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Reconsidering first-line treatment for obstructive sleep apnea: a systematic review of the literature

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Abstract

Background: Continuous positive airway pressure (CPAP) is typically recommended as first line therapy for obstructive sleep apnea, but the adherence rate of CPAP is problematic. This study's objective was to systematically review the literature relating to CPAP as first line therapy for OSA and compare it to surgical literature on the same topic.

Methods: A systematic review was conducted according to PRISMA guidelines, examining Medline-Ovid, Embase, and Pubmed databases. The primary search objective was to identify all papers reporting the results of (1) randomized clinical trials (RCT) of CPAP for the treatment of adults with OSA; and (2) both randomized and non-randomized clinical trials and case series on the surgical treatment of OSA in adults. A PhD-level biostatistician first screened papers, and then those that met study criteria were retrieved and analyzed using standardized forms for each author. The primary outcomes were adherence rates of CPAP.

Results: A total of 82 controlled clinical trials for CPAP and 69 controlled and non-controlled surgery trials were identified for analysis. Variation in CPAP use within reported RCT trials were identified, and the majority of patients in the studies would eventually be considered non-adherent to CPAP.

Conclusions: When considering the numerous patient-related factors that come into play when CPAP is prescribed, the concept of CPAP as gold-standard therapy for OSA should be reconsidered. In many cases surgery can provide a better overall outcome. This study's results suggest that certain patients with OSA may be managed more effectively with surgery than CPAP, without confounding issues of treatment adherence.

Keywords: Obstructive sleep apnea, Uvulopalatoplasty, CPAP

Background

Obstructive sleep apnea (OSA) is considered part of a group of disorders that cover a continuum ranging from habitual snoring (simple snoring) to moderate or severe OSAS. OSA is characterized by repetitive apnea and/or hypopnea during sleep. Due to relaxation of the upper airway pharyngeal and tongue muscles during sleep the airway narrows and collapses resulting in hypoxaemia, increased sympathetic overdrive, increased blood pressure, and hypercapnia. These add hypoxic stress to the brain and heart. Apneic and hypopneic events may occur numerous times per night, resulting in arousals from sleep and sleep disruptions causing sleep fragmentation leading to excessive daytime sleepiness. These repeated cyclic oxygen desaturations and a fragmented sleep architecture lead to sympathetic overdrive, interrupted sleep, and reduced percentage of slow wave sleep, translating into symptoms of daytime somnolence, morning headaches, poor concentration, memory loss, a higher risk of car accidents, depression and marital discord.

OSA has a strong association with hypertension, atherosclerosis, and cerebrovascular accidents (strokes) [1]. Studies have also shown a higher mortality rate among patients with cardiovascular disease who also have OSA [1]. It has been long purported that nasal continuous

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positive airway pressure (CPAP) is the "gold" standard in the treatment of OSA, and there is no doubt that CPAP is effective when used properly and according to AASM standards. However, it is also well known that due to problematic patient adherence, the real world effectiveness of CPAP is low, with a large proportion of users abandoning the machine within one year of prescription. Such patients cannot be said to be effectively treated. Surgery for OSA on the other hand does not rely on any form of long-term patient adherence, and when the right patient is matched with the right pharyngeal procedure in order to maximize success, long-term strong results have been shown. When considering all OSA patients it is recognized that overall treatment success rates with surgery are lower than via CPAP, but this does not hold true for the subset of patients with appropriate apnea-specific surgical anatomy wherein rates of successful surgical OSA treatment are very high. Moreover the issue of CPAP adherence has generally not been examined during these debates; to make an effective comparison adherence must be taken into account when studying the impact on OSA of CPAP versus surgery. CPAP, an efficacious therapy with inconsistent adherence, can potentially be equivalent to surgery, that being a "partial" therapy with complete adherence. It is the issue of treatment effectiveness versus adherence (the relationship of the two defining success) that is at the crux of the matter.

This study's objective was to systematically review the literature relating to CPAP as first line therapy for OSA and then compare it to surgical literature on the same topic.

Methods

Our review was carried out in accordance with the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. A comprehensive systematic literature review was conducted using the Medline-Ovid, Embase, and Pubmed databases.

The primary search objective was to identify all papers reporting the results of (1) randomized clinical trials (RCT) of CPAP for the treatment of adults with OSA; and (2) both randomized and non-randomized clinical trials and case series on the surgical treatment of OSA in adults. The first step was a locate and review all of the studies listed for analysis in three major literature reviews, a Cochrane Collaboration review [1] and a second systematic literature review published by the National Institutes of Health Research (NIHR) [2] on the use of CPAP for the treatment of OSA, and a second Cochrane Collaboration review on its surgical management [3]. The second step was an extensive search of the PubMed/MedLine database, initiated using the following combined search terms: "randomized clinical trial and obstructive sleep apnea" ($n = 1083$); "CPAP and randomized clinical trial and obstructive sleep apnea" ($n = 357$); and "surgery and obstructive sleep apnea and clinical trial" ($n = 603$). From these lists, studies were identified that (a) did not replicate studies already found and (b) were otherwise eligible for inclusion. The third and final step was a review of all reference lists and tables of other studies found within papers identified in the second step. A PhD level biostatistician performed all three of the search steps.

Articles were considered for inclusion into the study by reviewing the titles and abstracts of all retrieved studies. The senior study authors BWR and KPP did this and results were compiled to ensure no studies were missed. The full text of selected studies were then analyzed to ensure that the following inclusion criteria were met: diagnosis of obstructive sleep apnea, no confounding data for central sleep apnea, and the paper referred to either CPAP or surgical treatment of OSA.

Results

A total of 82 controlled clinical trials for CPAP and 69 controlled and non-controlled surgery trials were identified for analysis (note that non-controlled trials were accepted for surgery because of the relatively few controlled trials). The CPAP studies included trials comparing CPAP versus sub-therapeutic (sham) CPAP [4–34], CPAP versus an oral placebo [33, 35–43], CPAP versus conservative or no therapy [10, 22, 44–54], CPAP versus an oral appliance [4, 5, 36, 51, 55–63], CPAP versus postural therapy [64–67], and CPAP alone assessing different means to modify adherence (e.g., with vs. without a humidifying element) [8, 21, 30, 68–79]. The surgical trials assessed a variety of single- and multi-stage procedures incorporating uvuloplasty [22, 80–117], mandibular advancement [118, 119], laser treatments [120–125], radiofrequency tissue reduction and other lingual procedures [117, 125–134], and palate implants [135–141], in addition to five trials specifically evaluating the safety versus risks of OSA surgery, including its safety as an outpatient/same-day procedure [142–146]. The PRISMA charts seen in Figs. 1 and 2 summarize the study flow, and Additional files 1, 2, and Table 1 summarize the results of the search strategy.

Discussion of findings

Currently, continuous positive airway pressure (CPAP) is considered the gold standard treatment for patients with obstructive sleep apnea, be it mild, moderate or severe. This is the conclusion expressed in both a recently-published Cochrane Collaboration review [1] and a second systematic literature review published by the National Institutes of Health Research (NIHR) [2]. Surgical approaches are hardly discussed at all in either of these two

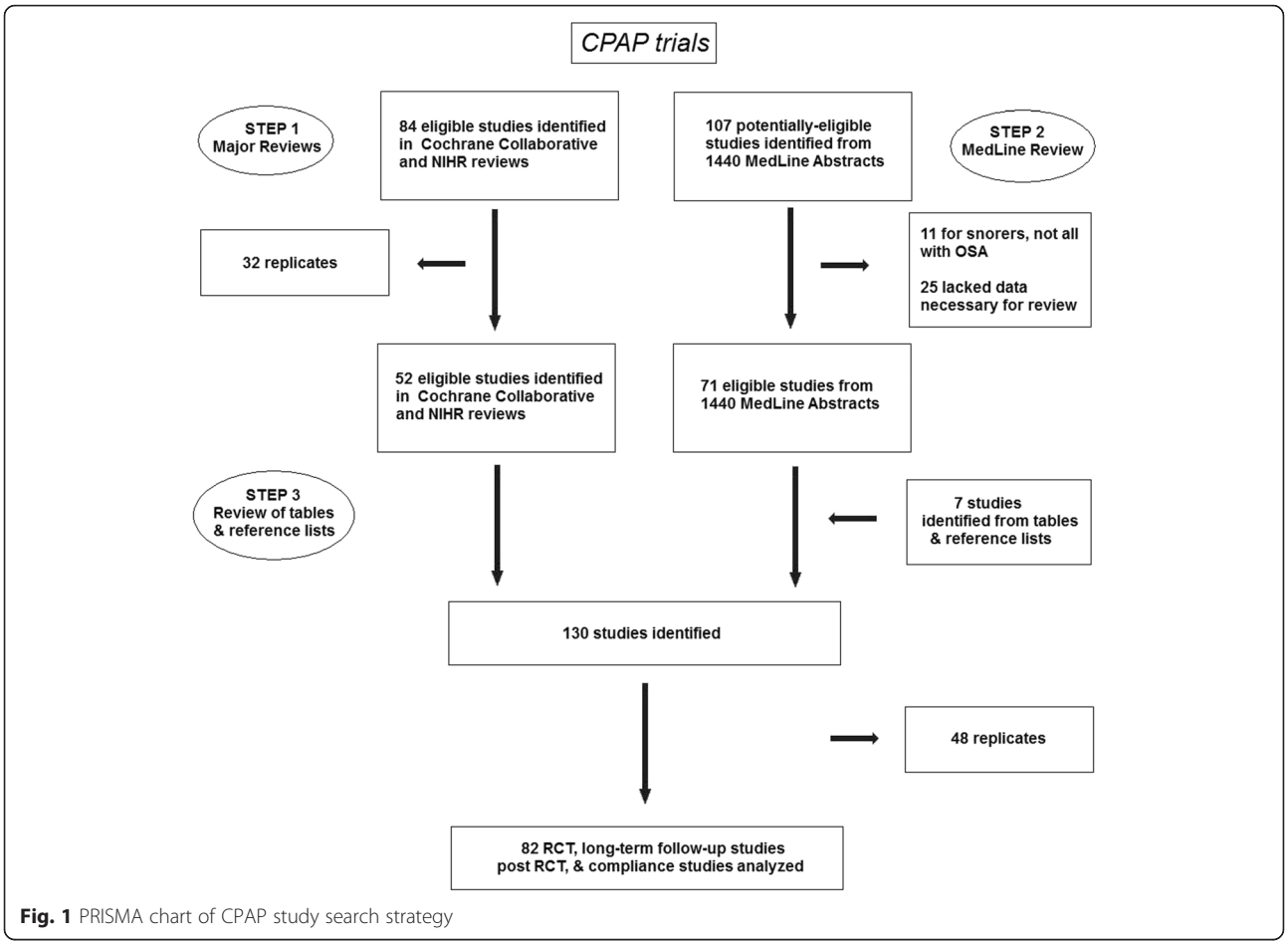

Fig. 1 PRISMA chart of CPAP study search strategy

reviews, largely on the basis of the lack of randomized controlled trials (RCTs). A closer look at the evidence however reveals that surgery may indeed play a primary role in many patients with OSA.

First, although a large number of RCTs have been published documenting the benefits of CPAP relative to sub-therapeutic (sham) CPAP [3–33], an oral placebo [32, 34–43], conservative or no therapy [9, 21, 42, 44–53], various oral appliances [3, 4, 35, 50, 54–62], and postural therapy [63–66], numerous limitations of these RCTs must be considered. First among these is the short duration of follow-up that has been almost ubiquitous amongst CPAP trials, the vast majority having final assessments within weeks of the initial treatment, and only a small handful extending beyond 3 to 4 months [46, 56], 6 months [3, 52], 1 year [9, 21], or beyond [44]. A couple of additional long-term cohort studies emerged from RCT, following patients, open label, to and beyond 1 year [3, 62]. This contrasts, however, with the much more long-term follow-up generally performed for surgical trials, where follow-up to and beyond 6 months is the norm, with several investigative groups reporting on outcomes beyond 1 year.

A second issue pertains to adherence with CPAP, a well-documented problem that warrants concern. In our review of 83 CPAP trials (Additional file 1), the average patient in bed for 7 h across these 83 closely supervised clinical trials was not using it an average of 32.9 % of the time. When the nights per week of CPAP non-use have been examined, the percentages range from 10 to 40 % [5, 35, 50, 55, 67–70] These are problematic percentages given that several published RCT have documented that at least a minimum level of CPAP use of 5–6 h per night is required to reap benefits from it [9, 37, 40, 68, 71]. There is therefore a sizeable subset of patients on CPAP who either cease to use it altogether, or fail to use it enough hours per night and/or nights per week to achieve clinically-significant benefits.

The issue of adherence is generally a non-issue with surgery, especially beyond the initial recovery period. Once a patient's anatomy is changed, it should remain so. How effective is surgery? Admittedly, there are far fewer EBM (evidence-based medicine) level 1 RCT and many more EBM level 4 case series for OSA surgery, as should be expected given the ethical and methodological obstacles associated with performing double-blinded or

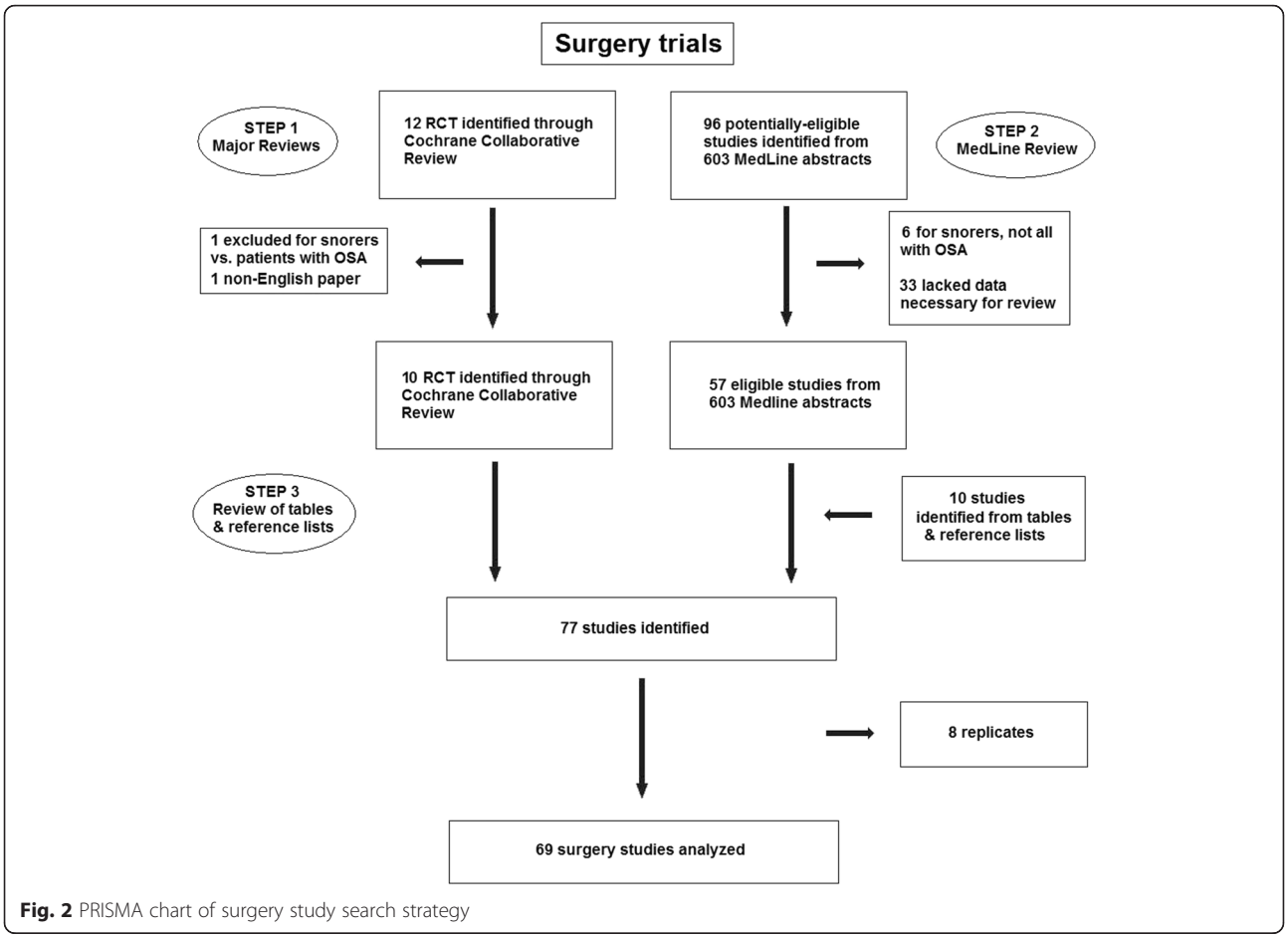

Fig. 2 PRISMA chart of surgery study search strategy

Table 1 CPAP versus surgery comparisons

First author - year	EBM rating	Study design	Treatment groups	Study findings	Study limitations/issues
Woodson 2003	1	RCT	nCPAP vs. RFTR vs. sham RFTR	Relative to sham Rx, rxn time & fastest rxn time both improved post-RFTR ($p = 0.03$ & 0.02) but not on CPAP.	Very poor CPAP complance (~16 h/week);
				ESS ↓ similarly with RFTR & CPAP (−2.1 vs. −2.3, $p = 0.005$ & 0.02). SNORE25 score ↓ w/both ($p < 0.001$ vs. 0.005)	Different # of Rx sessions in RFTR (4.5) vs. sham RFTR (2.9) groups
Ceylan 2009	3	nonRCT	TC-RFTR vs. nCPAP	Both RFTR & CPAP → ↓AHI (28.5 → 15.7 vs 29.6 → 16.1, both $p < 0.001$; NS); ↓ESS (11.1 → 8.4, $p = 0.003$ vs 10.8 → 8.2, $p = 0.003$; NS);	Non-random allocation to Rx/potential selection bias;
				↓CT90 (15.2 → 11.1 % vs 14.3 → 10.7 %, both $p < 0.001$; NS); & ↑LSAT (88.4 → 93.5, $p = 0.03$ vs 86.8 → 94.6 %, $p < 0.001$, NS). 53.8 vs. 52.4 % responders	Compliance with CPAP not reported
Weaver 2004	1	pop. survey	UPPP ± TE ± SP ± other vs. CPAP	1339/18,754 (7.1 %) died w/ CPAP vs. 71/2072 (3.4 %) post-op. Adjusting for age, gender, race, year of Rx & co-morbidities,	Retrospective analysis; potential confounders missing
				MR ↑ 31 % (95 % CI 3–67 %) w/CPAP ($p = 0.03$)	(e.g., severity of OSA, overall health status)

even controlled surgical trials. This being said, only 24 of the CPAP RCT described above were truly blinded, pitting therapeutic CPAP against sub-therapeutic (and thereby, sham) CPAP, rendering all comparisons, especially of subjective measures like the patient's level of sleepiness and quality of life, at least somewhat suspect. Clearly, all subjects in these studies knew that they were using an oral appliance, an oral placebo or nothing versus nasal CPAP. Interestingly, and harkening back to the issue of adherence, though CPAP tended to improve objective measures of OSA to a greater degree than oral appliances, patients consistently and decidedly preferred the latter [35, 55, 57, 60].

The limitations of EBM level 4 evidence set aside, among the 1802 patients who underwent OSA surgery across the 53 studies we analyzed, more than half (957, 53.1 %) were deemed to have experienced a 'good response'. This is despite the consistent use of strict criteria for a 'response' that ranged from Sher's criteria of no less than a 50 % reduction in AHI to a level of 20 events/hour or less [79], criteria that were used in 20 of the studies [80–99]; to being as stringent as no less than a 50 % reduction in RDI (which is similar to the AHI but also incorporates near-hyponeic events) to a level of 20 events/hour or less [100–106]; no less than a 50 % reduction in either AHI or RDI (the latter also incorporating near-hyponeic events) to a level of 15 or even 10 events/hour or less [91, 107–110]; and reducing AHI or RDI to ≤10 or even 5 events/hour [111–114] (Additional file 2). Mandibular/maxillo-mandibular advancement procedures had an especially high success (good response) rate of 87.0 % [84, 107, 115]. Moreover, there appeared to be a dose–response effect, with more aggressive procedures incorporating UPPP more effective than less aggressive procedures like tongue tissue ablation (Additional file 2), and more repetitions of treatments like laser- or radiofrequency- aided tissue reduction more effective than fewer repetitions [116].

Only three studies directly have compared CPAP and OSA surgery: one a randomized clinical trial comparing therapeutic radiofrequency-aided tissue reduction (RFTR), sham RFTR and nasal CPAP [117]; one a non-randomized clinical trial comparing RFTR and nasal CPAP [83]; and the third a population survey assessing long-term mortality among over 20,000 U.S. veterans who underwent either UPPP or CPAP therapy between October 1997 and September 2001 within the Veterans Affairs hospital system [118]. These results are summarized in Table 1. With the first study [117], subjective sleepiness, as measured with the Epworth Sleepiness scale (ESS), decreased to the same extent with RFTR & CPAP (−2.1 vs. −2.3, $p = 0.005$ & 0.02), as did the patients' level of snoring, as measured with the SNORE25 ($p < 0.001$ vs. 0.005), both effects superior to sham RFTR ($p < 0.001$). However, objective sleepiness, measured as each patient's average and shortest reaction time, only improved with RFTR ($p = 0.03$ and $p = 0.02$ versus sham therapy, respectively). In the non-randomized trial [83], RFTR and CPAP significantly reduced AHI versus baseline ($28.5 \rightarrow 15.7$ vs. $29.6 \rightarrow 16.1$, both $p < 0.001$; no significant inter-treatment difference), with similar significant reductions noted for the ESS score ($11.1 \rightarrow 8.4$, $p = 0.003$ vs. $10.8 \rightarrow 8.2$, $p = 0.003$; NS) and the percentage of time with oxygen saturation below 90 % ($15.2 \rightarrow 11.1$ % vs. $14.3 \rightarrow 10.7$ %, both $p < 0.001$; NS). The two treatments also produced a similar increase in the patient's lowest recorded nocturnal oxygen saturation level ($88.4 \rightarrow 93.5$, $p = 0.03$ vs. $86.8 \rightarrow 94.6$ %, $p < 0.001$; NS). Overall, 53.8 and 52.4 % of patients were deemed to be treatment 'responders' (NS).

Perhaps most alarming of these results are those of the survival study [118], in which 1339 out of 18,754 patients on CPAP died over the course of observation (7.1 %) versus just 71 of 2072 (3.4 %) post-operatively. Adjusting for patient age, gender, race, year of treatment and co-morbid illnesses, there still was a 31 % (95 % CI: 3–67 %) increase in mortality among CPAP patients ($p = 0.03$) versus their post-UPPP counterparts. It may be that some patients receiving CPAP were considered too ill to be surgical candidates, a confounder that would falsely elevate the CPAP mortality rate. It is also important to acknowledge that the study authors were not able to adjust for OSA severity or account for CPAP adherence. Nonetheless, it is clear that all prior assumptions that CPAP is both more effective and safer than surgery as first-line treatment for OSA warrant re-evaluation.

In summary, though it is true that the evidence supporting CPAP over surgery as first-line therapy for OSA is more strongly supported by EBM level 1 evidence, closer inspection reveals major limitations of that evidence and reasons to suspect that this long-held assumption should now be questioned. Among these limitations are the very short-term follow-up of almost all CPAP trials (versus the longer follow-up of surgical trials); the very high degree of CPAP non-adherence that, in the vast majority of trials, was not accounted for by intent-to-treat analysis; failure to identify any significant advantage of CPAP over surgery in the two trials in which these two approaches were compared directly; and the apparent 30 % increased mortality observed in veterans who received CPAP versus surgical treatment in the U.S. between 1997 and 2001. Surgery appears to be clinically successful long-term in at least half of OSA patients, in terms of reducing their AHI to normal or near-normal levels. Given all of this, the time has come to rethink our CPAP-first approach to the OSA patient, especially in those patients in whom adherence, for whatever reason, might be considered an issue. Within

that context however it is also imperative that surgeons understand that changing the current care ladder means also stressing the importance of correct patient selection and an appropriate consent process.

As a systematic review, this study is limited to the quality of the included studies. Because it is a collection of findings from various other studies, it provides an overview of the direction of literature but is unable to show new findings. This study is also limited in the fact that only English language articles are considered, which may introduce a language bias. However, studies are published from a variety of centers internationally. Because this study is not a meta-analysis, study results have not been statistically combined for more powerful results. One additional caveat is that studies were only graded by a traditional EBM approach as opposed to the more sophisticated Cochrane GRADE tool. This may introduce some level of bias to the priorities given to the various studies. However the large volume of literature reviewed for this paper should adequately compensate for that.

Conclusion

This review illustrates the need for an in-depth, thorough and critical analysis of the available treatment options for the OSA patient. Although CPAP is often documented as the gold standard or mandatory first line therapy for patients with OSA, a careful assessment of the outcomes provided by the literature does not support this assertion, especially when the concept of CPAP adherence is taken into account. Clinicians should consider a patient-centered approach to care wherein the patient's individual anatomical characteristics are evaluated in context of their OSA severity and treatment goals, and then tailor intervention to individual needs. In many patients beneficial surgical results may supplant the role of the CPAP machine when considering first line therapy.

Additional files

Additional file 1: Table S1. CPAP comparisons. (DOCX 60 kb)

Additional file 2: Table S2. Surgery findings. (DOCX 43 kb)

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

BR conducted the study design, and the majority of the writing. KP and EP assisted with writing, as well as compiling the data tables. CV assisted with intellectual contributions and editing of the paper. All authors read and approved the final manuscript.

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