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Nasal dilator strip therapy for chronic sleep-maintenance insomnia and symptoms of sleep-disordered breathing: a randomized controlled trial

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Abstract To test the impact of nasal dilator strips (NDSs) on insomnia severity, sleep-disordered breathing (SDB) symptoms, sleep quality, and quality of life. Randomized, controlled trial of 4 weeks' duration. Community sample of nonobese, adults with a primary sleep complaint of chronic sleep-maintenance insomnia and mild to moderate SDB symptoms (treatment, n=42; control, n=38). Primary outcomes were four validated scales: Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Functional Outcomes of Sleep Questionnaire (FOSQ), and Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ). Secondary outcomes were sleep indices, nonrestorative sleep ratings, and SDB symptoms, assessed retrospectively and prospectively. Both groups received nonspecific education about sleep disorders. Treatment group also received a brief SDB education and nasal strip instructions. At 4 weeks' follow-up, the treatment group demonstrated significant (p=.0001), large improvements in ISI and PSQI (mean Cohen's d=1.18) and significant (p<.02), medium-sized improvements in FOSQ and QLESQ (mean d=0.51) compared to small, nonsignificant changes in control group (Cohen's d range=0.36–0.09). Treatment group change scores among all four primary variables were significantly correlated (mean r=0.50, p=0.01). Secondary prospective and retrospective outcomes showed medium to large improvements in treatment compared to controls for sleep indices (mean d=0.52 vs 0.28), nonrestorative sleep ratings (mean d=0.69 vs 0.11), and sleep breathing symptoms (mean d=0.47 vs 0.09). Significance was obtained for prospective sleep indices (p=0.01), retrospective, and prospective nonrestorative sleep ratings (p=0.003, <0.05), and retrospective sleep breathing symptoms (p=0.03). SDB education and NDSs demonstrated therapeutic efficacy in a select sample of insomnia patients with SDB symptoms. Replication of results requires placebo controls and objectively confirmed SDB cases.

Keywords Insomnia · Nonrestorative sleep · Sleep quality · Impairment · Sleep-disordered breathing

Introduction

More than 30 years ago, Guilleminault et al. (1973) described three cases of sleep-maintenance insomnia caused by sleep-disordered breathing [1]. More recent studies demonstrated strong associations between these two common sleep disorders [2–4], and several studies showed higher-than-expected prevalence of obstructive sleep apnea (OSA) or

upper airway resistance syndrome (UARS) among chronic insomnia patients in select populations [5–10]. One study measured flow limitation events, consistent with upper airway resistance, at three times the rate of apneas and hypopneas [5].

A sleep fragmentation mechanism was proposed through which sleep-disordered breathing (SDB) causes or aggravates insomnia, and UARS might be the predominant or earliest form of SDB among affected insomnia patients [11]. Upper airway resistance is associated with craniofacial abnormalities, including deviated septum, arched or narrow hard palates, and excessive soft palate tissue [12] as well as somatic conditions, including allergic rhinitis and nasal congestion [13, 14]. The nasal resistance observed in these conditions has been associated with insomnia [13, 15, 16].

Rappai et al. (2003) reviewed salient relationships between nasal resistance and SDB, concluding that "technologies and treatments aimed at facilitation of nasal breathing should be explored further in the context of SDB [17]." Treatment of nasal resistance in SDB among insomnia patients has been studied rarely. Guilleminault et al. (2002) conducted the only prospective, randomized controlled trial (RCT) to test a specific nasal resistance treatment (turbinectomy) on insomnia parameters [15]. Of 30 postmenopausal women receiving continuous positive airway pressure (CPAP) or radiofrequency turbinectomy, the latter group achieved more consistent improvements in fatigue, sleep quality, and objective polysomnography (PSG) sleep parameters; however, overall results were mixed, and no validated insomnia scales were measured [15]. In a case series, three chronic insomnia patients with suspected SDB reported substantial improvements in sleep quality and insomnia with nasal dilator strip (NDS) therapy [18]. In 11 other NDS studies, improvements were exhibited in respiratory, sleep, and arousal indices as well as daytime sleepiness [19–29]. However, only three studies were RCTs [25, 27, 29], and their significant findings seemed dependent on patient types, tending to show modest benefits for those with less severe Apnea/Hypopnea Index (AHI) and/or minimal obesity [25, 27, 29].

The current pilot study was an RCT, testing NDS therapy on a select sample of nonobese, sleep-maintenance insomnia patients, with mild to moderate SDB symptoms. We hypothesized that NDS therapy would produce small to moderate improvements in insomnia, sleep quality, SDB symptoms, and quality of life.

Materials and methods

Patient sample and study design

The study was approved by the institutional review boards of Sandia National Laboratories and the University of New Mexico Health Sciences Center. All participants provided informed consent after a complete description of the study. Financial compensation was not provided. Three waves of recruitment (June 2002 thru December 2003) attracted volunteers from community sources, including working individuals in an occupational health setting, elderly adults through advertisements on a classical music radio station, and the general population through advertisements on a talk-radio station, electronic bulletins, and flyers. To attract patients with sleep-maintenance insomnia and SDB symptoms, advertising included two sets of symptoms: for sleep-maintenance insomnia (middle-of-the-night awakenings and difficulty returning to sleep) and for SDB (breathing symptoms, nocturia, awakening with a dry mouth, and morning headaches).

The study was an RCT of NDSs involving two arms. Both the control and treatment groups received a nonspecific educational review of their current sleep complaints (described below), and the treatment group also received a brief SDB education and NDS instruction.

Screening and eligibility

A screening questionnaire queried demographics, insomnia type, severity, and chronicity, current and past insomnia treatments, medical and psychiatric history, and medications for sleep and mental health. All screened patients responded to five categorical questions about well-described physiological symptoms of SDB: snoring [30], gasping or choking during sleep [30], dry mouth upon awakening [30], nocturia [31], and morning headache [32]. These symptoms, along with information from the subsequent intake measures, were used to confirm sleep-maintenance insomnia and to presumptively distinguish between individuals with severe SDB symptoms (exclusion criteria) and those with mild to moderate SDB symptoms (inclusion criteria).

Of 251 screened cases, 229 reported a primary sleep complaint of chronic sleep-maintenance insomnia defined as moderate difficulties sustaining sleep at night or wake time after sleep onset of 30 min or greater as well as related impairment [33]. Of these 229 patients, 223 reported one or more screening SDB symptoms (mean=2.75 symptoms). To reduce our sample to patients with mild to moderate SDB symptoms without complicating factors, 80 patients were excluded due to obesity [body mass index (BMI)>30], signs, symptoms, or previous PSG diagnosis of severe OSA, other comorbid sleep disturbances (e.g., restless legs, leg jerks, chronic nightmares, circadian rhythm disturbances), previously diagnosed severe or unstable breathing disorders [e.g., chronic obstructive pulmonary disease (COPD)], current psychiatric disorder or psychotropic medication usage, including sedatives or other sleep aids, untreated or uncontrolled allergic rhinitis, or other severe or unstable med-

ical conditions (Fig. 1). Patients were not excluded if they had briefly used nasal strips for allergies or colds at a distant point in the past. If patients reported allergic rhinitis, they were included only if their symptoms were essentially eliminated with assorted treatments prior to completing the baseline intake and actual protocol.

Intake and prerandomization sleep log

Of 143 eligible participants, 118 completed a full individual intake, which was then reviewed to reconfirm SDB symptoms, based on American Academy of Sleep Medicine self-report research criteria (1999) [34]. PSG must be performed

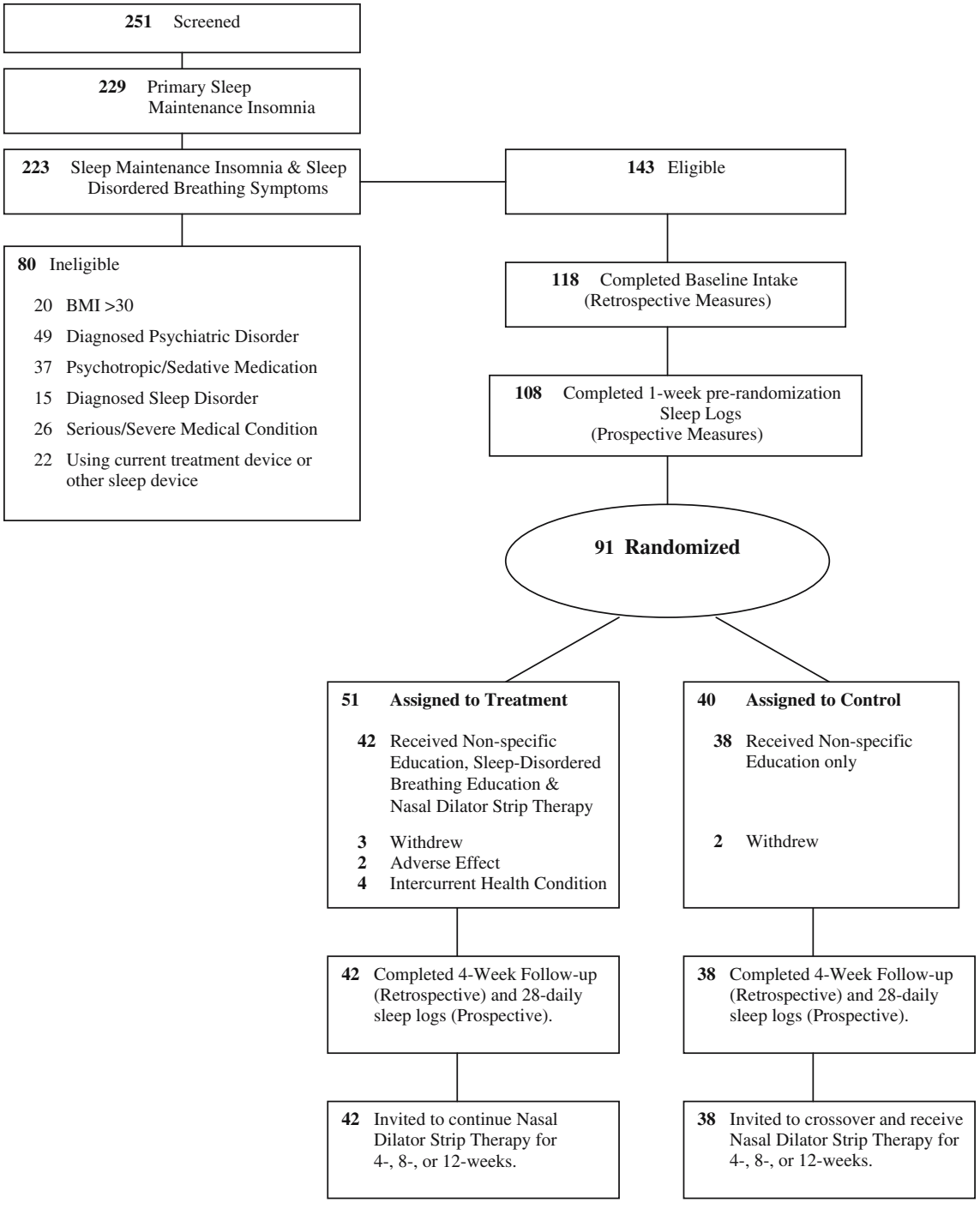

Fig. 1 Participant flow chart. For ineligible participants, 60% had more than one exclusion criteria. Adverse effects noted for two participants were skin irritation for one and nasal congestion for the other. For those that withdrew, time commitment was the reason noted

to confirm an SDB diagnosis, but for this pilot study, objective testing was not conducted due to funding restrictions. After reviewing the intakes and completing physical exams (see below), another ten patients who reported very severe or frequent breathing symptom reports such as regular episodes of witnessed apneas, appeared more obese than in their screening reports, or showed signs of uncontrolled allergies were excluded. One hundred-eight remaining participants completed sleep logs for 7 consecutive days, submitted electronically each morning. The log phase prospectively confirmed sleep-maintenance insomnia, familiarized participants with recording procedures, and clarified participants' capacity to complete the program. Another 17 patients withdrew because they deemed logs as too burdensome. Ninety-one individuals were eligible for randomization.

Randomization and blinding procedures

After completing the 1-week, prerandomization sleep log, an individual interview was conducted in which all participants, prior to randomization, received nonspecific educational reviews of their sleep logs and intake questionnaires. The responses on the logs and the intake questionnaires were reviewed with the patient, who was permitted to raise questions about sleep problems. However, no therapeutic recommendations were offered. For example, two patients said, "It seems I spend a lot of time in bed not sleeping," and the interviewer replied by rephrasing the statement without interpreting the point or recommending an action, thereby avoiding cognitive-behavioral instructions [35]. Prior to randomization, all patients—whose group status was unknown to the patient and therapist at the time—received this nonspecific, educational review.

Afterwards, a sealed envelope was opened to reveal randomization status to the control group, whose members only received the encounter just described, or to the treatment group, whose members also received individual education about SDB and NDS instructions. Data were coded and entered by a technician who was masked to group status as well as to the nature of the experimental manipulation.

Patient encounters and treatment delivery

All sessions were completed by the first, second or third author, and all were supervised by the principal investigator (PI; first author). Participants randomized to treatment received SDB education, which included a picture of the upper airway to demonstrate how SDB manifests through obstruction or resistance at various sites, provoking an increase in brain activity to correct disrupted breathing, which then stimulates arousals and awakenings, which then induces sleep fragmentation and subsequent insomnia. A single-teaching PSG epoch with an SDB-induced arousal was reviewed with the participant. No cognitive-behavioral therapy directed at psychophysiological conditioning, sleep hygiene, or other elements of insomnia was provided.

After discussing the SDB paradigm, NDS education involved proper sizing, positioning, application, and removal. Breathe Right® Nasal Strips (CNS Inc., Minneapolis, MN) are small adhesive strips containing a flexible tine, which is placed below the bridge of the nose, above or over the nasal flanges of the nostrils. When correctly placed, the tine causes expansion of the nasal valve region of the nose, presumably by stabilizing the lateral vestibular walls of the nose, which in turn increases its minimum cross-sectional area.

Measurements

Three widely used sleep scales, previously validated with PSG, were chosen as primary outcomes and were completed at intake and 4-week follow-up to test the three main sleep hypotheses: Insomnia Severity Index (ISI) [36], which assesses insomnia severity; Pittsburgh Sleep Quality Index (PSQI) [37], which assesses global sleep quality; and Functional Outcomes of Sleep Questionnaire (FOSQ) [38], which assesses sleepiness-related impairment likely due to suspected SDB. Because of the critical importance in demonstrating change in quality of life following insomnia treatment [35], the Quality of Life Enjoyment and Satisfaction Questionnaire [39] summary sheet (QLSESQ) was also used as the fourth primary outcome.

Secondary measures provided additional tests of insomnia severity, sleep quality, and SDB symptoms in three sets of related variables, respectively, composed of:

1. Five standard sleep indices [33], including sleep-onset latency (SOL), total sleep time (TST), calculated sleep efficiency (SE%), estimated awakenings at night (WAKES), and time awake after sleep onset (WASO), measured retrospectively at baseline and follow-up on a sleep medicine history form as well as monitored prospectively in a daily sleep log;
2. Five standard ratings of nonrestorative sleep [33] (including refreshing sleep, sleep quality, depth of sleep, ability to sustain sleep, and ability to return to sleep if awakened) were measured on the sleep history, and the first three items were monitored on the sleep log;
3. Seven standard outcome measures for SDB [30–34] (nocturia, morning headache, dry mouth upon awakening, impaired memory, impaired concentration, sleepiness, and tiredness) were measured on the sleep history, and the first three items were measured on the sleep log.

Retrospective and prospective items were measured with visual analog scales from 0 to 10 (e.g., sleepiness), rating

scales from 0=no difficulty to 4=severe difficulty (e.g., impaired concentration), or by actual count (e.g., episodes of nocturia). Typical SDB tools such as the Epworth Sleepiness Scale were not used because, anecdotally, we find that many insomnia patients underestimate their sleepiness when asked to link this condition to behavioral circumstances. The sleep log was the same one used during prerandomization and was completed for 28 days during the randomized controlled period and submitted daily by fax or email.

Physical examination and acoustic rhinometry

All randomized participants underwent a brief physical examination (conducted or supervised by the PI) of the face, nose, and upper airway to assess structural abnormalities suggestive of SDB [40]. Airway crowding was determined using Mallampati classification [41]. At baseline, control and treatment patients underwent acoustic rhinometry (Hood Laboratories, Pembroke, MA; Eccovision Software) in an upright, seated position [42]. Treatment patients also underwent acoustic rhinometry following instructional NDS placement to measure changes in minimum cross-sectional area of the nasal valve region.

Follow-up

Of 91 randomized participants, 11 did not complete the trial, including 4 with intercurrent illness, 5 who withdrew due to time constraints, and 2 who developed adverse effects, which may have been due to nasal strips. Eighty participants, including 42 in treatment and 38 in control groups, completed the 4-week RCT (Fig. 1).

All patients monitored results and adverse effects by completing daily logs for 28 days, and this log supplied the prospective data for the study, with the initial week of data prior to randomization serving as the baseline. Participants informed the clinician of any adverse effect such as skin irritation or increased nasal congestion from using nasal strips. Missing information on sleep logs, although rare, was retrieved by phone. The ISI and QLESQ were completed at the halfway mark in the protocol. All patients completed a follow-up appointment at the end of 4 weeks, during which the four primary outcome scales and other retrospective measurements were reassessed. After the study, all participants were provided the opportunity to continue or start NDS therapy for several weeks, and these crossover and longitudinal data will be the subject of a separate report.

Treatment receipt, adherence, and fidelity

To ensure participants understood the information provided in the SDB treatment session, a 10-question quiz was given, and incorrect answers were discussed with participants. Treatment adherence was measured through participants' completion of questions on the daily log about NDS use, indicating number of nights used and number of hours used each night, the latter equivalent to time in bed. To insure treatment fidelity, the PI completed mock treatments (control and treatment arms) with the second and third authors, and then he completed sessions for the initial four randomized patients with the second and third authors observing. Afterwards, the second author, a registered PSG technologist with 6 years of experience in working with sleep patients, completed 27 sessions, and the third author, a sleep research coordinator with 4 years of experience in working with sleep patients, completed the remaining 49 sessions. The PI supervised the clinicians and, at the conclusion of each session, reviewed lingering patient questions or concerns about NDS therapy (average time <5 min).

Data analysis

To reduce the possibility of Type I errors due to the use of more than 30 dependent variables, repeated-measure multivariate analysis of variance (MANOVA) was conducted on seven related sets of variables. All tests used a Treatment×Group design, predicting that the interaction would demonstrate significantly greater changes in the treatment group compared to the control group. The primary MANOVA tested the four validated scales (ISI, PSQI, FOSQ, and QLESQ). In the treatment group, change scores were correlated for these four primary outcomes.

The remaining secondary MANOVAs tested retrospective and prospective sleep indices, nonrestorative sleep ratings, and SDB physiological symptoms. Prospective data were collected daily and aggregated into five weekly time points. Testing of the repeated measures using the five weekly time points revealed no systematic differences compared to testing baseline and end point prospective values; therefore, the two-point analysis (baseline vs endpoint) was used for both retrospective (Sleep History) and prospective (Sleep Log) items in the MANOVAs. Repeated categorical measurements were analyzed using a Z test for difference in change proportions between groups, and treatment patients' self-assessments of NDS therapy were analyzed with one-sample t tests, which compared participant ratings to the measurement scale midpoint labeled "no change."

For continuous measures, within-subjects' effect sizes are reported separately for treatment and control groups as Cohen's d, the standardized mean difference, based on mean group change scores divided by the pooled standard deviation. The difference in treatment vs control d reflects the net treatment effect, a measure that controls for spontaneous improvements in the control group and preexisting random group differences at baseline. By convention, Cohen's d effect sizes are described as small (0.20), medium (0.50), or large (>0.80) [43]. For categorical

measurements, effect sizes were reported as the difference in proportions between baseline and end point, with the net treatment effect indicated by the difference in the change proportions between groups. An alpha of p=0.05 was used.

Results

Sample characteristics and treatment credibility

Baseline characteristics of the two groups were not significantly different for all primary and secondary variables, sociodemographics, mental health history as well as for chronicity, prior assessments, and treatments of sleep problems. Features of airway crowding were omnipresent, with 100% showing at least one site of nasal or oral airway obstruction. For possible sites of nasal obstruction, 86% had at least one, and 32% exhibited at least two or more (Table 1). Acoustic rhinometry at baseline was equivalent for both groups. For the treatment group, the mean change in minimum cross-sectional area of the nasal valve region, pre- and post-NDS, was 0.52 cm^2 ($F_{1,41}$=91.29, p<0.0001; d=1.39). Actual NDS use was consistent with a mean of 27.05 days of the 28-day period and a nightly average of 7.53 h, indicative of time in bed and not hours of sleep. Only five patients missed more than 2 days of use (range 3–9 days).

Primary outcome analyses

All four primary variables intercorrelated (mean r=0.41) at baseline among all participants. For the four validated scales, the Treatment×Group interaction was highly significant ($F_{4,75}$=5.197, p<0.001), with large sized improvement in insomnia severity (ISI) and sleep quality (PSQI) in the treatment group compared to small- to moderate-sized changes in the control group (Fig. 2a and b). Sleepiness impairment scores (FOSQ) and quality of life (QLESQ) summary scores demonstrated medium-sized improvements in the treatment group but only very small-sized changes in the control group (Fig. 2c and d). Among 42 participants in treatment, change scores were highly correlated for all four primary variables (Table 2).

Secondary outcome analyses

Testing insomnia severity on sleep indices (SOL, TST, SE %, WAKES, and WASO) with retrospective data showed

Table 1 Sociodemographic and clinical characteristics[a]

Characteristics	Treated (N=42)	Control (N=38)	p
	Mean (SD)		
Age (years)	53.1 (12.3)	54.2 (13.5)	0.70
	n (%)		
Men	22 (52)	23 (61)	0.24
White, non-Hispanic	33 (81)	33 (87)	0.76
	Mean (SD)		
Body mass index (kg/m^2)	25.1 (3.0)	25.5 (2.7)	0.51
Insomnia duration (years)	11.2 (8.9)	12.7 (9.6)	0.46
Possible sites of nasal airway obstruction	n (%)		
Palpably unequal airflow between nostrils	6 (14)	6 (16)	0.81
Collapse of nares on inspiration	8 (21)	12 (32)	0.27
Deviated anterior septum	17 (47)	13 (39)	0.51
Hard palate elevated, arched, or narrow	32 (40)	27 (34)	0.60
Possible sites of oral airway obstruction	n (%)		
Tongue large compared to lower dental arch	24 (57)	21 (55)	0.87
Excessive soft palate tissue or elongated uvula	30 (71)	26 (68)	0.77
Mallampati III classification (severe crowding)	27 (64)	29 (76)	0.24
Chin small or retrognathic	25 (60)	26 (70)	0.32
	Mean (SD)		
Nasal valve minimum cross-sectional area (cm^2)	1.17 (0.34)	1.16 (0.32)	0.83
	n (%)		
Chronic allergic rhinitis[b]	30 (71)	20 (53)	0.08
Reported classic sleep disordered breathing symptoms[c]	22 (52)	23 (60)	0.46

[a]Characteristics listed in this table were analyzed as moderating variables of treatment, none of which showed any systematic effect

[b]All allergies had to be well controlled for the participant to be randomized

[c]These patients reported infrequent to occasional snoring, gasping, choking, or struggling for breathing, and/or apnea

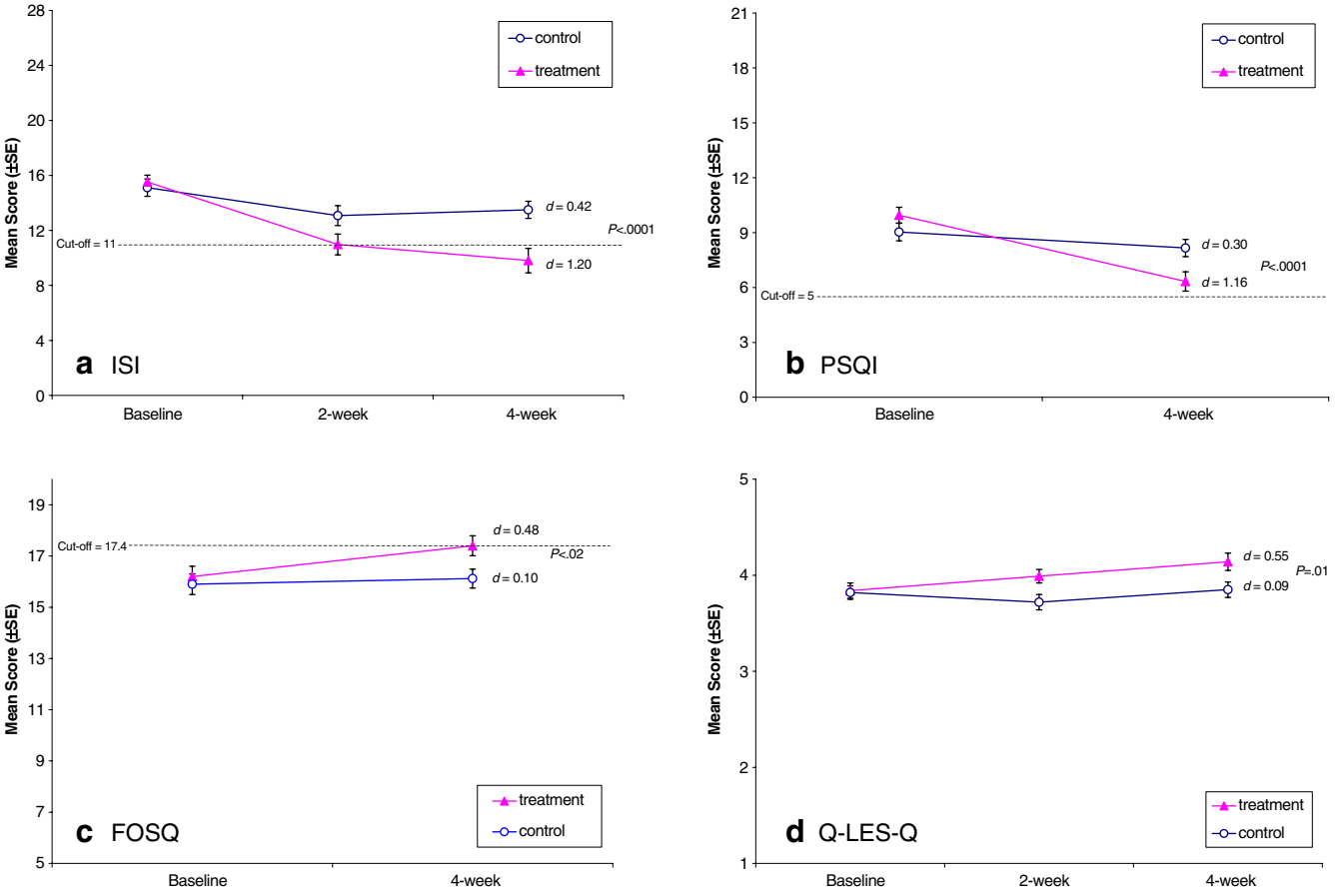

Fig. 2 **a**–**d** Four primary outcomes for treated (*N*=42) and control (*N*=38) participants at baseline and end point. The *dashed line* represents the clinical cutoff. The Insomnia Severity Index (ISI) quantifies perceived insomnia severity using seven items on 5-point scales (0–4) with a total range of 0–28. Scores greater than or equal to 11 reflect clinically meaningful insomnia. The Pittsburgh Sleep Quality Index (PSQI) assesses global sleep quality and disturbances on 18 items on 4-point scales (0–3), with a total score range from 0 to 21. Scores greater than or equal to *5* represent poor sleep quality. Functional Outcomes of Sleep Questionnaire (FOSQ) assesses the impact of daytime fatigue and sleepiness on daily functioning on 30 items on 5-point scales, with a global score range of 5–20. Scores less than 17.4 reflect clinically meaningful daytime impairment. The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) summary sheet assesses the degree of enjoyment and overall satisfaction levels in various areas of daily functioning using 16 questions scored on a 5-point scale (1–5) to provide an average item score. A Q-LES-Q score of 3 equals "fair," and a score of 4 equals "good." An inverse scoring model exists for the FOSQ and the Q-LES-Q; the lower the score, the greater the impairment. All participants completed a 2-week ISI and Q-LES-Q; therefore, 2-week time points are displayed in the *graphs* for these instruments. Cohen's *d* represents the actual standardized unit change from baseline to 4-week, that is, the effect size. *P* values represent the Treatment×Group interaction from a repeated-measures ANOVA

no differences ($F_{5,74}$=0.936, p=0.46), but prospective data revealed a significant Treatment×Group interaction ($F_{5,74}$=3.122, p=0.01). The treatment group showed consistently larger effect sizes for both retrospective and prospective (mean d=0.52) sleep indices compared to small effect sizes in the control group (mean d=0.27) (Table 3).

Testing for sleep quality with retrospective nonrestorative sleep ratings (refreshing sleep, sleep quality, depth of sleep, ability to sustain sleep, and ability to return to sleep) was significant ($F_{5,74}$=3.999, p=0.003), as were prospective ratings (refreshing sleep, sleep quality, and depth of sleep) ($F_{3,76}$=3.012, p<0.05). The treatment group showed consistently larger changes retrospectively and prospec-

Table 2 Pearson correlation coefficients (*r*) between all change scores for Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Functional Outcomes of Sleep Questionnaire (FOSQ), and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) for the treatment group (*N*=42)

	PSQI	FOSQ	Q-LES-Q
ISI	0.79**	−0.37*	−0.41**
PSQI		−0.43**	−0.55**
FOSQ			0.43**

For PSQI and ISI, higher scores represent greater severity, but for FOSQ and QLESQ, lower scores represent greater impairment. Thus, the pattern of intercorrelations among these four scales indicates consistent covariance of severity and impairment
*p<0.05; **p<0.01

Table 3 Mean (SD) for sleep indices from retrospective sleep history and prospective sleep log[a]

Indices	Baseline	Endpoint	Cohen's d[b]	Treatment main effect[c]		Treatment×Group interaction[d]	
				F_{df}	P	F (1,79)	P
Sleep onset latency (min)							
Sleep history							
Treated	18.74 (16.57)	13.31 (10.03)	0.40	$10.15_{1,41}$	.003	0.04	.84
Control	20.33 (22.65)	15.45 (13.64)	0.26	$5.66_{1,37}$	.02		
Sleep log							
Treated	19.17 (13.90)	15.55 (10.15)	0.30	$4.96_{1,41}$	.03	2.23	.13
Control	19.33 (14.51)	19.41 (17.82)	−0.01	$.01_{1,37}$	.97		
Total sleep time (h)							
Sleep history							
Treated	5.89 (1.12)	6.29 (1.12)	−0.36	$6.42_{1,41}$	.02	0.48	.49
Control	5.92 (.93)	6.18 (.92)	−0.28	$4.52_{1,37}$	.04		
Sleep log							
Treated	5.98 (.89)	6.49 (.99)	−0.54	$26.61_{1,41}$	.0001	5.67	.02
Control	6.31 (.86)	6.48 (.85)	−0.20	$3.23_{1,37}$	.08		
Sleep efficiency (%)							
Sleep history							
Treated	78 (14)	88 (25)	−0.49	$5.11_{1,41}$	.03	1.40	.24
Control	77 (12)	81 (12)	−0.33	$4.70_{1,37}$	.04		
Sleep log							
Treated	80 (10)	86 (11)	−0.57	$28.31_{1,41}$	.0001	1.54	.22
Control	80 (10)	84 (11)	−0.38	$8.92_{1,37}$	.005		
Wake after sleep onset, min.							
Sleep history							
Treated	72.60 (47.65)	48.12 (62.16)	0.44	$6.14_{1,41}$	.02	1.01	.32
Control	69.75 (39.41)	58.21 (45.62)	0.27	$2.09_{1,37}$	.16		
Sleep log							
Treated	66.20 (39.15)	42.90 (42.44)	0.57	$21.57_{1,41}$	.0001	0.04	.83
Control	71.97 (42.99)	50.07 (32.10)	0.58	$24.39_{1,37}$	.0001		
Number of awakenings, no.							
Sleep history							
Treated	2.74 (1.03)	1.88 (1.03)	0.83	$24.98_{1,41}$	.0001	3.96	.05
Control	3.58 (1.86)	3.25 (1.39)	0.20	$2.57_{1,37}$	.12		
Sleep log							
Treated	2.70 (1.15)	1.91 (1.10)	0.70	$24.04_{1,41}$	.0001	2.32	.13
Control	3.10 (1.64)	2.74 (1.27)	0.25	$6.01_{1,37}$	.02		

[a]Sleep history was completed retrospectively at baseline and endpoint, whereas sleep logs were completed prospectively on a daily basis. Daily sleep log data were collapsed into five weekly points, but only baseline week and endpoint week data are reported
[b]Cohen's d is the standardized mean difference
[c]Repeated-measures ANOVA on the groups separately, which are the simple main effects for treatment
[d]Repeated-measures ANOVA for Treatment×Group interaction

tively (mean d=0.69) compared to very small improvements in the control group (mean d=0.11) (Table 4).

Testing SDB symptom reports on retrospective data (dry mouth upon awakening, morning headache, nocturia, impaired memory, impaired concentration, daytime sleepiness, and daytime tiredness) were significant ($F_{7,72}$=2.366, p=0.03), but prospective data (dry mouth upon awakening, morning headache, and nocturia) were not significant ($F_{3,76}$=1.695, p=0.18). The treatment group demonstrated consistently larger improvements retrospectively and prospectively (mean d=0.47) compared to negligible changes in the control group (mean d=0.09) (Table 5).

Table 4 Mean (SD) for restorative sleep measures from retrospective sleep history and prospective sleep log[a]

Measures	Baseline	End point	Effect size[d]	Treatment main effect[b]		Treatment×Group interaction[c]	
				Statistic	*p*	Statistic	*p*
Refreshing sleep	Mean (SD)						
Sleep history							
Treated	1.04 (0.66)	1.71 (0.84)	0.89	$19.46_{1,41}$	0.0001	$14.02_{1,79}$	0.0001
Control	1.21 (0.58)	1.21 (0.47)	0.00	$0.00_{1,37}$	1.00		
Sleep log							
Treated	2.29 (0.67)	2.93 (0.84)	0.84	$20.69_{1,41}$	0.0001	$17.61_{1,79}$	0.003
Control	2.50 (0.60)	2.60 (0.61)	0.17	$1.01_{1,37}$	0.32		
Sleep quality							
Sleep history							
Treated	5.48 (0.97)	4.19 (1.58)	0.98	$23.61_{1,41}$	0.0001	$10.60_{1,79}$	0.002
Control	5.26 (0.95)	5.03 (1.00)	0.24	$1.93_{1,37}$	0.17		
Sleep log							
Treated	3.70 (0.85)	3.00 (1.13)	0.70	$13.52_{1,41}$	0.001	$6.30_{1,79}$	0.01
Control	3.55 (0.72)	3.46 (0.81)	0.12	$0.52_{1,37}$	0.48		
Sleep depth							
Sleep history							
Treated	1.10 (0.69)	1.69 (0.72)	0.84	$25.29_{1,41}$	0.0001	$10.67_{1,79}$	0.002
Control	1.18 (0.65)	1.26 (0.45)	0.14	$0.60_{1,37}$	0.45		
Sleep log							
Treated	2.44 (0.81)	2.81 (0.79)	0.46	$7.33_{1,41}$	0.01	$2.60_{1,79}$	0.11
Control	2.52 (0.63)	2.61 (0.72)	0.13	$1.04_{1,37}$	0.32		
Wake up a lot[e]	Percentage (*n*)						
Sleep history							
Treated	86 (36)	45 (19)	0.41	4.18	0.0001	16.80	0.0001
Control	95 (36)	90 (34)	0.05	0.91	0.36		
Trouble returning to sleep[e]	Percentage (*n*)						
Sleep history							
Treated	83 (35)	43 (18)	0.40	3.67	0.0002	10.04	0.0001
Control	82 (31)	82 (31)	0	0	0		

[a]Sleep history was completed retrospectively at baseline and end point, whereas sleep logs were completed prospectively on a daily basis. Daily sleep log data were collapsed into five weekly points, but only baseline and end point data are reported
[b]For variables described with mean (SD), the F_{df} statistic is a repeated-measures ANOVA. For categorical variables, the statistic is a *z* test for the difference of proportions
[c]For variables described with mean (SD), the F_{df} statistic is a repeated-measures ANOVA for Treatment×Group interaction. For categorical variables, the statistic is a *z* test for the difference of proportions for Treatment×Group
[d]For variables described with mean (SD), effect size is Cohen's *d*, which is the standardized mean difference. For categorical variables, the effect size is the difference of proportions
[e]Repeated categorical variables

Moderating variables

Moderating variables, including baseline characteristics and Table 1 items, were tested for interactions with treatment- and group-independent variables, but no systematic differences were observed. For example, when comparing 45 participants who reported infrequent to occasional classic breathing symptoms (loud snoring, gasping or choking for breath, and rare witnessed apnea) to 35 participants who did not report breathing symptoms, no systematic differences were observed. No effects were observed for the two groups based on past history of allergic rhinitis. In addition, surprisingly, no effects were dependent upon potential sites of nasal or oral airway obstruction. Last, no significant differences in outcomes were demonstrated, based on the three clinicians conducting sessions or on the three sources of recruitment.

Table 5 Mean (SD) for sleep disordered breathing symptoms from retrospective sleep history and prospective sleep log[a]

Indices	Baseline	End point	Cohen's d[d]	Treatment main Effect[b]		Treatment×Group interaction[c]	
				F_{df}	p	$F(1,79)$	p
	Mean (SD)						
Nocturia, number of times							
Sleep history							
Treated	1.30 (0.86)	0.83 (0.72)	0.59	$17.11_{1,41}$	0.0001	2.65	0.11
Control	1.87 (1.17)	1.65 (0.88)	0.21	$5.67_{1,37}$	0.02		
Sleep log							
Treated	1.09 (0.81)	0.79 (0.60)	0.43	$8.56_{1,41}$	0.006	2.41	0.13
Control	1.33 (0.98)	1.25 (0.87)	0.09	$6.01_{1,37}$	0.02		
Morning headache							
Sleep history							
Treated	0.98 (0.95)	0.52 (0.63)	0.57	$11.59_{1,41}$	0.001	2.07	0.15
Control	0.87 (0.78)	0.68 (0.66)	0.26	$2.01_{1,37}$	0.164		
Sleep log							
Treated	0.43 (0.47)	0.32 (0.41)	0.25	$1.71_{1,41}$	0.198	2.69	0.11
Control	0.42 (0.44)	0.48 (0.51)	−0.13	$1.09_{1,37}$	0.30		
Awakening with dry mouth							
Sleep history							
Treated	1.38 (0.96)	0.69 (0.72)	0.81	$26.50_{1,41}$	0.0001	4.84	0.03
Control	1.58 (1.03)	1.26 (0.86)	0.38	$9.87_{1,37}$	0.003		
Sleep log							
Treated	0.78 (0.63)	0.53 (0.65)	0.39	$5.99_{1,41}$	0.02	1.68	0.20
Control	1.14 (0.77)	1.07 (0.84)	0.09	$0.58_{1,37}$	0.45		
Difficulty with Concentration							
Sleep history							
Treated	1.31 (0.92)	1.07 (0.87)	0.27	$4.13_{1,41}$	0.05	2.97	0.09
Control	1.13 (0.70)	1.16 (0.64)	−0.04	$0.08_{1,37}$	0.79		
Difficulty with memory							
Sleep history							
Treated	1.45 (0.92)	1.07 (0.92)	0.41	$9.65_{1,41}$	0.003	9.81	0.002
Control	1.18 (0.83)	1.29 (0.77)	−0.14	$1.35_{1,37}$	0.25		
Sleepiness							
Sleep history							
Treated	5.40 (1.74)	3.95 (2.11)	0.75	$17.95_{1,41}$	0.0001	8.21	0.005
Control	5.63 (1.95)	5.34 (1.92)	0.15	$2.19_{1,37}$	0.15		
Tiredness							
Sleep history							
Treated	5.69 (1.94)	4.36 (2.27)	0.63	$13.96_{1,41}$	0.001	7.18	0.009
Control	5.37 (1.90)	5.26 (2.04)	0.06	$0.15_{1,37}$	0.71		

[a]Sleep history was completed retrospectively at baseline and end point, whereas sleep logs were completed prospectively on a daily basis. Daily sleep log data were collapsed into five weekly points, but only baseline week and end point week data are reported
[b]Repeated-measures ANOVA
[c]Repeated-measures ANOVA for Treatment×Group interaction
[d]Cohen's d is the standardized mean difference

Self-assessment and side effects

On average, 42 treatment patients indicated they perceived a moderate, systematic effect of nasal strips in improving breathing and sleep quality as well as decreasing insomnia symptoms (Fig. 3), and no other intercurrent factors were reported by the patients as affecting their results. Two patients withdrew because of perceived side effects from the nasal strips, described as itchiness around the nose and increased nasal congestion.

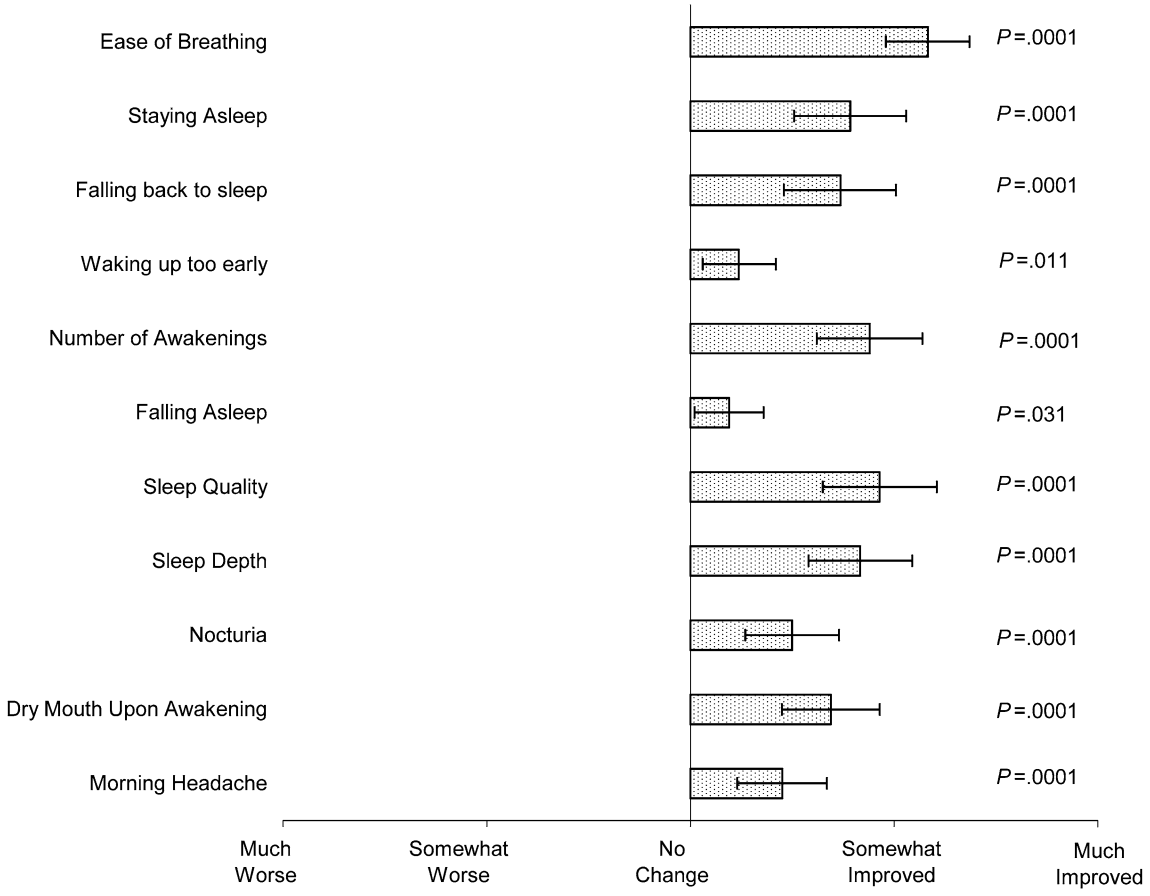

Fig. 3 Treated participants' (N=42) self-assessment of nasal dilator strip therapy. At 4 weeks follow-up, NDS-treated participants assessed the overall impact of NDS therapy on their ease of breathing, insomnia, sleep quality, and SDB symptoms. Ease of breathing refers to the sensation of increased airflow through the nasal passages while awake. Using one-sample t tests, all improvements were statistically significant. *Error bars* represent the 95% confidence interval of the difference

Discussion

In a pilot investigation of NDS therapy, this over-the-counter, nasal breathing aide proved unexpectedly efficacious in the treatment of a select sample of insomnia patients with SDB symptoms. Consistent improvements were demonstrated on validated scales for insomnia severity, sleep quality, sleepiness-related impairment, and quality of life, albeit retrospectively assessed and prospectively monitored sleep variables were less consistent in attaining reliable differences between groups. Although effect sizes were consistently larger for primary and secondary variables in the NDS group compared to controls, these results require cautious interpretation and replication with PSG testing of participants.

For this select sample of patients with insomnia and SDB symptoms, the findings support the theory that SDB-induced awakenings and sleep fragmentation contribute to sleep-maintenance insomnia [1, 7, 11, 44]. This pathophysiological mechanism might occur in the following way: If nasal strips decreased nasal resistance, which improved sleep breathing, then sleep fragmentation and related arousals would decrease, resulting in greater consolidation of sleep and improved sleep quality. This consolidation would decrease insomnia at night and decrease fatigue and sleepiness during the daytime, which, in turn, would be expected to improve quality of life. Consistent with this mechanism, change scores in the treatment group for the four primary outcomes (insomnia severity, sleep quality, sleepiness impairment, and quality of life) were moderately to strongly correlated. However, because of the complex nature of these hypothesized relationships, this proposed mechanism remains speculative and must be tested with PSG and evidence-based SDB treatments.

Limitations include the lack of a placebo device compared to NDS, the delivery of an unblinded therapy, and the absence of PSG corroboration of SDB diagnoses and NDS effects. In our view, nasal strip placebos are inadequate. Innovative protocols might include a three-way comparison among NDS, sedatives, and a placebo pill, or nasal strips could be tested in two groups of insomniacs, one with and one without SDB. A blinded SDB therapy requires the

use of other devices such as CPAP-placebo [45], which should be attempted to measure CPAP efficacy in the treatment of insomnia in those with comorbid SDB. However, because the relationship between SDB and insomnia is not intuitive, protocols must incorporate SDB education to attain reasonable perceptions of treatment credibility, which, in turn, could create bias and demand characteristics as might have occurred in our protocol. Without PSG corroboration of SDB diagnoses and NDS effects on breathing, the interpretation of these unexpected findings must be properly tempered. Moreover, the absence of testing in this protocol should not be construed as an indication that PSG is not required for diagnosing SDB. In fact, all patients in the study were strongly encouraged to follow-up at local sleep centers to undergo PSG and seek evidence-based therapies for SDB. To date, among 17 patients tested, all SDB diagnoses were confirmed. Last, the results do not establish NDS as a proven SDB therapy.

Caution is also advised because other factors may have influenced outcomes. For example, our treatment patients did not monitor turning from the supine to the lateral sleeping position, which is known to affect SDB events [27]. In addition, our sample was predominantly non-Hispanic white, whereas the nasal contour of individuals of another ethnicity may limit NDS therapy [46, 47]. Overall, our sample represents a select group of patients; therefore, this study lacks generalizability to a substantial number of insomnia patients who may or may not suffer from SDB.

Conclusion

The current work highlights pertinent clinical relationships between insomnia and SDB. First, certain insomnia patients may be suffering from resistance in the upper airway. Second, treatment of this sleep-related respiratory disorder in relevant insomnia cases likely requires a much wider range of therapeutic options such as CPAP [48], oral appliances [49, 50], and site-specific surgery [40]. Finally, treatment of nasal resistance may prove highly informative in the investigation of sleep breathing among chronic insomnia patients.

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