REVIEW ARTICLES

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Efficacy versus Effectiveness in the Treatment of Obstructive Sleep Apnea: CPAP and Oral Appliances

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Obstructive sleep apnea (OSA) is a chronic disorder and effective long-term treatment is necessary to prevent associated health risks. Standard treatment remains continuous positive airway pressure which is highly efficacious but has well-recognized limitations, with suboptimal patient acceptance and adherence rates, which in turn obviates the desired health benefits. The leading alternative device treatment is oral appliances. Patients often report preferring oral appliances to CPAP treatment, with better usage rates. However, unlike CPAP, inter-individual variability in the efficacy of oral appliance therapy means that patients are often left with some residual OSA. Despite discrepancies in efficacy (apnea-hypopnea index [AHI] reduction) between CPAP and oral appliances, randomized trials show similar improvements in health outcomes between treatments, including sleepiness, quality of life, driving performance, and blood pressure. Similar results in terms of health outcomes suggests that although the two treatments have different efficacy and treatment usage profiles, these result in similar overall effectiveness. In this narrative review, we discuss efficacy versus effectiveness in relation to CPAP and oral appliance treatment of OSA.

Keywords: obstructive sleep apnea, treatment effectiveness, efficacy, CPAP, oral appliances

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Efficacy and effectiveness are important concepts to distinguish when evaluating treatment performance. Treatment efficacy refers to how well an intervention works under ideal circumstances whereas, effectiveness is how well an intervention performs in the real world where conditions are not controlled. Therefore treatment effectiveness is particularly important in management of chronic disease. Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repetitive upper airway obstruction leading to intermittent hypoxia and sleep fragmentation. There has been a dramatic increase in OSA prevalence over the last two decades, attributable to the obesity epidemic, with at least moderate OSA now evident in 17% of middle-aged men and 9% of middle-aged women.[1] OSA is associated with excessive daytime sleepiness and lower quality of life as well as increased risk of workplace and motor vehicle accidents, hypertension and cardiovascular disease, type 2 diabetes, and all-cause mortality.[2–9] Therefore effective management of this chronic disorder is imperative to not only improve symptoms but to prevent long-term health risks. Standard care is the highly efficacious treatment, continuous positive airway pressure (CPAP). This therapy involves delivery of pressurized air to the upper airway during sleep via a nasal mask interface and tube connected to a pump. The pressurized air acts to splint open the upper airway preventing it from collapsing during sleep. The effectiveness of this therapy is therefore dependent upon its ability to overcome airway collapse (efficacy) as well as the time course over which a patient applies it during sleep (compliance). While the efficacy of CPAP is generally high, in the real world long-term health effects of CPAP are likely to be compromised by low compliance and suboptimal hours of treatment use. Treatment usage as a proportion of the total sleep period when a patient is vulnerable to OSA is often overlooked as a confounder of efficacy. However, treatment usage compared to sleep time is an important aspect of real-world effectiveness. Importantly, treatment effectiveness warrants consideration when comparing effects of other OSA treatment options which may not have the same level of efficacy as CPAP but may have a better usage profile. In this review we discuss efficacy and effectiveness between first line OSA treatment CPAP and the leading alternative device treatment, oral appliances.

EFFICACY VERSUS EFFECTIVENESS IN OSA

Efficacy, in the context of OSA, reflects the ability of treatment to prevent the occurrence of obstructive breathing events during periods when the treatment is being physically applied. This is assessed by the number of obstructive breathing events *per hour of sleep* or apnea-hypopnea index (AHI). An AHI < 5 events/h indicates absence of disease or a completely efficacious treatment. In a fully compliant patient (using treatment for 100% of sleep time) efficacy measured as AHI on treatment ($AHI_{Treatment}$) will give an accurate reflection of OSA treatment effectiveness. However sleep time off treatment becomes an important consideration when compliance is suboptimal. The potential impact of suboptimal CPAP compliance on AHI has been considered using formulas that adjust $AHI_{Treatment}$ for sleep time off treatment when AHI can presumably revert to untreated levels ($AHI_{Untreated}$).[10,11] When the untreated portion of the night with OSA reoccurrence is taken into consideration, CPAP effectiveness can dramatically decrease depending on OSA severity and total sleep time. Good CPAP adherence is generally set at a benchmark of 4 h/night; however, the rationale for this benchmark is not overly evidence based. Moreover when taking into consideration sleep time off treatment, 4 h of CPAP use during an 8-h sleep period may only reduce

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the AHI by 50% due to reoccurrence of moderate OSA during the remaining 4 h without CPAP.[10] In this case, the true AHI is poorly represented by $AHI_{Treatment}$. It has therefore been proposed that treatment comparisons should be made on overall effectiveness after adjustment of efficacy for hours of usage over total sleep time.[12] In this context, although other OSA treatments such as surgery and oral appliances may be less efficacious, they offer more favorable compliance profiles (100% in the case of surgery), which may be an important determinant of the overall effectiveness, and may correlate more strongly with downstream health outcomes.

CPAP COMPLIANCE AND EFFECTIVENESS

Adequate CPAP compliance, based on reported average usage rates, is generally accepted as > 4 h on ≥ 70% if nights.[13] However, even with strategies to enhance patient acceptance and usage, only ~50% of patients use CPAP ≥ 4 h per night after 6 months.[14] The proportion of patients maintaining this minimally acceptable level of CPAP usage further drops to 17% after 5 years.[15] Furthermore this 4-h threshold is arbitrary and not necessarily adequate to convey benefits for *all* important health outcomes. In reality, a dose response relationship has been observed between hours of CPAP use and a range of subjective and objective health benefits with differing benefit thresholds for different outcomes.[16–18] For example, normalization of subjective sleepiness (ESS), objective sleepiness (multiple sleep latency test), and disease specific functional status (functional outcomes of sleep questionnaire [FOSQ]) requires 4, 6, and 7.5 h, respectively, of nightly CPAP usage.[18] In hypertensive OSA patients, ≥ 5.6 h of CPAP usage is required to sustain a long-term reduction in blood pressure.[19] CPAP usage > 6 h per night shows greatest reduction in mortality risk.[20] Therefore to maximize treatment benefits for all important health outcomes, CPAP needs to be consistently used for the majority, if not all, of the sleep period. Given that this is generally not a reality for most CPAP users, there is a clear rationale for conducting comparative effectiveness trials against alternative less efficacious treatments which may still be equally effective at improving health outcomes due to higher compliance rates.

ORAL APPLIANCES IN TREATMENT OF OSA

Oral appliances are the leading device alternative to CPAP. Oral appliances cover the upper and lower dental arches and are configured so that the lower jaw is held forward in a more protruded position. The action of mandibular advancement results in an increase in pharyngeal airway space and reduces airway collapsibility.[21,22] Oral appliances have a demonstrated role in improving snoring, obstructive apneas and hypopneas, and oxygen desaturation measures.[23] Oral appliances also have demonstrated benefit on health outcome measures such as daytime sleepiness and blood pressure.[23,24] However unlike CPAP which will prevent airway collapse in most people as long as sufficient pressure is applied, therapeutic response to oral appliance treatment shows intra-individual variability. In general terms, over a third of patients will show a complete response to oral appliance therapy with a reduction in AHI to < 5/h (or no OSA). Another third will have a clinically important response showing > 50% reduction in AHI,[25] although AHI remains > 5/h and a third will not achieve > 50% reduction in AHI. There are many factors which may contribute to differences in therapeutic response to oral appliance therapy including differences in devices and treatment protocols but also craniofacial, upper airway, and obesity characteristics of the patient.[25] Currently there is no validated clinical method to reliably pre-select patients who will receive sufficient benefit from oral appliance therapy from those who show minimal therapeutic response. Uncertainty around efficacy has essentially restricted oral appliance implementation to milder cases of OSA with consideration only in more severe OSA if CPAP fails.[26]

COMPARISON OF HEALTH EFFECTS OF CPAP AND ORAL APPLIANCE THERAPY

Although CPAP is clearly superior to oral appliances in terms of eliminating obstructive breathing events and improving nocturnal oxygen saturation,[27] this is not the case for health outcomes. In randomized controlled trials comparing CPAP to oral appliance treatment, CPAP consistently demonstrates normalization of AHI, whereas average AHI remains in the range of mild OSA on oral appliance treatment.[28–35] However the superiority of CPAP in terms of efficacy is generally not carried through to the actual health outcomes of treatment. A summary of randomized controlled trials comparing CPAP and oral appliances with commonly reported health outcomes is summarized in Table 1. Subjective daytime sleepiness, assessed by the Epworth Sleepiness Scale, does not differ following CPAP and oral appliance treatment.[36] This has also been shown in objective tests of sleepiness[32,37] and simulated driving performance.[35,38] Furthermore, in terms of cardiovascular outcomes there is no demonstrated difference between treatments in short-term effects on blood pressure.[29,34,35] In a small study both CPAP and oral appliances were found to improve endothelial function to the same degree.[39] To date short-term treatment studies comparing CPAP and oral appliance overall consistently show minimal to no difference in health outcome measures despite demonstrating a higher $AHI_{Treatment}$ with oral appliances. Longer term studies are lacking, although a recent 6-year observational study of untreated and treated (either CPAP or oral appliance) OSA patients found OSA treatment reduced the cardiovascular mortality rates regardless of whether CPAP or oral appliance treatment was used.[40]

A likely explanation for similarity in key health outcomes is that oral appliances are more consistently used for a greater proportion of the total sleep period, compared to CPAP. Greater usage may counterbalance the lower treatment efficacy and result in overall equivalent treatment effectiveness. Oral appliances were preferred to CPAP in four of six crossover trials asking for treatment preference at the end of the trial.[30–32,35] This preference for oral appliance treatment may translate to significantly more hours of usage. A review of reported treatment times in oral appliance studies suggests usage remains at a median of 77% of nights after one year of treatment.[41] However, it has been possible to objectively verify CPAP usage by data download for many years, while comparison to oral appliance

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Table 1—Efficacy and effectiveness of oral appliances versus CPAP: AHI and health outcome results from randomized trials.

Study	Study Design	N	Baseline AHI	Treatment AHI		Health Outcomes			
						Daytime Sleepiness		Health-Related Quality of Life	Blood Pressure
				CPAP	OA	Subjective (ESS)	Objective		
Aarab, 2010	parallel	57	20.9 ± 9.8	1.4 ± 13.1	5.8 ± 14.9	↔	N/A	↔	N/A
Barnes, 2004	crossover	80	21.5 ± 1.6	4.8 ± 0.5	14.0 ± 1.1	↔	↔ (MWT)	N/A	↔
Engleman, 2002	crossover	48	31 ± 26	8 ± 6	15 ± 16	CPAP	CPAP (MWT)	CPAP	N/A
Ferguson, 1997	crossover	20	26.8 ± 11.9	4.0 ± 2.2	14.2 ± 14.7	↔	N/A	N/A	N/A
Gagnadoux, 2009	crossover	59	34 ± 13	2 (1–8)#	6 (3–14)#	↔	↔ (OSLER)	OA	N/A
Hoekema, 2008	parallel	103	40.3 ± 27.6	2.4 ± 4.2	7.8 ± 14.4	↔	N/A	↔	N/A
Lam, 2007	parallel	101	23.8 ± 1.9^	2.8 ± 1.1	10.6 ± 1.7	CPAP	N/A	CPAP	↔
Phillips, 2013	crossover	108	25.6 ± 12.3	4.5 ± 6.6	11.1 ± 12.1	↔	N/A	↔	↔
Tan, 2002	crossover	21	22.2 ± 9.6	3.1 ± 2.8	8.0 ± 10.9	↔	N/A	↔	N/A

#Median (interquartile range). ^Mean ± standard error. Summary of AHI data with CPAP and oral appliances (OA) in randomized trials comparing treatments. Summary of commonly reported health assessments are presented. "CPAP" or "OA" indicates superior results were found with that treatment, ↔ indicates equivalent findings observed with both treatments. AHI data is mean ± standard deviation, unless otherwise indicated. ESS, Epworth Sleepiness Score; MWT, maintenance of wakefulness test; OSLER, oxford sleep resistance test.

usage has been limited to self-report until recently. Therefore, even though self-reported oral appliance usage appears to exceed that of objectively downloaded CPAP usage, it has been difficult to compare usage profiles between therapies. The recent advent of objective compliance monitors for oral appliances in the form of small embedded temperature-sensing chips[42] now makes verification of usage patterns possible. Initial studies of objective oral appliance usage confirm good usage of > 7 hours a night in the initial 3 months of oral appliance treatment[42] which is maintained at > 6 hours per night after one year.[43] Furthermore the discrepancy of over an hour between subjective and objective CPAP usage[13] does not seem to be apparent with oral appliance treatment, with initial studies reporting < 30 minutes difference between subjective estimates and objective data.[43] Regardless, initial evidence from oral appliance compliance monitors lends support to greater usage of oral appliance therapy than CPAP.

SLEEP ADJUSTED RESIDUAL AHI (SARAH INDEX) FOR ASSESSMENT OF TREATMENT EFFECTIVENESS

Evidence of equivalent health outcomes between oral appliances and CPAP suggest that real-world treatment effectiveness is not captured by the efficacy measure $AHI_{Treatment}$. However this is the metric on which clinical decisions are primarily made, although it is well recognized that CPAP is not used for all hours of sleep. The different treatment profiles of CPAP (high efficacy/low adherence) and oral appliances (moderate efficacy/high adherence) may conceptually result in similar profiles of treatment effectiveness. In the schematic in Figure 1, two identical sleep periods in which OSA can occur is represented by a grid (white boxes) for which CPAP and oral appliance are applied. Treatment effectiveness is a composite of efficacy (represented on the y axis of the grid) and hours of treatment usage (represented on the x axis). In this example MAS is only half as efficacious as CPAP, but compliance is twofold greater. Despite these different treatment profiles, both treatments have similar overall effectiveness in relieving OSA (shaded area). This conceptual example likely reflects many patients in the real world, for whom CPAP is highly efficacious but treatment usage is modest, while oral appliances may have more modest efficacy but are used for relatively more of the sleep period. Potentially a more representative measure of treatment effectiveness than $AHI_{Treatment}$ should also take into account hours ON treatment ($AHI_{Treatment}$) *and* hours OFF treatment ($AHI_{Untreated}$) for the TOTAL sleep period. We adopt the formula of Ravesloot and colleagues,[12] which accounts for these additional factors in order to assess a more accurate measure of treatment effectiveness, which we have called the Sleep Adjusted Residual AHI or SARAH Index. Potentially such an index which incorporates these currently overlooked factors could be a more accurate measure of treatment effectiveness and will better align with downstream health benefits. The formula is expressed below:

$$\text{Sleep Adjusted Residual AHI (SARAH Index)} = \frac{[AHI_{Treatment} \times Hours_{Treatment}] + [AHI_{Untreated} \times Hours_{Untreated}]}{Hours_{Total\ Sleep\ Time}}$$

COMPARISON OF AHI AND SLEEP ADJUSTED RESIDUAL AHI (SARAH INDEX) IN CPAP AND ORAL APPLIANCE TREATMENT

We have previously published a large cross-over study (108 completers) of one month each of optimized CPAP and oral appliance treatments.[35] This study found that oral appliances were non-inferior to CPAP across a range of health outcomes in predominantly moderate-severe patients. There were no between-treatment difference in cardiovascular (24-h

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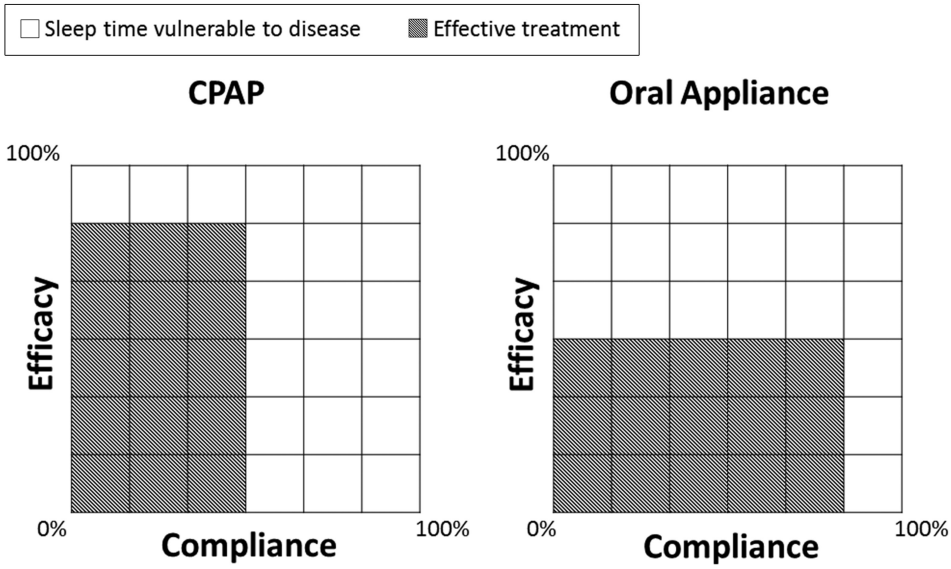
Figure 1—Comparison of treatment effectiveness profile of CPAP and oral appliances.



Efficacy (y axis) reflects the ability of treatment to prevent obstructive breathing events when it is physically applied. Compliance (x axis) reflects the hours the treatment is applied for over the total sleep time when obstructive events can occur. "Effectiveness" requires both efficacy and compliance and the balance of these likely reflects over health outcomes. This schematic illustrates the scenario of an oral appliance which is only half as efficacious as CPAP but has two-fold greater compliance which results in equivalent effectiveness (shaded area).

blood pressure, arterial stiffness), neurobehavioral (subjective sleepiness, driving simulator performance), or quality of life outcomes. In a subgroup of hypertensive patients, blood pressure during sleep reduced from baseline with both treatments, but more importantly, with no difference between them. In comparing the efficacy profiles of the two treatments, as expected, polysomnography confirmed OSA resolution on CPAP, whereas residual mild OSA was evident with oral appliance treatment (AHI 4.5 ± 6.6 vs. 11.1 ± 12.1/h). However, self-reported compliance favored oral appliances at an average 1.3 h more usage per night than CPAP. These efficacy and compliance profiles of CPAP and oral appliance treatment suggest that superior CPAP efficacy may be offset by greater oral appliance usage. We now use real data from this trial to compare AHI and SARAH Index between CPAP and oral appliance treatments across the spectrum of OSA severity.

Median treatment AHI on CPAP from this trial was 4.7/h (i.e., elimination of OSA). We have used $AHI_{Treatment}$ of 4.7/h to calculate the SARAH Index at different levels of treatment usage hours for an 8-h sleep period (healthy sleep time range[44]). Figure 2 shows the results from calculation of SARAH Index across a range of OSA severity ($AHI_{Untreated}$). If CPAP is used for the total 8-h sleep, OSA is indeed resolved (AHI = 4.7) for all levels of OSA severity. However, it is recognized that as many as 50% of CPAP treated patients are using their treatment < 4 h of total sleep time.[15] Using this example of an 8-h sleep period, the graph demonstrates that patients using their device for 4 and 2 h per night have at least mild OSA assessed by the SARAH Index, with much higher levels in those with more severe OSA. As total sleep time decreases, the SARAH Index reduces; however, for an average 8-h sleep period, the majority of CPAP users would be effectively under-treated based on known compliance rates. As CPAP usage further declines long term, CPAP treatment effectiveness may additionally become worse over time. This graph illustrates that when taking into consideration CPAP hours used over sleep time, OSA may not be well controlled, and even moderate-severe OSA may still be present in more severe and less compliant patients who sleep for longer periods. The SARAH Index calculation raises the possibility that despite high efficacy, CPAP users may not be effectively treated in practice.

Oral appliance usage data from this same trial[35] found median reported usage time to be 95% of total sleep time. We have used this 95% compliance rate to assess oral appliance treatment effectiveness by the SARAH Index. With good self-reported usage of nearly 100% of sleep time the influencing factor on treatment effectiveness for oral appliances is their efficacy, expressed as a percentage improvement in OSA from baseline levels. We show SARAH Index for different OSA severities across different levels of oral appliance efficacy of 25%, 50%, 75%, and 100% improvement in Figure 3. Oral appliance treatment effectiveness expressed by SARAH Index varies with efficacy and OSA severity. We have shown in a large audit of oral appliance treated patients that the majority (70%) will have ≥ 50% improvement in OSA using an oral appliance.[45] If we compare Figures 2 and 3, CPAP and oral appliance treatment effectiveness measured by the SARAH Index, conceptually we can see that many patients may be effectively undertreated with either treatment. However, with half of all CPAP treated patients using it < 4 h per night and two-thirds of oral appliance treated patients reducing OSA by at least half, theoretically many patients with incomplete efficacy on oral appliance may be no worse off than when on fully efficacious CPAP in terms of treatment effectiveness.

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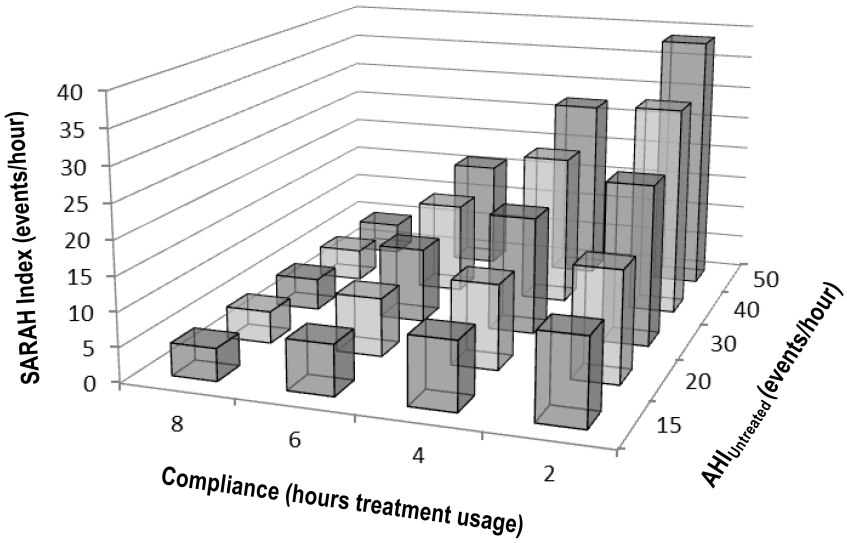
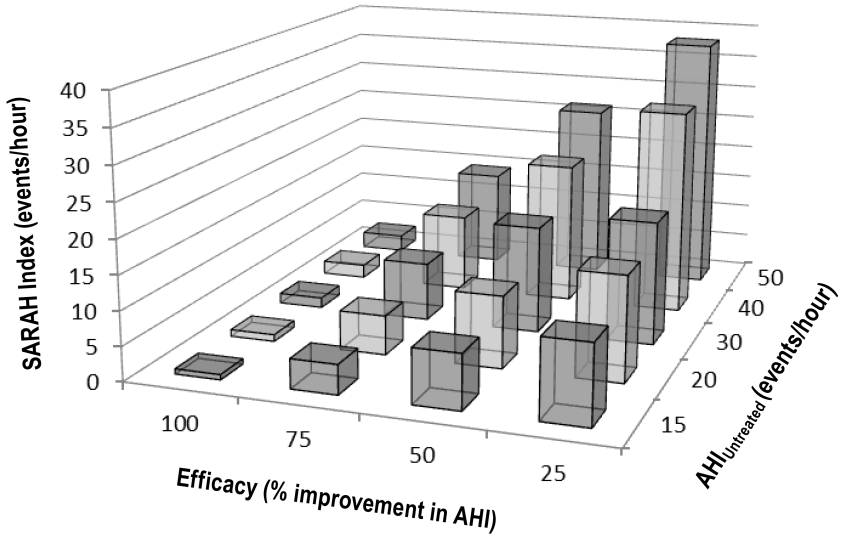
Figure 2—CPAP effectiveness assessed by the Sleep Adjusted Residual AHI (SARAH Index).



This figure illustrates SARAH Index for different levels of OSA severity ($AHI_{Untreated}$) for varying hours of treatment usage for an average 8-h sleep time. An $AHI_{Treatment}$ of 4.7 events/h is used (elimination of OSA). When taking into consideration CPAP hours used over sleep time, OSA may not be well controlled in moderate-severe patients using CPAP 4 hours or less for 8 h of sleep.

Figure 3—Oral appliance effectiveness assessed by the Sleep Adjusted Residual AHI (SARAH Index).



In contrast to CPAP, oral appliance hours of usage are reported to be high (95% of sleep time). However efficacy levels are variable with oral appliances. This figure illustrates SARAH Index for different levels of efficacy (% improvement in AHI). The majority of patients have 50% or greater improvement in $AHI_{Treatment}$ using an oral appliance. Therefore by SARAH Index calculation, many patients may not be worse off on oral appliance treatment despite $AHI_{Treatment}$ > 5/hour compared to CPAP used for minimal hours compared to total sleep time.

POTENTIAL CONFOUNDERS OF EFFECTIVENESS CALCULATION

Although treatment efficacy is not an adequate indicator of health benefit, effectiveness measures, such as the calculation presented as the SARAH Index, also have potential limitations. The formula assumes that OSA will return to baseline levels once treatment is removed before the end of the sleep period. Withdrawal of CPAP results in return of OSA.[46–48] However, short-term carryover effects after CPAP removal may occur resulting in reduced OSA despite being without treatment. Sustained effects of CPAP may be due to an ongoing increase in pharyngeal volume and airflow due to reduced soft tissue edema as a consequence of CPAP use.[49,50] The evidence for existence and duration of CPAP washout effects has been recently reviewed.[51] Studies re-assessing OSA after CPAP

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withdrawal for several nights to weeks find lower AHI levels then recorded at baseline, potentially more evident in severe OSA patients,[48] although this is not always observed.[47,52,53] Regardless of baseline severity, AHI does appear to deteriorate between the first and seventh night of CPAP withdrawal.[54] Furthermore, although some CPAP washout effect is observed in studies, the extent and duration is highly variable and potentially confounded by issues of night to night variability in measurement of sleep-disordered breathing.[55,56] In particular, it is unknown whether such a phenomenon occurs within a single night. In terms of oral appliances, OSA levels return to baseline after a week of a placebo oral appliance (no active advancement).[57] However residual effects of mandibular advancement once the lower jaw returns to normal position, or a washout effect, may be less plausible with oral appliances than CPAP.

This effectiveness assessment also does not take into account differences in OSA severity due to body position and sleep stage. OSA may become more severe in the supine position and REM sleep and treatment effectiveness, particularly of oral appliances, may vary under these conditions.[45] CPAP removal after several hours may leave the patient exposed to the portion of the night with more concentrated REM sleep, and hence more severe OSA. Treatment carryover effects and OSA variability due to body position and sleep stage are not captured in the simple assessment of time on versus off treatment at $AHI_{Treatment}$ and $AHI_{Baseline}$, and would be difficult to do so routinely. However, whether this approximation of effectiveness will be more clinically useful than relying only on a potentially false reassurance of $AHI_{Treatment}$ needs further assessment. If proven to give a more reliable measure of effectiveness, another obstacle to adopting an index such as SARAH Index would be related to technological limitations with estimating sleep time in the home setting. Although the growing adoption of lifestyle wearable devices that monitor aspects of sleep may prove useful in this regard.

CONCLUSIONS AND FUTURE DIRECTIONS

Although effectiveness, as a combined measure of real world usage and efficacy, is difficult to accurately assess, proposed formulas which account for sleep time on and off treatment potentially may be a more accurate marker of health outcome responses. However this remains to be assessed in prospective trials. There is limited evidence of comparative effectiveness of CPAP and oral appliance treatments longer-term. If equivalent short-term health outcomes are found to be sustained in the long term, this opens up treatment options for patients with this chronic disease. Comparative-effectiveness and Patient-Centered Outcomes Research aims to help patients (and their healthcare providers) to make informed decisions about health and healthcare options base on outcomes that are important to them.[58] We propose a greater emphasis on treatment effectiveness rather than efficacy as part of a chronic disease management approach. Future comparative effectiveness research of CPAP and Oral appliance treatment could allow patients more freedom to choose their preferred treatment over all aspects of treatment effectiveness and health outcomes.

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