



Efficacy of Antidepressants in the Treatment of Obstructive Sleep Apnea Compared to Placebo. A Systematic Review with Meta-Analyses.

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Abstract

Purpose To establish the efficacy of oral antidepressants compared to placebo in improving obstructive sleep apnea (OSA) as measured on a polysomnography study. Secondary outcomes included self-reported sleepiness.

Methods Authors identified prospective randomized placebo-controlled studies from MEDLINE through PubMed, Web of Science, the Cochrane Library and EMBASE up to February 2019 in English language. Antidepressants included tricyclic antidepressants (TCA), tetracyclic antidepressants (TeCA), selective serotonin reuptake inhibitors (SSRI), and serotonin receptor modulators (SRM). Studies were assessed for inclusion and exclusion criteria, as well as risk of bias based on the Cochrane handbook.

Results The initial search yielded 254 unduplicated references ultimately reduced to 8 relevant studies, in which 198 OSA participants were included. Patients with an average baseline AHI of 26.7 events/hour taking 15-45mg mirtazapine had a statistically significant reduction in apnea-hypopnea index compared to placebo by -10.5 events/hour ($p < 0.001$), apnea index by -3.6 events/hour ($p = 0.001$) and hypopnea index by -5.9 events/hour ($p = 0.037$). In one study, patients taking 100mg trazodone 1 night improved significantly in AHI compared to placebo group ($p < 0.001$). Arousal index, sleepiness, and sleep efficiency were not statistically significantly reduced with any antidepressant medication compared to placebo ($p > 0.05$).

Conclusions Of the five antidepressant medications studied, only mirtazapine and trazodone showed a statistically significant reduction in AHI in the treated groups but not in sleepiness scale nor an increase in sleep efficiency. In this review, the total sample sizes were small, adverse side effects of some of the antidepressant medications were clinically significant, overall risk of bias of the studies was high or unclear, and overall quality of the evidence was low. Based on the evidence available at this time, we cannot recommend the antidepressants studied in the treatment of OSA.

Keywords Obstructive sleep apnea · Antidepressants · Mirtazapine · Trazodone · Polysomnography · Apnea Hypopnea Index · apnea index · sleepiness

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Introduction

Treatment modalities of obstructive sleep apnea (OSA) include Continuous positive airway pressure (CPAP) and oral appliances. CPAP is the gold standard treatment for patients with OSA [1]; however, the effectiveness of CPAP is limited due to lack of compliance [2, 3]. Meta-analyses have shown that oral appliances, specifically mandibular advancement devices (MAD), are an effective alternative treatment modality to CPAP for the treatment of OSA and daytime sleepiness [1]. MADs generally fit to the teeth in each arch and mechanically protrude the mandible, bringing the tongue forward and therefore opening the airway. Historically, CPAP compliance was typically lowered due to nasal stuffiness, the sensation of cold air, noise from the machine and pressure from the mask [4]. It should be noted that latest generation machines are smaller and quieter with a variety of nasal cones and pillows available. Other alternative treatments include supine position avoidance, behavioral modifications including weight loss, surgery and nerve electrical stimulation for appropriately selected patients.

Alternative treatments to CPAP and MAD – such as pharmaceutical interventions – have been explored, by taking advantage of the effect that serotonin-promoting drugs have on the airway. Through 5-HT_{2A} receptors, serotonin provides a tonic excitatory input to hypoglossal motor neurons innervating the genioglossus and other upper airway dilating muscles [5]. By using drugs such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs), serotonin's breakdown or reuptake is inhibited, depending on the drug of choice. Specifically, SSRIs (i.e. paroxetine, citalopram, escitalopram, fluoxetine, sertraline, and vilazodone) cause a negative allosteric modulation of the presynaptic serotonin transporter, therefore inhibiting the reuptake of serotonin, as their name indicates [6]. Serotonin receptor modulators (SRMs) [trazodone, nefazodone, vilazodone or vortioxetine] also work via blockade of serotonin reuptake; however, SRMs directly modulate various serotonin receptors [7]. TCAs (i.e. desipramine, protriptyline, amitriptyline, amoxapine) work by blocking the uptake of monoamines into cerebral neurons [8], whereas tetracyclic antidepressants (TeCAs) [mirtazapine, mianserin and setiptiline] work by increasing noradrenergic and serotonergic neurotransmission via blockade of central α_2 -adrenergic auto- and heteroreceptors [9].

Excessive daytime sleepiness can be a symptom of OSA in some patients. However, sleepiness is not necessarily specific to OSA; sleepiness may be due to another sleep disorder, such as insomnia. It has been reported that some antidepressants may actually worsen or induce primary sleep disorders, such as restless legs syndrome, sleep bruxism, REM sleep behavior disorder, and nightmares [10]. Therefore, the effects of anti-

depressants on sleepiness may not necessarily be limited to the disease of interest (OSA).

Researchers have found that serotonin-enhancing drugs in the brain may be able to offset the apnea-promoting effect of serotonin in the peripheral nervous system [5], and that may be a mechanism to improve OSA. As per motor neurons specifically, certain studies [11, 12] have shown that serotonin has the capability to provide a tonic excitatory input to hypoglossal motor neurons innervating the genioglossus and other upper airway-dilating muscles; in fact, animal models have shown that withdrawal of serotonin can predispose to airway obstruction, leading to possible apneas [13]. Therefore, the objective of this review was to analyze the efficacy of antidepressant medications in improving OSA.

Methods

Research question

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [14]. The PICOS (Patient, Intervention, Comparison, Outcome, Setting) question was, “In patients with OSA, what is the efficacy of antidepressants in improving AHI and sleepiness compared to placebo?”

- Population: Patients with mild, moderate or severe OSA.
- Intervention: Antidepressants (TCA, SSRI, SRM, TeCA).
- Comparison: Placebo intervention.
- Outcomes: Primary: AHI; secondary: other polysomnographic measurements (apnea index, hypopnea index, AHI REM, AHI NREM), sleepiness (Epworth sleepiness scale, sleep efficiency).
- Setting: Sleep laboratories, university/hospital sleep centers.

Inclusion and exclusion criteria

Studies were limited to prospective randomized placebo-controlled clinical trials or crossover studies in the English language with human subjects. Studies without PSG were excluded. Systematic reviews and literature reviews were excluded, as were editorials, letters to the editor, case studies, animal studies, cost-effectiveness studies, pharmacokinetic studies and clinical guidelines.

Search methods for identification of studies

The MEDLINE via PubMed search was limited to English language and Humans: (Antidepressant OR Tricyclic Antidepressant OR Selective Serotonin Reuptake Inhibitor

OR SSRI OR Selective Serotonin Norepinephrine Inhibitor OR SNRI) AND (Obstructive Sleep Apnea OR OSA).

Three other electronic databases were searched (EMBASE, Cochrane Library, Web of Science). After our original search on 2/8/2018 documented on Online Resource 1, we re-ran the searches on 2/10/2019 with no further relevant references found.

Selection of studies, data extraction and management

The titles, abstracts and reports that resulted from our search strategy were independently evaluated by three review authors (M.R.A., M.A.G., S.W.J.). Disagreements were resolved by discussion with a fourth senior author (R.E.). Full manuscripts were reviewed where trials met our inclusion criteria or when the title or abstract did not allow for a clear inclusion or exclusion decision to be made. Studies rejected at this or later stages were recorded along with reasons for exclusion. Reviews, systematic reviews and all included studies were evaluated for relevant trials. Data were extracted independently and in triplicate using a previously prepared data extraction form. The form included the characteristics of trial subjects, interventions, control groups if appropriate and outcome measures.

Assessment of risk of bias in included studies

A risk of bias table was completed for each included study. The assessment of risk of bias in the included randomized controlled trials is consistent with the approach described in the Cochrane Handbook [15] and was undertaken independently and in triplicate as part of the data extraction process as described previously.

Meta-analyses

Randomized controlled trials comparing an antidepressant to a placebo intervention, reporting similar outcomes, were pooled into a paired meta-analysis. The analyses included only the available data (ignoring missing data). For one study [16], standard deviation (SD) was calculated from the standard error of the mean (SEM) and sample size (n) as $SD = SEM * \sqrt{n}$. For another study [17], we approximated mean = median and calculated SD from median and interquartile range (IQR) as follows: $SD = IQR / 1.35$.

Clinical heterogeneity was assessed by examining the participants, interventions, and outcomes measures included in the trials. Estimates of effect were combined using a random effects model. All the outcomes reported in this review were continuous variables. Review authors calculated estimates of effect as mean differences of post-treatment data for all outcomes with 95% Confidence

Intervals (CI) except for sleepiness scales. Review authors used the ‘standardized difference in means’ to compare the sleepiness scales as different scales were used by different authors. Subgroup analyses are presented in this review according to pharmacologic categories. Statistical analyses were conducted with Comprehensive Meta-analysis software version 3 (Biostat, Englewood, NJ, USA).

Levels of evidence and summary of the review findings

Quality of evidence assessment and summary of the review findings were conducted with the software GRADE profiler© (Grader©), following the Cochrane Collaboration and GRADE Working Group recommendations [15]. In this systematic review we considered the sample size of the meta-analysis as insufficient (small sample size) if less than 400 participants were included in the meta-analysis [18], downgrading the quality of the evidence.

Results

Search results

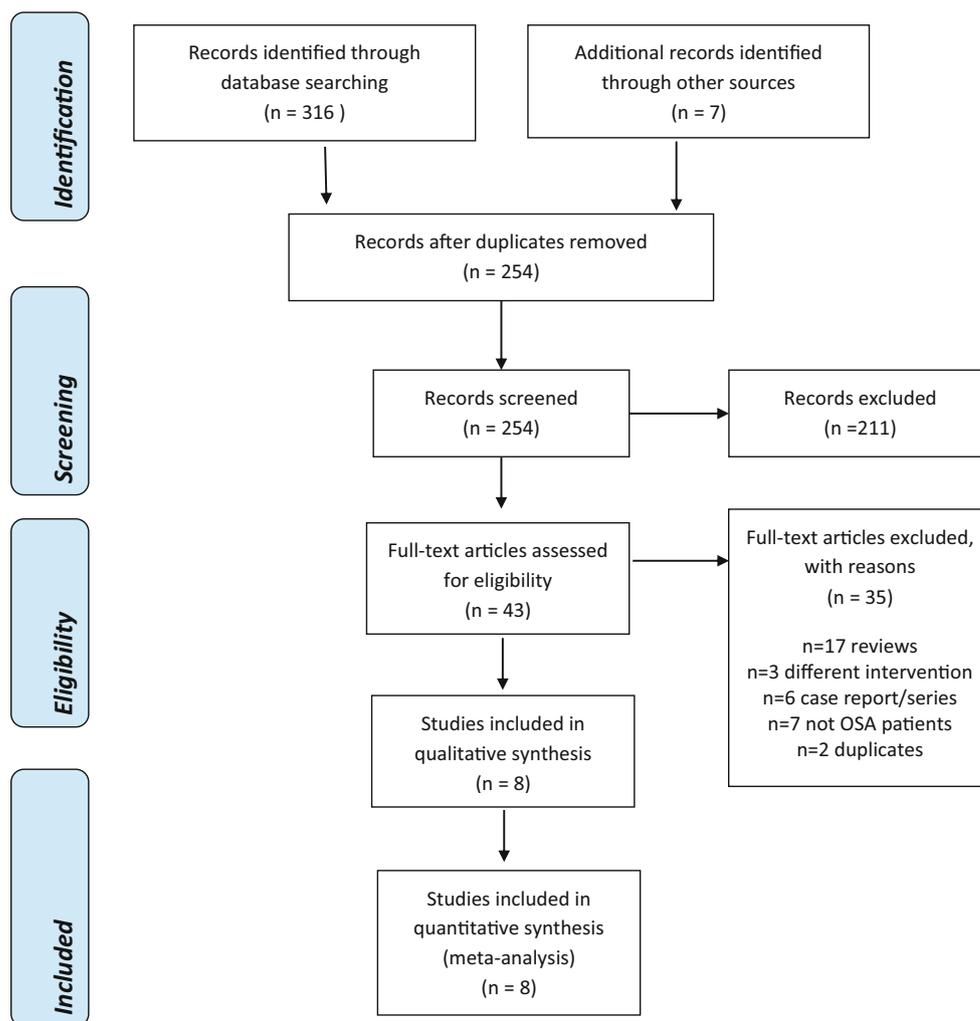
The initial search strategy yielded 247 unduplicated references, plus 7 records obtained by cross-referencing the bibliography sections of the included studies and reviews. 254 records were assessed independently by three review authors, and based on the abstracts and titles, these were reduced to 43 relevant manuscripts. All of the 43 manuscripts identified were searched for full-text and analyzed for inclusion independently by three review authors. 8 manuscripts were relevant for inclusion. The main reason for exclusions were that the reference was a literature review or systematic review (n=17), the intervention was not an antidepressant (n=7), the reference was a case report or a case series (n=6), the patients used were not OSA patients (n=7) and the reference was a duplicate (n=2). The PRISMA flowchart shows a summary of our results (Fig. 1). Table 1 shows a list of our included studies.

Summary of included studies

Eight crossover placebo-controlled studies were eligible for qualitative analysis, one single-blinded [19] and seven double-blinded [5, 16, 17, 20–25], (Table 1).

Population A total of 163 patients were included in this review. Patients had OSA as diagnosed by PSG. The minimum AHI used as inclusion criteria varied from study to study, but the minimum included AHI was 10 events/hour [16, 19, 24, 25]. In one study patients had to be naïve to any form of OSA

Fig. 1 PRISMA flow diagram [14]



treatment to be included [5]; in another, the patients either never had used CPAP or had used it for less than 4 days within the past year [16]. Patients were excluded from the studies for various other reasons, including taking a tricyclic antidepressant or SSRI during the study [20], clinically significant medical problems [5, 16], known psychiatric disease [19], smoking habits [24], and taking any current sleep medications or medications that affect sleep [16, 17, 24]. Four articles only included men [19–21, 25], and the other included both men and women; there were more males than females in all included studies. The number of participants ranged from 5 subjects [21] to 65 participants [16]. The ages of the patients ranged from 18 years old in two studies [5, 17], to 74 in another study [16]. The trials were conducted in four countries including Australia [16], Canada [27], Sweden [19], the United States [5, 17, 20, 24, 25]. The inclusion and exclusion criteria among the studies as well as the average age and gender distribution are presented in Table 1.

Interventions Antidepressants and placebo were used in a crossover manner in all trials and treatment duration

ranged from 1 night to 6 weeks for each intervention. In two of the reviewed articles, doses of paroxetine of either 20 mg or 40 mg were used [19, 20]; mirtazapine of varying doses – 4.5 mg compared to 15 mg in one study and 7.5 mg, 15 mg, 30 mg, and 45 mg in another study [5, 16], as well as protriptyline in 10 mg or 20 mg doses in two different crossover trials [21, 25]. The remaining investigations used trazadone 100 mg [24] and desipramine 200 mg [17]. The patients were placed into two [17, 19–25] or three [5, 16] randomized groups in each study. The protocol entailed administering the placebo or antidepressant first in a randomized manner, evaluating the patient via PSG, and then giving an alternative intervention (placebo or antidepressant) and evaluating via PSG for a second or third night. One included paper [16] used a 3-way crossover with mirtazapine, placebo, and mirtazapine in combination with another compound CD0012, a dopaminergic and serotonergic agent. The other article that used mirtazapine was a 3-way crossover design with two different doses of the drug [5]. In one of the trials, there was no washout period used [5].

Table 1 Summary of eligible randomized placebo-controlled crossover studies

Study	Country, Study Design	Sample size and interventions	Duration of intervention and washout period duration	Inclusion criteria	Gender and age (average±SD) [range] years	Summary of Risk of Bias	Baseline AHI mean±SD
Berry et al. 1999 [20]	USA, DBRC,	CROSSOVER N=8 -Paroxetine 40 mg -Placebo	Dose = 1 night Washout = 1 week	1 severe sleep apnea AHI>60	8M/0F 48.0±1.9 years	Unclear	AHI>60
Brownell et al. 1982 [21]	Canada, DBRC	CROSSOVER N=5 -Protriptyline 20mg -Placebo	Dose = 2 weeks Washout = 2 weeks	2 Obese men 3 OSA confirmed by PSG	5M/0F 45.8±5.3	HIGH	AHI not reported
Carley et al. 2007 [5]	USA, 3-way DBRC	CROSSOVER N=12 -Mirzapine 4.5 mg -Mirzapine 15 mg -Placebo	Dose = 1 week for each treatment Washout = None	1 OSA confirmed by PSG 2 Naïve to any form of treatment 3 Diagnosis of sleep apnea syndrome [22]	7M/5F 18-67 years Men: 39.0±18.3 Female: 43.4±14.2	HIGH	Baseline AHI Men: 22.0±11.2 Female: 24.1±22.8
Kraiczai et al. 1999 [19]	Sweden, Single-blind randomized crossover	CROSSOVER N=20 -Paroxetine 20 mg -Placebo	Dose = 6 weeks Washout = 4 weeks	1 OSA diagnosed in a previous overnight study (oxygen desaturation index based on self-reported sleep duration ≥10 hours) 2 aged 25-65 years 2 AHI of 10 to 40	20M/0F 52.1±8.7 [25 to 65]	HIGH	AHI not reported
Marshall et al. 2008 [16]	Australia, Study 1: 3-way DBRC --- Study 2: double-blind, 3-arm, parallel-group	Study 1: Crossover N=18 -Placebo -Mirzapine 7.5 mg -Mirzapine 15 mg -Mirzapine 30 mg -Mirzapine 45 mg --- Study 2: N=65 -Placebo (n=13) -Mirzapine 15 mg + placebo (n=26) -Mirzapine 15mg + CD0012 (n=25)	Study 1: Dose = 2 weeks at each of the 4 doses Washout = None between doses Study 2: Dose = 4 weeks for each treatment	3 body mass index (BMI) of 40 kg/m ² or less (Study 1) or had a BMI of 34 kg/m ² or less (Study 2) 4 either had never used CPAP or had used it for less than 4 days within the past year 5 Nonsmokers or had no history of smoking for at least 2 years, 6 Baseline Epworth Sleepiness Scale score higher than 10.	Study 1: 15M/3F mean: 47 [28 to 64] years Study 2: 56M/9F mean: 52 [30 to 74] years	HIGH	Baseline AHI Study 1: 24.1±8.0 --- Study 2: 27.4±11.1
Smales et al. 2015 [24]	USA, DBRC	CROSSOVER N=13 -Trazodone 100 mg -Placebo	Dose = 1 night Washout = 1 week	1 History of OSA with an AHI > 10 events/h during supine NREM sleep [23]	7M/6F 52±3 [26 to 69] years	UNCLEAR	AHI > 10
Stepanski et al. 1988 [25]	USA, DBRC	CROSSOVER N=8 -Protriptyline 10-20mg -Placebo	Dose = 3 weeks Washout = None	2 No known allergies to medications 1. daytime sleepiness 2. apnea index ≥ 10	8M/0F 44.9±7.8 [31 to 54] years	UNCLEAR	Apnea index ≥ 10
AHI > 15	Taranto-Montemurro et al. 2016 [17]	USA, DBRC	CROSSOVER N=14 -Desipramine 200 mg -Placebo	Dose = 1 night Washout = 1 week	1. AHI>15 events/hour [26] 2. aged 18-65 years [18 to 65] years	10M/4F 55 average [18 to 65] years	UNCLEAR

Abbreviations: DBRC: Double-blind randomized crossover; N: sample size; M: Male; F: Female; AASM: American Academy Sleep Medicine; AHI: Apnea-Hypopnea Index; SD: Standard deviation;

Table 2 Adverse effects reported by the studies

Study	Intervention group(s)	Adverse Events in Intervention Groups	Adverse Events in Placebo groups
Berry et al. 1999 [19]	N=8 Paroxetine 40mg	None Reported	None reported
Brownell et al. 1982 [20]	N= 5 Protriptyline 20 mg to >30mg	<i>Short-term</i> study (Protriptyline 20 mg): No adverse events reported <i>Long-term</i> (6 months, >30mg dose+): urinary retention, dry mouth	None reported
Carley et al. 2007 [5]	N=12 Mirtazapine 4.5mg Mirtazapine 15mg	None reported for either dosing group	None reported
Kraiczi et al. 1999 [18]	N=20 Paroxetine 20 mg	n=2 fatigue, n=3 ejaculation disturbances, n=2 decreased libido, n=1 nervousness, n=1 constipation, n=1 headache, n=1 , dizziness, n=1 somnolence, n=1 infectious pneumonia, n=1, Lyme disease, n=1 sweating	n=1 dizziness, n=1 fatigue and somnolence, n=1 dry mouth
Marshall et al. 2008 [15]	<i>Study 1: Crossover</i> -Mirtazapine 7.5 mg or 15 mg or 30 mg or 45 mg <i>Study 2: N=65</i> - Mirtazapine 15 mg + placebo (n=26) - Mirtazapine 15mg + CD0012 (n=25)	<i>Study 1 (7.5-45mg x 2 weeks):</i> n=2 withdrew due to excessive lethargy and resultant difficulty driving. <i>Study 2 (15mg x 4 weeks):</i> n=6 withdrew due to complaints of lethargy, difficulty driving or other side-effects 1.4 kg (~ 3 pounds) average weight gain in 4 weeks	None reported
Smales et al. 2015 [21]	N=13 Trazadone 100mg	None reported	None reported
Stepanski et al. 1988 [24]	N=8 Protriptyline 10mg-20mg	None reported	None Reported
Taranto-Montemurro et al. 2016 [16]	N=14 Desipramine 200mg	n=3, Worsening of AHI, worsening of collapsibility	None reported

Comparison groups Patients served as their own controls, as all studies included in this analysis followed a crossover design. Each used a placebo, although none of the included studies specified what was used as the placebo.

Outcomes The primary outcome measurement reported by the reviewed articles was comparison of AHI (Apnea Hypopnea Index) between antidepressants and placebo in patients with OSA. One study however, reported apneic events with measurements such as Total Number of Apneas/Total Sleep Time; it should be noted that “hypopneas” were not defined and measured at the time Brownell et al. published their results [21]. Secondary outcomes included Apnea Index (AI) [5, 16, 19, 21, 25], hypopnea index [5, 16, 19, 21], REM AHI [5, 16, 19], NREM AHI [5, 16, 19], sleep efficiency defined as “total sleep time divided by time in bed (%)” [5, 16, 19, 21–25] and sleepiness scales (ESS -Epworth Sleep Scale [16], Stanford Sleepiness Scale [5] and daytime sleepiness [19]).

Risk of bias in included studies

The assessment of risk of bias for each domain is presented in [Online Resource 2](#) & [Online Resource 3](#). In conclusion, an unclear overall risk of bias was assigned to four studies [17, 20, 24, 25], a high overall risk of bias was assigned to four

studies [5, 16, 19, 21]. A low overall risk was assigned to none of the studies (Fig. 2).

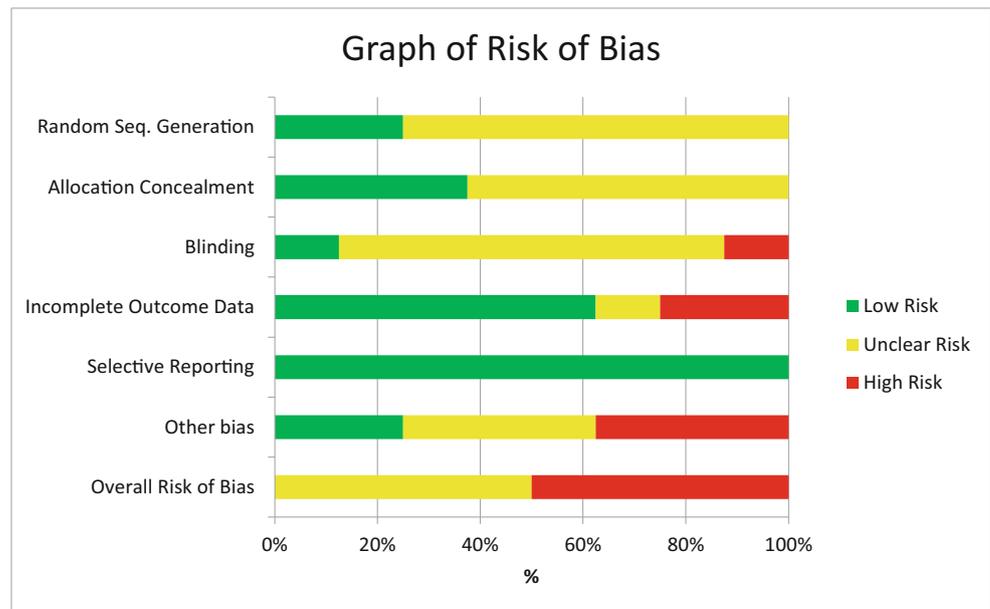
Meta-analyses

Our initial search strategy yielded 247 references, and 8 RCT studies were included in the meta-analyses which fulfilled the inclusion criteria for our systematic review on OSA patients comparing similar outcomes with the same interventions (antidepressants vs. placebo). Subgroup analyses are presented in this review according to pharmacologic categories.

Overall results

Antidepressants improved AHI significantly by -8.4 events/hour on average compared to placebo (95% CI= -10.8 to -6.0; $p < 0.001$; Fig. 3a). The baseline and post-treatment AHI reported by the original studies are shown in [Online Resource 5](#). Baseline AHI was only reported in two RCTs [5, 16] with an average of 26.7 events/hour; one RCT only reported inclusion criteria as baseline AHI > 10 [24] and another included participants with an AHI > 60 [20]. Because AHI was unknown in some studies, it is unclear if the -8.4 events/hour of improvement compared to placebo is clinically significant. Though overall AHI improved significantly compared to placebo, the average post-treatment AHI in the intervention groups was

Fig. 2 Summary of risk of bias of eligible RCT's



<15 events/hour in only one crossover trial [5], between 15-30 events/hour in three studies [16, 19, 24] and above 75 events/hour in Berry et al. 1999 [20] where the patients received 40mg paroxetine (Online Resource 5).

Antidepressants also improved NREM AHI ($p < 0.001$; Online Resource 4), REM AHI ($p < 0.001$; Online Resource 4) and apnea index ($p < 0.001$; Fig. 3b). Again, the baseline REM, NREM AHI, and arousal index for these studies are unknown. Our meta-analyses did not show a significant improvement ($p > 0.05$) compared to placebo on arousal index, hypopnea index, sleep efficiency (Online Resource 4) nor sleepiness (Fig. 3c).

Sensitivity analyses: Of the included RCTs, three studies had a length of antidepressant intervention of only one night [17, 20, 24]. Therefore, authors performed a second meta-analysis excluding these particular studies. These meta-analyses show similar results to the meta-analyses including the single-night intervention studies. Antidepressants improved overall AHI significantly by -10.5 events/hour on average compared to placebo ($p < 0.001$; Online Resource 6) and did not show a significant improvement ($p > 0.05$) compared to placebo on arousal index nor sleep efficiency (Online Resource 6).

Subgroup analyses by class of antidepressant

TeCAs Patients taking 15mg-45mg of mirtazapine, a tetracyclic antidepressant, had a significant improvement compared to controls receiving placebo in AHI by -10.5 events/hour ($p < 0.001$; Fig. 3a) [5, 16]. These two studies reported an average baseline AHI of 26.7 events/hour [5, 16]. TeCAs also showed significant efficacy by decreasing REM AHI by -11.2 events/hour [5] ($p < 0.001$) and NREM AHI by -

9.9 events/hour [16] ($p = 0.001$; Online Resource 4). Mirtazapine 15mg [5, 16] also significantly improved apnea index by -3.6 events/hour ($p = 0.001$; Fig. 3b). Hypopnea index was also improved significantly by -5.9 events/hour [16] ($p = 0.037$; Online Resource 4). However, TeCAs did not significantly improve sleepiness [5, 16], arousal index nor sleep efficiency ($p > 0.05$; Online Resource 4).

SRMs Our meta-analyses indicated that trazodone (SRM) was significantly effective in reducing AHI by -10.2 events/hour compared to placebo in one study [24] ($p < 0.001$; Fig. 3a). However, trazodone did not significantly improve arousal index nor sleep efficiency (total sleep time divided by time in bed (%)) [24] (Online Resource 4).

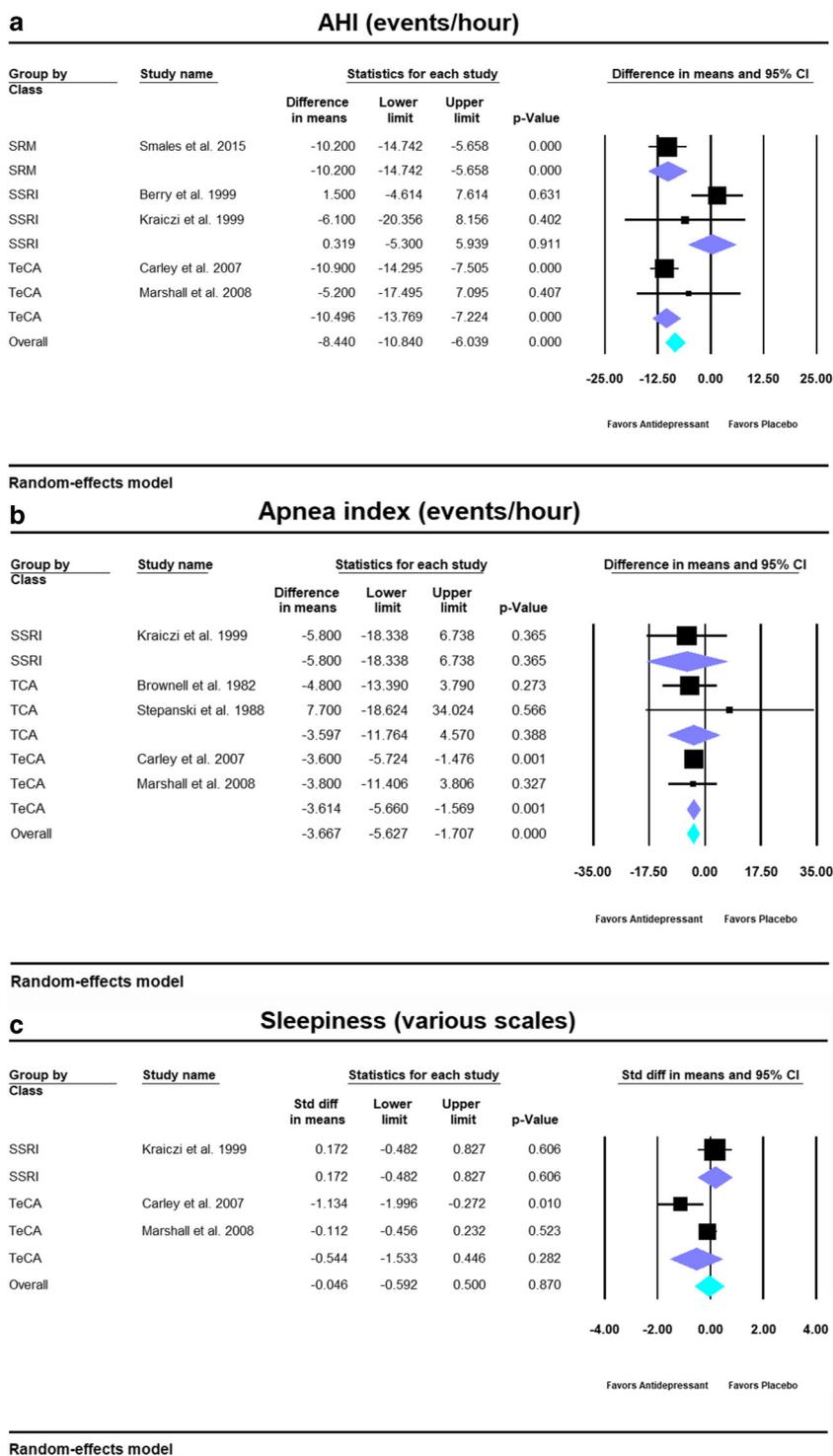
Sensitivity analyses: Smales et al. [24] reported results on trazodone where the authors employed only a 1-night trial using this medication; therefore, it is believed that the results should be taken with caution.

SSRIs Paroxetine 20mg or 40mg [19] did not significantly improve AHI, apnea index or sleepiness (Fig. 3), hypopnea index, arousal nor sleep efficiency according to our random-effects models (Online Resource 4).

Sensitivity analyses: Similar results were found after excluding the study by Berry et al. [20] (Online Resource 6); this study was excluded due to the fact that it only used 1 night of paroxetine to determine their results.

TCAs (protriptyline 10-20mg and desipramine 200mg) Our subgroup analyses indicated that TCAs did not significantly improve apnea index in two studies [21, 25], nor arousal index [21], hypopnea index [25] nor sleep efficiency [17, 25] (Online Resource 4).

Fig. 3 Effect of antidepressants in AHI (A), apnea index (B) and sleepiness (C)



Sensitivity analyses: Similar results were found after excluding the Taranto-Montemurro et al. study [17] (Online Resource 6) as it only employed 1-night intervention.

Adverse effects reported by the authors One study reported patients taking TeCA's (mirtazapine) presented with weight gain (1.4 kg or 3 pounds average weight gain in 4 weeks) as

a side effect ($p < 0.01$) as well as unacceptable lethargy while taking medication for study [5]. Treatment with SSRI presented adverse events during active treatment including fatigue, ejaculation disturbances, decreased libido, nervousness, constipation, headache, dizziness, somnolence, infectious pneumonia, Lyme disease, and sweating [19]. The crossover trial also presented adverse effects with placebo treatment which

included one patient reporting dizziness, one reporting fatigue and somnolence, and one reporting dryness of the mouth [19]. One patient experienced mild dizziness in the morning after desipramine administration (TCA). The symptom lasted for a few hours and the patient spontaneously recovered [17] (Table 2).

Summary of the evidence and quality of the findings (GRADE)

The quality of the evidence was *very low* for arousal index due to high risk of bias, inconsistency in reporting and imprecision of measurements in the included studies. The quality of evidence was *low* for all other outcomes due to risk of bias and inconsistency of reported outcomes in the included studies (Online Resource 7); *low* evidence grading indicates that further research is very likely to have an important impact on our confidence in the estimate of effect and it is likely to change the estimate.

Discussion

Primary outcome

The primary outcome measurement reported by the original studies was overall AHI in events/hours. According to our meta-analyses, AHI improved in average -8.4 events/hour after interventional antidepressants compared to placebo. One limitation of this systematic review is the lack of a clear baseline AHI reported in the original RCTs. Only two studies provided a baseline mean and SD for AHI [5, 16], with a wide variability of inclusion criteria from OSA patients $AHI \geq 10$ [24] to severe OSA patients ($AHI > 60$) [20]. The average post-treatment AHI was between 11 and 75 events/hour in the included studies. Sensitivity analyses excluding three studies with only 1 night treatment showed similar results.

Our subgroup analyses showed that only 15–45mg mirtazapine, a tetracyclic antidepressant (TeCA) was effective in improving AHI, NREM AHI, REM AHI, apnea index and hypopnea index but not sleepiness, arousal index nor sleep efficiency. AHI improved in average by -10.5 events/hour ($p < 0.001$) in two studies with a baseline AHI of 26.7 events/hour with patients taking 15–45mg of mirtazapine [5, 16] compared to placebo, further research is needed to confirm these results, as well as the optimal dosage. Though statistically significant, these outcomes may not be clinically significant.

Agreements and disagreements with other studies or reviews

Our review of the evidence has shown that 15–45mg mirtazapine improved AHI, NREM AHI, REM AHI and apnea Index but did not show improvement in clinical OSA findings such as sleepiness or sleep efficiency. This review is in partial disagreement with Rosenberg et al. [28] who in

a review in 2008 of mirtazapine and its impact on AHI summarized Marshall et al. 2008 [16] as follows, “No measurement of OSA severity was improved by mirtazapine”; however, our meta-analysis did not only include Marshall et al. [16] but also Carley et al. 2007 [5] showing overall significant improvement on AHI, NREM AHI, REM AHI, apnea Index and hypopnea index with mirtazapine [5, 16].

This study finds a general agreement with other review’s conclusions that antidepressants may have a slightly beneficial effect on one or more parameters of measuring OSA [29–37]. While reviewing 33 trials covering 27 different drugs, Kohler et al. 2009 [37] found the mechanisms by which antidepressants are supposed to improve OSA include, among others, an increase in tone of the upper airways, an increase in ventilatory drive, a reduction in airway resistance, and alterations in surface tension forces in the upper airway; however, Kohler et al. 2009 [37] found that in most of these studies, there was no statistically significant effect on OSA observed. Additionally, in a review by Grunstein et al. 2001 [31], authors concluded that TCAs showed a beneficial effect on sleep apnea as well as improved daytime somnolence. Abad and Guilleminault 2006 [36] concluded that, in a review of the pharmacological management of sleep apnea including serotonergic drugs, that SSRIs do not have a role in the treatment of OSA; however, this paper does report that mirtazapine was found to reduce AHI by $\sim 50\%$, with an increase in subjective perception of sleepiness and weight gain while using the drug [36]. It is important to note that overall positive clinical findings were minimal if at all reported, daytime sleepiness was not improved and potential adverse side effects may outweigh the small positive impact on reduction of NREM and REM AHI.

Overall completeness and applicability of evidence

Crossover placebo-controlled studies were identified from four electronic data bases including MEDLINE through PubMed, Web of Science, the Cochrane Library and EMBASE limited to English language. Oral antidepressants included TCAs, SSRIs, SRM, and TeCAs. The results of this systematic review apply to mild to severe OSA patients with an $AHI > 10$ between the ages of 18 to 74 years old both female and male. The trials were conducted in four countries only (Australia, Canada, Sweden and USA) and may not reflect or apply to other countries.

Quality of the evidence

Only randomized placebo-controlled trials were included in this systematic review by choice of the authors, as high-quality RCTs can provide the best evidence in comparing the effects of oral antidepressants in the treatment of OSA. However, of the 8 RCTs included in the quantitative analysis, four of the studies were at overall unclear risk of bias and four

were at high risk. The quality of the evidence was low to very low due to risk of bias, inconsistency, and imprecision (a small total sample size below 400 participants [18]), with a small number of eligible studies in each meta-analysis due to heterogeneity of the outcomes reported and in some cases, wide variance of point estimates and statistical heterogeneity (Online Resource 7).

Heterogeneity of the review

This systematic review included only RCTs comparing antidepressants with placebo with similar reported outcomes. The main outcomes were AHI, NREM AHI, REM AHI, Apnea index, Sleepiness, Arousal index, Hypopnea index, and Sleep efficiency. These outcomes were mainly measured with PSG (objective outcomes) and questionnaires (subjective outcomes) before and at the end of each treatment. The patients' severity of OSA ranged from mild to severe. Some degree of clinical heterogeneity was found in terms of numerous factors. The studies included in this review were all crossover trials and treatment duration ranged from 1 night to 6 weeks for each intervention. Different types of antidepressants were utilized in the included studies with varied mechanisms of action, dosages and schedules.

Future research

The results of our study of eight randomized controlled clinical trials indicate that although there was statistical significance of the studied antidepressants to have a slightly beneficial effect on one or more parameters of measuring OSA, the clinical significance of these medications is still in question.

Further research is needed to understand why mirtazapine was effective in reducing AHI compared to placebo. It is suggested to include RCTs with larger subject sample sizes and longer study periods. It would be beneficial to include newer medications that may have specific profiles that show improvement of the deep sleep and REM sleep stages. Ideally, pharmaceutical interventions should be targeted to a "personal" therapeutic approach.

Conclusions

The use of antidepressants as an option in treating patients suffering with mild to severe obstructive sleep apnea is a subject of interest to providers of care and to patients who have failed assistive devices such as CPAP and MADs. This review of five different antidepressant medications shows a statistically significant difference, though there might not be a clinical significance. This review found favorable effect of 15mg-45mg mirtazapine, a tetracyclic antidepressant, compared to placebo in two studies including OSA patients with an average of 26.7

events/hour. The quality of the evidence was low due to high risk of bias, small sample size and heterogeneity. Mirtazapine reduced some of the measured parameters of OSA (AHI, REM AHI, NREM AHI, apnea index and hypopnea index) but no reduction in daytime sleepiness nor sleep efficiency was found. Adverse effects of TeCAs in one study included weight gain and sedation. This indicates caution for practitioners in use of TeCAs as weight gain could be a contributing factor for OSA. Therefore, close weight monitoring is highly recommended while using TeCA. Trazodone, a Serotonin Receptor Modulator, showed a statistically significant effect in reducing AHI compared to placebo in one study with one night of treatment, with no improvement in arousal index or sleep efficiency, so no strong recommendation can be made at this point.

This study finds a general agreement with other reviews' conclusions that antidepressants may have a slightly beneficial effect on one or more parameters of measuring OSA, albeit at a low quality of evidence. However, daytime sleepiness was not improved and potential adverse side effects including daytime sedation and weight gain may outweigh the statistically significant positive impact on reduction of NREM and REM AHI. Therefore, at this time we cannot support the use of the studied antidepressant medications as an intervention for patients who have tried and failed with CPAP and or MADs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent For this type of study (systematic review), formal consent is not applicable.

Ethical approval For this type of study (systematic review), ethical approval is not applicable.

Abbreviations CPAP, continuous positive airway pressure;; MAD, mandibular advancement device;; OSA, obstructive sleep apnea;; RCT, randomized controlled trial;; M.R.A, Dr. Magda R AbdelFattah;; S.W.J, Dr. Song Woo Jung;; M.A.G, Dr. Melvin A Greenspan;; R.E, Dr. Reyes Enciso;; AASM, American Academy of Sleep Medicine;; AHI, Apnea-hypopnea index;; CI, confidence interval;; PSG, polysomnography;; TCAs, Tricyclic antidepressants;; TeCAs, Tetracyclic antidepressants;; SSRIs, Selective serotonin reuptake inhibitors;; SRMs, Serotonin receptor modulators;; SNRIs, Selective serotonin-norepinephrine reuptake inhibitors;; MAOs, Monoamine oxidase inhibitors;; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses;; PICO, Patient, intervention, comparison and outcome;; REM, Rapid eye movement;; NREM, Non-rapid eye movement;; SD, Standard deviation;; SEM, Standard error of the mean;; IQR, Interquartile range

References

1. Bratton DJ, Gaisl T, Schlatzer C, Kohler M (2015) 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* 3: 869–878. [https://doi.org/10.1016/S2213-2600\(15\)00416-6](https://doi.org/10.1016/S2213-2600(15)00416-6)
2. Wolkove N, Elkholy O, Baltzan M, et al (2007) Sleep and aging: 2. Management of sleep disorders in older people. *CMAJ* 176:1449–1454. <https://doi.org/10.1503/cmaj.070335>
 3. Weaver TE, Grunstein RR (2008) Adherence to Continuous Positive Airway Pressure Therapy: The Challenge to Effective Treatment. *Proc Am Thorac Soc* 5:173–178. <https://doi.org/10.1513/pats.200708-119mg>
 4. Douglas NJ, Engleman HM (1998) CPAP therapy: outcomes and patient use. *Thorax* 53(Suppl 3):S47–S48
 5. Carley DW, Olopade C, Ruijt GS, Radulovacki M (2007) Efficacy of mirtazapine in obstructive sleep apnea syndrome. *Sleep* 30:35–41
 6. Stahl SM (1998) Not so selective serotonin reuptake inhibitors. *J Clin Psychiatry* 59:343–344. [https://doi.org/10.1016/S0165-0327\(98\)00221-3](https://doi.org/10.1016/S0165-0327(98)00221-3)
 7. D'Agostino A, English CD, Rey JA (2015) Vortioxetine (brintellix): a new serotonergic antidepressant. *P T* 40:36–40. <https://doi.org/10.4088/JCP.14027ah1>
 8. Ritter J, Lewis L, Mant T, Ferro A (2008) A textbook of clinical pharmacology and therapeutics, 5th edn. CRC Press, London (England)
 9. Davis R, Wilde M (1996) Mirtazapine A Review of its Pharmacology and Therapeutic Potential in the Management of Major Depression. *CNS Drugs* 5:389–402
 10. Wichniak A, Wierzbicka A, Walecka M, Jernajczyk W (2017) Effects of Antidepressants on Sleep. *Curr Psychiatry Rep* 19:1–7. <https://doi.org/10.1007/s11920-017-0816-4>
 11. Douse MA, White DP (1996) Serotonergic effects on hypoglossal neural activity and reflex responses. *Brain Res* 726:213–222. [https://doi.org/10.1016/0006-8993\(96\)00335-6](https://doi.org/10.1016/0006-8993(96)00335-6)
 12. Berger AJ, Bayliss DA, Viana F (1992) Modulation of neonatal rat hypoglossal motoneuron excitability by serotonin. *Neurosci Lett* 143:164–168. [https://doi.org/10.1016/0304-3940\(92\)90257-8](https://doi.org/10.1016/0304-3940(92)90257-8)
 13. Veasey SC, Panckeri KA, Hoffman EA et al (1996) The Effects of Serotonin Antagonists in an Animal Model of Sleep-Disordered Breathing. *Am J Respir Crit Care Med* 153:776–786. <https://doi.org/10.1164/ajrccm.153.2.8564132>
 14. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6:e1000097. <https://doi.org/10.1371/journal.pmed.1000097>
 15. Higgins J, Green S (editors) (2011) *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011].
 16. Marshall NS, Yee BJ, Desai AV et al (2008) Two randomized placebo-controlled trials to evaluate the efficacy and tolerability of mirtazapine for the treatment of obstructive sleep apnea. *Sleep* 31:824–831
 17. Taranto-Montemurro L, Sands SA, Edwards BA et al (2016) Desipramine improves upper airway collapsibility and reduces OSA severity in patients with minimal muscle compensation. *Eur Respir J* 48:1340–1350. <https://doi.org/10.1183/13993003.00823-2016>
 18. Schwingshackl L, Knüppel S, Schwedhelm C, Hoffmann GMB, Stelmach-Mardas M, Dietrich S, Eichelmann F, Kontopantelis EIK, Aleksandrova K, Lorkowski S, Leitzmann MF, Kroke ABH (2017) Perspective: NutriGrade: A Scoring System to Assess and Judge the Meta-Evidence of Randomized Controlled Trials and Cohort Studies in Nutrition Research. *Adv Nutr An Int Rev J* 8: 789–790. <https://doi.org/10.3945/an.117.016188>
 19. Kraiczki H, Hedner J, Dahlof P et al (1999) Effect of serotonin uptake inhibition on breathing during sleep and daytime symptoms in obstructive sleep apnea. *Sleep* 22:61–67
 20. Berry RB, Yamaura EM, Gill K, Reist C (1999) Acute effects of paroxetine on genioglossus activity in obstructive sleep apnea. *Sleep* 22:1087–1092
 21. Brownell LG, West P, Sweatman P et al (1982) Protriptyline in obstructive sleep apnea: a double-blind trial. *N Engl J Med* 307: 1037–1042. <https://doi.org/10.1056/NEJM1982102103071701>
 22. No authors. (1999) Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 22:667–689
 23. Iber C, Ancoli-Israel S, Chesson A, Quan S. (2007) *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*, 1st Ed. Westchester, Illinois
 24. Smales ET, Edwards BA, Deyoung PN et al (2015) Trazodone effects on obstructive sleep apnea and non-REM arousal threshold. *Ann Am Thorac Soc* 12:758–764. <https://doi.org/10.1513/AnnalsATS.201408-399OC>
 25. Stepanski EJ, Conway WA, Young DK et al (1988) A double-blind trial of protriptyline in the treatment of sleep apnea syndrome. *Henry Ford Hosp Med J* 36:5–8
 26. Berry RB, Budhiraja R, Gottlieb DJ, et al. (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin sleep Med*. 8(5):597-619. <https://doi.org/10.5664/jcsm.2172>
 27. Brownell LG, Perez-Padilla R, West P, Kryger MH (1983) The role of protriptyline in obstructive sleep apnea. *Bull Eur Physiopathol Respir* 19:621–624
 28. Rosenberg R, Doghramji P (2009) Optimal treatment of obstructive sleep apnea and excessive sleepiness. *Adv Ther* 26:295–312. <https://doi.org/10.1007/s12325-009-0016-7>
 29. Lin CM, Huang YS, Guilleminault C (2012) Pharmacotherapy of obstructive sleep apnea. *Expert Opin Pharmacother* 13:841–857. <https://doi.org/10.1517/14656566.2012.666525>
 30. Jayaraman G, Sharafkhan H, Hirshkowitz M, Sharafkhan A (2008) Pharmacotherapy of obstructive sleep apnea. *Ther Adv Respir Dis* 2:375–386. <https://doi.org/10.1177/17534658080898225>
 31. Grunstein RR, Hedner J, Grote L (2001) Treatment options for sleep apnoea. *Drugs* 61:237–251. <https://doi.org/10.2165/00003495-200161020-00007>
 32. Levy P, Pepin JL, Mayer P et al (1996) Management of simple snoring, upper airway resistance syndrome, and moderate sleep apnea syndrome. *Sleep* 19:S101–S110
 33. Ballard RD (2008) Management of patients with obstructive sleep apnea. *J Fam Pract* 57:S24–S30
 34. Smith I, Lasserson TJ, Wright J (2006) Drug therapy for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev*:CD003002. <https://doi.org/10.1002/14651858.CD003002.pub2>
 35. Heck T, Zolezzi M (2015) Obstructive sleep apnea: Management considerations in psychiatric patients. *Neuropsychiatr Dis Treat* 11: 2691–2698. <https://doi.org/10.2147/NDT.S90521>
 36. Abad V, Guilleminault C (2006) Pharmacological management of sleep apnoea. *Expert Opin Pharmacother* 7:11–23
 37. Kohler M, Bloch KE, Stradling JR (2009) Pharmacological approaches to the treatment of obstructive sleep apnoea. *Expert Opin Investig Drugs* 18:647–656. <https://doi.org/10.1517/13543780902877674>