CNS Drugs
https://doi.org/10.1007/s40263-025-01175-7

SYSTEMATIC REVIEW

Comparative Efficacy and Safety of Multiple Wake-Promoting Agents for the Treatment of Residual Sleepiness in Obstructive Sleep Apnea Despite Continuous Positive Airway Pressure: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

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Accepted: 26 February 2025

Abstract

Background and objectives Residual sleepiness can occur in adult patients with obstructive sleep apnea (OSA) despite adequate treatment with continuous positive airway pressure (CPAP). Various wake-promoting agents (WPAs) have been shown to reduce residual sleepiness in CPAP-treated patients with OSA. This systematic review and network meta-analysis aimed to compare the efficacy and safety of WPAs in this setting.

Methods We searched MEDLINE, Scopus, and ClinicalTrials.gov up to 9 January 2025 for randomized controlled trials (RCTs) examining WPAs for treating sleepiness in patients with OSA. Included were all RCTs that explored the efficacy and/or safety of any approved WPAs (i.e., modafinil, armodafinil, solriamfetol, or pitolisant) in patients with OSA (aged ≥ 18 years) treated with CPAP but who are still sleepy [Epworth sleepiness scale (ESS) score ≥10]. Studies that were conducted in patients whose comorbidities cause daytime somnolence [i.e., psychiatric conditions (other than depression), other sleep disorders, medical or surgical conditions], open label extension studies, and studies published in a language other than English were excluded. The primary outcomes included ESS, maintenance of wakefulness test (MWT), and adverse events. Two authors independently assessed the risk of bias using the revised Cochrane risk-of-bias tool for randomized trials 2.0.

Results In total, 14 RCTs studying four WPAs (total $N = 2969$) including modafinil (six RCTs; 200–400 mg/day), armodafinil (four RCTs; 150–250mg/day), solriamfetol (two RCTs; 37.5–300 mg/day), and pitolisant (two RCTs; 5–40 mg/day) were included. Solriamfetol, modafinil, and armodafinil were efficacious in reducing subjective sleepiness as measured by ESS [mean difference (95% confidence interval) at ≤ 4 weeks: −3.84 (−5.60, −2.07), −2.44 (−3.38, −1.49), and −2.41 (−3.60, −1.21) for solriamfetol, modafinil, and armodafinil, respectively; at > 4 weeks: −4.11 (−6.14, −2.08), −2.88 (−3.85, −1.91), −2.46 (−3.68, −1.24) for solriamfetol, armodafinil, and modafinil, respectively] and clinical global impression of change, as well as the objective MWT [at ≤ 4 weeks: 11.66 min (9.70, 13.61), 3.61 min (2.48, 4.73), and 2.52 min (1.27, 3.76) for solriamfetol, modafinil, and armodafinil, respectively; at > 4 weeks: 10.34 min (4.16, 16.52) for solriamfetol]. Pitolisant showed later improvements in ESS [at > 4 weeks: −2.70 (−3.66, −1.73)], with limited data on MWT. Sensitivity analyses restricted to U.S. Food and Drug Administration-approved solriamfetol dosages (37.5–150 mg/day) still showed higher efficacy, but lower anxiety risk.

Conclusions Among all WPAs, solriamfetol demonstrated the highest efficacy on ESS and MWT, with the latter being significant. Modafinil demonstrated the best clinician impression, albeit not statistically significant. All four WPAs were associated with a low risk of serious or adverse events.

Registration PROSPERO registration number, CRD42022359237

1 Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse occurring during sleep despite ongoing respiratory effort, leading to oxygen desaturations, and/or arousals. OSA is a risk factor for cardiovascular disease [1] and may result in neurobehavioral performance deficits [2]. One of the cardinal symptoms of OSA is excessive daytime sleepiness (EDS), which causes significant impairment in health-related quality of life [3]. Continuous positive airway pressure (CPAP) therapy, the first-line treatment for OSA, has been shown to alleviate EDS symptoms as evidenced from several randomized controlled trials (RCTs) [4–6]. However, residual sleepiness has been reported to

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Key Points

In adult obstructive sleep apnea patients with daytime sleepiness despite the use of continuous positive airway pressure, wake-promoting agents, such as modafinil, armodafinil, solriamfetol, and pitolisant, were well-tolerated offering different levels of efficacy in reducing daytime sleepiness, regardless of improvements in the Epworth sleepiness scale.

Solriamfetol showed the best efficacy for improvement on the Epworth sleepiness scale and maintenance of wakefulness test over a 12-week treatment period.

The 12-week modafinil treatment demonstrated the best clinician impression of change for the proportion of patients who were minimally, much, or very much improved.

Although pitolisant showed the most limited evidence of efficacy for this indication, it had a favorable safety profile and also improved sleepiness later (> 4 weeks), as assessed by the Epworth sleepiness scale.

persist in 12–65% of patients adequately treated with CPAP [7, 8]. In addition to airway-focused therapy, wake-promoting agents (WPAs) have an adjunctive role in alleviating residual sleepiness in patients with OSA.

Recently the US Food and Drug Administration (FDA) has approved WPAs including, modafinil, armodafinil, and solriamfetol for the treatment of residual sleepiness in patients with adequately-treated OSA [9–11]. However, the European Medical Agency (EMA) has approved only solriamfetol [12], due to limited evidence and potential cardiovascular safety concerns for the other agents [13]. In addition, the EMA has also approved pitolisant (the first agent of the histamine H_3 receptor (H_3R) class) on the basis of evidence from several randomized controlled trials [14]. Given the availability of various WPAs, balancing the efficacy and side effect profile of these agents is crucial for the treating clinician.

To date, head-to-head comparative studies of the efficacy and safety of modafinil, armodafinil, solriamfetol, and pitolisant have not been performed. However, a network meta-analysis (NMA) allows indirect comparisons for these treatments using information from common comparator arms. Recently, two NMAs were conducted to directly compare the efficacy and adverse events of treatments for EDS related to OSA. However, one NMA [15] did not include pitolisant while the other included drugs that were not clinically available and included patients with inadequate CPAP treatment [16]. As such, we aimed to conduct a systematic review and NMA focusing specifically on RCTs that compared the efficacy and safety of all currently available medications for the treatment of residual sleepiness in patients with adequately treated OSA.

2 Methods

2.1 Protocol and Registration

The review protocol was registered at PROSPERO (number CRD42022359237). The study was conducted according to the PRISMA guidelines [17] and the extension statement for reporting of network meta-analyses (PRISMA-NMA) [18].

2.2 Information Sources and Literature Search

A literature search was performed on three major electronic databases including MEDLINE, Scopus, and ClinicalTrials.gov from inception to 9 January 2025. Search terms were constructed according to participants, intervention, comparator, and outcome as follows: "OSA (MeSH)" OR "obstructive sleep apnea" AND ("modafinil" OR "armodafinil" OR "solriamfetol" OR "pitolisant" OR "stimulant") AND ("epworth sleepiness scale" OR "maintenance of wakefulness test" OR "multiple sleep latency test" OR "daytime sleepiness"). Full search strategies are listed in Supplementary Appendix 1a–1c.

2.3 Eligibility Criteria and Exclusion Criteria

Any RCT was included if it met all of the following inclusion criteria: (1) included adult patients (aged ≥ 18 years) with OSA (diagnosed as defined per individual trial criteria) who had been treated with CPAP, but had residual sleepiness [defined by Epworth sleepiness scale (ESS) score ≥ 10]; (2) compared any pair of active treatments involving any WPAs (i.e., modafinil, armodafinil, solriamfetol, or pitolisant) or compared with placebo; and (3) had at least one of the outcomes of interest regarding efficacy on EDS symptoms [ESS, maintenance of wakefulness test (MWT)] or quality of life [clinical global impression of change (CGI-C), patient global impression of change (PGI-C), functional outcomes of sleep questionnaire (FOSQ), 36-item short-form health survey (SF-36), Euro-quality of life (QoL) 5-dimension scale (EQ-5D)] or drug safety [safety reporting of adverse events (AEs) including overall AEs, serious AEs (SAEs), AEs leading to discontinuation, specified AEs, such as headache, nausea, insomnia, anxiety, etc.]

The exclusion criteria for studies were any of the following: (1) included patients with comorbid psychiatric

conditions (other than depression), other sleep disorders, medical or surgical conditions that cause daytime somnolence; (2) open label extension studies; and (3) published in a language other than English.

2.4 Study Selection

All identified articles were combined and duplicates were removed. Studies were independently screened by two authors (P.T., V.T.) based on titles and abstracts; if a decision could not be made based on these, full articles were retrieved. Disagreements between reviewers were adjudicated by a third reviewer (A.T.).

2.5 Data Extractions

Two reviewers (P.T., V.T.) independently extracted relevant data from the shortlisted RCTs including: (1) general study characteristics including author, publication year, study design, and number of participants; (2) participant characteristics (age, sex, ethnicity, and body mass index) and baseline clinical data (i.e., AHI, ESS, MWT, etc.); and (3) clinical outcomes for ESS, MWT, FOSQ, SF-36, and EQ-5D reported as mean and standard deviation (SD), and number of patients reporting improvement in CGI-C and AEs during the treatment exposure. Any disagreement was discussed and resolved by consensus within the review team.

2.6 Risk of Bias Assessment

The same two reviewers independently assessed risk of bias for the included studies using the revised Cochrane risk-of-bias tool for randomized trials 2.0 (RoB 2), which consists of five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results [19]. A rating of "low risk" of bias, "high risk" of bias, or "some concerns" of bias was provided for each domain. Any discordance between reviewers was discussed and resolved via consensus.

2.7 Data Synthesis and Statistical Analysis

2.7.1 Direct Meta-Analysis (DMA)

DMA of each comparison was performed for all outcomes if there were at least three studies. The mean and SD were used to calculate the mean differences (MD) and the 95% confidence interval (CI) for continuous outcomes (ESS, MWT, and FOSQ). When necessary, SDs were calculated from reported p values, t values, standard error or CI limits, or were calculated from graphics using web plot digitizer version 4.2. The risk ratios (RR) with 95% CIs were calculated for the dichotomous outcomes of CGI-C and AEs, and were then pooled across studies using an inverse variance method if heterogeneity was low (i.e., $I^2 < 25\%$ and Q test p value > 0.1); otherwise, the Der-Simonian and Laird method was applied. Meta-regression was used to explore source(s) of heterogeneity [i.e., age, sex, ethnicity, body mass index (BMI), baseline apnea-hypopnea index (AHI) during CPAP, baseline ESS, or baseline MWT]. Effect estimates of mean difference or relative risk with a 95% CI were used to create league tables of results. Funnel plots, including contour-enhanced funnel plots [20], and Egger's tests [21] were used to check for publication bias.

2.7.2 Indirect Network Meta-Analysis (NMA)

Treatments were numerically coded from 0 to 4 for placebo, modafinil, pitolisant, armodafinil, and solriamfetol, respectively. A two-stage NMA with a consistency model and a common between-study variance was applied to assess relative treatment effects across the network [22]. Multiple treatment comparisons were estimated and tested accordingly. The consistency assumption was assessed using the design-by-treatment interaction model, and transitivity was explored by comparing patient characteristics between the treatment and comparison groups. Publication bias was assessed using comparison-adjusted funnel plots.

All analyses were performed using Stata version 16.1 (Stata Corp, College Station, Texas, USA). Statistical significance was set as $p < 0.05$ (two-sided), except for heterogeneity where a threshold of 0.1 was used.

3 Results

3.1 Study Selection

Study selection was performed as described in Fig. 1. A total of 817 records were initially identified from the database search from inception to 9 July 2024, from which 36 full-text articles were retrieved and assessed for eligibility after removing duplicates and screening. Of these, 21 articles were excluded due to missing outcomes of interest ($n = 4$), not using CPAP ($n = 6$), different comparisons ($n = 1$), secondary analyses ($n = 8$), pooled analysis ($n = 1$), and open-label study ($n = 1$). One additional study was identified following an updated database search from 10 July 2024 to 9 January 2025. Thus, 14 RCTs (total $N = 2969$), reported in 16 publications, were ultimately considered eligible for qualitative and quantitative analyses.

3.2 Study Characteristics

All study participants were adults (age ≥ 18 years) who had OSA with residual sleepiness after CPAP treatment. Study characteristics are described in Table 1 [23–38]. Criteria for defining OSA, residual sleepiness, and effective CPAP therapy [use ≥ 4 h per night, for at least 70% of nights] were similar between most trials. Participant demographics were generally similar across the trials included, i.e., mean age of 50 years, male predominance, and BMI of greater than 30. However, the Inoue study included Asian participants with lower BMI (27.57 versus ≥ 32 kg/m^2) than other studies [28]. The majority of studies predominantly included Caucasian participants, however, ethnicity was not reported for some studies. ESS scores at baseline were similar across studies. All of the trials had placebo as a comparator. The study by Herring et al. included two arms of WPAs, i.e., modafinil and mk-0249; the latter treatment is a compound that has not been clinically approved and so this arm was excluded from our analysis [29].

Overall, six, four, two, and two RCTs compared modafinil, armodafinil, solriamfetol, and pitolisant with placebo, respectively. Modafinil dosages were 200 mg/day (two RCTs) [28, 29], 300 mg/day (one RCT) [27], and 400 mg/day (three RCTs) [23–26]. Armodafinil dosages were 150 mg/day (one RCT) [31], 200 mg/day (one RCT) [33], and 150 and 250 mg/day (two RCTs) [30, 32]. Solriamfetol dosages varied from 37.5 to 300 mg/days (two RCTs) [34–36] whereas pitolisant dosages varied from 5 to 40 mg/day (two RCTs) [37, 38]. Most RCTs (11 RCTs) [23–28, 30–33, 35–38] were parallel-arm designs, while 2 were crossover designs [29], and another was a withdrawal design [34]. All RCTs evaluated outcomes at 2–12 weeks, which was categorized for further analyses as < 4 weeks and 4–12 weeks (Table 1).

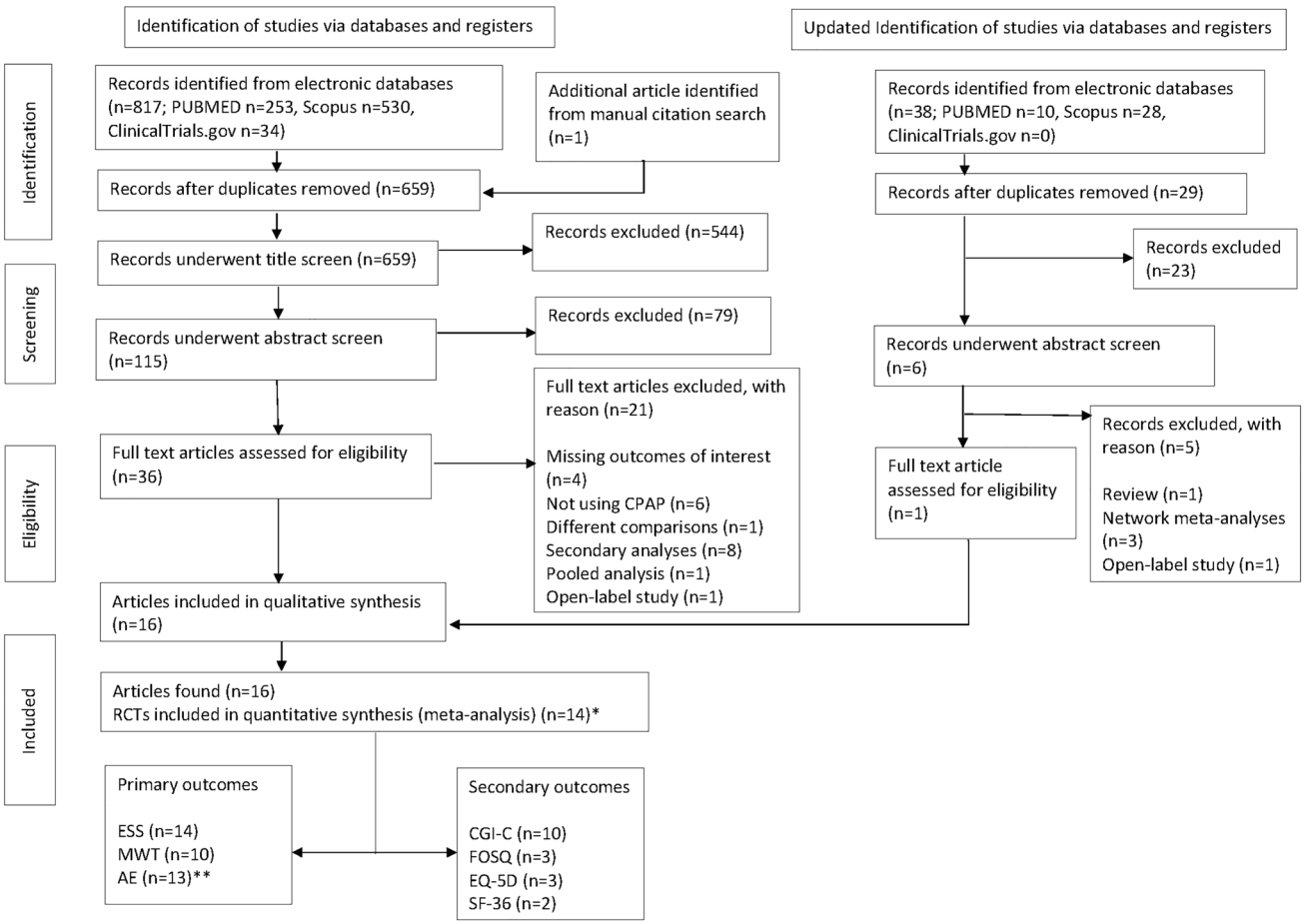

Fig. 1 PRISMA flow chart for study selection of wake-promoting agents for the treatment of residual sleepiness in obstructive sleep apnea despite continuous positive airway pressure. *As two articles were follow-up analyses for other randomized controlled trials (RCTs), 14 RCTs were included in meta-analysis but only **13 RCTs included AE data that could be analyzed. *AE*, adverse event; *CGI-C*, clinical global impression of change; *EQ-5D*, Euro-QoL 5-dimension scale; *ESS,* Epworth sleepiness scale; *FOSQ*, functional outcomes of sleep questionnaire; *MWT*, maintenance of wakefulness test; *SF-36*, 36-item short-form health survey

Table 1. Study characteristics and outcomes of interest

Study	Design	Trial duration, weeks	Sample size	Intervention versus comparator	Participant characteristics					Criteria for OSA diagnosis	Criteria for defining stable CPAP therapy	Criteria for effective CPAP therapy	Definition of residual sleepiness while on CPAP	Time of assessments	
					Mean age, years	Males, %	White Ethnicity, %	Mean BMI, kg/m^2	Baseline ESS					≤ 4 weeks	> 4–12 weeks
Modafinil															
Kingshott RN et al. 2001 [23]	DB-RCT (1:1), cross-over	2	44	Modafinil 400 mg/day versus placebo	53	90	–	32	15	AHI ≥ 15 using PSG or AHI ≥ 30 using limited recorder	CPAP ≥ 1 month	CPAP ≥ 4 h/night, ≥ 10/14 nights, with posttreatment AHI ≤ 15	ESS ≥ 11	ESS 2 weeks MWT20 2 weeks FOSQ 2 weeks CGI-C 2 weeks SF-36 2 weeks AE	n/a
Pack AI et al. 2001 [24]	DB-RCT (1:1), parallel	4	157	Modafinil titrated up to 400 mg/day (200 mg/day for weeks1, 400 mg/day for weeks 2–4) versus placebo	50	76.45	–	35.44	14.3	RDI ≥ 15	CPAP ≥ 2 months	CPAP ≥ 4 h/night, ≥ 5/7 nights, with posttreatment AHI < 10	ESS ≥ 10	ESS 1, 4 weeks CGI-C 1, 4 weeks AE	n/a
Dinges D et al. 2003 [25][a]														FOSQ 4 weeks AE	n/a
Black JE et al. 2005 [26]	DB-RCT (1:1:1), parallel	12	309	Modafinil 200 mg/day, modafinil 400 mg/day versus placebo	49.34	75.74	–	36.8	–	ICSD criteria	CPAP ≥ 1 month	CPAP ≥ 4 h/night, ≥ 70% of nights, with posttreatment AHI < 10	ESS ≥ 10	ESS 4 weeks MWT20 4 weeks FOSQ 4 weeks CGI-C 4 weeks AE	ESS 8, 12 weeks MWT20 8, 12 weeks FOSQ 8, 12 weeks CGI-C 8, 12 weeks

Table 1. (continued)

Study	Design	Trial duration, weeks	Sample size	Intervention versus comparator	Participant characteristics					Criteria for OSA diagnosis	Criteria for defining stable CPAP therapy	Criteria for effective CPAP therapy	Definition of residual sleepiness while on CPAP	Time of assessments	
					Mean age, years	Males, %	White Ethnicity, %	Mean BMI, kg/m^2	Baseline ESS					≤ 4 weeks	> 4–12 weeks
Bittencourt LR et al. 2008 [27]	DB-RCT (1:1), parallel	3	22	Modafinil 300 mg/day versus placebo	53	85	–	33.5	14.7	AHI > 15	CPAP ≥ 1 month	CPAP > 5 h/night, with posttreatment AHI < 5	ESS > 10	ESS 3 weeks MWT20 3 weeks CGI-C 3 weeks SF-36 3 weeks AE	n/a
Inoue Y et al. 2013 [28]	DB-RCT (1:1), parallel	4	114	Modafinil 200 mg/day versus placebo	49.82	96.48	–	27.57	14.46	ICSD criteria	CPAP ≥ 3 months	CPAP ≥ 4 h/night, ≥ 70% of nights, with posttreatment AHI ≤ 10	ESS ≥ 11	ESS 1, 4 weeks MWT20 4 weeks AE	n/a
Herring WJ et al. 2013 [29]	DB-RCT (1:1:1), x-over	2	125	Modafinil 200 mg/day versus, MK-0249 (5, 8, 10, 12 mg/day) versus placebo	48.6	80	81.6	-	15.03	AHI ≥ 15	CPAP ≥ 2 months	CPAP ≥ 4 h/night, ≥ 70% of nights, with posttreatment AHI ≤ 10	ESS ≥ 10	ESS 2 weeks MWT30 2 weeks CGI-C 2 weeks SF-36 3 weeks AE	n/a
Armodafinil															
Roth T et al. 2006 [30]	DB-RCT (1:1:1), parallel	12	395	Armodafinil 150 mg/day versus Armodafinil 250 mg/day versus placebo	49.5	70.4	84.96	36.67	15.57	ICSD-2	CPAP ≥ 1 month	CPAP ≥ 4 h/night, ≥ 70% of nights, with posttreatment AHI < 10	ESS ≥ 10	ESS 4 weeks MWT30 4 weeks CGI-C 4 weeks AE	ESS 8, 12 weeks MWT30 8, 12 weeks CGI-C 8, 12 weeks

Table 1. (continued)

Study	Design	Trial duration, weeks	Sample size	Intervention versus comparator	Participant characteristics					Criteria for OSA diagnosis	Criteria for defining stable CPAP therapy	Criteria for effective CPAP therapy	Definition of residual sleepiness while on CPAP	Time of assessments	
					Mean age, years	Males, %	White Ethnicity, %	Mean BMI, kg/m^2	Baseline ESS					≤ 4 weeks	> 4–12 weeks
Hirshkowitz M et al. 2007 [31]	DB-RCT (1:1), parallel	12	259	Armodafinil 150 mg/day versus placebo	50.6	73.49	84	33.54	15.8	ICSD-2	CPAP ≥ 1 month	CPAP ≥ 4 h/night, ≥ 70% of nights, with posttreatment AHI ≤ 10	ESS ≥ 10	ESS 4 weeks MWT30 4 weeks CGI-C 4 weeks AE	ESS 8, 12 weeks MWT30 8, 12 weeks CGI-C 8, 12 weeks
Krystal AD et al. 2010 [32]	DB-RCT (1:1), parallel	12	249	Armodafinil 150–250 mg/day versus placebo	49.5	46.5	90	36.75	14.8	ICSD-2	CPAP ≥ 1 month	CPAP ≥ 4 h/night, ≥ 70% of nights, with posttreatment AHI ≤ 10	ESS ≥ 10	ESS 4 weeks MWT30 4 weeks CGI-C 4 weeks AE	ESS 8, 12 weeks MWT30 8, 12 weeks CGI-C 8, 12 weeks
Greve DN et al. 2014 [33]	DB-RCT (1:1), parallel	2	40	Armodafinil 200 mg/day versus placebo	50.28	77.68	82.43	32.78	15.5	AHI > 15	CPAP ≥ 1 month	CPAP ≥ 4 h/night, ≥ 70% of nights, with posttreatment AHI ≤ 10	ESS ≥ 10	ESS 2 weeks AE	n/a

Table 1. (continued)

Study	Design	Trial duration, weeks	Sample size	Intervention versus comparator	Participant characteristics					Criteria for OSA diagnosis	Criteria for defining stable CPAP therapy	Criteria for effective CPAP therapy	Definition of residual sleepiness while on CPAP	Time of assessments	
					Mean age, years	Males, %	White Ethnicity, %	Mean BMI, kg/m^2	Baseline ESS					≤ 4 weeks	> 4–12 weeks
Solriamfetol															
Strollo PJ, Jr. et al. 2019 (TONES 4) [34]	DB-randomized-withdrawal (1:1)	4	174 (Adherence: nonadherence ≈ 80:20)	Solriamfetol (combined dosage up to 300 mg/day: 75, 150, and 300 mg/day) versus placebo	55.4	61.8	77.1	33.3	15.5	ICSD-3	–	Adherence group: current or prior use of a primary OSA therapy including PAP, mandibular advancement device, or surgical intervention (CPAP ≥ 4 h/night, ≥ 70% of nights, if CPAP used; oral appliance use ≥ 70% of nights by daily diary; or history of a surgical intervention for OSA deemed to be effective in treating the obstruction) Nonadherence group: use of a primary therapy at a level that did not meet the above criteria; no device used at all; or prior history of a surgical intervention deemed to be no longer effective)	ESS ≥ 10	ESS 2 weeks (weeks4 versus weeks6) MWT40 2 weeks (weeks4 versus weeks6) FOSQ 2 weeks (weeks4 versus weeks6) CGI-C 2 weeks (weeks4 versus weeks6) AE	n/a
Schweitzer PK et al. 2019 (TONES 3) [35] Weaver TE et al. 2020 [36][b]	DB-RCT (1:1:2:2:2), parallel	12	476 (Adherence: nonadherence ≈ 70:30)	Solriamfetol 37.5 mg/day, Solriamfetol 75 mg/day, Solriamfetol 150 mg/day, Solriamfetol 300mg/day versus placebo	53.94	62.65	76.17	33.26	15.21	ICSD-3	–		ESS ≥ 10	ESS 1, 4 weeks MWT40 1, 4 weeks CGI-C 1, 4 weeks AE FOSQ 1, 4 weeks EQ-5D 1, 4 weeks SF-36 4 weeks	ESS 8, 12 weeks MWT40 12 weeks CGI-C 8, 12 weeks FOSQ 8, 12 weeks EQ-5D 8, 12 weeks SF-36 8, 12 weeks

Table 1. (continued)

Study	Design	Trial duration, weeks	Sample size	Intervention versus comparator	Participant characteristics					Criteria for OSA diagnosis	Criteria for defining stable CPAP therapy	Criteria for effective CPAP therapy	Definition of residual sleepiness while on CPAP	Time of assessments	
					Mean age, years	Males, %	White Ethnicity, %	Mean BMI, kg/m^2	Baseline ESS					≤ 4 weeks	> 4–12 weeks
Pitolisant															
Pepin JL et al. 2021 [37]	DB-RCT (3:1), parallel	12	244	Pitolisant (combined dosage up to 20mg/day: 5, 10, 20 mg/day) versus placebo	53.1	82.8	-	32.58	14.83	ICSD-2	CPAP ≥ 3 months	CPAP ≥ 4 h/night, ≥ 70% of nights, with posttreatment AHI ≤ 10	ESS ≥ 12	ESS 2, 3 weeks	ESS 7, 12 weeks CGI-C 12 weeks EQ-5D 12 weeks AE
Dauvilliers Y et al. 2024 [38]	DB-RCT (2:1), parallel	12	361	Pitolisant (combined dosage up to 40 mg/day: 10, 20, and 40 mg/day) versus placebo	52.4	73.7	-	34.9	14.34	ICSD-2	CPAP ≥ 3 months	Adherence group: CPAP ≥ 4 h/night, with posttreatment AHI ≤ 10 Refusing or intolerant group: refusing or not adhering to CPAP therapy despite AHI ≥ 15	ESS ≥ 12	ESS 2, 3 weeks	ESS 7, 12 weeks CGI-C 12 weeks EQ-5D 12 weeks AE

AE, adverse event; *AHI*, apnea-hypopnea index; *BMI*, body mass index; *CGI-C*, clinical global impression of change; *CPAP*, continuous positive airway pressure; *DB-RCT*, double blind-randomized controlled trial; *EQ-5D*, Euro-QoL 5-dimension scale; *ESS*, Epworth sleepiness scale; *FOSQ*, functional outcomes of sleep questionnaire; *ICSD*, international classification of sleep disorders; *MSLT*, multiple sleep latency test; *MWT20*, 20-min maintenance of wakefulness test; *MWT30*, 30-min maintenance of wakefulness test; *MWT40*, 40-min maintenance of wakefulness test; *n/a*, not available; *OSA*, obstructive sleep apnea, *PGI-C*, patient global impression of change; *PAP*, positive airway pressure; *PSG*, polysomnography; *RCT*, randomized controlled trial; *RDI*, respiratory disturbance index

[a]Follow-on publication to Pack et al. [24]

[b]Follow-on publication to Schweitzer et al. [35]

3.3 Risk of Bias and Publication Bias

All studies showed low risk of bias. The funnel plots showed no evidence of publication bias (Supplementary Appendix 2-Fig. 1, Appendix 3-Fig. 1, Appendix 4-Figs. 1 and 2, Appendix 5-Figs. 1–7, and Appendix 6-Fig. 1).

3.4 Epworth Sleepiness Scale (ESS)

All 14 RCTs [23, 24, 26–35, 37, 38] assessed the effects of the four WPAs on ESS scores; 6 [23, 24, 26–29] and 4 [30–33] of these RCTs compared modafinil and armodafinil with placebo. A DMA suggested that modafinil significantly reduced ESS score (compared with placebo) within 4 weeks by −2.44 points (95% CI −3.61, −1.27) (Supplementary Appendix 2-Table 1); likewise, armodafinil also significantly reduced ESS scores by −2.38 points (−3.21, −1.55) at ≤ 4 weeks and by −2.88 points (−3.85, −1.91) at 4–12 weeks after treatment.

A NMA of ESS measured at ≤ 4 weeks included four treatments (N = 2,634) [23, 24, 26–35, 37, 38] (Fig. 2a). Compared with placebo, ESS was significantly reduced by solriamfetol, modafinil, and armodafinil, but not pitolisant, with pooled MDs of −3.84 (−5.60, −2.07), −2.44 (−3.38, −1.49), −2.41 (−3.60 to −1.21), and −0.86 (−2.36, 0.63), respectively (Table 2). Comparing active WPAs, only solriamfetol significantly reduced ESSs when compared to pitolisant with a pooled MD of −2.98 (−5.29, −0.66).

A network map of the four WPAs on ESS at 4–12 weeks was constructed (N = 1935) [26, 30–32, 35, 37, 38] (Fig. 2d). ESS scores at 4–12 weeks were significantly reduced with pooled MDs (95% CI) of −4.11 (−6.14, −2.08), −2.88 (−3.85, −1.91), −2.70 (−3.66, −1.73), and −2.46 (−3.68, −1.24) for solriamfetol, armodafinil, pitolisant, and modafinil relative to placebo, respectively (Table 2).

3.5 Maintenance of Wakefulness Test (MWT)

Five [23, 26–29] and three [30–32] RCTs compared the effect of modafinil and armodafinil relative to placebo on MWT (Supplementary Appendix 3-Table 1). A DMA indicated both treatments significantly increased MWT within 4 weeks with corresponding pooled MDs (95% CI) of 3.62 (2.48, 4.76) and 2.52 (1.27, 3.76).

A NMA was performed using data from 10 RCTs [23, 26–32, 34, 35]; 3 treatments including solriamfetol, modafinil, and armodafinil were included for assessing MWT ≤ 4 weeks (N = 1764) [23, 26–32, 34, 35] (Fig. 2b). Compared with placebo, MWT improved with solriamfetol, modafinil, and armodafinil with pooled MDs (95% CI) of 11.66 min (9.70, 13.61), 3.61 min (2.48, 4.73), and 2.52 min (1.27, 3.76), respectively (Table 3). In addition, solriamfetol significantly improved MWT relative to modafinil and armodafinil with pooled MDs of 8.05 min (5.79, 10.31) and 9.14 min (6.82, 11.46) (Table 3).

Considering outcomes at 4–12 weeks (N = 1298) [26, 30–32, 35] (Fig. 2e), only solriamfetol significantly improved MWT relative to placebo with pooled MD of 10.34 min (4.16, 16.52); this effect was also significant relative to modafinil and armodafinil with pooled MD of 7.88 mins (0.73, 15.03) and 7.83 min (1.10, 14.56), respectively (Table 3).

3.6 Clinical Global Impression of Change (CGI-C)

Three RCTs each compared the effects of modafinil [24, 26, 27] and armodafinil [30, 32, 33] relative to placebo on CGI-C (Supplementary Appendix 4-Table 1); pooling these treatment effects measured ≤ 4 weeks by a DMA yielded pooled RRs (95% CI) of 1.68 (1.35, 2.09) and 1.39 (0.91, 2.13), respectively. In addition, the effect of armodafinil persisted > 4 weeks, with pooled RR (95% CI) of 1.48 (1.13, 1.93).

Seven RCTs (N = 1253) [24, 26, 27, 30, 32, 33, 35] with three interventions (i.e., modafinil, armodafinil, and solriamfetol) were included in a NMA of CGI-C measured at ≤ 4 weeks (Fig. 2c). Compared with placebo, modafinil and armodafinil showed significant improvement in CGI-C of 76% (RR = 1.76; 95% CI 1.20, 2.59) and 40% (RR = 1.40; 95% CI 1.00, 1.97), respectively; there was a trend toward improvement for solriamfetol but this was not significant (RR = 1.50; 95% CI 0.89, 2.51) (Table 4). There were no significant differences among the three active WPA treatments at this early time point.

A NMA of CGI-C measured at the later time point of 4–12 weeks was also performed from data from seven RCTs (N = 1921) [26, 30–32, 35, 37, 38] (Fig. 2f). Compared with placebo, modafinil, solriamfetol, and armodafinil but not pitolisant significantly improved CGI-C, with pooled RRs (95% CI) of 1.86 (1.16, 2.97), 1.66 (1.10, 2.49), 1.47 (1.15, 1.88), and 1.29 (0.97, 1.72), respectively (Table 4). Comparing active WPAs, modafinil improved CGI-C compared with pitolisant, armodafinil, and solriamfetol but this was not significant, with pooled RRs (95% CI) of 1.44 (0.83, 2.50), 1.26 (0.74, 2.14), and 1.12 (0.60, 2.09).

3.7 Overall Safety Assessment

Severe adverse events (SAE) along with individual adverse events were reported, including headache, nausea, insomnia, anxiety, diarrhea, and discontinuation (Supplementary Appendix 5). Incidence and risk effects were estimated and

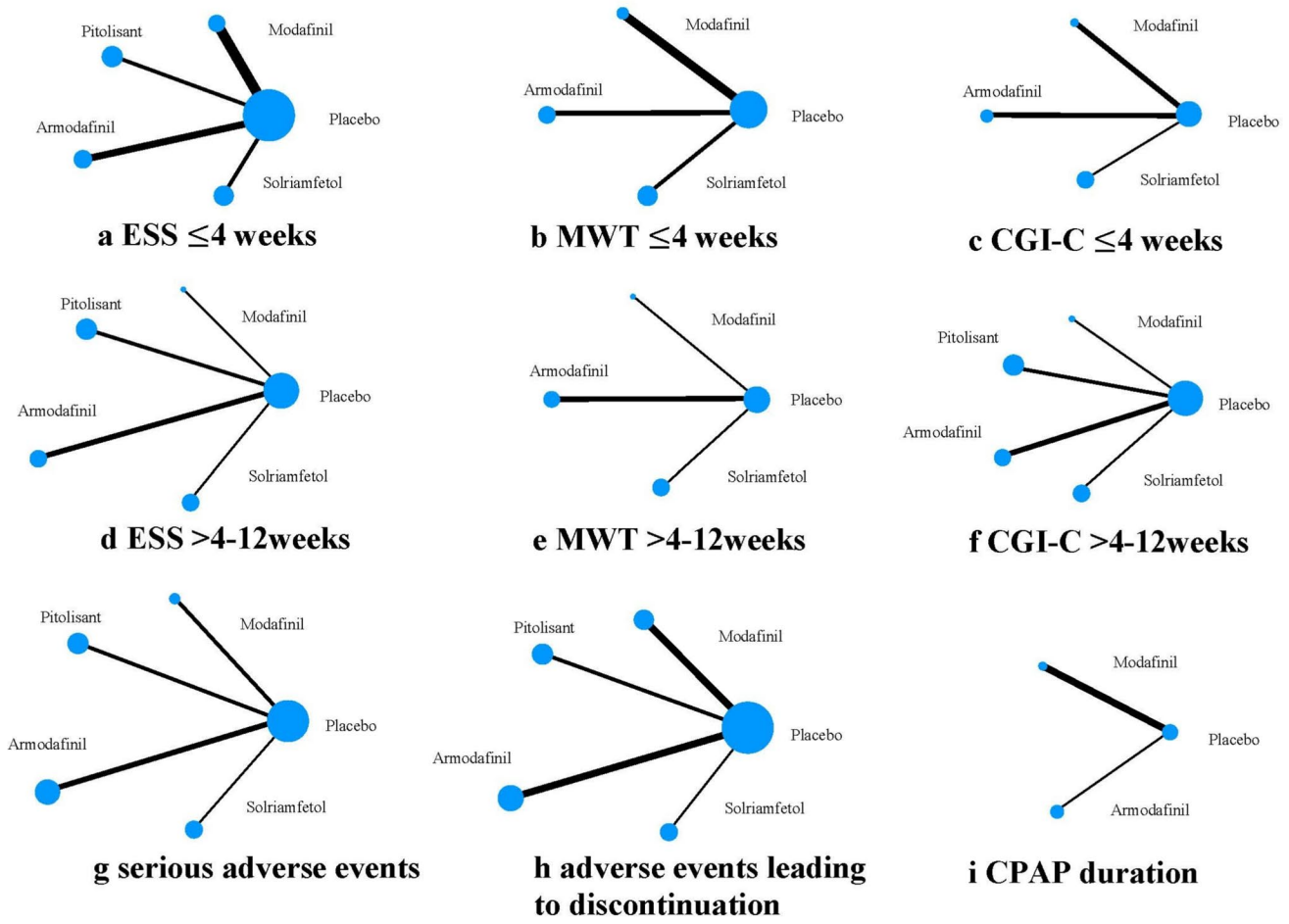

Fig. 2 Network of eligible comparisons for efficacy at ≤ 4 weeks and at >4-12 weeks and safety at study endpoint. Efficacy (ESS, MWT, and CGI-C) was analyzed at ≤ 4 weeks and at >4-12 weeks. Duration in CPAP use and patients experiencing serious adverse events, adverse events leading to discontinuation, and specified adverse events were analyzed at study endpoint. Size of nodes was weighted by number of subjects. Size of edges was weighted by number of studies in each comparison. *CGI-C*, clinical global impression of change; *CPAP*, continuous positive airway pressure; *ESS*, Epworth sleepiness scale; *MWT*, maintenance of wakefulness test

pooled across RCTs (Supplementary Appendix 5-Table 1 and 2).

In total, eight RCTs [24, 29–32, 35, 37, 38] (N = 2362) with four WPAs were included in a NMA of serious adverse events. Results showed that none of the WPAs had greater serious adverse events than placebo (Table 5; Fig. 2g). However, NMA of 10 RCTs [23, 24, 26, 27, 30–33, 35, 37, 38] (N = 2738) showed that only modafinil had a significantly higher risk of discontinuation owing to adverse events compared with placebo with a pooled RR (95% CI) of 3.12 (1.48, 6.59) (Table 5; Fig. 2h). Comparing active WPAs, modafinil had a significantly higher risk of discontinuation owing to adverse events than pitolisant, with a pooled RR (95% CI) of 6.31 (1.20, 33.21). Considering specific adverse events, modafinil also had significantly higher risk of headache, nausea, insomnia and anxiety than placebo, with pooled RRs (95% CI) of 1.78 (1.25, 2.54), 3.38 (1.31, 8.66), 4.12 (1.29, 13.16), 3.25 (1.08, 9.80), respectively (Supplementary Appendix 5-Table 3).

Likewise, armodafinil had significantly higher risk of headache, insomnia, and anxiety with pooled RRs (95% CI) of 1.98 (1.32, 2.97), 4.35 (1.53, 12.39), and 4.93 (1.63, 14.96), solriamfetol only had significantly higher risk of anxiety with a pooled RR (95% CI) of 17.19 (1.05, 280.22), whereas pitolisant showed nonsignificant risks of headache, insomnia or anxiety similar to placebo (Supplementary Appendix 5-Table 3).

Other efficacy (i.e., FOSQ, EQ-5D, and SF-36) and safety outcomes (i.e., any treatment-emergent AEs and other

Table 2. Relative treatment effect on Epworth sleepiness scale score: a network meta-analysis

ESS score ≤ 4 weeks					
Reference treatment	MD (95% CI)				
	Placebo	Solriamfetol	Armodafinil	Pitolisant	Modafinil
Placebo		-3.84 (-5.60, -2.07) *	-2.41 (-3.60, -1.21) *	-0.86 (-2.36, 0.63)	-2.44 (-3.38, -1.49) *
Solriamfetol	3.84 (2.07, 5.60) *		1.43 (-0.70, 3.56)	2.98 (0.66, 5.29) *	1.40 (-0.60, 3.40)
Armodafinil	2.41 (1.21, 3.60) *	-1.43 (-3.56, 0.70)		1.54 (-0.37, 3.46)	-0.03 (-1.56, 1.49)
Pitolisant	0.86 (-0.63, 2.36)	-2.98 (-5.29, -0.66) *	-1.54 (-3.46, 0.37)		-1.58 (-3.35, 0.19)
Modafinil	2.44 (1.49, 3.38) *	-1.40 (-3.40, 0.60)	0.03 (-1.49, 1.56)	1.58 (-0.19, 3.35)	
ESS score > 4-12 weeks					
Reference treatment	MD (95% CI)				
	Placebo	Solriamfetol	Armodafinil	Pitolisant	Modafinil
Placebo		-4.11 (-6.14, -2.08) *	-2.88 (-3.85, -1.91) *	-2.70 (-3.66, -1.73) *	-2.46 (-3.68, -1.24) *
Solriamfetol	4.11 (2.08, 6.14) *		1.23 (-1.02, 3.48)	1.41 (-0.84, 3.66)	1.65 (-0.72, 4.02)
Armodafinil	2.88 (1.91, 3.85) *	-1.23 (-3.48, 1.02)		0.18 (-1.19, 1.55)	0.42 (-1.14, 1.98)
Pitolisant	2.70 (1.73, 3.66) *	-1.41 (-3.66, 0.84)	-0.18 (-1.55, 1.19)		0.24 (-1.31, 1.79)
Modafinil	2.46 (1.24, 3.68) *	-1.65 (-4.02, 0.72)	-0.42 (-1.98, 1.14)	-0.24 (-1.79, 1.31)	

Network meta-analysis results are presented as mean difference (MD) of Epworth sleepiness scale (ESS) score. MD of less than 0 indicates that the treatment specified in the column reduced ESS score better than that specified in the row

CI, confidence interval; *ESS*, Epworth sleepiness scale; *MD*, mean difference

*Denotes statistically significant p-value < 0.05

specified AEs) were reported in fewer than three studies for each WPA, and so were not amenable to NMA.

3.8 Mean Change in Duration of CPAP Use

Post hoc analyses were conducted to evaluate changes in duration of CPAP use with WPAs. A DMA was used to pool CPAP duration use/night between modafinil and placebo indicating no significant difference (Supplementary Appendix 6-Table 1). A NMA of modafinil and armodafinil (five RCTs; $N = 728$) showed no difference in duration of CPAP use between WPAs and placebo, with pooled MD (95% CI) of 0.04 h/night (−0.21, 0.28) and −0.20 h/night (−0.42, 0.02), respectively (Fig. 2i; Supplementary Appendix 6-Table 2).

3.9 Sensitivity Analyses

To explore the robustness of our analyses, we conducted an additional sensitivity analysis by restricting to US FDA-approved doses of solriamfetol (i.e., 37.5–150 mg/d). We excluded the study of Strollo et al., [34] which did not present separate data for each dose and the outcomes of solriamfetol at 300 mg/day from the study by Schweitzer et al. [35] (Supplementary Appendix 7). These analyses produced results consistent with the primary analysis. Solriamfetol still demonstrated the highest efficacy on ESS and MWT at two different time intervals and showed later improvement in CGI-C at > 4–12 weeks, while not having serious adverse events, discontinuation due to adverse events, or specific adverse events. Compared with placebo, a statistically significant reduction in ESS persisted both at ≤ 4 weeks, with a pooled MD (95% CI) of −3.11 (−5.55, −0.67) and at > 4–12 weeks, with a pooled MD (95% CI) of −3.67 (−5.83,−1.51) (Supplementary Appendix 7-Table 1). Compared with

Table 3. Relative treatment effect on maintenance of wakefulness test sleep latency in minutes: a network meta-analysis

MWT ≤ 4 weeks				
Reference treatment	MD (95% CI)			
	Placebo	Solriamfetol	Armodafinil	Modafinil
Placebo		11.66 (9.70, 13.61) *	2.52 (1.27, 3.76) *	3.61 (2.48, 4.73) *
Solriamfetol	-11.66 (-13.61, -9.70) *		-9.14 (-11.46, -6.82) *	-8.05 (-10.31, -5.79) *
Armodafinil	-2.52 (-3.76, -1.27) *	9.14 (6.82, 11.46) *		1.09 (-0.59, 2.77)
Modafinil	-3.61 (-4.73, -2.48) *	8.05 (5.79, 10.31) *	-1.09 (-2.77, 0.59)	
MWT > 4 weeks				
Reference treatment	MD (95% CI)			
	Placebo	Solriamfetol	Armodafinil	Modafinil
Placebo		10.34 (4.16, 16.52) *	2.51 (-0.16, 5.18)	2.46 (-1.15, 6.07)
Solriamfetol	-10.34 (-16.52, -4.16) *		-7.83 (-14.56, -1.10) *	-7.88 (-15.03, -0.73) *
Armodafinil	-2.51 (-5.18, 0.16)	7.83 (1.10, 14.56) *		-0.05 (-4.54, 4.44)
Modafinil	-2.46 (-6.07, 1.15)	7.88 (0.73, 15.03) *	0.05 (-4.44, 4.54)	

Network meta-analysis results are presented as mean difference (MD) of maintenance of wakefulness test (MWT) sleep latency in minutes. MD of more than 0 indicates that the treatment specified in the column improved MWT sleep latency better than that specified in the row

CI, confidence interval; *MWT*, maintenance of wakefulness test; *MD*, mean difference

*Denotes statistically significant p-value < 0.05

placebo, a statistically significant improvement in MWT persisted both at ≤ 4 weeks, with a pooled MD (95% CI) of 8.13 min (3.10, 13.16) and at > 4–12 weeks, with a pooled MD (95% CI) of 9.31 min (2.87, 15.75). Comparing active WPAs, the impact of solriamfetol on MWT at ≤ 4 weeks remained statistically significant relative to armodafinil, with a pooled MD of 5.61 min (0.43, 10.80) (Supplementary Appendix Table 2). In addition, solriamfetol still showed significant improvement in CGI-C at > 4–12 weeks relative to placebo, yielding a pooled RR (95% CI) of 1.58 (1.05, 2.38) (Supplementary Appendix 7-Table 3). Considering serious adverse events and discontinuation owing to adverse events, the risks remained comparable to placebo, with pooled RRs (95% CI) of 0.75 (0.13, 4.45) and 1.26 (0.40, 3.92), respectively (Supplementary Appendix 7-Table 4). Upon restricting to FDA-approved solriamfetol doses, risk of anxiety became comparable to placebo, with a pooled RR (95% CI) of 9.58 (0.56, 163.20) (Supplementary Appendix 7-Table 5).

4 Discussion

We conducted a systematic review and NMA to compare the efficacy and safety of four WPAs for the treatment of residual sleepiness in adult patients with OSA despite receiving adequate CPAP treatment. Our results, based on 14 RCTs, showed that 12-week treatment of solriamfetol (37.5–300 mg/day), modafinil (200–400 mg/day), armodafinil (150–250 mg/day), and pitolisant (5–40 mg/day) were all effective in reducing residual EDS compared with placebo, as measured by both subjective and objective measures (i.e., ESS and MWT), and clinical global impression, with low risk of serious adverse events or discontinuation.

Solriamfetol, modafinil, and armodafinil showed better improvements than placebo on both subjective reports of sleepiness (ESS; range 2.41–3.84 points) and objectively documented sleepiness (MWT; range 2.52–11.66 min) within 4 weeks; these clinical benefits were still sustained up to 12 weeks on both ESS (4.11 points) and MWT (10.34 min) for solriamfetol, and on ESS (2.46 and 2.88 points) for modafinil and armodafinil. However, pitolisant showed more delayed improvement of sleepiness (ESS; 2.70 points) after 4 weeks.

Solriamfetol showed the greatest improvement in EDS, based both on ESS and MWT at ≤ 4weeks and at > 4–12 weeks, in particular with significantly higher improvement on MWT compared with other WPAs. However, modafinil and armodafinil had higher overall clinical global impressions of improvement (CGI-C) at ≤ 4weeks and at > 4–12 weeks; solriamfetol appeared to have greater improvement

Table 4. Relative treatment effects on clinical global impression of change: a network meta-analysis

CGI-C ≤ 4 weeks					
Reference treatment	RR (95% CI)				
	Placebo	Pitolisant	Solriamfetol	Armodafinil	Modafinil
Placebo			1.50 (0.89,2.51)	1.40 (1.00,1.97) *	1.76 (1.20,2.59) *
Pitolisant					
Solriamfetol	0.67 (0.40, 1.12)			0.94 (0.51, 1.73)	1.18 (0.62, 2.24)
Armodafinil	0.71 (0.51, 1.00) *		1.07 (0.58, 1.98)		1.26 (0.75, 2.10)
Modafinil	0.57 (0.39, 0.83) *		0.85 (0.45, 1.62)	0.79 (0.48, 1.33)	
CGI-C > 4 weeks					
Reference treatment	RR (95% CI)				
	Placebo	Pitolisant	Solriamfetol	Armodafinil	Modafinil
Placebo		1.29 (0.97, 1.72)	1.66 (1.10, 2.49) *	1.47 (1.15, 1.88) *	1.86 (1.16, 2.97) *
Pitolisant	0.77 (0.58, 1.03)		1.28 (0.78, 2.11)	1.14 (0.78, 1.66)	1.44 (0.83, 2.50)
Solriamfetol	0.60 (0.40, 0.91) *	0.78 (0.47, 1.28)		0.89 (0.55, 1.43)	1.12 (0.60, 2.09)
Armodafinil	0.68 (0.53, 0.87) *	0.87 (0.60, 1.27)	1.12 (0.70, 1.81)		1.26 (0.74, 2.14)
Modafinil	0.54 (0.34, 0.86) *	0.69 (0.40, 1.21)	0.89 (0.48, 1.66)	0.79 (0.47, 1.35)	

Network meta-analysis results are presented as risk ratio (RR) of clinical global impression of change (CGI-C). RR of more than 1 indicates that the treatment specified in the column got more proportion of patients who were minimally, much, or very much improved than that specified in the row

CI, confidence interval; *CGI-C*, clinical global impression of change; *RR*, risk ratio

*Denotes statistically significant *p*-value < 0.05

on CGI-C only at > 4–12weeks; pitolisant did not show any effects. Among the agents, modafinil demonstrated the best impression of change on CGI-C at ≤ 4 weeks and at > 4–12 weeks, although no significant differences between these four WPAs was found.

Although data for duration of CPAP use were only provided for modafinil and armodafinil studies, our analysis showed no difference in duration of CPAP use compared with placebo; this supports the conclusion that the reduction in EDS resulted from the efficacy of WPAs per se, without compromising the duration of CPAP use. All four WPAs demonstrated low rates of serious AE and discontinuation-associated treatment-emergent AEs, although modafinil showed a higher risk of AE leading to discontinuation. Although solriamfetol showed the highest efficacy on EDS, there was a markedly higher rate of anxiety (RR = 17.19, pooled incidence rate 7.0%).

Our analysis was concordant with four previous meta-analyses of modafinil and armodafinil and two NMAs on various WPAs in alleviating residual sleepiness in patients with OSA treated with CPAP [15, 16, 39–42], with overall reduction in ESS scores by 2–4.5 points, and increased sleep onset latency on MWT by 2.5–6.0 min.

Our NMA differed from these previous meta-analyses and NMAs in several ways. First, all studies in our analysis included participants with adequate CPAP treatment, whereas prior meta-analysis/NMA included studies in which participants did not use CPAP [16, 42]. Second, two meta-analyses [39, 41] and one NMA [16] combined modafinil and armodafinil together for the pooled outcome estimates while our NMA analyzed both medications separately on the basis of their somewhat different pharmacologic properties, e.g., higher plasma concentration later in the day for armodafinil [43]. Third, our NMA analyzed outcomes according to two different time intervals (at ≤ 4weeks,

Table 5. Relative treatment effects on severe adverse events and discontinuity: a network meta-analysis

Serious adverse events					
Reference treatment	RR (95% CI)				
	Placebo	Pitolisant	Solriamfetol	Armodafinil	Modafinil
Placebo		2.04 (0.24, 17.35)	0.50 (0.09, 2.97)	0.70 (0.15, 3.31)	0.76 (0.08, 6.78)
Pitolisant	0.49 (0.06, 4.16)		0.25 (0.02, 3.97)	0.34 (0.02, 4.82)	0.37 (0.02, 7.92)
Solriamfetol	1.99 (0.34, 11.76)	4.06 (0.25, 65.57)		1.39 (0.13, 14.76)	1.50 (0.09, 25.30)
Armodafinil	1.43 (0.30, 6.77)	2.92 (0.21, 41.10)	0.72 (0.07, 7.62)		1.08 (0.07, 15.89)
Modafinil	1.32 (0.15, 11.86)	2.70 (0.13, 57.89)	0.67 (0.04, 11.20)	0.93 (0.06, 13.63)	
Adverse events discontinuation					
Reference treatment	RR (95% CI)				
	Placebo	Pitolisant	Solriamfetol	Armodafinil	Modafinil
Placebo		0.49 (0.11, 2.17)	2.18 (0.78, 6.12)	1.61 (0.93, 2.81)	3.12 (1.48, 6.59) *
Pitolisant	2.03 (0.46, 8.91)		4.41 (0.73, 26.84)	3.27 (0.67, 15.90)	6.31 (1.20, 33.21) *
Solriamfetol	0.46 (0.16, 1.29)	0.23 (0.04, 1.38)		0.74 (0.23, 2.39)	1.43 (0.40, 5.12)
Armodafinil	0.62 (0.36, 1.08)	0.31 (0.06, 1.49)	1.35 (0.42, 4.35)		1.93 (0.76, 4.90)
Modafinil	0.32 (0.15, 0.68) *	0.16 (0.03, 0.83) *	0.70 (0.20, 2.50)	0.52 (0.20, 1.31)	

Network meta-analysis results are presented as risk ratio (RR) of severe adverse events and discontinuity. RR of less than 1 indicates that the treatment specified in the column got less proportion of severe adverse events and discontinuity than that specified in the row

CI, confidence interval; *RR*, risk ratio

*Denotes statistically significant p-value < 0.05

and at > 4–12 weeks) to evaluate the onset of efficacy. As such, our pooled data solely represented the efficacy of WPAs as an adjunctive therapy in OSA patients with residual sleepiness after receiving primary treatment.

Our indirect NMA was also able to demonstrate that modafinil and armodafinil had similar efficacy estimates based on ESS, MWT, and CGI-C. However, there were some differences in safety endpoints. Compared with placebo, modafinil had higher risks of adverse events leading to discontinuation, headache, nausea, insomnia, and anxiety, while armodafinil had higher reports of headache, insomnia, and anxiety.

Consistent with previous NMAs, solriamfetol showed the highest efficacy in lowering EDS despite the fact that lower dosage (37.5 mg) was also included in our indirect NMA. When restricting our analyses to FDA-approved dosages, we found no evidence of variable effects for solriamfetol. Pitolisant also showed later improvement (> 4–12 weeks) on ESS, with a paucity of other efficacy data.

The mechanisms underlying residual EDS in OSA patients are unclear. Experimental evidence in murine models suggests that chronic intermittent hypoxia and sleep fragmentation might lead to oxidative injury and irreversible neuronal damage involving particular dopaminergic and noradrenergic wake-promoting neuronal circuits, while preserving histaminergic neurons [44–46]. Neuroimaging studies in humans also demonstrate alterations in white and grey matter associated with OSA and residual sleepiness [47]. This supports the results of NMA for the more potent effect of WPAs that inhibit reuptake of dopamine and/or norepinephrine (i.e., modafinil/armodafinil and solriamfetol) than WPAs that enhance histaminergic signaling (i.e., pitolisant). Solriamfetol has the pharmacological action of increasing both central dopaminergic and norepinephrinergic neuronal activity by inhibiting their transporters [48]. Thus, solriamfetol demonstrated a robust effect in improving residual sleepiness in patients with OSA.

Pitolisant selectively binds to the H_3 auto-receptor located in the presynaptic region of histamine-containing neurons. Since pitolisant does not increase central dopamine neurotransmission, it has minimal abuse potential and does not show other amphetamine-like properties that were reported for modafinil, solriamfetol, and amphetamine in preclinical in vivo studies [49]. Although our NMA demonstrated that pitolisant had a delayed effect on ESS reduction, its safety concerns were minimal. There is limited evaluation of pitolisant efficacy using an objective outcome (MWT), hence further studies are needed for this agent.

This NMA has a number of strengths. First, our NMA expanded the scope of pairwise comparisons enabling us to estimate indirect differences in efficacy and safety outcomes between active treatments that have not previously been directly compared in RCTs. We included any RCT design, i.e., parallel-arm design, crossover design, and randomized-withdrawal design. The low heterogeneity observed for most outcomes supports the robustness of the NMA results. Furthermore, the funnel plots were not suggestive of publication bias. Second, on the basis of our extensive search and inclusion criteria, more data on objective outcomes (MWT) were included as well as subjective outcomes (ESS and CGI-C) compared with previous reviews. Third, our NMA pooled endpoints according to two timeframes (≤ 4weeks, and at > 4–12 weeks), thereby providing a timeline for evaluation for WPAs efficacy for clinical practice.

The present study has several limitations. First, we excluded patients with physical or mental comorbidities (other than depression) and other sleep disorders that cause EDS, which limits the generalizability of the results. Second, various dosages of WPAs were pooled to strengthen the efficacy estimates. Notably, some dosages of WPAs are not approved for this indication, such as modafinil at 400 mg/day and solriamfetol at 300 mg/day. Third, given that some data were reported as graphics, conversions were approximated from graphs using web plot digitizer. Although imputations were recommended following Cochrane reviews for dealing with missing data [50], these methods might be inaccurate.

5 Conclusions

This NMA compared the efficacy and safety of four WPAs (solriamfetol, modafinil, armodafinil, and pitolisant) for treating residual sleepiness despite adequate use of CPAP in adult OSA patients. Solriamfetol, modafinil, and armodafinil had efficacy in improving EDS on the basis of ESS and MWT, and impressions of change on CGI-C during a 12-week treatment period; this clinical benefit began within 4 weeks. While pitolisant improved subjective EDS (i.e., ESS) later than the other three agents, there were a limited number of studies and lack of data on MWT. Among all WPAs, solriamfetol demonstrated the greatest efficacy with a significant difference on MWT. Modafinil appeared to offer the optimum clinician impression for change in CGI-C, although this was not statistically significant. All WPAs were associated with an acceptable safety profile.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40263-025-01175-7.

Declarations

Conflicts of Interest The authors declare no conflicts of interest.

Availability of Data and Material The database of studies and extracted data can be shared upon reasonable request to the corresponding author.

Ethics Approval Not applicable.

Funding Open access funding provided by Mahidol University.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability Not applicable.

Author Contributions Pongsakorn Tanayapong: conceptualization, methodology, investigation, data curation, formal analysis, writing—original draft preparation, writing—review and editing, and visualization. Visasiri Tantrakul: conceptualization, methodology, investigation, data curation, formal analysis, writing—original draft preparation, writing—review and editing, and visualization. Somprasong Liamsombut: writing—review and editing. Sukanya Siriyotha: data curation, software, formal analysis, visualization, and writing—review and editing. Gareth McKay: writing—review and editing. John Attia: writing—review and editing. Ammarin Thakkinstian: conceptualization, methodology, formal analysis, supervision, and writing—review and editing. All authors have read and approved the final version for submission and agree to be accountable for the work.

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