CHEST

Factors Contributing to Unintentional Leak During CPAP Treatment

A Systematic Review

Marius Lebret, PT, MSc; Jean-Benoit Martinot, MD, PhD; Nathalie Arnol, MSc; Daniel Zerillo, PT, MSc; Renaud Tamisier, MD, PhD; Jean-Louis Pepin, MD, PhD; and Jean-Christian Borel, PT, PhD

CPAP is the first-line treatment for moderate to severe OSA syndrome. Up to 25% of patients with OSA syndrome discontinue CPAP treatment due to side effects. Unintentional leakage and its associated annoying consequences are the most frequently reported adverse effects of CPAP. Successive technological improvements have not succeeded in addressing this issue. A systematic review was conducted (1) to assess the impact of different technological advances on unintentional leaks and (2) to determine if any patient characteristics have already been identified as determinants of unintentional leakage. No CPAP modality was superior to another in reducing unintentional leaks and, surprisingly, oronasal masks were associated with higher unintentional leaks. Nasal obstruction, older age, higher BMI, central fat distribution, and male sex might be associated with an increased risk of unintentional leakage. Such leaks remain an important problem. Further studies are needed to improve the understanding of underlying clinical factors so that patients at risk of unintentional leaks may be identified and individualized solutions applied. CHEST 2017; 151(3):707-719

KEY WORDS: compliance; CPAP; mask; sleep apnea; unintentional leakage

CPAP is the first-line treatment for moderate to severe OSA syndrome.[1] Several randomized controlled and observational cohort studies have demonstrated beneficial effects regarding cardiovascular,[2-4] quality of life, and daytime vigilance outcomes.[5] Adherence to CPAP is crucial to improve symptoms[6] and cardiometabolic consequences[3,4]; however, up to 25% of patients with OSA syndrome discontinue CPAP treatment.[7,8] Unintentional leakage through the mouth or around the mask contributes to the occurrence of annoying side effects such as oral dryness or nasal congestion.[9,10] Unintentional leakage is associated with a higher risk of low adherence to CPAP[11,12] and induces sleep fragmentation.[13] To reduce such leakage, the mask must be correctly fitted or, in the case of mouth leaks, a chin strap may be added or an oronasal mask used.[14] Technological innovations have also focused on reducing

ABBREVIATIONS: HH = heated humidification; PAP = positive airway pressure; RCT = randomized controlled trial

AFFILIATIONS: From the Department of Research and Development (Dr Borel, Messrs Lebret and Zerillo; and Ms Arnol), Association AGIR à dom, HP2 Laboratory, INSERM U 1042, Meylan, France; CHU UCL (Dr Martinot), Site Sainte Elisabeth, Namur, Belgium; Thorax and Vessels Division (Drs Tamisier Pepin, and Borel), Sleep Laboratory, Grenoble Alpes University, HP2 Laboratory, INSERM U 1042, Grenoble, France.

FUNDING/SUPPORT: The study was funded by AGIRadom, a French nonprofit home care provider.

Drs Pepin and Borel are co-senior authors.

CORRESPONDENCE TO: Marius Lebret, PT, MSc, Agir à dom, 36 Chemin du Vieux Chêne, 38244 Meylan, France; e-mail: mariuslebret@gmail.com

DOI: http://dx.doi.org/10.1016/j.chest.2016.11.049

leakage by improving the interfaces (eg, shape, sealing, ergonomic straps, comfort) and CPAP algorithms and providing accessories (heated humidifiers, chin straps, heated tubes, gel plaster). However, despite all these efforts, unintentional leaks remain the most frequently reported adverse effect of CPAP treatment[9,15-19] and constitute a daily challenge for both physicians and home-care providers. For instance, in the Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) trial,[20] although it relates to a different clinical context, it was suggested that the primary use of oronasal masks (probably provided to reduce unintentional leakage) may have contributed to low adherence to treatment.[21] Thus, to date, technological improvements have not succeeded in overcoming this adverse effect, and a better understanding of the underlying determinants of unintentional leakage is needed.

The objectives of this systematic review were (1) to assess the impact of different technological features on unintentional leakage and (2) to determine if any patient characteristics have already been identified as determinants of unintentional leaks.

Systematic Review and Literature Selection

We searched MEDLINE and the Cochrane Library for publications in English or French from 1990 to March 2016. The following search algorithm was used: ("Sleep Apnea" OR "sleep apnoea/apnea") AND ("Continuous Positive Airway Pressure" OR "Positive airway pressure" or "cpap") AND ("leak" OR "air leak" OR "leakage"). We selected all the randomized controlled trials (RCTs) that reported unintentional leaks in patients with OSA syndrome using CPAP. We also reviewed all the RCTs cited in all the meta-analyses found on the subject of CPAP interfaces and CPAP modes,[5,19,22-26] Only full-length original articles were selected. When no RCTs were available, cohort studies reporting unintentional leaks were included.

A total of 113 studies were identified from the literature search. After reviewing the full texts, 21 RCTs were included based on the selection criteria (Fig 1). Finally, other studies were selected based on our expertise, and their relevance was validated by two authors (M. L. and J. C. B.). Other articles were also included to provide background information and context but were not included in the analysis.

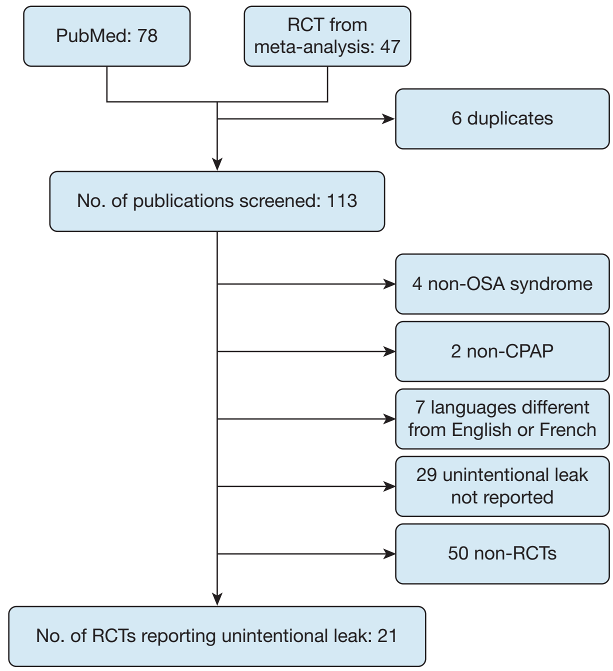

Figure 1 – *Randomized controlled trials selection. RCT = randomized controlled trial.*

Technological Features and Unintentional Leakage

Impact of Mask Type on Unintentional Leakage

Several types of masks are currently available: (1) nasal masks, (2) oronasal masks (full face), and (3) nasal pillows and (4) oral masks. Nasal masks are the most commonly used interface,[27,28] and oronasal masks are used by about 10% to 25% of patients who cannot tolerate an exclusively nasal route for positive airway pressure (PAP) delivery or who are unable to maintain sufficient mouth closure during sleep. Nasal pillows are used by about 10% of patients and offer the advantage of greatly reducing both the size and cutaneous contact area of the mask.[9,29] The least commonly used is the oral mask, which delivers PAP exclusively through the mouth.

Nasal vs oronasal masks: Five RCTs assessed unintentional leaks and compared nasal and oronasal masks (Table 1). All but one found that oronasal masks were associated with higher unintentional leakage than were nasal masks.[18,30-32] The other study found higher unintentional leaks with oronasal masks than with nasal pillows but found no significant difference between nasal and oronasal masks.[33] Although the time frames, settings, and objectives of these five studies differed, the high-quality methodology (ie, randomized designs)

TABLE 1] Studies Reporting the Impact of the Type of Masks on Unintentional Leakage

Study/Year	Primary Objective	Population	Sample Size[a]	Study Design and Intervention	Key Findings	Unintentional Leaks Related to the Type of Mask	Difference Reported in Unintentional Leakage Between Masks
Mortimore et al[30]/ 1998	To assess compliance and side effects related to the mask type	Mean age: 52 ± 3 y Mean BMI: 32 ± 1 kg/m^2 Male sex: ND Mean AHI: 34 ± 5.2/h CPAP-naive OSA syndrome	20/20	RCT NM vs ONM Time frame: 1 mo	Higher compliance with an NM (5.3 ± 0.4 vs 4.3 ± 0.5 h/night; $P = .01$) Lower Epworth score with NM (8.2 ± 0.9 vs 9.8 ± 0.9; $P < .01$)	ONM was associated with higher unintentional leakage; $P = .003$	6/10 (ONM) vs 1/10 (NM) (10-cm visual analog scale)
Teo et al[32]/ 2011	To assess if the use of ONM requires a higher pressure treatment to maintain upper airway patency compared with an NM	Mean age: 51.3 ± 13.3 y Mean BMI: 33.8 ± 9.4 kg/m^2 Male sex: 75% Mean AHI: 35.9 ± 15.8/h CPAP-naive OSA syndrome	24/24	RCT crossover NM + chin strap vs ONM Time frame: 2 consecutive nights	No difference in pressure treatment between the 2 masks	ONM was associated with higher unintentional leakage; $P > .0001$	22.1 ± 9.9 (ONM) vs 11.2 ± 8.8 (NM) (95th percentile leak in L/min)
Ebben et al[33]/ 2012	To compare the efficacy of ONM, NM, and NP during a CPAP titration study	Mean age: from 51.8 ± 13.5 y to 58.5 ± 14.7 y Mean BMI: from 31.1 ± 6.6 to 35.6 ± 7.9 kg/m^2 Male sex: 66% Mean AHI: 39.8 ± 21.4/h (group NM); 37.9 ± 24.5/h (group NP); oronasal 30.3 ± 20.3/h (group ONM) CPAP-naive OSA	55/55	RCT NM vs ONM vs NP Time frame: 1 night	No significant difference in residual AHI between masks Significant difference in final pressure delivered with an ONM ($P < .001$)	ONM was associated with higher unintentional leakage compared with NP; $P < .000$ No significant difference between ONM and NM	ND "Patients titrated with oronasal masks had a significantly higher mask leakage compared to nasal pillows […] but not to standard nasal masks"

(Continued)

TABLE 1] *(Continued)*

Study/Year	Primary Objective	Population	Sample Size[a]	Study Design and Intervention	Key Findings	Unintentional Leaks Related to the Type of Mask	Difference Reported in Unintentional Leakage Between Masks
Bakker et al[31]/ 2012	To assess the pressure requirement, the residual AHI, or unintentional leaks between NM, ONM, and under-chin ONM	Mean age: 48.8 ± 11.2 y Mean BMI: 37.7 ± 59 kg/m^2 Male sex: 91.7% Mean AHI: 59.8 ± 28.6/h CPAP-naive OSA syndrome	13/12	RCT crossover NM vs ONM vs under-chin ONM (CPAP vs automatic CPAP) Time frame: 2 × 7 nights (3 nights NM; 2 nights ONM; 2 nights under-chin ONM)	No significant difference in pressure delivered between masks Significant difference in residual AHI in favor of nasal mask ($P < .002$)	ONM was associated with higher unintentional leakage; $P < .01$ No difference between the 2 ONMs	automatic CPAP mode: 9.4 ± 10.9 (NM) vs 35.2 ± 32 (under-chin ONM) vs 34.1 ± 31.1 (ONM) CPAP mode: 15 ± 10.8 (NM) vs 54.4 ± 37 (under-chin ONM) vs 36.9 ± 33.8 (ONM) (95th percentile leakage in L/min)
Ebben et al[18]/ 2014	To investigate if switching from an ONM to an NM or vice versa after titration will result in a change in residual respiratory events	Mean age: 62 ± 2 y Mean BMI: 30 ± 7 kg/m^2 Male sex: 78.6% (Mean AHI: 36.4 ± 14.5/h) CPAP-naive OSA syndrome	21/14	RCT crossover ONM vs NM Time frame: 2 × 3 wk	Significant difference in residual AHI in favor of nasal mask ($P < .001$)	ONM was associated with higher unintentional leaks; $P < .05$	17.2 ± 12.5 (ONM) vs 8.6 ± 6.2 (NM) (leakage in L/min)

AHI = apnea-hypopnea index; ND = not described; NM = nasal mask; NP = nasal pillow; ONM = oronasal mask; RCT = randomized controlled trial.
[a]No. at enrollment/final No.

permits us to say with confidence that the performance of oronasal masks regarding control of unintentional leakage is poorer than that of nasal masks.

Comparison between other types of interfaces: Four studies assessed the performance of oral masks compared with conventional nasal or oronasal masks.[34-37] Two of the four studies compared unintentional leakage between oral and nasal masks.[35,36] Khanna and Kline[35] found less unintentional leakage with the use of oral masks than with nasal masks, whereas Anderson et al[36] did not find any difference between interfaces. The results of these two studies should be interpreted with caution, since unintentional leakage was not objectively measured by the CPAP devices but was self-estimated by the patients using adverse-effects questionnaires.

Three RCTs evaluated unintentional leaks from nasal pillows.[33,38,39] Zhu et al[38] and Ryan et al[39] found no difference in patients self-reported unintentional leakage using nasal pillows compared with nasal masks. The study by Ebben et al[33] did not report the comparison of nasal pillows and nasal masks; however, they found less unintentional leakage with nasal pillows than with oronasal masks. Thus, it appears that the level of unintentional leakage from nasal pillows is similar to that from nasal masks but lower than leakage from oronasal masks. Furthermore, the level of pressure was similar between nasal pillows and nasal masks[38] but was higher with oronasal masks.[33]

Many technological innovations, including customized cushions, have been designed to adapt the mask as much as possible to the patient's face. From a theoretical point of view, this might be a good strategy to limit unintentional leakage; however, the only study that investigated customized cushions found no difference in the occurrence of unintentional leakage.[40]

Overall, oronasal masks are associated with a higher level of unintentional leakage when compared with purely nasal masks or pillows. In contrast, oral masks and nasal pillows do not appear to be associated with higher unintentional leakage than that seen with nasal masks.

Impact of CPAP Modality on Unintentional Leaks

Alternative CPAP modalities have been developed to overcome pressure intolerance. The aim of automatic CPAP is to automatically adjust the applied PAP in response to persistent obstructive respiratory events (flow limitation or hypopnea/apnea), with the goal of maintaining upper airway patency whatever the body position or stage of sleep.[41] This CPAP modality is commonly used during pressure titration[22] as well as for long-term CPAP treatment.[42] As mean CPAP pressure during the night is reduced, automatic CPAP might potentially modulate unintentional leakage compared with standard fixed CPAP treatment.

More recently, CPAP modes with flexible pressure delivery have been commercialized by different manufacturers (C-Flex and A-Flex, Philips-Respironics; Expiratory Pressure Relief, ResMed; eAdapt, Breas Medical). These advanced CPAP options reduce the pressure delivered at the beginning of exhalation and then restore the therapeutic pressure level for the latter part of exhalation and subsequent inhalation.[19,43,44]

Comparison of automatic CPAP vs fixed CPAP: Twenty-four RCTs compared fixed CPAP with automatic CPAP. Table 2 shows the six RCTs that objectively reported the amount of leakage from both automatic CPAP and fixed CPAP devices. Although there was a trend toward less unintentional leakage with automatic CPAP, four of six studies did not show any significant effect of automatic CPAP in reducing unintentional leakage compared with fixed CPAP,[42,45-47] despite a lower median pressure in the automatic CPAP mode. Only one study reported a significantly lower risk of unintentional leaks with automatic CPAP.[48] Bakker et al[31] also reported a lower level of leakage with automatic CPAP than with fixed CPAP but did not report whether this difference was statistically significant. Taken together, these studies suggest a nonsignificant or marginal effect of automatic CPAP modes on unintentional leaks.

Comparison of pressure relief modes vs fixed CPAP: Nine RCTs compared pressure relief modes to standard CPAP; however, only three of these studies reported unintentional leaks (Table 3).[19,43,49] The two studies that compared C-Flex and CPAP found no differences in unintentional leakage.[43,49] In contrast, Kushida et al[19] reported a significantly lower average level of unintentional leakage with the A-Flex compared with fixed CPAP after 3 and 6 months of treatment. The reasons for this difference remain unclear. There were no differences in the 95th percentile pressure between the A-Flex mode vs CPAP; however, median pressure was not reported, and we cannot exclude that it was lower with the A-Flex mode. This reduction in unintentional leakage with the A-Flex mode was not associated with an improvement in compliance. It is

TABLE 2] Studies Reporting Unintentional Leak Between Automatic-CPAP Mode and Fixed-CPAP

Study/Year	Primary Objective	Population	Sample Size[a]	Study Design and Intervention	Key Findings	Leaks Related to CPAP Modes	Difference Reported in Unintentional Leak Between Modes
Teschler et al[13]/ 2000	To test whether APAP produce the same reduction in AHI as conventional manually titrated fixed-CPAP	Mean age: 52 ± 2 y Mean BMI: 33.8 ± 1.3 kg/m^2 Male sex: 100% AHI: >20/h CPAP-naive OSA syndrome	10/10	RCT, double-blinded, crossover APAP vs fixed-CPAP Time frame: 2 × 2 mo	The AHI reduction with APAP was maintained after 2 mo of treatment and was comparable to that seen during fixed-CPAP	No difference between automatic-CPAP and fixed-CPAP regarding leaks	10 ± 3 (APAP) vs 13 ± 3 (fixed-CPAP) (time spent with mask-on with leak > 0.4 L/min)
Hukins[48]/ 2004	To compare compliance and treatment response between fixed-CPAP and APAP, and to develop selection criteria for the use of APAP	Mean age: from 49 ± 12.5 y to 51 ± 11.9 y Mean BMI: from 34.3 ± 6.3 y to 35.8 ± 6.7 kg/m^2 Male sex: 87% Mean AHI: from 49.3 ± 12.5/h to 51.0 ± 11.9/h CPAP-naive OSA syndrome	58/46	RCT, crossover APAP vs fixed-CPAP Time frame: 2 × 2 mo	No significant difference in compliance between treatment modes	Significantly less leak with automatic-CPAP compared with fixed-CPAP ($P < .001$)	0.23 ± 0.15 (APAP) vs 0.43 ± 0.42 (fixed-CPAP) (95th percentile leak in L/s)
West et al[42]/ 2006	To establish whether sleepiness, blood pressure, self-reported health status, or CPAP usage were different regarding three different methods of titration, including automatic-CPAP	Median (5th/95th centile) age: from 43 (33.5/60) y to 48 (33/66.6) y Median BMI: ND Male sex: 85% Mean AHI: ND CPAP-naive OSA syndrome	98/80	RCT, double-blinded APAP vs APAP titration (then switched to fixed-CPAP at DAY 7) vs fixed-CPAP	No significant difference between the three groups regarding the clinical outcomes measures	No difference between groups regarding leaks	0.3 (0/1.5) (APAP) vs 0.3 (0/0.7) (APAP then fixed-CPAP) vs 0.3 (0/0.7) (fixed-CPAP) (median (5th/95th centile) of 95th percentile leak in L/s)
Galetke et al[47]/ 2008	To compare the effect of APAP and fixed-CPAP on treatment efficacy and adherence based on an analysis of pressure and mask leakage	Mean age: 55.5 ± 8.6 y Mean BMI: 29.3 ± 4.1 kg/m^2 Male sex: 80% Mean AHI: 32.9 ± 19.1/h CPAP-naive OSA syndrome	20/20	RCT, single-blinded, crossover APAP vs fixed-CPAP Time frame: 2 × 8 wk	APAP is as affective as fixed-CPAP	No difference between automatic-CPAP and fixed-CPAP regarding leaks	25 ± 49 (APAP) vs 31 ± 57 (fixed-CPAP) (mean leakage time per night in min/night)

(Continued)

TABLE 2] *(Continued)*

Study/Year	Primary Objective	Population	Sample Size[a]	Study Design and Intervention	Key Findings	Leaks Related to CPAP Modes	Difference Reported in Unintentional Leak Between Modes
Damjanovic et al.[46] 2009	To test whether an intensive support during the first 6 mo of CPAP can enhance adherence and improve clinical outcomes compared with standard support	Mean Age: 57 ± 12 years Mean BMI: 31±5 kg/m^2 Male sex: 78% Mean AHI : 43.8±3.6/h (Intensive support group); 43.6±3.4/h, (standard support group) CPAP naive OSA	100/78	RCT APAP vs fixed-CPAP (standard support vs intensive support) Time frame: 9 mo	Intensive support can enhance long-term adherence The reduction of the AHI appeared to be stronger with intensive support	No difference between automatic-CPAP and fixed-CPAP regarding leaks	0.29 (0.03) (APAP) vs 0.36 (0.04) (fixed-CPAP) (mean (95th percentile) leakage, in L/s)
Bakker et al[31]/ 2012	To assess the pressure requirement, the residual AHI, or unintentional leaks between NM, ONM and underchin-ONM	Mean age: 48.8 ± 11.2 y Mean BMI: 37.7 ± 59 kg/m^2 Male sex: 91.7% Mean AHI: 59.8 ± 28.6/h CPAP-naive OSA syndrome	13/12	RCT, crossover NM vs ONM vs underchin-ONM (CPAP vs automatic-CPAP) Time frame: 2 × 7 nights (3 nights NM; 2 nights ONM; 2 nights underchin-ONM)	No significant difference in pressure delivered between masks Significant difference in residual AHI in favor of nasal mask ($P < .002$)	Difference of leak levels between CPAP and APAP not assessed	From 9.4 ± 10.9 to 35.2 ± 32 (APAP) vs from 15 ± 10.8 to 54.5 ± 37 (fixed-CPAP) (95th percentile leak in L/min)

APAP = automatic CPAP. See Table 1 legend for expansion of other abbreviations.
[a]No. at enrollment/final No.

TABLE 3] Studies Reporting Unintentional Leakage Between Flexible Pressure Modes and Fixed CPAP

Study/Year	Primary Objective	Population	Sample Size[a]	Study Design and Intervention	Key Findings	Unintentional Leakage Related to CPAP modes	Difference Reported in Unintentional Leakage Between Modes
Leidag et al[49]/ 2008[b]	To compare the leak between CPAP and C-Flex	Mean age: 55.4 ± 11.7 y Mean BMI: 32 ± 7.4 kg/m^2 Male sex: 73% Mean AHI: 35.4 ± 24.8/h CPAP-naive OSA syndrome	30/18	RCT, double-blind crossover C-Flex vs fixed CPAP Time frame: 2 × 6 wk	No difference regarding leaks between fixed CPAP and C-Flex Significant patient preference for C-Flex	No difference between C-Flex and fixed CPAP regarding leaks	28 ± 10 (C-Flex) vs 27.5 ± 11.5 (fixed CPAP) (leakage in L/min)
Bakker et al[43]/ 2010	To evaluate the effectiveness of C-Flex vs fixed CPAP by analyzing mean objective compliance over 1 and 3 mo	Mean age: 49.7 y (range, 30-77 y) Mean BMI: 35.6 ± 7.8 kg/m^2 Male sex: 77% Mean AHI: 60.2 ± 32.9/h CPAP-naive OSA syndrome	80/76	RCT, double blind C-Flex vs fixed CPAP Time frame: 3 mo	No difference in median objective compliance between the two treatment arms after either 1 or 3 mo	No difference between C-Flex and fixed CPAP regarding leaks	59.8 ± 20.8 (fixed CPAP) vs 54.8 ± 19.5 (C-Flex) (90th percentile in L/min)
Kushida et al[19]/2011	To determine the efficacy of automatic CPAP with comfort feature (A-Flex) at reducing apnea and hypopnea	Mean age: from 48.3 ± 10 to 49.1 ± 11.6 y Mean BMI: 33.0 ± 6.6 to 35.6 ± 8.3 kg/m^2 Male sex: 76% Mean AHI: from 36.87 ± 30/h to 41.1 ± 31.5/h CPAP-naive OSA syndrome	168/ 140	RCT, double blind A-Flex vs fixed CPAP vs automatic CPAP (then switched to fixed CPAP at d 14) Time frame: 180 d	No differences between modes on efficacy, adherence, and functional outcomes after either 3 or 6 mo	Lower average leak level (in L/min) with A-Flex vs fixed CPAP after both 3 mo (*P* = .005) and 6 mo (*P* = .007)	32.0 ± 10.4 (A-Flex) vs 38.3 ± 12.6 (fixed CPAP) after 3 mo 30.3 ± 10.8 (A-Flex) vs 36.5 ± 12.8 (CPAP) after 6 mo Average leak in L/min)

C-Flex and A-Flex are automatic modes with a flexible pressure delivery. See Table 1 legend for expansion of abbreviations.
[a]No. at enrollment/final No.
[b]This study is the only one with unintentional leak as a primary objective.

interesting to note that the reduction in leakage with the A-Flex mode was found only for the average leakage values (L/min) but not for the time spent with high levels of unintentional leaks. There is thus a lack of evidence to support the theory that pressure relief or automatic modes reduce unintentional leakage.

The Effect of Chin Straps on Unintentional Leakage

Both clinical practice and uncontrolled studies suggest that the addition of a chin strap to PAP therapy is a useful method to reduce unintentional leakage by limiting mouth opening.[50,51] However, the true effectiveness of this accessory for avoiding unintentional leaks, as well as its long-term tolerance, have been poorly documented, with only two studies available.[50,52]

Bachour et al[52] found that the use of a chin strap decreased mouth leakage in the majority of patients but failed in a subgroup who had a high level of mouth leakage. This may be explained by several factors. The chin strap keeps the jaw, but not the lips, closed, and it can also move throughout the night. Likewise, in some cases, the chin strap may not counteract the mouth opening when this latter phenomenon is due to nasal obstruction[53] or persistent pharyngeal obstruction.[54,55] A more recent study[50] also showed that chin straps were associated with less unintentional leakage. However, age was found to be a stronger contributor to unintentional leakage than the use of a chin strap in the multivariate analysis. This suggests that physiological factors such as facial morphologic characteristics, nasal obstruction, loss of teeth, or skin elasticity might be determining factors of unintentional leaks.

Heated Humidification

In clinical practice, heated humidification (HH) is often used with CPAP to improve tolerance, despite the fact that a Cochrane review found no evidence that HH significantly improves compliance or side effects.[23]

The effect of HH on unintentional leaks was reported in four RCTs. None of the studies found any significant differences in leakage with the use of HH.[56-59] One experimental study in eight patients with nasal symptoms (chronic obstruction, rhinitis, sneezing) showed that HH improved the relative humidity of the upper airway during nasal CPAP ($P < .01$), and this was associated with a trend toward a decrease in the time spent with mouth leakage (18% $\pm$ 23% of the total sleep time; $P = .09$).[60] It is likely that the relief of the nasal congestion (because of the HH) reduced mouth breathing and subsequently also mouth leakage.[53,61]

In summary, these findings, while based on relatively small sample sizes, suggest that technological improvements, without specific assessment of the clinical context, have limited effects on unintentional leakage. In contrast, patient physiology and characteristics such as persistent upper airway resistance and nasal obstruction, as well as age, BMI, and sex might be important factors relating to unintentional leakage.

Relationship Between Patient Characteristics and Unintentional Leaks

Nasal Obstruction and Unintentional Leaks

Numerous observational studies have demonstrated that nasal obstruction is associated with snoring, daytime sleepiness, and mild OSA syndrome, but only a few studies have found the link between nasal obstruction and unintentional leakage during CPAP treatment.[17,60,62,63]

Although it has been shown that mouth opening is not always associated with mouth breathing, since the tongue and the soft palate can be in close apposition, preserving nasal breathing,[64] nasal obstruction forces patients to open the mouth.[53] This mouth opening often favors mouth leaks,[17,65-68] which increases the blood flow of the nasal mucosa, which in turn increases nasal congestion further,[62,63] creating a pathologic vicious circle.

It is thus important to bear in mind that nasal resistance is an important factor relating to unintentional leaks, and that it is necessary to treat any nasal obstruction prior to initiating CPAP and attempting sophisticated technological solutions.

Relationship Between Age, BMI, Fat Distribution, Sex, and Unintentional Leakage

A large retrospective study that included 4,281 patients showed that the risk of unintentional leaks was twice as high in older patients (> 70 years) as in younger patients (< 40 years).[69] This was also found by Knowles et al,[50] who suggested that the positive association between age and unintentional leakage may be explained by changes in facial morphologic characteristics due to (1) loss of teeth, (2) changes in skin elasticity, or (3) a decrease in subcutaneous fat.

Obesity is considered a major risk factor for the development and progression of sleep apnea.[70-72] Only a few studies have assessed the relationship between BMI and unintentional leakage. Sopkova et al[73] and Dorkova et al[74] found a strong relationship between BMI and unintentional leakage; the higher the BMI, the higher the level of unintentional leakage (n = 51: $r = 0.579$; $P < .00$[73]; n = 32: $r = 0.686$; $P < .001$[74]). Their results suggested that central fat distribution (waist circumference) might be associated with a higher risk of unintentional leakage.[73] This is consistent with results in a previous study by our group showing a correlation between mouth opening and neck circumference,[17] which is a surrogate marker of central fat distribution. By increasing the work of breathing, central fat distribution might favor open-mouthed breathing[75,76] and lead to mouth leaks.[17,77] Accordingly, Guerrero et al[78] showed that patients with an overlap syndrome (COPD + OSA syndrome) exhibited a higher level of unintentional leakage with CPAP than did patients with OSA syndrome without COPD.[78] We hypothesize that this type of clinical condition, which involves higher airway resistance and an increase in the work of breathing, may promote mouth opening during sleep and therefore leaks.

Conclusions

The issue of unintentional leakage has been considered a challenge to be resolved by technological developments. However, new technologies have only partially solved the problem. Although current published studies are heterogeneous regarding design, devices used, and time frame, this review suggests that (1) the different CPAP modes are not effective in reducing unintentional leaks and (2) oronasal masks seem, surprisingly, to be associated with higher unintentional leakage, despite the fact that in clinical practice they are commonly used to overcome this problem.

Moreover, other issues, such as patient-related factors, that are not yet understood well enough may play a significant role in the occurrence of unintentional leaks. Figure 2 summarizes these potential factors: anthropometric features such as obesity (high BMI or central fat distribution, or both), male sex, craniofacial variability, pharyngeal anatomy, and physiological factors such as nasal resistance are known to be causes of upper airway collapse and could also be associated with mouth opening and therefore unintentional leaks. Likewise, sensory impairment of the pharynx reduces the efficacy of the protective pharyngeal reflexes and might contribute to mouth opening because of increased respiratory effort. Finally, sleep stages, body position,

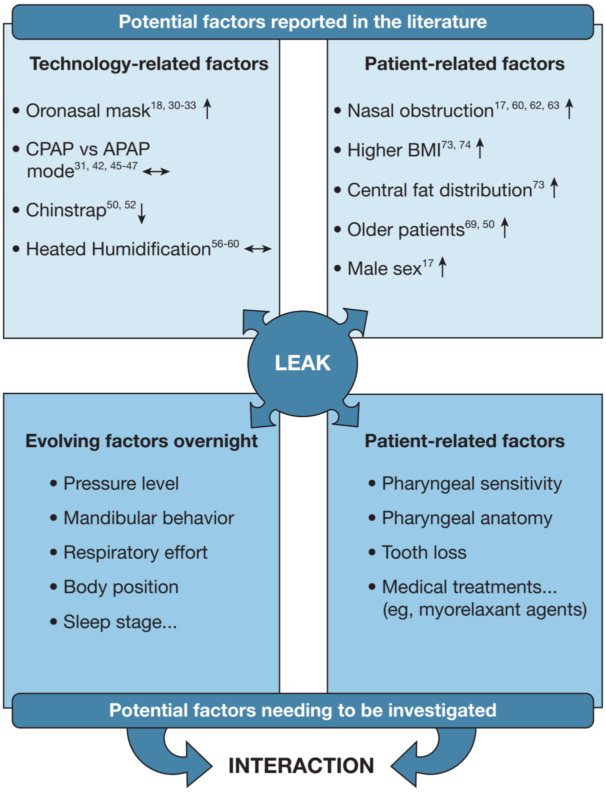

Figure 2 – *Potential contributing factors associated with unintentional leakage. Arrow pointing up = the factor is associated with increased unintentional leakage. Horizontal arrows = no difference observed between modes regarding unintentional leakage. Arrow pointing down = chin strap is associated with less unintentional leakage but is poorly documented. APAP = automatic CPAP.*

medical treatments that can alter upper airway and mandibular muscle tone (ie, myorelaxant agents)[79] might also participate in mouth opening with CPAP.

Future Directions to Improve Understanding of the Determining Factors of Unintentional Leak

Additional studies are clearly needed to improve the understanding of factors that underlie unintentional leaks associated with CPAP to provide a phenotype of patients "at risk of leaks" and thus anticipate problems and propose personalized solutions.

First, the leak threshold above which there is a decrease in CPAP efficacy and patient adherence is still unknown. Interventional trials using CPAP should systematically report leak levels to better characterize the intervention. Also, measurements and terminology used to report unintentional leakage are inconsistent between manufacturers, which is confusing for clinicians. Further studies are needed to determine a threshold for clinically meaningful leaks (reported as an absolute value [L/min] or time spent with leakage, or both) in different brands of equipment.

Finally, studies are needed to define the main anthropometric, anatomic, and physiological features associated with occurrence of leaks to identify patients "at risk of leaks" and to provide close specific follow-up, particularly in the early course of CPAP treatment.

Acknowledgments

Author contributions: J. C. B. had full access to all the data in the study and takes responsibility for the content of the manuscript. M. L., J. L. P and J. C. B. are responsible for conception of the study. J. C. B. and M. L. are responsible for the bibliographic analysis. M. L., D. Z., J. B. M., J. L. P., R. T., and J. C. B. are responsible for data interpretation. M. L., N. A., J. B. M., J. L. P., R. T., and J. C. B. are responsible for drafting or revising the manuscript. All authors agree with manuscript results and conclusions.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: M. L., N. A., D. Z., and J. C. B. are employees of AGIR à dom, a nonprofit home-care provider. J. C. B. has received grants, personal fees, and nonfinancial support from Philips Healthcare and ResMed outside the context of the submitted work. J. C. B. also has a patent with NOMICS SA. None declared (J. B. M., R. T., J. L. P.)

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: We thank Johana Robertson, PhD (medical writer) funded by AGIRadom for language editing.

References

1. Lévy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers*. 2015;1:15015.
2. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005;365(9464): 1046-1053.
3. Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA*. 2012;307(20):2169-2176.
4. Pépin J-L, Tamisier R, Barone-Rochette G, Launois SH, Lévy P, Baguet J-P. Comparison of continuous positive airway pressure and valsartan in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med*. 2010;182(7):954-960.
5. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev*. 2006;(3):CD001106.
6. Weaver TE, Maislin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep*. 2007;30(6):711-719.
7. Veale D, Chailleux E, Hoorelbeke-Ramon A, et al. Mortality of sleep apnoea patients treated by nasal continuous positive airway pressure registered in the ANTADIR observatory. Association Nationale pour le Traitement A Domicile de l'Insuffisance Respiratoire chronique. *Eur Respir J*. 2000;15(2): 326-331.
8. Gagnadoux F, Le Vaillant M, Goupil F, et al. Influence of marital status and employment status on long-term adherence with continuous positive airway pressure in sleep apnea patients. *PloS One*. 2011;6(8):e22503.
9. Borel JC, Tamisier R, Dias-Domingos S, et al. Type of mask may impact on continuous positive airway pressure adherence in apneic patients. *PloS One*. 2013;8(5):e64382.
10. Pépin JL, Leger P, Veale D, Langevin B, Robert D, Lévy P. Side effects of nasal continuous positive airway pressure in sleep apnea syndrome: study of 193 patients in two French sleep centers. *Chest*. 1995;107(2):375-381.
11. Bachour A, Maasilta P. Mouth breathing compromises adherence to nasal continuous positive airway pressure therapy. *Chest*. 2004;126(4):1248-1254.
12. Valentin A, Subramanian S, Quan SF, Berry RB, Parthasarathy S. Air leak is associated with poor adherence to autoPAP therapy. *Sleep*. 2011;34(6):801-806.
13. Teschler H, Stampa J, Ragette R, Konietzko N, Berthon-Jones M. Effect of mouth leak on effectiveness of nasal bilevel ventilatory assistance and sleep architecture. *Eur Respir J*. 1999;14(6):1251-1257.
14. Kushida CA, Chediak A, Berry RB, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. *J Clin Sleep Med*. 2008;4(2):157-171.
15. Neuzeret P-C, Morin L. Impact of different nasal masks on CPAP therapy for obstructive sleep apnea: a randomized comparative trial [published online ahead of print January 18, 2016]. *Clin Respir J*. http://dx.doi.org/10.1111/crj.12452.
16. Bachour A, Vitikainen P, Maasilta P. Rates of initial acceptance of PAP masks and outcomes of mask switching. *Sleep Breath*. 2016;20(2):733-738.
17. Lebret M, Arnol N, Contal O, et al. Nasal obstruction and male gender contribute to the persistence of mouth opening during sleep in CPAP-treated obstructive sleep apnoea. *Respirology*. 2015;20(7): 1123-1130.
18. Ebben MR, Narizhnaya M, Segal AZ, Barone D, Krieger AC. A randomised controlled trial on the effect of mask choice on residual respiratory events with continuous positive airway pressure treatment. *Sleep Med*. 2014;15(6):619-624.
19. Kushida CA, Berry RB, Blau A, et al. Positive airway pressure initiation: a randomized controlled trial to assess the impact of therapy mode and titration process on efficacy, adherence, and outcomes. *Sleep*. 2011;34(8):1083-1092.
20. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med*. 2015;373(12):1095-1105.
21. Bradley TD, Floras JS. The SERVE-HF trial. *Can Respir J*. 2015;22(6): 313.
22. Gao W, Jin Y, Wang Y, et al. Is automatic CPAP titration as effective as manual CPAP titration in OSAHS patients? A meta-analysis. *Sleep Breath*. 2011;16(2):329-340.
23. Smith I, Lasserson TJ. Pressure modification for improving usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2009;(4): CD003531.
24. Ayas NT, Patel SR, Malhotra A, et al. Auto-titrating vs standard continuous positive airway pressure for the treatment of obstructive sleep apnea: results of a meta-analysis. *Sleep*. 2004;27(2):249-253.
25. Bakker JP, Marshall NS. Flexible pressure delivery modification of continuous positive airway pressure for obstructive sleep apnea does not improve compliance with therapy: systematic review and meta-analysis. *Chest*. 2011;139(6):1322-1330.
26. Ip S, D'Ambrosio C, Patel K, et al. Auto-titrating vs fixed continuous positive airway pressure for the treatment of obstructive sleep apnea: a systematic review with meta-analyses. *Syst Rev*. 2012;1(1):1-24.
27. Chai CL, Pathinathan A, Smith B. Continuous positive airway pressure delivery interfaces for obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2006;(4):CD005308.
28. Lemarié E, Valeyre D, Housset B, Godard P. Sleep apnea syndrome: clinical practice guidelines [in French]. *Rev Mal Respir*. 2010;27(7): 804-805.
29. Bachour A, Vitikainen P, Virkkula P, Maasilta P. CPAP interface: satisfaction and side effects. *Sleep Breath*. 2013;17(2):667-672.
30. Mortimore IL, Whittle AT, Douglas NJ. Comparison of nose and face mask CPAP therapy for sleep apnoea. *Thorax*. 1998;53(4): 290-292.

31. Bakker JP, Neill AM, Campbell AJ. Nasal vs oronasal continuous positive airway pressure masks for obstructive sleep apnea: a pilot investigation of pressure requirement, residual disease, and leak. *Sleep Breath*. 2012;16(3):709-716.

32. Teo M, Amis T, Lee S, Falland K, Lambert S, Wheatley J. Equivalence of nasal and oronasal masks during initial CPAP titration for obstructive sleep apnea syndrome. *Sleep*. 2011;34(7): 951-955.

33. Ebben MR, Oyegbile T, Pollak CP. The efficacy of three different mask styles on a PAP titration night. *Sleep Med*. 2012;13(6):645-649.

34. Smith PL, O'Donnell CP, Allan L, Schwartz AR. A physiologic comparison of nasal and oral positive airway pressure. *Chest*. 2003;123(3):689-694.

35. Khanna R, Kline LR. A prospective 8 week trial of nasal interfaces vs. a novel oral interface (Oracle) for treatment of obstructive sleep apnea hypopnea syndrome. *Sleep Med*. 2003;4(4):333-338.

36. Anderson FE, Kingshott RN, Taylor DR, Jones DR, Kline LR, Whyte KF. A randomized crossover efficacy trial of oral CPAP (Oracle) compared with nasal CPAP in the management of obstructive sleep apnea. *Sleep*. 2003;26(6):721-726.

37. Beecroft J, Zanon S, Lukic D, Hanly P. Oral continuous positive airway pressure for sleep apnea: effectiveness, patient preference, and adherence. *Chest*. 2003;124(6):2200-2208.

38. Zhu X, Wimms AJ, Benjafield AV. Assessment of the performance of nasal pillows at high CPAP pressures. *J Clin Sleep Med*. 2013;9(9): 873-877.

39. Ryan S, Garvey JF, Swan V, Behan R, McNicholas WT. Nasal pillows as an alternative interface in patients with obstructive sleep apnoea syndrome initiating continuous positive airway pressure therapy. *J Sleep Res*. 2011;20(2):367-373.

40. Cheng Y-L, Hsu D-Y, Lee H-C, Bien M-Y. Clinical verification of patients with obstructive sleep apnea provided with a customized cushion for continuous positive airway pressure. *J Prosthet Dent*. 2015;113(1):29-34.e1.

41. Farré R, Montserrat JM, Rigau J, Trepat X, Pinto P, Navajas D. Response of automatic continuous positive airway pressure devices to different sleep breathing patterns. *Am J Respir Crit Care Med*. 2002;166(4):469-473.

42. West SD, Jones DR, Stradling JR. Comparison of three ways to determine and deliver pressure during nasal CPAP therapy for obstructive sleep apnoea. *Thorax*. 2006;61(3):226-231.

43. Bakker J, Campbell A, Neill A. Randomized controlled trial comparing flexible and continuous positive airway pressure delivery: effects on compliance, objective and subjective sleepiness and vigilance. *Sleep*. 2010;33(4):523-529.

44. Pépin J-L, Muir J-F, Gentina T, et al. Pressure reduction during exhalation in sleep apnea patients treated by continuous positive airway pressure. *Chest*. 2009;136(2):490-497.

45. Teschler H, Wessendorf TE, Farhat AA, Konietzko N, Berthon-Jones M. Two months auto-adjusting vs conventional nCPAP for obstructive sleep apnoea syndrome. *Eur Respir J*. 2000;15(6):990-995.

46. Damjanovic D, Fluck A, Bremer H, Müller-Quernheim J, Idzko M, Sorichter S. Compliance in sleep apnoea therapy: influence of home care support and pressure mode. *Eur Respir J*. 2009;33(4): 804-811.

47. Galetke W, Anduleit N, Richter K, Stieglitz S, Randerath WJ. Comparison of automatic and continuous positive airway pressure in a night-by-night analysis: a randomized, crossover study. *Respiration*. 2008;75(2):163-169.

48. Hukins C. Comparative study of autotitrating and fixed-pressure CPAP in the home: a randomized, single-blind crossover trial. *Sleep*. 2004;27(8):1512-1517.

49. Leidag M, Hader C, Keller T, Meyer Y, Rasche K. Mask leakage in continuous positive airway pressure and C-Flex. *J Physiol Pharmacol*. 2008;59(suppl 6):401-406.

50. Knowles SR, O'Brien DT, Zhang S, Devara A, Rowley JA. Effect of addition of chin strap on PAP compliance, nightly duration of use, and other factors. *J Clin Sleep Med*. 2014;10(4):377-383.

51. Vorona RD, Ware JC, Sinacori JT, Ford ML, Cross JP. Treatment of severe obstructive sleep apnea syndrome with a chinstrap. *J Clin Sleep*. 2007;3(7):729-730.

52. Bachour A, Hurmerinta K, Maasilta P. Mouth closing device (chin strap) reduces mouth leak during nasal CPAP. *Sleep Med*. 2004;5(3): 261-267.

53. Koutsourelakis I, Minaritzoglou A, Zakynthinos G, Vagiakis E, Zakynthinos S. The effect of nasal tramazoline with dexamethasone in obstructive sleep apnoea patients. *Eur Respir J*. 2013;42(4): 1055-1063.

54. Hollowell DE, Suratt PM. Mandible position and activation of submental and masseter muscles during sleep. *J Appl Physiol (1985)*. 1991;71(6):2267-2273.

55. Miyamoto K, Ozbek MM, Lowe AA, et al. Mandibular posture during sleep in patients with obstructive sleep apnoea. *Arch Oral Biol*. 1999;44(8):657-664.

56. Salgado SM da ST, Boléo-Tomé JPCF, Canhão CMS, et al. Impact of heated humidification with automatic positive airway pressure in obstructive sleep apnea therapy. *J Bras Pneumol*. 2008;34(9):690-694.

57. Worsnop CJ, Miseski S, Rochford PD. Routine use of humidification with nasal continuous positive airway pressure. *Intern Med J*. 2010;40(9):650-656.

58. Mador MJ, Krauza M, Pervez A, Pierce D, Braun M. Effect of heated humidification on compliance and quality of life in patients with sleep apnea using nasal continuous positive airway pressure. *Chest*. 2005;128(4):2151-2158.

59. Yu C-C, Luo C-M, Liu Y-C, Wu H-P. The effects of heated humidifier in continuous positive airway pressure titration. *Sleep Breath*. 2013;17(1):133-138.

60. Martins De Araújo MT, Vieira SB, Vasquez EC, Fleury B. Heated humidification or face mask to prevent upper airway dryness during continuous positive airway pressure therapy. *Chest*. 2000;117(1): 142-147.

61. Koutsourelakis I, Vagiakis E, Perraki E, et al. Nasal inflammation in sleep apnoea patients using CPAP and effect of heated humidification. *Eur Respir J*. 2011;37(3):587-594.

62. Hayes MJ, McGregor FB, Roberts DN, Schroter RC, Pride NB. Continuous nasal positive airway pressure with a mouth leak: effect on nasal mucosal blood flux and nasal geometry. *Thorax*. 1995;50(11):1179-1182.

63. Richards GN, Cistulli PA, Ungar RG, Berthon-Jones M, Sullivan CE. Mouth leak with nasal continuous positive airway pressure increases nasal airway resistance. *Am J Respir Crit Care Med*. 1996;154(1): 182-186.

64. Meurice JC, Marc I, Carrier G, Sériès F. Effects of mouth opening on upper airway collapsibility in normal sleeping subjects. *Am J Respir Crit Care Med*. 1996;153(1):255-259.

65. Georgalas C. The role of the nose in snoring and obstructive sleep apnoea: an update. *Eur Arch Otorhinolaryngol*. 2011;268(9): 1365-1373.

66. Enoz M. Effects of nasal pathologies on obstructive sleep apnea. *Acta Medica (Hradec Kralove)*. 2007;50(3):167-170.

67. McLean HA, Urton AM, Driver HS, et al. Effect of treating severe nasal obstruction on the severity of obstructive sleep apnoea. *Eur Respir J*. 2005;25(3):521-527.

68. Shikata N, Ueda HM, Kato M, et al. Association between nasal respiratory obstruction and vertical mandibular position. *J Oral Rehabil*. 2004;31(10):957-962.

69. Woehrle H, Graml A, Weinreich G. Age- and gender-dependent adherence with continuous positive airway pressure therapy. *Sleep Med*. 2011;12(10):1034-1036.

70. Romero-Corral A, Caples SM, Lopez-Jimenez F, Somers VK. Interactions between obesity and obstructive sleep apnea. *Chest*. 2010;137(3):711-719.

71. Weihu C, Jingying Y, Demin H, Boxuan W. Relationship of body position, upper airway morphology, and severity of obstructive sleep apnea/hypopnea syndrome among Chinese patients. *Acta Otolaryngol*. 2011;131(2):173-180.

72. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA*. 2000;284(23):3015-3021.

73. Sopkova Z, Dorkova Z, Tkacova R. Predictors of compliance with continuous positive airway pressure treatment in patients with obstructive sleep apnea and metabolic syndrome. *Wien Klin Wochenschr*. 2009;121(11-12):398-404.

74. Dorkova Z, Petrasova D, Molcanyiova A, Popovnakova M, Tkacova R. Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnea and metabolic syndrome. *Chest*. 2008;134(4):686-692.

75. Pankow W, Hijjeh N, Schuttler F, et al. Influence of noninvasive positive pressure ventilation on inspiratory muscle activity in obese subjects. *Eur Respir J*. 1997;10(12):2847-2852.

76. Stadler DL, McEvoy RD, Sprecher KE, et al. Abdominal compression increases upper airway collapsibility during sleep in obese male obstructive sleep apnea patients. *Sleep*. 2009;32(12):1579-1587.

77. Senny F, Maury G, Cambron L, Leroux A, Destiné J, Poirrier R. Mandible behavior in obstructive sleep apnea patients under CPAP treatment. *Open Sleep J*. 2012;5:1-5.

78. Guerrero A, Montserrat JM, Farre R, Masa F, Duran J, Embid C. Automatic CPAP performance in patients with sleep apnea plus COPD. *COPD*. 2012;9(4):382-389.

79. Jullian-Desayes I, Revol B, Chareyre E, et al. Impact of concomitant medications on obstructive sleep apnea [published online ahead of print October 13, 2016]. *Br J Clin Pharmacol*. http://dx.doi.org/10.1111/bcp.13153.