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CLINICAL REVIEW

Efficacy of pharmacotherapy for OSA in adults: A systematic review and network meta-analysis

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SUMMARY

Pharmacotherapy represents a desirable potential therapeutic alternative for patients with obstructive sleep apnoea (OSA). We aimed to summarize evidence on the efficacy of pharmacotherapy in adults with OSA and delineate the underlying mechanisms.

Seven databases were systematically screened for randomised controlled trials (RCTs) from their inception to September 2018. According to a pre-registered study protocol (PROSPERO-ID-CRD42018086446) network meta-analysis was performed to obtain intervention effects on the apnoea-hypopnoea-index (AHI) based on data extracted from published reports.

We identified 58 RCTs ($n = 1710$ patients) investigating 44 different drugs or drug-combinations. Interventions were classified into seven pathomechanism-groups and summarized narratively. A meta-analysis of 17 trials for seven drugs (acetazolamide, donepezil, mirtazapine, ondansetron, paroxetine, protriptyline, theophylline) indicated a small effect for acetazolamide (mean difference in AHI −9.6/h [−17.7; −1.4]; $p = 0.02$). In the network meta-analysis ($I^2 = 50\%$) nine drugs (tramazoline, liraglutide, spironolactone/furosemide, acetazolamide, dronabinol, zonisamide, phentermine, spironolactone, and ondansetron/fluoxetine) significantly lowered the AHI compared to placebo.

Although some trials indicate favorable outcomes, these results are only valid for distinctive OSA-phenotypes or were not clinically significant. The effect sizes were small, the majority of trials were not adequately powered. There is currently insufficient evidence to recommend any pharmacotherapy for OSA and no phase-III trials are available.

Introduction

Obstructive sleep apnoea (OSA) is a major public health problem, causing high blood pressure, excessive daytime sleepiness, and impaired quality of life [1–4]. The prevalence of OSA is primarily affected by age and body-mass-index (BMI) but also depends on by other (potentially modifiable) traits, including alcohol consumption, menopause, distinct craniofacial features, connective tissue disorders, and nasal congestion [5–8]. On an individual level, it has been recognized that poor muscle responsiveness, an oversensitive ventilatory control system (i.e., high loop gain), and a low respiratory arousal threshold are intrapersonal traits contributing to OSA [9]. The possibility to phenotype this heterogeneous disease on an epidemiologic and individual level and to further quantify the relative contribution of each factor to disease severity, enables a new potential for personalized treatment [9].

The current gold standard treatment, continuous positive airway pressure (CPAP) therapy, effectively counteracts all mechanisms stated above and represents an effective treatment of all OSA phenotypes. However, a successful initiation of long-term CPAP-therapy is only tolerated in approximately 40–60% of all patients, and thus represents a major limitation in OSA treatment [10]. Alternative OSA therapies usually target one specific disease trait, which often achieves promising results in carefully selected patients but the overall efficacy falls short when compared to CPAP [2,11]. Mandibular advancement devices, upper airway surgery, and hypoglossal nerve stimulation represent some of the alternative therapies for certain patients who decline or fail to adhere to CPAP [3].

Besides established OSA-therapies, which rely on mechanical interventions, pharmacotherapy represents an easily applicable

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Glossary of terms

AHI	apnoea-hypopnoea-index
BMI	body-mass-index
CPAP	continuous positive airway pressure
IQR	interquartile range
OSA	obstructive sleep apnoea
PROSPERO	international prospective register of systematic reviews
RCT	randomised controlled trial
SD	standard deviation

and attractive alternative for the treatment of OSA. Despite the huge number of potential drug-targets in the field of sleep apnoea [12], there is currently no approved pharmacotherapy available to reduce OSA severity. Although societies such as the American Academy of Sleep Medicine regularly monitor potential pharmacological candidates for OSA treatment, the outlook and evolution of this research area remains vague [13]. Previous reviews in this field either have concentrated on a single aspect of this development or did not distinguish the underlying mechanisms of pathophysiology [14–18].

The specific aims of this systematic review were to (1) summarize all available evidence from randomised controlled trials (RCTs) on the efficacy of pharmacotherapy in OSA, (2) examine the underlying mechanisms of pharmacotherapy in OSA, and (3) ascertain the research activity in this field to create a framework for future research on this topic. To achieve these aims, we performed a systematic review and network meta-analysis of RCTs including adults with OSA.

Methods

Search strategy and inclusion criteria

Due to the expected heterogeneity in this field, trials were narratively summarized according to their pathomechanism-group, trials on the same drug were included in a meta-analysis, and finally the data was incorporated in an overall network model. Eligible, trials must have randomised patients aged ≥18 y with a diagnosis of OSA defined by an apnoea-hypopnoea index (AHI) of ≥5 per hour to any combination of at least one pharmacotherapy, an inactive control (e.g., placebo), or established OSA-therapy (e.g., CPAP).

Trials investigating oxygen-therapy, the perioperative/-procedural period (i.e., involvement of anaesthetics), central sleep apnoea, and OSA at high-altitude were not considered eligible for this review. RCTs including patients with a concurrent disease (i.e., Parkinson disease, Alzheimer disease, diabetes mellitus and cardiovascular disease including obesity, psoriasis) were considered eligible for inclusion; however, trials investigating pharmacological treatment of OSA-associated conditions (e.g., hypertension, cardiovascular consequences, excessive daytime sleepiness, etc.) were not considered eligible and are summarized elsewhere [19–21]. Furthermore, trials with the additional use of CPAP (i.e., parallel to pharmacotherapy), mandibular advancement devices and oxygen therapy were excluded. The protocol for this study was generated a priori, reviewed, registered (CRD42018086446), and published by the international prospective register of systematic reviews (PROSPERO) and is available in the supplementary files. The screening process (for strategy see Tables 1–8, supplementary files) considered seven databases (Medline, EMBASE, Cochrane, Web of Science, PsycInfo, Clinicaltrials.gov, ICTRP-WHO) from their inception to September 01 2018. Study bibliographies were also reviewed. Additional information is available in the supplementary files.

Data analysis

Two authors independently extracted summary estimates from eligible trials. If standard errors were reported, these were converted to standard deviation (SD) by multiplying by the square root of the sample size. If median and interquartile range (IQR) were reported, we treated the median as a mean (assuming approximate normality), and converted the IQR to a SD by dividing half the IQR by 0.6745. Treatment effects were computed using the *escalc()* function from the metafor package [22] in R (R Core-Team 2018). Meta-analysis was performed the *rma()* function from the metafor package, using the random effects model. Network meta-analysis was performed using both, consistency and inconsistency models with the *rma.mv()*-function [23]. The statistical analysis was performed using R (R-version 3.4.4).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 58 RCTs investigating 44 different drugs or combinations met the inclusion criteria (Fig. 1) [24–39,40–81]. Summaries of the characteristics of included RCTs are presented in Table 1 and a more detailed summary can be found in the supplementary files. Five trials were excluded from quantitative analysis due to lack of reporting for AHI or oxygen-desaturation index [25,28,43,70,79], and two trials were excluded because they only compared the intervention to CPAP [77,81]. There was no evidence for a publication bias (Fig. 1, supplementary files). Considering all drugs included in the quantitative analysis, patients treated with drugs had an AHI that was on average 4.6 (−4.6, 95% CI −6.7 to −2.6, $p < 0.0001$ [consistency]) points lower than patients treated without medication. In the inconsistency model, the treatment effect of all drugs was similar (−4.7, −6.9 to −2.6, $p < 0.0001$ [inconsistency]). We note that in this case, the consistency and inconsistency models are exactly the same.

17 trials investigating seven drugs versus placebo were summarized in a meta-analysis (Fig. 2) with only acetazolamide showing a statistically significant result. Finally, 51 RCTs with 44 different drugs or combinations versus placebo were included in the network meta-analysis (Fig. 3), nine drugs significantly lowered the AHI. We also investigated the predicted effects on AHI and oxygen-desaturation index by drug categories (Figs. 3–4, supplementary files), only antidepressants, antihypertensives, and drug-combinations successfully lowered the AHI. As expected, heterogeneity between the studies was high (AHI: $I^2 = 50\%$, oxygen desaturation index: $I^2 = 66\%$). However, there was no significant heterogeneity in the studies when we considered only the seven drugs that were studied in more than one RCT. All RCTs and ongoing trials (Table 10, supplementary files) were categorized into seven pathomechanism groups (Fig. 4) and are summarized below.

Drugs proposed to act on the upper airway muscle tone

Most recent pharmacological approaches in the treatment of OSA have focused on modulating serotoninergic and cholinergic activities, as both have been shown to augment pharyngeal muscle

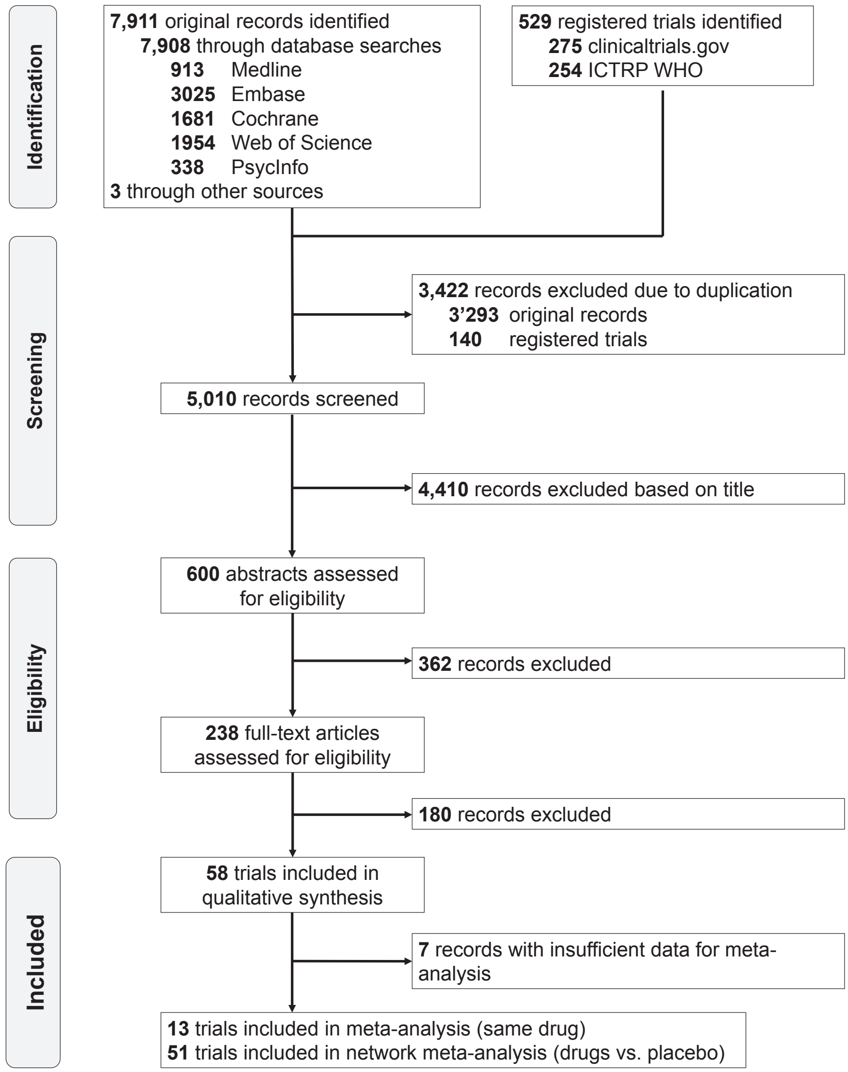

Fig. 1. PRISMA study flow chart. Screening, assessment for eligibility (TG, ST), data extraction (TG, MO) was completed independently by two authors. Disagreements in study identification and in extracted data between investigators were resolved by discussion and consensus.

tone. Overall, 13 RCTs tested interventions with antidepressants (fluoxetine [63], mirtazapine [30,58], paroxetine [26,53], protriptyline [28,67,75], desipramine [71], buspirone [59], and trazodone [66]) or antiemetics (ondansetron [63,68]) involving the serotonin-pathway. While the intervention with ondansetron alone had no effect on OSA-severity [68], the combination with fluoxetine was generally well tolerated and resulted in a ~40% reduction from baseline AHI in a non-phenotyped OSA population [63]. It is noted that this effect lasted for 28 nights but daytime sleepiness was not affected by the intervention [63].

The intervention with mirtazapine initially showed promising results in a pilot-study [30] but these findings could not be reproduced in two larger phase-IIa trials [58]. Considering the significant weight-gain under mirtazapine, this intervention is an unlikely candidate for successful OSA treatment (Fig. 2), as obesity itself contributes to the pathogenesis of OSA. One RCT described an augmented inspiratory genioglossus activity after an intervention with paroxetine. However, this effect was also not sufficient to conclusively lower the AHI in two OSA-populations (Fig. 2) [26,53]. Regarding the change in AHI, three RCTs testing protriptyline did not find any effect on this outcome (Fig. 2) [28,67,75]. Interestingly, one RCT testing desipramine in an unselected OSA population did not show any significant effects regarding AHI but when patients were phenotyped post-hoc, those patients with a minimal upper airway response at baseline showed the greatest reduction in AHI [71].

While trials testing buspirone were inconclusive [59], one trial on trazodone reported a statistically significant reduction in AHI in 15 patients undergoing a cross-over design. Unfortunately, the intervention lasted only one night, therefore the clinical significance of this relatively small effect remains unclear [66].

Four RCTs on parasympathomimetics (physostigmine [45], donepezil [44,60,69]) involving the cholinergic pathway have tried to modulate muscle contraction via muscle end-plate depolarization at the neuromuscular junction. During the nocturnal infusion of physostigmine a ~20% AHI reduction was reported [45]. Another RCT by the same group reported on the orally available donepezil, where the intervention reduced the AHI by 31%, but this effect was mostly limited to REM sleep only [44,45]. RCTs on donepezil in the following years consistently reported a similar (but moderate) AHI reduction (−20% over one month [69] to −50% over three months [60]) which also corresponded with an improvement in daytime sleepiness [69]. Meta-analysis on donepezil (Fig. 2), however, did not show a statistically significant reduction in AHI.

Other RCTs testing drugs with potential effects on the upper airway muscle tone (the sympathomimetic salmeterol [64] and the GABA-receptor antagonist flumazenil [65]) were negative.

Table 1

Included RCTs by pathomechanism. The mean age of the included study-population (n = 1697 patients) was 50.1 ± 5.6 y and 84.8% were male. Included studies recruited a median of 30 (IQR 10-34) patients; one study contributed more than 20% of all patients (n = 359) to this review [27]].

Study	Design	n	Age ±SD	%Male	Drug	Description	Application	Dosage	Proposed mechanism	Control	Duration
Drugs proposed to act on the upper airway muscle tone											
Berry et al., 1999 [26]	2-way cross-over	8	48 ± 5	100	Paroxetine	SSRI (antidepressant)	oral	1 × 40 mg	Airway muscle tone	Placebo	2 × 1 night
Brownell et al., 1982 [28]	2-way cross-over	5	46 ± 5	100	Protriptyline	(Non-sedating) Tricyclic antidepressant	oral	1 × 20mg	Airway muscle tone	Placebo	2 × 14 nights
Carley et al., 2007 [30]	3-way cross-over	12	41 ± 16	58	Mirtazapine	NaSSA (α2-antagonist)	oral	1 × 4.5 or 1 × 15 mg	Airway muscle tone	Placebo	3 × 7 nights
Hedner et al., 2003 [45]	2-way cross-over	10	43 ± 7	100	Physostigmine	AChEI (parasympathomimetic)	intravenously	1 × 0.12 μg/min/kg	Respiratory coordination/Airway muscle tone	Placebo	2 × 1 night
Hedner et al., 2005 [44]	2-way cross-over	38	52	unclear	Donepezil	AChEI (parasympathomimetic)	oral	1 × 5 mg	Ventilatory drive	Placebo	2 × 1 nights
Kraiczi et al., 1999 [53]	2-way cross-over	20	52 ± 9	100	Paroxetine	SSRI (antidepressant)	oral	1 × 20 mg	Airway muscle tone	Placebo	2 × 42 nights
Marshall et al., 2008 [58]	3-parallel-groups	65	52 ± 7	86	Mirtazapine/ Compound CF0012	NaSSA (atypical antidepressant) (α2-antagonist)	oral	1 × 15 mg (M) and unclear (C)	Airway muscle tone	Placebo	1 × 28 nights
Mendleson et al., 1991 [59]	2-way cross-over	5	45 ± 3	100	Buspirone	Selective partial agonists at 5-HT_{1A} (anxiolytic)	oral	20 mg	Ventilatory drive	Placebo	2 × 1 night
Moraes et al., 2008 [60]	2-parallel-groups	23	75 ± 9	35	Donepezil	AChEI (parasympathomimetic)	oral	1 × 5 mg and 1 × 10 mg	Ventilatory drive	Placebo	1 × 90 nights
Prasad et al., 2010 [63]	4-parallel-groups	35	48 ± 10	66	Ondansetron/ Fluoxetine	5-HT_3 rezeptor antagonist (Antiemetic)/SSRI (antidepressant)	oral	1 × 12 or 24 mg (O) and 5 and 10 mg (F)	Airway muscle tone	Placebo	1 × 21 nights
Rasche et al., 1999 [64]	2-way cross-over	20	53 ± 8	80	Salmeterol	LABA (bronchodilator)	oral	1 × 50 μg	Airway muscle tone	Placebo	2 × 1 night
Schönhofer et al., 1996 [65]	2-way cross-over	10	55 ± 8	100	Flumazenil	Benzodiazepin-antagonist	intravenously	1 × 2 mg	Airway muscle tone	Placebo	2 × 1 night
Smales et al., 2015 [66]	2-way cross-over	15	52 ± 3	60	Trazodone	SARI (antidepressant)	oral	100 mg	Arousal Threshold	Placebo	2 × 1 night
Stepanski et al., 1988 [67]	2-way cross-over	8	45 ± 8	100	Protriptyline	(Non-sedating) Tricyclic antidepressant	oral	1 × 10 mg to 1 × 20 mg	Airway muscle tone	Placebo	2 × 21 nights
Stradling et al., 2003 [68]	2-way cross-over	10	53 ± 11	90	Ondansetron	5-HT_3 receptor antagonist (Antiemetic)	oral	1 × 16 mg	Airway muscle tone	Placebo	2 × 1 night
Sukys-Claudino et al., 2012 [69]	2-parallel-groups	21	52 ± 9	100	Donepezil	AChEI (parasympathomimetic)	oral	1 × 5 mg and 1 × 10 mg	Airway muscle tone	Placebo	1 × 28 nights
Taranto-Montemurro et al., 2016 [71]	2-way cross-over	14	55 ± 13	71	Desipramine	(Non-sedating) Tricyclic antidepressant (TCA)	oral	200 mg	Airway muscle tone	Placebo	2 × 1 night
Whyte et al., 1988 [75]	3-way cross-over	10	52 ± 11	80	Protriptyline/ Acetazolamide	(Non-sedating) TCA/Carbonic anhydrase inhibitor	oral	1 × 20 mg (P) or 500 mg −1000 mg (A)	Airway muscle tone/ Ventilatory drive	Placebo	3 × 14 nights
Drugs proposed to act on mucosa surface											
Jokic et al., 1998 [50]	2-way cross-over	10	49 ± 10	100	Phosphocholinamin	Mineral oil	topical	4 × 0.4 ml	Surface tension forces	Placebo	2 × 1 night
Morrell et al., 2002 [61]	2-way cross-over	7	41 ± 17	100	Surfactant	Detergent	topical	1 × 1 ml	Surface tension forces	Placebo	1 × 1 night
Drugs proposed to act on airway diameter											
Acar et al., 2013 [24]	4-parallel-groups	80	unclear	68	Desloratadine/ Mometasone furoate	Antihistamine/Topical corticosteroid	oral	1 puff per nostril	Upper airway diameter	Placebo	1 × 24 nights
Clarenbach et al., 2008 [33]	2-way cross-over	12	49 ± 11	83	Xylometazoline	Local vasoconstrictor (nasal decongestant)	topical	2 × 0.15 mg	Upper airway diameter	Placebo	2 × 7 nights
Fiori et al., 2015 [80]	3-parallel-groups	54	45 ± 9	100	Spironolactone/ Furosemide	Diuretic (Antimineralocorticoid, Loop diuretic)	oral	1 × 100 mg/ 20 mg	Upper airway diameter	Placebo	1 × 7 nights
Kiely et al., 2004 [51]	2-way cross-over	23	46 ± 17	83	Fluticasone	Topical Corticosteroids (Anti-inflammatory)	topical	2 × 100μg	Upper airway diameter	Placebo	2 × 28 nights
Koutsourelakis et al., 2013 [52]	2-way cross-over	21	38 ± 8	62	Tramazoline/ dexamethasone	α-Sympathomimetic/ Corticosteroide	topical	120 μg/20 μg	Upper airway diameter	Placebo	2 × 7 nights
Smith et al., 2017 [79]	2-parallel-groups	26	57 ± 12	unclear	Montelukast/ Fluticasone		topical/oral	unclear	Upper airway diameter	Placebo	1 × 24 nights

(continued on next page)

Table 1 (*continued*)

Study	Design	n	Age ±SD	%Male	Drug	Description	Application	Dosage	Proposed mechanism	Control	Duration
						LTRA (bronchodilator)/ Corticosteroide (anti-inflammatory)					
Yang et al., 2016 [78]	2-parallel-groups	30	44 ± 13	unclear	Spironolactone	Aldosteron-antagonist (antihypertensive)	oral	20 mg–40 mg	unclear	Placebo	1 × 48 nights
Drugs proposed to act on lower airway tract											
Blackman et al., 2016 [27]	2-parallel-groups	359	49 ± 10	72	Liraglutide	Incretin mimetic (antidiabetic)	subcutaneous	3.0 mg	Weight loss	Placebo	1 × 224 nights
Cook et al., 1989 [34]	2-way cross-over	10	51 ± 10	100	Medroxyprogesterone Acetate	Progesterone (contraceptive)	oral	1 × 150 mg	Airway muscle tone	Placebo	2 × 7 nights
Eskandari et al., 2014 [39]	3-parallel-groups	47	51 ± 12	93	Zonisamide	Sodium channel blocker (anticonvulsant)	oral	100–300 mg	Weight loss	Placebo/CPAP	3 × 28 nights and 2 × 140 nights
Hoyos et al., 2012 [48]	2-parallel-groups	67	49 ± 2	100	Testosterone undecanoate	Androgen (steroide)	intramuscular	1000 mg	Redistribution of body-fat	Placebo	1 × 126 nights
Liu et al., 2016 [55]	2-parallel-groups	45	51 ± 11	67	Pioglitazone	Thiazolidinedione (antidiabetic)	oral	45 mg	Weight loss	Placebo	1 × 32 nights
Winslow et al., 2012 [76]	2-parallel-groups	45	52 ± 6	53	Phentermine/ extended-release Topiramate	Amphetamin (appetite depressant)/Glutamate antagonist (anticonvulsive)	oral	15 mg (P)/ 92 mg (T)	Weight loss	Placebo	1 × 196 nights
Drugs proposed to act on ventilatory drive											
Atkinson et al., 1985 [25]	2-way cross-over	10	46	80	Naloxone	Opiate receptor antagonist	intravenously	5 mg/h	Ventilatory drive	Placebo	2 × 1 nights
Carley et al., 2018 [31]	3-parallel-groups	66	56 ± 7	60	Dronabinol	Tetrahydrocannabinol (antiemetic)	oral	1 × 2.5 mg or 10 mg	Ventilatory drive	Placebo	1 × 42 nights
Diamond et al., 1982 [36]	2-way cross-over	4	unclear	unclear	Naloxone	Opiate receptor antagonist	oral	1 × 2 mg	Ventilatory drive	Placebo	unknown
Edwards et al., 2012 [38]	2-way cross-over	13	50 ± 2	unclear	Acetazolamide	Carbonic anhydrase inhibitor	oral	2 × 500 mg	Ventilatory drive	Placebo	2 × 1 night
Eskandari et al. [81]	3-way cross-over	13	64 ± 7	100	Acetazolamide	Carbonic anhydrase inhibitor	oral	3 × 250 mg	Ventilatory drive	CPAP	3 × 14 nights
Espinoza et al., 1987 [40]	2-way cross-over	10	53 ± 4	100	Aminophylline	Xanthine (bronchodilator)	intravenously	1 × 0.7 mg/kg/h	Ventilatory drive	Placebo	2 × 1 night
Ferber et al., 1993 [41]	2-way cross-over	12	60 ± 11	83	Naltrexone	(competitive) Opiate receptor antagonist	oral	1 × 50 mg	Ventilatory drive	Placebo	2 × 2 nights
Hedner et al., 1996 [43]	2-way cross-over	12	49 ± 10	92	Sabeluzole	NMDA receptor antagonist (neuroprotective) (Alzheimer-dementia)	oral	2 × 10 mg	Ventilatory drive	Placebo	2 × 28 nights
Hein et al., 2000 [46]	2-way cross-over	14	50 ± 8	86	Theophylline	Xanthine (bronchodilator)	oral	1 × 12 mg/kg	Ventilatory drive	Placebo	2 × 14 nights
Mangin et al., 1983 [57]	2-way cross-over	9	55 ± 10	100	Almitrine	(Diphenylmethylpiperazine derivative) (respiratory stimulant)	oral	2–3 mg/kg	Ventilatory drive	Placebo	2 × 5 nights
Martino et al., 1999 [35]	2-parallel-groups	50	51 ± 11	88	Theophylline	Xanthine (bronchodilator)	oral	300–500 mg	Ventilatory drive	Placebo	1 × 10 wks
Mulloy et al., 1992 [62]	2-way cross-over	12	48 ± 11	100	Theophylline	Xanthine (bronchodilator)	oral	1 × 200 to 1 × 800 mg	Ventilatory drive	Placebo	2 × 4 wks
Suratt et al., 1986 [70]	2-way cross-over	4	47 ± 10	100	Doxapram	Morpholin derivate (respiratory stimulant)	oral	0.5 mg/kg	Ventilatory drive	Placebo	2 × 1 night
Torvaldsson et al., 2005 [73]	2-way cross-over	15	52 ± 4	100	NMDA receptor antagonist AR-R15896AR	NMDA receptor antagonist	intravenously	1 × 120 to 350 mg	Ventilatory drive	Placebo	2 × 1 night
Drugs proposed to act on arousal threshold											
Carter et al., 2016 [32]	2-way cross-over	12	49 ± 3	75	Zopiclone	Z-compound (hypnotic)	oral	1 × 7.5 mg	Arousal threshold	Placebo	2 × 1 night
Eckert et al., 2011 [37]	2-way cross-over	17	45 ± 5	59	Eszopiclone	Z-compound (hypnotic)	oral	1 × 3 mg	Arousal threshold	Placebo	2 × 1 night
Li et al., 2016 [54]	2-way cross-over	41	52 ± 11	66	Donepezil	AChEI (parasympathomimetic)	oral	10 mg	Arousal Threshold	Placebo	2 × 1 night
Taranto-Montemurro et al., 2017 [72]	2-way cross-over	14	58 ± 12	57	Tiagabine	GABA agonist (anticonvulsant)	oral	12 mg	Arousal Threshold	Placebo	2 × 1 night
Wang et al., 2011 [74]	2-way cross-over	20	44 ± 12	100	Temazepam	GABA agonist (hypnotic)	oral	1 × 10 mg	Arousal Threshold	Placebo	2 × 1 night

Other mechanisms											
Bruckert et al., 2010 [29]	2-parallel-groups	34	56 ± 6	65	Fenofibrate	Fibrate (cholesterol lowering drug)	oral	1 × 145 mg	Anti-inflammatory	Placebo	1 × 28 nights
Grote et al., 2000 [42]	2-way cross-over	54	50 ± 1	100	Cilazapril	ACE-inhibitor (antihypertensive)	oral	1 × 2.5 mg	Blood pressure surges	Placebo	2 × 8 nights
Heitmann et al., 1998 [47]	2-parallel-groups	53	51 ± 8	100	Mibefradil	Calcium channel blocker (antihypertensive)	oral	1 × 50 mg	Vasoactive	Placebo	1 × 8 nights
Issa 1992 [49]	2-way cross-over	8	43 ± 9	100	Clonidine	α_2-receptor agonist (antihypertensive)	oral	1 × 0.2 mg	Vasoactive	Placebo	2 × 10 nights
Maari et al., 2014 [56]	2-parallel-groups	20	52 ± 12	90	Adalimumab	TNFα-inhibitor (antibody)	subcutaneous	40–80 mg	Cytokines	Placebo	1 × 56 nights
Wu et al., 2016 [77]	2-parallel-groups	28	43 ± 11	100	Carbocysteine	Mucolytic	oral	1500 mg	Oxidative stress	CPAP	1 × 24 nights

5-HT = 5-hydroxytryptamine; ACE = Angiotensin converting enzyme; AChEI = Acetylcholinesterase inhibitor; LABA = Long-Acting β2 adrenergic agonist; LTRA = Leukotriene receptor antagonists; NaSSA=Noradrenergic and specific serotonergic antidepressant; NMDA=N-Methyl-D-aspartic acid; SARI=Serotonin antagonist and reuptake inhibitor; SSRI=Selective serotonin reuptake inhibitor; TNF = Tumor necrosis fractor.

Currently ongoing trials are capitalizing on the relatively new ability to phenotype patients and the conclusions from sub-group analysis [69,71]. These RCTs investigate off-label-use (atomoxetine and oxybutynin [82]) or new drugs (DAW1033D [83]; BAY2253651 [84]) in carefully selected patients which might profit from an increased genioglossus-muscle tone.

Drugs proposed to act on the mucosal surface

The influence of mucosal factors on pharyngeal lumen caliber was subject to investigation in two specific studies. One RCT investigating surfactant [61] and another one investigating the mineral oil lubricating and coating agent phosphocholinamin [50] (similar to human surfactant) hypothesized that alteration of the mucosal surface might reduce inspiratory pharyngeal resistance at peak negative pressure and also result in a reduction of the pharyngeal re-opening pressure, thus stabilizing the upper airway and reduce OSA severity. Both studies reported a modest reduction in AHI [50] or respiratory disturbance reduction [61] in an unselected OSA-population, but both studies failed to prove a significant difference in sleep architecture and sleepiness was not assessed [50,61]. Apart from yet unresolved issues regarding the administration and duration of effectiveness of the investigated drugs the two studies serve as proof-of-principle for the role of surface tension forces in the pathogenesis of OSA.

Drugs proposed to act on airway diameter

Upper airway congestion and nocturnal rostral fluid shifts reduce upper-airway diameter, which results in an increased risk of collapse of the narrowest regions. Furthermore, nasal congestion itself may promote oral breathing and thus the propensity to OSA. Five RCTs addressed this mechanism with an intervention of one of the following topical nasal decongestants: alpha-adrenergic agonists (xylometazoline [33]), corticosteroids (fluticasone [51]), or a corticosteroid-combination therapy (desloratadine & mometasone furoate [24], tramazoline/dexamethasone [52], montelukast, and fluticasone [79]). Three trials included only patients with diagnosed nasal congestion [24,33,51] and two trials performed the intervention on patients with normal nasal resistance [52,79]. All three trials using a corticosteroid (or a prodrug) in patients with nasal congestion [24,51,52] reported a 20–25% reduction in AHI, whereas the trials only testing an alpha-adrenergic agonist or a unselected study population were negative [33,79]. Two trials also objectified a lower nocturnal nasal conductance in the intervention group [33,51], confirming the role of upper airway congestion in the pathophysiology of OSA. Based on these promising results, the exact role of additional alpha-adrenergic agonists (oxymetazoline) [85] in addition to fluticasone in OSA-patients with rhinitis is currently being studied in a significantly larger cohort.

Two RCTs tried to modulate OSA severity with the intervention of diuretics (spironolactone and furosemide which may prevent nocturnal rostral fluid shift) [80] or spironolactone alone [78]. Due to the small effect sizes [80] and risk of bias [78] this intervention cannot be evaluated conclusively from the available data.

Drugs proposed to act on the lower airway tract

A markedly decreased functional residual capacity that occurs in sleep significantly increases upper airway collapsibility. One RCT hypothesized that medroxyprogesterone acetate [34] may optimize respiratory muscle function towards a favorable outcome, which was not the case.

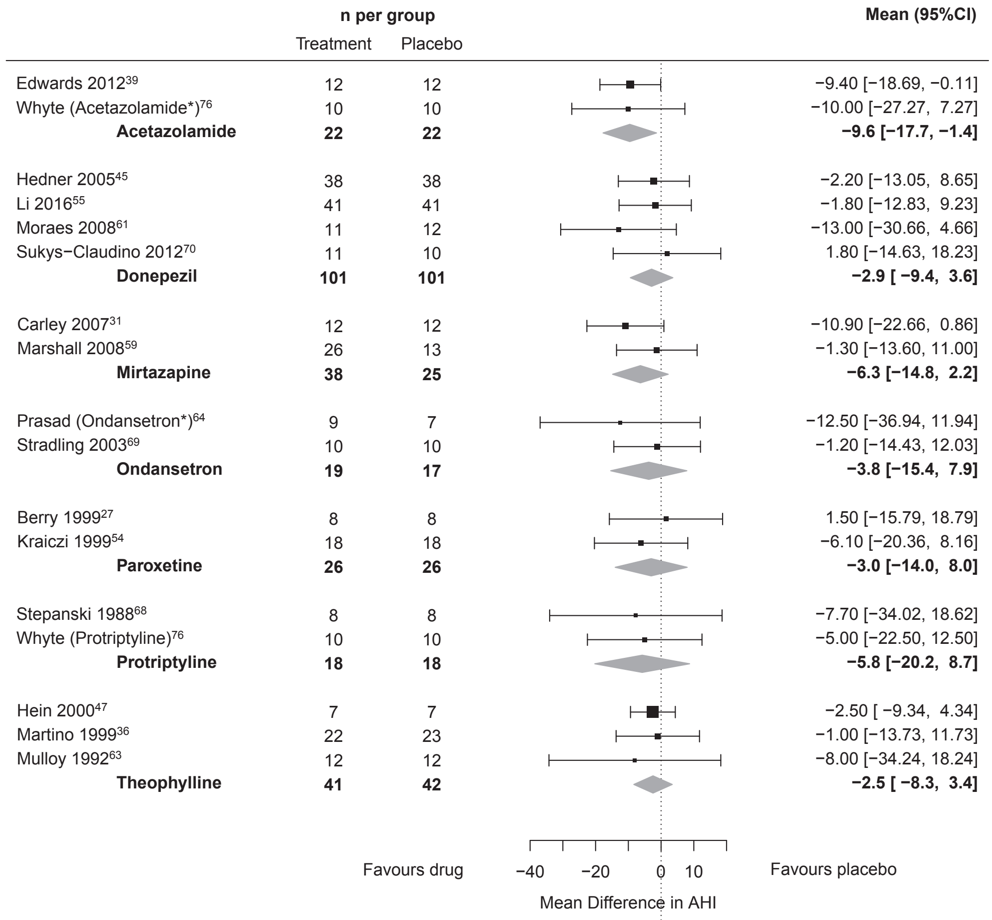

Fig. 2. Meta-analysis on seven drugs in more than one RCT vs. placebo. Heterogeneity among those trials (n = 17) was low. There were not enough studies reporting an oxygen desaturation index to perform a meta-analysis for this index. * = data only for the corresponding drug extracted.

In practice, the single main risk factor contributing to this mechanism is central adiposity (i.e., accumulation of fat around the neck and the abdominal area). Due to the high influence of this risk factor, even minor changes in body-fat distribution have a significant impact on OSA-severity. Five RCTs attempted to assess the potential of weight loss with the help of the following drugs: weight loss induced by an antidiabetic (pioglitazone [55], liraglutide [27]), weight loss as a side effect of an anticonvulsant (zonisamide [39]) or in combination with an appetite depressant (phentermine [76]), or redistribution of body fat due to sexual hormones (testosterone [48]). These studies were performed exclusively with obese OSA-participants (BMI>30 kg/m^2) and an appropriate follow-up time from 4 to 7.5 mo [27,39,48,76]. A single study with a short follow-up of 56 days failed to prove an effect of the intervention [55]. Three studies described an AHI reduction when compared to the placebo-arm, which was associated with the amount of weight-loss achieved due to the study intervention [27,39,76]. The biggest reduction was achieved in a phase-II-RCT using phentermine plus extended-release topiramate and after a follow-up of 28 wks [76]. All trials incorporated an adjunct diet and exercise regimen in both study arms. Finally, the testosterone-intervention in obese men with OSA mildly worsens OSA in a time-dependent manner, irrespective of the initial testosterone concentrations [48].

Drugs proposed to act on the ventilatory drive

The concept of loop gain describes ventilatory feedback loops (e.g., those involving chemoreceptors) and their internal amplification. An enhanced “loop gain” or in other words an oversensitive ventilatory control system, predisposes to respiratory control instability (i.e., hypopnoeas) along with diminished effectiveness of the upper airway to prevent an obstruction or to reopen the obstructed airspace. Various RCTs have tried to modulate these feedback loops.

In the ‘80s and ‘90s, several research groups investigated the role of opioid receptor antagonists (naloxone [25,36] or naltrexone [41]) on the severity of OSA. It was hypothesized that these antagonists may counteract the respiratory depression of endogenous opiates. Sample sizes were generally small and although some effect on the AHI was documented [25,41], the nocturnal intravenous infusion of opioid receptor antagonists influenced the overall sleep architecture which made interpretation of the results impossible and the clinical usefulness of these drugs questionable [25,36,41].

Several RCTs used respiratory stimulants as an intervention to take advantage of the central stimulatory effect, mainly on the medullary respiratory center (theophylline [35,46,62], aminophylline [40], doxapram [70], almitrine [57]), via NMDA receptors (sabeluzole [43], AR-R15896AR [73]), or via a metabolic acidosis (acetazolamide [38,75,81]). These interventions were either negative [40,43,70,73] or showed a relatively small effect on the AHI (usually 15–20% reduction [35,38,46,57,62,75], Fig. 2) owing to a massive deterioration in sleep quality (i.e., lower sleep efficiency and massive sleep fragmentation). With this in mind, the observed effect for theophylline in the experimental group diminished after a longer follow-up [35]. Although acetazolamide consistently lowered the AHI, clinical outcomes (i.e., daytime sleepiness) did not improve and side effects were common (e.g., paresthesia) [38,75,81].

Recently, a phase-II RCT reported an average dose-dependent 40–50% AHI reduction for six weeks when moderate-to-severe OSA patients were given a cannabinoid (dronabinol [31]). Considering the

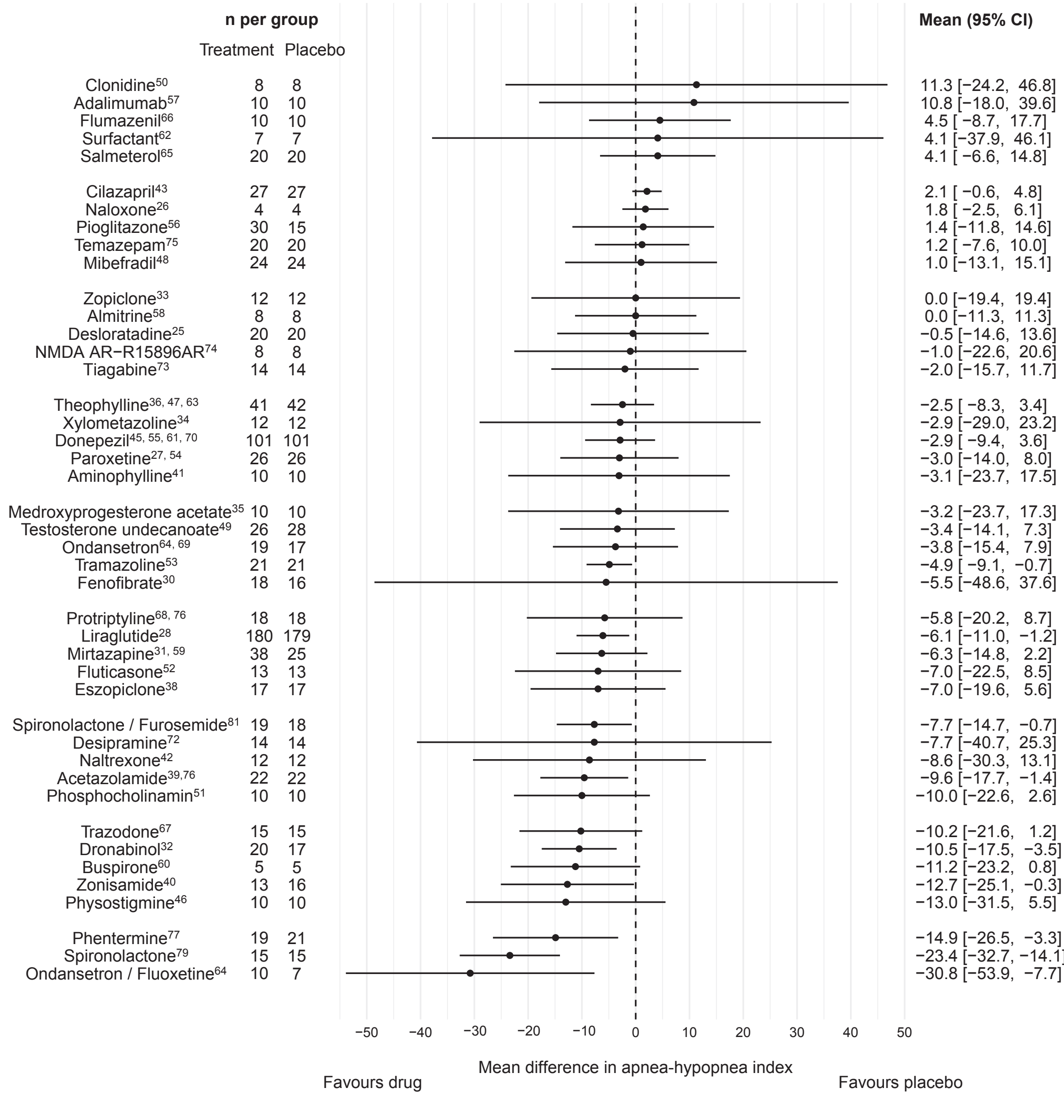

Fig. 3. Network meta-analysis on predicted effects of each drug vs. placebo on AHI. Of 58 RCTs, 51 trials on 44 drugs (or combinations) were included in the network meta-analysis. Five trials did not report sufficient data for effect estimation [25,28,43,70,79] and two trials did not include a placebo (only CPAP as a comparator) [77,81]. Whiskers represent the 95% confidence interval.

relatively low rate of adverse drug reactions and relatively large effect sizes in an unselected OSA-population, this drug may be regarded as an interesting candidate for future investigations. However, due to the unknown clinical significance and unreliable delivery methods, further data is needed to assess this drug in the context of sleep apnoea. Currently, an industry-sponsored follow-up phase-II trial is conducted with a slightly altered substance [86].

Drugs proposed to act on the arousal threshold

Arousals from sleep destabilize the breathing cycle and can trigger further obstructive events after an initial event has occurred. Implications include a significantly reduced OSA-severity during slow-wave sleep [87]. Following this argument, several RCTs investigated the effects of hypnotics (zopiclone [32], eszopiclone [37], temazepam [74], or tiagabine [72]) and parasympathomimetics (donepezil [54]) on the arousal threshold and OSA-severity. Ultimately, two studies were able to successfully demonstrate an increase in the arousal threshold [32,37] whereas two studies did not [54,72]. Regardless of the arousal-threshold and the studied drug, there was no statistically significant effect on the AHI [32,37,54,72,74]. These studies, however, mostly recruited a general population of diverse OSA patients without any specific phenotype [32,72,74]. Subgroup analysis suggested that patients with a low arousal threshold may actually profit from this therapy [32,37].

Other drugs

Animal studies suggested that airway collapsibility is directly affected by systemic arterial pressure [88]. Thus, several studies in the '90s tried to modulate sleep apnoea with vasoactive substances (mibefradil [47], clonidine [49], or cilazapril [42]) without any effect. Other RCTs with negative findings tried to alter the oxidative stress-/cytokine-pathway in OSA patients (fibrate [29], carbocysteine [77], or adalimimab [56]) without success. Currently, in one other RCT the investigators are trying to accomplish the same oxidative stress reduction with melatonin [89].

Bias assessment

Most of the included studies (86%) were considered of unclear or low bias. Only nine studies were rated as "high probability of bias"

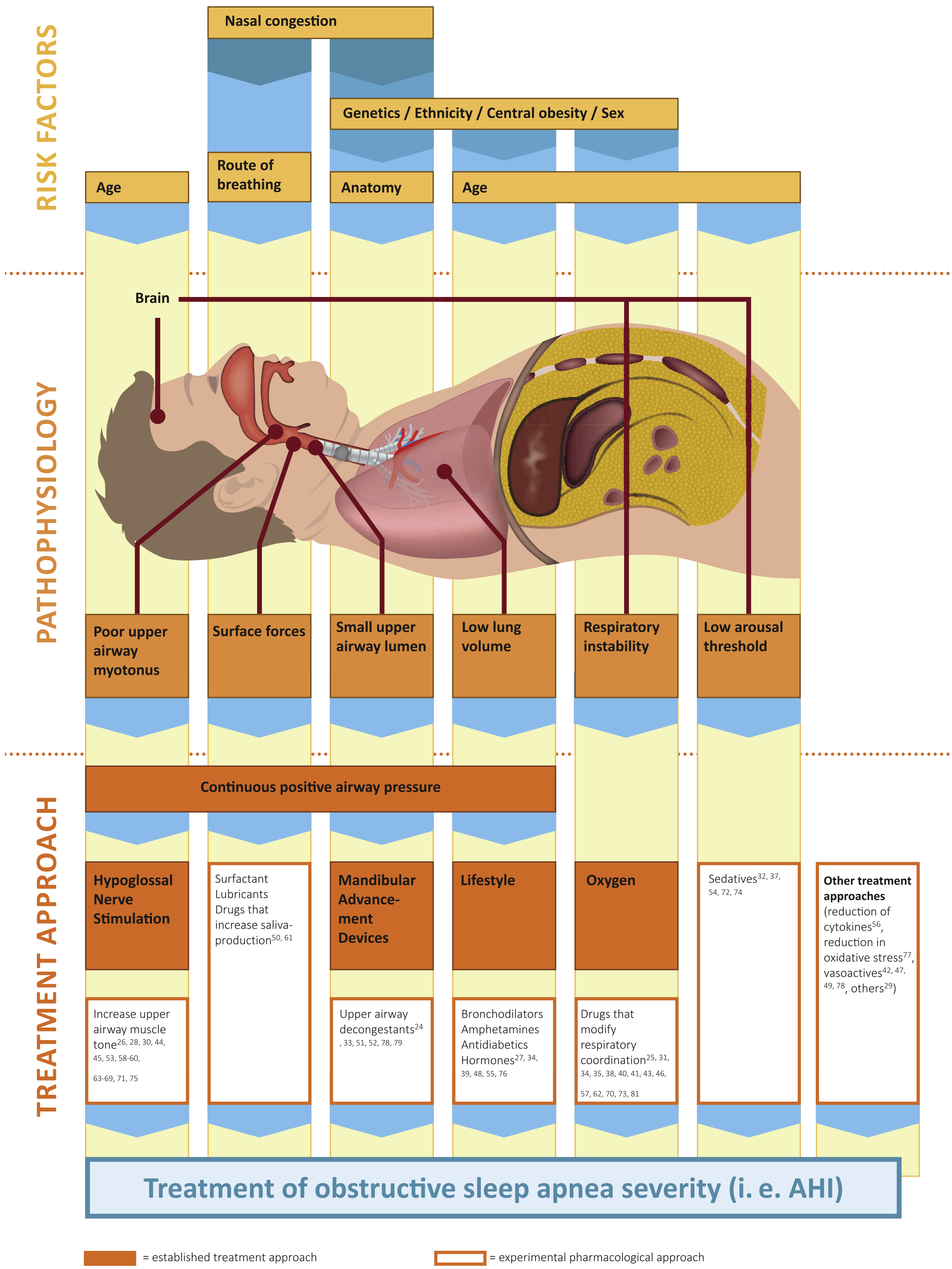

Fig. 4. Risk factors, pathophysiology, and treatments for OSA. Different risk factors affect one or more downstream pathophysiological mechanisms in each patient. Usually, a combination of different traits contribute to disease severity in OSA. Continuous positive airway pressure treats OSA irrespective of the underlying traits, whereas alternative treatments are designed to target only specific mechanisms of this heterogeneous disease. Correspondingly, pharmacological randomised controlled trials have tried to address each single mechanism of the disease, mainly in an OSA-subpopulation which is selected based on the respective trait. Considering the architecture of the pathophysiology, it seems unlikely that a single pharmacological intervention might moderate disease severity for all OSA patients.

either due to issues in the blinding process (participants, personnel, outcome assessment) [35,38,55,61,65,77,78,81] or the random sequence generation process [57] (Table 11, supplementary files). 35% of trials were supported by a pharmaceutical company or the industry.

Discussion

This systematic review summarizes the existing evidence on pharmacotherapy for OSA and delineates the underlying mechanisms of pharmacotherapy for OSA. It serves as a documentation of the significant increase in trials on this topic over the past five decades. As expected, the field of pharmacotherapy for OSA is extremely heterogeneous and only a few RCTs ($n = 17$) investigated the same drug. OSA was not completely treated by any drug and the effect sizes were generally small. Contrary to general opinion, one meta-analysis suggests that there are also no pharmacological compounds (e.g., opioids or hypnotics) that have a deleterious effect on OSA severity [90]. Currently, only mechanical interventions seem to effectively modulate OSA.

Pathomechanisms

Generally, the most interesting (yet preliminary) results in this field gravitate around three main mechanisms: 1) antidepressants to change upper airway muscle activity [26,28,53,58,63,66,67,71,75], 2) spironolactone [78,80], and 3) drug combinations addressing multiple disease traits at once [24,52,58,63,75,76,79,80]. There is currently insufficient evidence for a recommendation of any pharmacotherapy for OSA and phase-III studies are lacking. There was evidence of “high risk of bias” in an RCT involving spironolactone [78]. Thus, results for this drug should be interpreted with caution. Only a few trials assessed additional clinical outcomes e.g., sleepiness [24,27,39,51,52,69,76], quality of life, or blood pressure [27,39,81].

As far as modifying factors on the effectiveness of pharmacotherapy for OSA are concerned, subgroup analysis of various RCTs in this review consistently indicated that the largest effect on AHI-reduction was found in patients with mild to moderate obstructive sleep apnoea [31,35]. This finding is in contrast to pooled data from mechanical OSA-treatment (i.e., CPAP and mandibular advancement devices), where baseline AHI levels are significantly associated with the observed AHI reduction [91,92]. These contrasting findings may indicate, that observations so far suggest only an adjunct role for pharmacotherapy in the treatment of OSA, rather than a stand-alone therapy.

From a pathophysiological viewpoint, the results of all included studies support the fact that OSA is a multifactorial disorder and different OSA-phenotypes may respond distinctively to a pharmacological intervention (which is not the case for CPAP). Vice versa, current evidence suggests that pharmacotherapy in OSA should target carefully selected subgroups to achieve an adequate efficacy. In theory, one possibility to overcome this limitation is a combination of two treatments. This approach has already shown promising results in an RCT where multiple traits (i.e., loop gain and arousal threshold) were targeted with a combination of eszopiclone and oxygen in carefully phenotyped OSA patients [93]. Due to the use of oxygen (exclusion criterion in the study protocol), this RCT was not covered in the main analysis.

We also considered the possibility that pharmacotherapy may alter sleep stages and thus might ultimately affect OSA severity [43–45]. However, there was no overall effect on sleep stages (i.e., % REM of total sleep time) and the AHI changes did not correlate with changes in sleep stages (Table 14, supplementary files).

Until recently, RCTs did not carefully select the study population that was investigated. Most of the trials in this review included OSA patients irrespective of their phenotype, except trials for weight loss (exclusively obese participants [27,39,48,55,76]), trials investigating a topical nasal decongestant [24,33,51], or trials investigating the intervention in a specific population (e.g., Alzheimer disease [60], hypertension [42,78], or psoriasis [56]). Only one RCT in this review objectively phenotyped patients based on a low arousal threshold before study inclusion [37]. We noticed, that these trials were among the few adequately powered and/or studies with positive outcomes among all included RCTs. This narrative meta-analysis adds further evidence that in terms of pharmacotherapy, there is no CPAP-like “one size fits all” approach in the field of OSA and a careful a-priori consideration of pathomechanisms and inclusion criteria is required.

In terms of inclusion criteria, a more general problem arises when comparing studies on OSA. Since ‘80s, the criteria for scoring and the diagnostic thresholds were modified. Some trials in this RCT incorporated an AHI-inclusion threshold of five [32,37,46,47,50,54,60,64,74,79] while others went up to 60 [26]. It is also noted that symptomatic daytime sleepiness (in any form) as a diagnostic criterion for OSA was only required in nine trials [34,39,40,46,50,55,58,67,75]. Bearing this in mind, it can be extremely difficult to interpret or compare findings from different trials on the same drug, let alone the same mechanism of action.

Statistical considerations

Most RCTs on OSA in this review are poorly reported and generally underpowered (i.e., they have low sensitivity). Most RCTs that were included in this review failed to achieve statistical significance for AHI even with very large effect sizes (Fig. 5, supplementary files). Of the 11 trials with effects between 5 and 10 AHI points in either direction, only three were statistically significant. This indicates that most trials were powered to detect only large effects or that the variability was larger than expected when the investigators performed sample size calculations. Furthermore, it should be noted that 26 RCTs had observed effect sizes less than five points in either direction, which would have likely been smaller than the planned minimally relevant effect size used for sample size considerations. In short, while it is clear that most trials of medication use in OSA are underpowered, increased sample sizes would not have changed the results and conclusion of the large number of studies with no clinically-relevant effect. A study with low statistical power has a reduced chance of detecting a true effect but it is also important to note that low power also reduces the likelihood that a statistically significant result reflects a true effect [94]. This review demonstrates that RCTs in the field of pharmacology in OSA are generally underpowered and their (positive) conclusions should be interpreted with caution. In this light, it should also be mentioned that most newly discovered true (non-null) associations often have inflated effects compared with the true effect sizes [95] as it was already demonstrated in this field [30,58].

Outlook

None of the included RCTs in this review would classify as a phase-III trial and there is currently no ongoing phase-III trial registered in this regard on major trial registries. Most trials only investigated a single night, thus not assessing the potential symptomatic benefit in OSA patients. Therefore, the prospects for a general pharmacological treatment in OSA remains open. For the first time, industry-sponsored trials are now established in this promising field [84,86]. Besides off-label use of already established drugs [82,85,89] new substances for the single purpose of treating OSA are being developed [83,84].

Strengths and limitations

Given the number of drugs tested here, it is of course possible that a significant effect is purely an artifact of multiple testing. We only included RCTs and the study protocol of the review was pre-registered and the results are presented accordingly in a replicable manner. All eleven methodological domains of the AMSTAR-tool for systematic reviews were considered [96]. With this approach we were able to identify approximately 41% more RCTs [25,26,35,38,42,45,48,61,65,73,74,76] than comparable reviews [14] in an overlapping period of time (1982–2012). Ultimately, the decision to include an RCT to a review will always involve a degree of subjectivity. For example, a review investigating deleterious effects of drugs on OSA-severity [52] also included two RCTs which contributed to this review and the case for treating/modulating sleep apnoea is not always clear [37,74].

It has not escaped our notice that in some cases, more than one pathomechanism may be accountable for the effect of the drug and the authors always chose the "most appropriate" mechanism in this context. For example, RCTs on parasympathomimetics [44,45,54,60,69] which are proposed to act on the upper airway muscle tone, may also capitalize on other mechanisms such as alteration of the mucosa surface via an increased nocturnal saliva secretion or impact on loop gain. However, no study specifically presented evidence for this mechanism or measured an outcome in this regard.

Finally, the nature of this review is prone to publication bias in the field of pharmacotherapy. However, funnel plots (Fig. 1, supplementary files) did not suggest a major bias for the primary outcome since an expected number of RCTs also showed an effect into the opposite direction (i.e., worsening of OSA).

Conclusion

Although some RCTs indicate favourable outcomes, these results are only valid for distinctive OSA-phenotypes or were not clinically significant. Future trials need to capitalize on the ability to phenotype OSA and measure clinically meaningful outcomes. Based on the current evidence, it seems unlikely that a single pharmacological intervention might lower disease severity for all OSA patients. There is currently insufficient evidence to recommend any pharmacotherapy for OSA.

Author contributions

TG and SH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: TG, MK. Acquisition, analysis, or interpretation of data: TG, ST, MO. Drafting of the manuscript: TG. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: SH. Administrative, technical, or material support: TG, MK. Study supervision: MK.

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Practice points

- Considering the architecture of the pathophysiology, it seems unlikely that a single pharmacological intervention might lower disease severity for all OSA patients.
- Top candidates requiring further investigation include antidepressants to change upper airway muscle activity and drug combinations addressing multiple disease traits at once.
- There is currently insufficient evidence to recommend any pharmacotherapy for OSA and no phase-III trials are available.

Research agenda

- There is a need for robust clinically-applicable tools to phenotype OSA.
- Future investigations should identify underlying pathomechanisms (phenotypes) in the selected patient population and adjust treatment (or better: treatment combinations) accordingly.
- There is a need for adequately powered trials which account for the time needed for pathomechanisms or clinical outcomes to change (e.g., sleepiness, quality of life, blood pressure, etc.).
- A consensus for reporting objective diagnostic and clinically meaningful outcome criteria is needed when OSA is treated.

Conflicts of interest

TG and MK served as consultants for Bayer AG for the conduction of a phase-II trial (BAY2253651) in pharmacotherapy in OSA. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2019.04.009.

References

[1] Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3(4):310–8.
[2] Bratton DJ, Gaisl T, Schlatzer C, Kohler M. Comparison of the effects of continuous positive airway pressure and mandibular advancement devices on sleepiness in patients with obstructive sleep apnoea: a network meta-analysis. Lancet Respir Med 2015;3(11):869–78.
[3] Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: a systematic review and meta-analysis. JAMA – J Am Med Assoc 2015;314(21):2280–93.

* The most important references are denoted by an asterisk.

[4] Kuhn E, Schwarz EI, Bratton DJ, Rossi VA, Kohler M. Effects of CPAP and mandibular advancement devices on health-related quality of life in OSA: a systematic review and meta-analysis. Chest 2017;151(4):786–94.
[5] Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. JAMA – J Am Med Assoc 2004;291(16):2013–6.
[6] Gaisl T, Giunta C, Bratton DJ, Sutherland K, Schlatzer C, Sievi N, et al. Obstructive sleep apnoea and quality of life in Ehlers-Danlos syndrome: a parallel cohort study. Thorax 2017;72(8):729–35.
[7] Scanlan MF, Roebuck T, Little PJ, Redman JR, Naughton MT. Effect of moderate alcohol upon obstructive sleep apnoea. Eur Respir J 2000;16(5):909–13.
[8] Kohler M, Blair E, Risby P, Nickol AH, Wordsworth P, Forfar C, et al. The prevalence of obstructive sleep apnoea and its association with aortic dilatation in Marfan's syndrome. Thorax 2009;64(2):162–6.
[9] Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am J Respir Crit Care Med 2013;188(8):996–1004.
[10] Stepnowsky Jr CJ, Moore PJ. Nasal CPAP treatment for obstructive sleep apnea: developing a new perspective on dosing strategies and compliance. J Psychosom Res 2003;54(6):599–605.
[11] Iftikhar IH, Bittencourt L, Youngstedt SD, Ayas N, Cistulli P, Schwab R, et al. Comparative efficacy of CPAP, MADs, exercise-training, and dietary weight loss for sleep apnea: a network meta-analysis. Sleep Med 2017;30:7–14.
[12] Horner RL, Grace KP, Wellman A. A resource of potential drug targets and strategic decision-making for obstructive sleep apnoea pharmacotherapy. Respirology 2017;22(5):861–73.
[13] Ramar K, Rosen IM, Kirsch DB, Chervin RD, Carden KA, Aurora RN, et al., American Academy of Sleep Medicine Board of D. Medical cannabis and the treatment of obstructive sleep apnea: an American Academy of sleep medicine position statement. J Clin Sleep Med – JCSM – Off Publ Am Acad Sleep Med 2018;14(4):679–81.
[14] Mason M, Welsh EJ, Smith I. Drug therapy for obstructive sleep apnoea in adults. Cochrane Database Syst Rev 2013;5:CD003002.
[15] Kohler M, Bloch KE, Stradling JR. Pharmacological approaches to the treatment of obstructive sleep apnoea. Expert Opin Investig Drugs 2009;18(5): 647–56.
[16] Kohler M, Stradling JR. Pitfalls of clinical trials on pharmacological treatment for obstructive sleep apnoea: future directions. Expert Opin Investig Drugs 2011;20(8):1033–7.
[17] Lin CM, Huang YS, Guilleminault C. Pharmacotherapy of obstructive sleep apnea. Expert Opin Pharmacother 2012;13(6):841–57.
[18] White DP. Pharmacologic approaches to the treatment of obstructive sleep apnea. Sleep Med Clin 2016;11(2):203–12.
[19] Avellar AB, Carvalho LB, Prado GF, Prado LB. Pharmacotherapy for residual excessive sleepiness and cognition in CPAP-treated patients with obstructive sleep apnea syndrome: a systematic review and meta-analysis. Sleep Med Rev 2016;30:97–107.
[20] Chapman JL, Vakulin A, Hedner J, Yee BJ, Marshall NS. Modafinil/armodafinil in obstructive sleep apnoea: a systematic review and meta-analysis. Eur Respir J 2016;47(5):1420–8.
[21] Khurshid K, Yabes J, Weiss PM, Dharia S, Brown L, Unruh M, et al. Effect of antihypertensive medications on the severity of obstructive sleep apnea: a systematic review and meta-analysis. J Clin Sleep Med – JCSM – Off Publ Am Acad Sleep Med 2016;12(8):1143–51.
[22] Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36(3):48.
[23] Law M, Jackson D, Turner R, Rhodes K, Viechtbauer W. Two new methods to fit models for network meta-analysis with random inconsistency effects. BMC Med Res Methodol 2016;16:87.
[24] Acar M, Cingi C, Sakallioglu O, San T, Fatih Yimenicioglu M, Bal C. The effects of mometasone furoate and desloratadine in obstructive sleep apnea syndrome patients with allergic rhinitis. Am J Rhinol Allergy 2013;27(4):e113–6.
[25] Atkinson RL, Suratt PM, Wilhoit SC, Recant L. Naloxone improves sleep apnea in obese humans. Int J Obes 1985;9(4):233–9.
[26] Berry RB, Yamaura EM, Gill K, Reist C. Acute effects of paroxetine on genioglossus activity in obstructive sleep apnea. Sleep 1999;22(8):1087–92.
[27] Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes (2005) 2016;40(8):1310–9.
*[28] Brownell LG, West P, Sweatman P, Acres JC, Kryger MH. Protriptyline in obstructive sleep apnea: a double-blind trial. N Engl J Med 1982;307(17): 1037–42.
[29] Bruckert E, Duchene E, Bonnefont-Rousselot D, Hansel B, Ansquer JC, Dubois A, et al. Proof of concept study: does fenofibrate have a role in sleep apnoea syndrome? Curr Med Res Opin 2010;26(5):1185–92.
[30] Carley DW, Olopade C, Ruigt GS, Radulovacki M. Efficacy of mirtazapine in obstructive sleep apnea syndrome. Sleep 2007;30(1):35–41.
[31] Carley DW, Prasad B, Reid KJ, Malkani R, Attarian H, Abbott SM, et al. Pharmacotherapy of apnea by cannabimimetic enhancement, the PACE clinical trial: effects of dronabinol in obstructive sleep apnea. Sleep 2018;41(1).
*[32] Carter SG, Berger MS, Carberry JC, Bilston LE, Butler JE, Tong BK, et al. Zopiclone increases the arousal threshold without impairing genioglossus activity in obstructive sleep apnea. Sleep 2016;39(4):757–66.
[33] Clarenbach CF, Kohler M, Senn O, Thurnheer R, Bloch KE. Does nasal decongestion improve obstructive sleep apnea? J Sleep Res 2008;17(4): 444–9.
[34] Cook WR, Benich JJ, Wooten SA. Indices of severity of obstructive sleep apnea syndrome do not change during medroxyprogesterone acetate therapy. Chest 1989;96(2):262–6.
[35] Di Martino E, Saadi R, Emmerling O, Werner E. [Drug therapy of sleep apnea syndromes: results of short-term treatment with theophylline]. Laryngo-Rhino-Otol 1999;78(3):120–4.
[36] Diamond E, Druz W, D'Souza V, Sharp JT. Effect of Naloxone in obstructive sleep apnoea. Am Rev Respir Dis 1982;125(Suppl. 4):235.
[37] Eckert DJ, Owens RL, Kehlmann GB, Wellman A, Rahangdale S, Yim-Yeh S, et al. Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. Clin Sci 2011;120(12):505–14.
[38] Edwards BA, Sands SA, Eckert DJ, White DP, Butler JP, Owens RL, et al. Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. J Physiol 2012;590(5):1199–211.
*[39] Eskandari D, Zou D, Karimi M, Stenlof K, Grote L, Hedner J. Zonisamide reduces obstructive sleep apnoea: a randomised placebo-controlled study. Eur Respir J 2014;44(1):140–9.
*[40] Espinoza H, Antic R, Thornton AT, McEvoy RD. The effects of aminophylline on sleep and sleep-disordered breathing in patients with obstructive sleep apnea syndrome. Am Rev Respir Dis 1987;136(1):80–4.
[41] Ferber C, Duclaux R, Mouret J. Naltrexone improves blood gas patterns in obstructive sleep apnoea syndrome through its influence on sleep. J Sleep Res 1993;2(3):149–55.
[42] Grote L, Wutkewicz K, Knaack L, Ploch T, Hedner J, Peter JH. Association between blood pressure reduction with antihypertensive treatment and sleep apnea activity. Am J Hypertens 2000;13(12):1280–7.
[43] Hedner J, Grunstein R, Eriksson B, Ejnell H. A double-blind, randomized trial of sabeluzole–a putative glutamate antagonist–in obstructive sleep apnea. Sleep 1996;19(4):287–9.
[44] Hedner J, Kraiczi H, Peker Y, Grote L. Reduction of sleep apnea after the orally available cholinesterase inhibitor donepezil. Sleep Med 2005;6(2):54–5.
[45] Hedner J, Kraiczi H, Peker Y, Murphy P. Reduction of sleep-disordered breathing after physostigmine. Am J Respir Crit Care Med 2003;168(10):1246–51.
[46] Hein H, Behnke G, Jorres RA, Magnussen H. The therapeutic effect of theophylline in mild obstructive sleep Apnea/Hypopnea syndrome: results of repeated measurements with portable recording devices at home. Eur J Med Res 2000;5(9):391–9.
[47] Heitmann J, Grote L, Knaack L, Kohler U, Hinder M, Peter JH. Cardiovascular effects of mibefradil in hypertensive patients with obstructive sleep apnea. Eur J Clin Pharmacol 1998;54(9–10):691–6.
[48] Hoyos CM, Killick R, Yee BJ, Grunstein RR, Liu PY. Effects of testosterone therapy on sleep and breathing in obese men with severe obstructive sleep apnoea: a randomized placebo-controlled trial. Clin Endocrinol 2012;77(4): 599–607.
[49] Issa FG. Effect of clonidine in obstructive sleep apnea. Am Rev Respir Dis 1992;145(2 Pt 1):435–9.
[50] Jokic R, Klimaszewski A, Mink J, Fitzpatrick MF. Surface tension forces in sleep apnea: the role of a soft tissue lubricant: a randomized double-blind, placebo-controlled trial. Am J Respir Crit Care Med 1998;157(5 Pt 1):1522–5.
[51] Kiely JL, Nolan P, McNicholas WT. Intranasal corticosteroid therapy for obstructive sleep apnoea in patients with co-existing rhinitis. Thorax 2004;59(1):50–5.
[52] 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):1055–63.
[53] Kraiczi H, Hedner J, Dahlof P, Ejnell H, Carlson J. Effect of serotonin uptake inhibition on breathing during sleep and daytime symptoms in obstructive sleep apnea. Sleep 1999;22(1):61–7.
[54] Li Y, Owens RL, Sands S, Orr J, Moraes W, DeYoung P, et al. The effect of donepezil on arousal threshold and apnea-hypopnea index. A randomized, double-blind, cross-over study. Ann Am Thorac Soc 2016;13(11):2012–8.
[55] Liu A, Kim SH, Ariel D, Abbasi F, Lamendola C, Cardell J, et al. Does enhanced insulin sensitivity improve sleep measures in patients with obstructive sleep apnea: a randomized, placebo-controlled pilot study. Sleep Med 2016;22: 57–60.
[56] Maari C, Bolduc C, Nigen S, Marchessault P, Bissonnette R. Effect of adalimumab on sleep parameters in patients with psoriasis and obstructive sleep apnea: a randomized controlled trial. J Dermatol Treat 2014;25(1):57–60.
[57] Mangin P, Krieger J, Kurtz D. Effect of oral almitrine on the sleep apnea syndrome. Rev Fr Mal Respir 1983;11(6):899–906.
[58] Marshall NS, Yee BJ, Desai AV, Buchanan PR, Wong KK, Crompton R, et al. Two randomized placebo-controlled trials to evaluate the efficacy and tolerability of mirtazapine for the treatment of obstructive sleep apnea. Sleep 2008;31(6):824–31.
[59] Mendelson WB, Maczaj M, Holt J. Buspirone administration to sleep apnea patients. J Clin Psychopharmacol 1991;11(1):71–2.
[60] Moraes W, Poyares D, Sukys-Claudino L, Guilleminault C, Tufik S. Donepezil improves obstructive sleep apnea in Alzheimer disease: a double-blind, placebo-controlled study. Chest 2008;133(3):677–83.

[61] Morrell MJ, Arabi Y, Zahn BR, Meyer KC, Skatrud JB, Badr MS. Effect of surfactant on pharyngeal mechanics in sleeping humans: implications for sleep apnoea. Eur Respir J 2002;20(2):451–7.
[62] Mulloy E, McNicholas WT. Theophylline in obstructive sleep apnea. A double-blind evaluation. Chest 1992;101(3):753–7.
[63] Prasad B, Radulovacki M, Olopade C, Herdegen JJ, Logan T, Carley DW. Prospective trial of efficacy and safety of ondansetron and fluoxetine in patients with obstructive sleep apnea syndrome. Sleep 2010;33(7):982–9.
*[64] Rasche K, Duchna HW, Lauer J, Orth M, Kotterba S, Bauer TT, et al. Obstructive sleep apnea and hypopnea efficacy and safety of a long-acting beta2-agonist. Sleep Breath = Schlaf & Atmung 1999;3(4):125–30.
[65] Schonhofer B, Kohler D. Benzodiazepine receptor antagonist (flumazenil) does not affect sleep-related breathing disorders. Eur Respir J 1996;9(9):1816–20.
[66] Smales ET, Edwards BA, Deyoung PN, McSharry DG, Wellman A, Velasquez A, et al. Trazodone effects on obstructive sleep apnea and non-REM arousal threshold. Ann Am Thorac Soc 2015;12(5):758–64.
[67] Stepanski EJ, Conway WA, Young DK, Zorick FJ, Wittig RM, Roth T. A double-blind trial of protriptyline in the treatment of sleep apnea syndrome. Henry Ford Hosp Med J 1988;36(1):5–8.
[68] Stradling J, Smith D, Radulovacki M, Carley D. Effect of ondansetron on moderate obstructive sleep apnoea, a single night, placebo-controlled trial. J Sleep Res 2003;12(2):169–70.
[69] Sukys-Claudino L, Moraes W, Guilleminault C, Tufik S, Poyares D. Beneficial effect of donepezil on obstructive sleep apnea: a double-blind, placebo-controlled clinical trial. Sleep Med 2012;13(3):290–6.
[70] Suratt PM, Wilhoit SC, Brown ED, Findley LJ. Effect of doxapram on obstructive sleep apnea. Bull Eur Physiopathol Respir 1986;22(2):127–31.
[71] Taranto-Montemurro L, Sands SA, Edwards BA, Azarbarzin A, Marques M, de Melo C, et al. Desipramine improves upper airway collapsibility and reduces OSA severity in patients with minimal muscle compensation. Eur Respir J 2016;48(5):1340–50.
[72] Taranto-Montemurro L, Sands SA, Edwards BA, Azarbarzin A, Marques M, de Melo C, et al. Effects of tiagabine on slow wave sleep and arousal threshold in patients with obstructive sleep apnea. Sleep 2017;40(2).
[73] Torvaldsson S, Grote L, Peker Y, Basun H, Hedner J. A randomized placebo-controlled trial of an NMDA receptor antagonist in sleep-disordered breathing. J Sleep Res 2005;14(2):149–55.
[74] Wang D, Marshall NS, Duffin J, Yee BJ, Wong KK, Noori N, et al. Phenotyping interindividual variability in obstructive sleep apnoea response to temazepam using ventilatory chemoreflexes during wakefulness. J Sleep Res 2011;20(4):526–32.
[75] Whyte KF, Gould GA, Airlie MA, Shapiro CM, Douglas NJ. Role of protriptyline and acetazolamide in the sleep apnea/hypopnea syndrome. Sleep 1988;11(5):463–72.
*[76] Winslow DH, Bowden CH, DiDonato KP, McCullough PA. A randomized, double-blind, placebo-controlled study of an oral, extended-release formulation of phentermine/topiramate for the treatment of obstructive sleep apnea in obese adults. Sleep 2012;35(11):1529–39.
*[77] Wu K, Su X, Li G, Zhang N. Antioxidant carbocysteine treatment in obstructive sleep apnea syndrome: a randomized clinical trial. PLoS One 2016;11(2):e0148519.
[78] Yang L, Zhang H, Cai M, Zou Y, Jiang X, Song L, et al. Effect of spironolactone on patients with resistant hypertension and obstructive sleep apnea. Clin Exp Hypertens 2016;38(5):464–8.
[79] Smith DF, Ishman SL, Spiceland CP, Romaker AM. Effects of medical therapy on mild obstructive sleep apnea in adult patients. Sleep 2017;40:A208. Abstract Suppl.
[80] Fiori CZ, Martinez D, Goncalves SC, Montanari CC, Fuchs FD. Effect of diuretics and sodium-restricted diet on sleep apnea severity: study protocol for a randomized controlled trial. Trials 2015;16:188.
*[81] Eskandari D, Zou D, Grote L, Hoff E, Hedner J. Acetazolamide reduces blood pressure and sleep-disordered breathing in patients with hypertension and obstructive sleep apnea: a randomized controlled trial. J Clin Sleep Med – JCSM – Off Publ Am Acad Sleep Med 2018;14(3):309–17.
[82] David Andrew Wellman BaWsH. Atomoxetine and oxybutynin in obstructive sleep apnea (ATOSA). 2016 [cited 2018 22.10.2018]; Available from: https://clinicaltrials.gov/ct2/show/NCT02908529.
[83] David Andrew Wellman BaWsH. DAW1033D in obstructive sleep apnea (OSAstimD). 2017 [cited 2018 22.10.2018]; Available from: https://clinicaltrials.gov/ct2/show/NCT03383887.
[84] AG B. Obstructive sleep apnea (OSA) treated with a potassium channel inhibitor (SANDMAN). 2018 [cited 2018 22.10.2018]; Available from: https://clinicaltrials.gov/ct2/show/NCT03603678.
[85] UoS Florida. Effect of oxymetazoline hydrochloride in combination with fluticasone propionate on the apnea hypopnea index (AHI) in subject with persistent nasal congestion and mild obstructive sleep apnea. 2015 [cited 2018 22.10.2018]; Available from: clinicaltrials.gov.
[86] Ltd TB. A study to examine the efficacy of a therapeutic THX-110 for obstructive sleep apnea. 2018 [cited 2018 22.10.2018]; Available from: https://clinicaltrials.gov/ct2/show/NCT03646552.
*[87] Dingli K, Fietze I, Assimakopoulos T, Quispe-Bravo S, Witt C, Douglas NJ. Arousability in sleep apnoea/hypopnoea syndrome patients. Eur Respir J 2002;20(3):733–40.
[88] Schwartz AR, Rowley JA, O'Donnell C, King ED, Mayor A, Smith PL. Effect of hypertension on upper airway function and sleep apnoea. J Sleep Res 1995;4(S1):83–8.
[89] University of California SD. The effect of melatonin on sleep and ventilatory control in obstructive sleep apnea. 2015 [cited 2018 22.10.2018]; Available from: https://clinicaltrials.gov/ct2/show/NCT02484300.
[90] Mason M, Cates CJ, Smith I. Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. Cochrane Database Syst Rev 2015;7:CD011090.
[91] Koretsi V, Eliades T, Papageorgiou SN. Oral interventions for obstructive sleep apnea. Dtsch Arzteblatt Int 2018;115(12):200–7.
[92] Liu T, Li W, Zhou H, Wang Z. Verifying the relative efficacy between continuous positive airway pressure therapy and its alternatives for obstructive sleep apnea: a network meta-analysis. Front Neurol 2017;8:289.
[93] Edwards BA, Sands SA, Owens RL, Eckert DJ, Landry S, White DP, et al. The combination of supplemental oxygen and a hypnotic markedly improves obstructive sleep apnea in patients with a mild to moderate upper airway collapsibility. Sleep 2016;39(11):1973–83.
[94] Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci 2013;14(5):365–76.
[95] Ioannidis JP. Why most discovered true associations are inflated. Epidemiology 2008;19(5):640–8.
[96] Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007;7:10.