0.26
REM time, min	60.31 $\pm$ 40.62	64.10 $\pm$ 42.16	45.38 $\pm$ 60.07	.01	0.40
Breathing indices, mean $\pm$ SD					
AHI, events/h	3.63 $\pm$ 6.85	2.97 $\pm$ 4.89	6.25 $\pm$ 11.48	.02	0.48
RDI, events/h	17.23 $\pm$ 16.18	16.06 $\pm$ 15.29	21.83 $\pm$ 18.87	.07	0.36
Post-sleep questionnaire data‡					
Sleep quality rating	4.97 $\pm$ 1.16	5.32 $\pm$ 1.11	3.98 $\pm$ 2.69	.044	0.86
Anticipated trouble adapting, $n$ (%)§					
Yes	10 (6.8)	2 (1.7)	8 (27.6)		
No	109 (74.1)	99 (83.9)	10 (34.5)		
Unsure	28 (19.1)	17 (14.4)	11 (37.9)	.001	NA

User status was based on positive airway pressure use evidence following most recent re-titration only.

\* Determined using one-way analysis of variance for continuous variables.

† Used to determine effect size for unequal sample sizes.

‡ Questionnaire given to all subjects the morning following titration polysomnography containing 2 questions: (1) rank quality of sleep during the titration relative to a normal night's sleep at home on a 7-point Likert scale (0 = much worse and 6 = much better) and (2) anticipated trouble adapting to positive airway pressure at home (yes, no, or unsure).

§ Eleven subjects did not answer this question on the post-sleep questionnaire.

AHI = apnea-hypopnea index

RDI = respiratory disturbance index

NA = not applicable

events/h. When available, central apnea index was negligible ( $<1$  event/h).

## Discussion

In this large case series of subjects with clinically relevant PAP failure and most with psychiatric comorbidity, technological solutions, including extensive changes in masks ( $n = 249$  [91.2%]), modes ( $n = 265$  [97.1%]), and pressure settings ( $n = 264$  [96.7%]) were associated with improvements in objective and subjective sleep markers and immediate post-re-titration subjective impressions, all of which appeared to be salient factors in a 72% PAP renewal rate among a cohort who had previously abandoned or rejected PAP at another sleep center. Technological solutions were necessary in the face of repeated episodes of unresolved pathophysiological effects of sleep-disordered breathing (residual breathing events) or iatrogenic side effects (mask discomfort and leak, mouth breathing, and expiratory pressure intolerance) and required repeated adjustments with technological interfaces (masks, modes, pressures), including pressure changes to accommo-

date mask and mode changes. By subject self-report, these issues were not adequately addressed before PAP failure at the original sleep center. Among a subset comprising more than half of the user group, greater re-initiation of PAP therapy was significantly associated with multiple re-titrations compared with a single REPAP protocol.

Our study also replicates past work demonstrating changes in technology in association with several objective and subjective improvements in sleep, including greater objective sleep consolidation<sup>47</sup> as well as greater self-reports of better sleep or easier adaptability to PAP.<sup>33,34</sup> Conversely, non-users showed greater sleep fragmentation, fewer REM minutes, lower REM percentage, more Stage 1 NREM, reports of no change in or worse sleep quality, and concerns about adaptability. Taken together, although speculative, the findings reflect favorably on this experiential, re-titration model to assist failing patients in re-initiating and using PAP therapy by addressing specific barriers through technology to yield a more efficacious response, both objectively and subjectively.

The subjective rating of the morning-after experience was the most predictive factor of subsequent use,<sup>33,34</sup> al-

## REPAP PROTOCOL FOLLOWING PAP FAILURE

Table 3 Parameters From Multiple Logistic Regression Predicting Positive Airway Pressure Use Following Initial and Most Recent Re-Titration Polysomnographs Based on Subjective and Objective Data

Titration	$\beta \pm SE$	Wald	P	OR (95% CI)
Initial				
Constant	1.428 $\pm$ 0.900	2.518	.11	4.172
Ethnicity				
Caucasian (reference)				
Hispanic	-0.662 $\pm$ 0.413	2.575	.11	0.516 (0.230–1.158)
Marital status*				
Single (reference)				
Married	0.827 $\pm$ 0.365	5.128	.02	2.287 (1.118–4.680)
BMI	-0.021 $\pm$ 0.019	1.261	.26	0.979 (0.944–1.016)
RDI	0.010 $\pm$ 0.011	0.781	.38	1.010 (0.988–1.032)
ISI	0.051 $\pm$ 0.033	2.478	.12	1.053 (0.987–1.122)
Depression	-1.203 $\pm$ 0.370	10.563	.001	0.300 (0.145–0.620)
Macro sleep†	0.244 $\pm$ 0.192	1.276	.21	1.276 (0.875–1.860)
Stage‡	0.588 $\pm$ 0.242	5.887	.02	1.800 (1.120–2.894)
Subjective§	0.748 $\pm$ 0.226	10.987	.001	2.112 (1.357–3.287)
Most recent				
Constant	1.053 $\pm$ 1.607	0.429	.51	2.865
Ethnicity				
Caucasian (reference)				
Hispanic	0.909 $\pm$ 0.805	1.275	.26	2.481 (0.512–12.010)
Marital status*				
Single (reference)				
Married	2.256 $\pm$ 0.847	7.101	.01	9.548 (1.816–50.193)
BMI	0.018 $\pm$ 0.033	0.301	.58	1.019 (0.954–1.088)
RDI	-0.031 $\pm$ 0.029	1.091	.30	0.970 (0.916–1.027)
ISI	0.007 $\pm$ 0.064	0.014	.91	1.008 (0.889–1.142)
Depression	-2.519 $\pm$ 0.813	9.610	.002	0.081 (0.016–0.396)
Objective	0.620 $\pm$ 0.401	2.389	.12	1.860 (0.847–4.084)
Quality¶	2.332 $\pm$ 0.693	11.320	.001	10.297 (2.647–40.053)

\* For marital status, single includes divorced or widowed subjects, and married includes subjects living with their significant others.

† Factor reflecting sleep onset latency and sleep efficiency.

‡ Percentage stage 1 and stage REM.

§ Post-sleep questionnaire sleep quality assessment and anticipated problems adapting to positive airway pressure at home.

|| Objective total sleep time, sleep onset latency, wake after sleep onset, and percentage of total sleep time spent in REM.

¶ Post-sleep questionnaire sleep quality assessment, anticipated problems adapting to positive airway pressure at home, and stage 1 sleep.

$\beta$  = parameter estimate

Wald = Wald statistic

OR = odds ratio, the increased probability of an individual becoming a positive airway pressure user

BMI = body mass index

RDI = respiratory disturbance index, the sum of all apneas, hypopneas, and respiratory effort-related arousals divided by total hours of sleep (events/h)

ISI = insomnia severity index

beit in our clinical practice, we perceive these subjective impressions as a direct consequence of enhanced technology, because our REPAP protocol stresses regular modifications to technology (mask, modes, pressures) to fine-tune patients' experiences. Ironically, it cannot go without saying that technology issues not only seem to act as prime movers causing PAP failure,<sup>48</sup> but technology also appears to solve some of these problems. Parsimoniously, discomfort (defined as physically distressing sensations and worse sleep) caused PAP failure. However, new technology en-

hanced comfort; and, greater comfort resulted in enhanced adaptability and use, which aligns with a rationale to make PAP more user-friendly to improve self-efficacy and ultimately increase adherence.<sup>2,3,8,48</sup> These findings may be especially relevant to psychiatric patients with OSA/upper-airway resistance syndrome who comprised the predominant phenotype in our sample and for whom vulnerability to expiratory pressure intolerance appears more pronounced.<sup>26,30</sup> Practically, newer models of care involving home testing for OSA diagnosis and auto-titration devices may also be applied to rescue PAP failure cases of lesser complexity,<sup>11</sup> notwithstanding the potential confounds in the assessment and treatment of respiratory effort-related arousals exhibited in either diagnosed upper-airway resistance syndrome cases or as residual breathing events in patients with OSA who are titrated suboptimally.<sup>1</sup>

The two most common changes in the treatment regimen were switches to full face masks and auto-adjusting dual-pressure systems (ABPAP, ASV). We wish to reiterate that we never use auto-adjusting devices in the laboratory set simply to auto mode,<sup>31</sup> because research has shown that auto modes do not produce an optimal titration per AASM standards.<sup>31,49,50</sup> Typically, use of auto-adjusting devices prescribed without an attended PSG requires a wider range between maximum inspiratory and minimum expiratory pressures. When we use auto mode, our sleep technologists manually override and adjust the system as necessary to determine a more precise and delimited set of therapeutic pressure ranges to titrate respiratory effort-related arousals while preventing expiratory intolerance. This protocol appears to improve tolerability and efficacy and speculatively may decrease the time interval to adherence. The major goal to normalize the air-flow curve for as much of the night as possible to consolidate sleep as much as possible serves the desired outcome of self-reported higher quality of sleep, an experience that may reinforce patients' motivation.<sup>47</sup> Because our findings are consistent with these points (ie, significantly less time in Stage 1 NREM and greater time and percentage in Stage REM), it is thought-provoking that among subjects undergoing multiple re-titrations, a significantly lower AHI and a trend for a lower RDI manifested in the users compared with the non-users. Such findings do not prove but are compatible with a dose-response paradigm<sup>25,51</sup> in which fine-tuning treatment of a collapsible airway with repeat titrations (REPAP protocol) further stabilizes the patency of the breathing passages (fewer residual events), which in turn probably decreases the "apnea burden" (weighted AHI), a concept defined by Bianchi et al<sup>7</sup> to suggest that a patient would be able to tolerate more hours of PAP use.

AASM guidelines suggest that re-titrations may be needed for patient discomfort or intolerance at high pressures, for persisting breathing events, or for assessment of alternative PAP modes when failing PAP,<sup>1</sup> yet the same

## REPAP PROTOCOL FOLLOWING PAP FAILURE

AASM guidelines using a titration grading scale only recommend re-titrations based on the supposed adequacy or inadequacy of the PSG and not on outcomes.<sup>1</sup> In contrast, another guideline published in 2006 from an AASM Task Force stipulated "... logic encourages recheck [re-titration] for persistent adherence problems or the recurrence of symptoms ...."<sup>35</sup> Regardless of what may or may not be paradoxical recommendations, current guidelines imply that a patient's first titration settings are sufficient,<sup>21</sup> and consensus statements<sup>1,35</sup> further imply that these initial settings should be adequate as a long-term prescription for PAP in most patients, a premise frequently disproven in other areas of medical care (eg, when initially prescribing medications for numerous health conditions).<sup>52-54</sup>

Speculatively, this cluster of guidelines may represent a potential shortcoming in treatment approaches to sleep apnea, particularly for vulnerable psychiatric patients with OSA/upper-airway resistance syndrome. If PAP therapy were equated to a dosage of medicine to treat breathing events, it is an anomalous perspective to imagine that the dosage does not change with time or circumstances. Notwithstanding concerns about health-care costs, sleep medical centers possess reasonably effective tools to subjectively measure sleep apnea patient outcomes (validated scales, clinical encounters, bedpartner reports) and workable objective tools to monitor responses to PAP therapy (PSG re-titration, objective data download). However, in light of the widely published poor rates of adherence,<sup>8,55-57</sup> our findings suggest that PAP modes and pressure settings as well as masks may need changes more routinely and expeditiously in the care of at-risk sleep apnea patients. Although a REPAP model would be associated with increased initial costs, sufficient evidence indicates that health problems associated with failure to use PAP are ultimately more expensive.<sup>58-60</sup> For example, if our sample of subjects had received their re-titrations at the initial sleep center, this expedited care might have decreased health-care costs by eliminating their extended period without a PAP device (ie, the time following equipment return to the durable medical equipment company and before re-initiating therapy through our center). Instead, a lack of follow-up, inadequate resolution of mask issues, untreated residual breathing events, emergent central apneas, and no option to use advanced PAP devices to resolve expiratory PAP pressure (all contributing to suboptimal sleep-disordered breathing treatment) resulted in PAP failure and cessation for these patients and ultimately persuaded them to seek second opinions from our facility.

Future studies are warranted to examine the REPAP model versus the objective data download model,<sup>11</sup> both for efficacy and cost-effectiveness for specific cohorts of patients; and, as evidenced by this study, special attention should be given to the effects of unmarried status and comorbid depression in light of lower adherence associ-

ated with each factor. Clearly, because the REPAP protocol is not required in every PAP failure case, prospective studies are needed to determine appropriate patients who may benefit from this in-depth intervention.

The most specific limitation of this study, given its lack of prospective design and absence of a formal control group, is the inability to affirm that technological solutions caused re-initiation of PAP therapy in our cohort. Many other variables may have contributed to subjects becoming PAP users: "fresh start" patient motivation, greater education and awareness of the problem through passage of time, referring physician persistence, or specific worsening of symptoms that enhanced the risk-benefit ratio toward motivation and away from avoidance. Also, the long lapse between the initial diagnostic PSG at the original sleep center and the return to our center averaged >5 y, during which many other changes in sleep, medical, or psychiatric history could have influenced patient attitudes and our findings. The inability to repeat diagnostic PSG in all subjects due to insurance barriers or subject preference also limited measurement of baseline status upon entry into our system. The absence of data downloads in more than half of the subjects also limited our analyses. Even the finding of greater use among multiple-titration subjects must be viewed with caution because many confounding factors may persuade patients to return to the laboratory and others to resist doing so. Variability among sleep technologists must be considered as well.

In addition, extensive hands-on education<sup>61</sup> is a requisite element of our experiential model. Patients are taught why and how a full face mask resolves mouth breathing, why and how dual pressure systems produce greater comfort to overcome pressure intolerance, and why and how specific pressure settings are required to normalize breathing, all in an attempt to enhance subjective and objective sleep quality and to encourage a user-friendly perspective toward PAP. Education is a crucial factor in managing OSA/upper-airway resistance syndrome patients, and its impact on various barriers to adherence has been deemed an essential element of high-quality care,<sup>2,9,48,61</sup> despite research demonstrating that education alone does not appreciably improve PAP adherence.<sup>62</sup> Nonetheless, we are persuaded that the effects of education are greatly amplified when patients actually undergo the *experience* of re-titrations, including the experience of greater comfort achieved through advanced technology. Even so, data from Table 2 clearly show the difficulty in attempting to eliminate all breathing events; thus, our findings, although favorable for this cohort of predominantly psychiatric subjects who had previously abandoned PAP at other sleep centers, still indicate a need for more scientific advancements to definitively treat all breathing events in patients with OSA or upper-airway resistance syndrome.

## REPAP PROTOCOL FOLLOWING PAP FAILURE

## Conclusions

Practically, the conventional sleep medicine model of single exposure to a titration may prove inadequate for certain patients with OSA/upper-airway resistance syndrome, particularly those with co-morbid mental health conditions. With poor adherence rates routinely described in general sleep medicine practices,<sup>18,63</sup> our findings support the need to investigate residual breathing events as well as expiratory pressure intolerance in non-adherent patients. Such research could explore the potential for advanced PAP pressure delivery modes applied in the REPAP model to ameliorate pathophysiological and iatrogenic barriers as well as to increase use and adherence rates. Studying the dose-response effects of PAP therapy may also shed light on the common problem of PAP failure,<sup>25,51</sup> and we believe that such research is crucial to the advancement of greater therapeutic precision in the treatment of OSA/upper-airway resistance syndrome, despite numerous policy changes aimed at diminishing the role of the sleep laboratory.<sup>64-66</sup>

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## REPAP PROTOCOL FOLLOWING PAP FAILURE

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