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REVIEW ARTICLES

Indirect treatment comparison of solriamfetol, modafinil, and armodafinil for excessive daytime sleepiness in obstructive sleep apnea

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Study Objectives: Excessive daytime sleepiness associated with obstructive sleep apnea affects 9%–22% of continuous positive airway pressure–treated patients. An indirect treatment comparison meta-analysis was performed to compare efficacy and safety of medications (solriamfetol, modafinil, and armodafinil) approved to treat excessive daytime sleepiness associated with obstructive sleep apnea.

Methods: Efficacy and safety measures assessed in this indirect treatment comparison included Epworth Sleepiness Scale (ESS), 20-minute Maintenance of Wakefulness Test (MWT20), Clinical Global Impression of Change (CGI-C), Functional Outcomes of Sleep Questionnaire (FOSQ), and incidence of treatment-emergent adverse events (any, serious, or leading to discontinuation).

Results: A systematic literature review identified 6 parallel-arm, placebo-controlled randomized controlled trials that randomized 1,714 total participants to placebo, solriamfetol, modafinil, or armodafinil. In this indirect treatment comparison, all comparators were associated with greater improvements than placebo on the ESS, MWT20, and CGI-C after 4, 8, and 12 weeks of treatment. Relative to comparators and placebo at 12 weeks, solriamfetol at 150 mg or 300 mg had the highest probabilities of improvement in the ESS, MWT20, and CGI-C. Modafinil (200 or 400 mg) and solriamfetol (150 or 300 mg) were associated with greater improvement on the FOSQ than placebo at 12 weeks. Less than 2% of patients using placebo or comparators experienced serious or discontinuation-related treatment-emergent adverse events.

Conclusions: The results of this indirect treatment comparison show 12 weeks of treatment with solriamfetol, modafinil, and armodafinil resulted in varying levels of improvement on the ESS, MWT20, and CGI-C and similar safety risks in participants with excessive daytime sleepiness associated with obstructive sleep apnea.

Keywords: obstructive sleep apnea, solriamfetol, modafinil, armodafinil, Epworth Sleepiness Scale

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Direct head-to-head comparisons of solriamfetol, a medication to treat excessive daytime sleepiness in obstructive sleep apnea, vs modafinil and armodafinil are not available, as pivotal trials for all 3 medications were performed using placebo as a comparator. Thus, an indirect treatment comparison was conducted, representing the first study to compare these 3 pharmacotherapies across wakefulness, sleepiness, functionality, patient and clinical impressions, and safety outcomes in patients with obstructive sleep apnea.

Study Impact: Findings demonstrated varying improvements in efficacy and similar safety outcomes for the 3 comparators vs placebo. This study provides essential comparative effectiveness and safety information for the obstructive sleep apnea patient population.

INTRODUCTION

Obstructive sleep apnea (OSA) is a serious disorder characterized by sleep fragmentation caused by repeated episodes of complete or partial upper airway obstruction during sleep.[1] The primary treatment for moderate and severe OSA is continuous positive airway pressure (CPAP).[2,3] Excessive daytime sleepiness (EDS) is the most common OSA symptom,[4] affecting 9%–22% of patients with OSA despite adherence to CPAP therapy.[5,6] In the United States, approximately 14% of men and 5% of women ages 30 through 70 years have OSA with EDS.[7] Compared with people without EDS, people with EDS experience substantial impairments in daily functioning, work productivity, cognition, and alertness,[8] resulting in greater disability,[9] greater health care resource utilization and health care costs,[10] and reduced quality of life.[8,11] In addition, EDS associated with OSA impacts public safety, as EDS is associated with an increased risk of motor vehicle accidents[12] and workplace accidents.[13]

In patients with persistent EDS following CPAP therapy or in patients who cannot manage CPAP therapy, adjunctive therapy with pharmacologic treatments may be beneficial.[14] Available pharmacologic treatment options for EDS vary by interactions with other drugs, narrow therapeutic windows, side effects, and abuse potential.[15] Traditional stimulants (eg, methylphenidate, amphetamine) are often used off-label in the United States in patients with EDS associated with OSA.[16] These medications have limited use due to the risks of adverse events and abuse potential.[15,17,18] Nonstimulant wake-promoting agents (WPAs) approved by the U.S. Food & Drug Administration for the treatment of adult patients with OSA-associated EDS include

solriamfetol (Sunosi, Jazz Pharmaceuticals, Inc., Palo Alto, CA), armodafinil (Nuvigil, Harmony Biosciences, Plymouth Meeting, PA), and modafinil (Provigil, Teva Pharmaceuticals USA, North Wales, PA).[19–21] Solriamfetol (Sunosi) is also approved by the European Medicines Agency,[22] but the European Medicines Agency marketing authorization for modafinil in the treatment of OSA-associated EDS was revoked in 2011,[23] and armodafinil is not authorized by the European Medicines Agency. All 3 medications are taken orally in the morning at the following recommended dosages: modafinil, 200 mg per day; armodafinil, 150 or 250 mg per day; solriamfetol, 37.5 to 150 mg per day.[24–26]

The pivotal trials for solriamfetol, modafinil, and armodafinil were performed using a placebo as a comparator; the comparative efficacy and safety of these medications have not been assessed in head-to-head studies.[24–26] Therefore, the objective of this study was to conduct an indirect treatment comparison (ITC) to compare the relative efficacy and safety of WPAs in patients with EDS associated with OSA.

METHODS

Methods of the literature review and ITC were specified in advance and documented in a study protocol and statistical analysis protocol. The systematic literature review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[27] and the ITC was guided by the PRISMA extension statement for reporting of network meta-analyses (PRISMA-NMA).[28] The ITC methods were specified in advance in a statistical analysis protocol consistent with the National Institute for Health and Care Excellence (NICE) Decision Support Unit recommendations for meta-analysis of randomized controlled trials (RCTs), as well as the guidelines contained within NICE's single technology appraisal user guide for company evidence submission template.[29,30] This approach is also consistent with the International Society for Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparison recommendations.[31–33]

Literature search

A systematic literature review was performed to identify RCTs investigating the comparative efficacy of solriamfetol, modafinil, and armodafinil for the treatment of EDS associated with OSA. The systematic literature search was conducted on October 11, 2019. Data sources included MEDLINE (1946–present); Embase (1947–present); the Cochrane Central Register of Controlled Trials (CENTRAL); the Cochrane Database of Systematic Reviews; ClinicalTrials.gov; the EU Clinical Trials Register; the International Clinical Trials Registry; the 2017, 2018, and 2019 Associated Professional Sleep Societies annual meetings; and the 2016 and 2018 European Sleep Research Society biannual meetings. Full search strategies are listed in **Table S1** in the supplemental material.

Eligibility criteria

The selection criteria included adult patients (≥ 18 years) with OSA and EDS (as defined per individual trial criteria). Treatments of interest included solriamfetol (75 mg, 150 mg, or 300 mg), modafinil (200 mg or 400 mg), armodafinil (150 mg or 250 mg), and placebo. Notably, modafinil is not approved at 400 mg and solriamfetol is not approved at 300 mg. The search included RCTs with a parallel-arm design or crossover design (if the results at first cross were reported) that reported at least 1 efficacy outcome of interest with a minimum sample size of 10 patients per trial arm; systematic reviews of RCTs were also included for identification of primary studies. Selection excluded EDS etiologies other than OSA; participant use of concurrent pharmacological interventions that could affect sleepiness/wakefulness; and nonrandomized trials, crossover trials without data to first cross, observational studies, case series/case reports, nonsystematic reviews, and trials with a follow-up length of 2 weeks or less.

Trial selection

Results of all literature searches were compiled into a common Microsoft Excel database. All eligible articles were screened by 2 independent reviewers. At each screening step, trial inclusion and exclusion were based on predefined selection criteria. After all relevant publications were identified and received, 2 independent reviewers extracted relevant data from the articles and reconciled any discrepancies. A third independent reviewer was consulted as necessary and adjudicated where consensus could not be reached. A full list of variables extracted is provided in **Table S2** in the supplemental material.

The Cochrane Risk of Bias tool was used to assess the methodological quality of trials included in the ITC.[34] The risk-of-bias assessment was conducted at the study level by 2 blinded reviewers and adjudicated by a third independent reviewer if necessary.

Outcome measures

Following the systematic literature review, a feasibility assessment was conducted to determine which outcomes were measured for more than 1 comparator of interest. Efficacy outcomes of interest included the Epworth Sleepiness Scale (ESS), Maintenance of Wakefulness Test (MWT), Physician's Global Impression of Change (PGI-C), Clinical Global Impression of Change (CGI-C), Functional Outcomes of Sleep Questionnaire (FOSQ), 36-item Short-Form Health Survey (SF-36), and EuroQoL 5-Dimension Scale (EQ-5D) scores. Safety outcomes of interest included incidence of any treatment-emergent adverse events (TEAEs), serious TEAEs, discontinuation due to TEAEs, and individual TEAEs experienced in ≥ 5% of patients in any trial arm.

Statistical analysis

A qualitative similarity assessment was performed to ensure comparability of trial, population, treatment, and outcome characteristics based on clinician and expert input. Network diagrams were developed for each outcome to demonstrate the trial arms (nodes, represented as circles) and direct comparisons made (edges, represented as connecting lines). A Bayesian ITC framework was used to generate estimates of relative effect and absolute change from baseline. Models were programmed and executed in

WinBUGS version 1.4 for Windows.[35] Quantitative assessment of heterogeneity was planned using a heterogeneity Q-statistic and I^2 statistic for outcomes where 2 or more studies for the same pairwise comparison were included into the ITC. Fixed-effects models were selected based on model fit diagnostics (such as deviance information criterion; **Table S3** in the supplemental material), heterogeneity testing (**Table S4** in the supplemental material), and the small sample of studies per comparison.

Mean within-arm changes from baseline and standard errors were used as model inputs for continuous outcomes (ie, ESS, MWT, FOSQ), with adjusted means (ie, least-squares means) favored as inputs over arithmetic means, when available. Sensitivity analyses were conducted to assess the impact of including adjusted (ie, least-squares) vs unadjusted (ie, arithmetic) means as inputs. For outcome values with missing standard deviations or standard errors (ie, ESS and MWT performed over 20 minutes [MWT20] outcomes at 4, 8, and 12 weeks from Black and Hirshkowitz;[36] ESS and MWT20 outcomes at 4 weeks from Inoue et al;[37] ESS outcomes at 4 weeks from Pack et al[38]), estimated values were imputed by assuming a within-group correlation value of 0.55 for active treatment arms and 0.75 for placebo arms, and then the standard error was calculated.[39] Sensitivity analyses were performed in which the within-group correlation values were set for both active treatment and placebo arms to 0.75 or to 0.55; a third sensitivity analysis imputed standard errors using guidance from the Cochrane Collaboration, using the weighted average of all other presented placebo arm standard errors as the imputed placebo arm standard error or the weighted average of all presented arm standard errors as the imputed active treatment arm standard error.[40] The sensitivity analyses revealed no change in MWT20 results and no change in ESS results. The incidence proportion (%) was used as the model input for discrete outcomes (ie, CGI-C, TEAEs). For discrete outcomes in which at least 1 trial arm reported 0 patients reporting an event, 0.5 was substituted for the numerator and 1 was added to the denominator (eg, 0/30 patients would become 0.5/31 patients);[41] this was done for serious TEAEs, anxiety, dry mouth, and insomnia. Without these adjustments, the models fail to converge, thus precluding the analysis of these safety outcomes.

Patient-level data were censored to enable comparisons for the MWT analysis. During the MWT, a participant is instructed to stay awake in soporific circumstances during repeated trials of a certain number of minutes (20, 30, or 40 minutes [MWT20, MWT30, or MWT40]). Patients who remain awake for the full length of the test are censored at that final time point; thus, trials that use the longer MWT test durations may show differences in treatments that are not observed when using shorter tests.[42,43] For this reason, studies of different MWT times were analyzed separately. This comparison required calculating censored patient-level outcome data for the solriamfetol Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness (TONES) 3 trial (obtained from the clinical study report), in which 40-minute individual patient outcome values were censored to 20- and 30-minute values.[44]

The relative effect of the WPA vs placebo at each time point was expressed as a mean difference from baseline to endpoint on the ESS, MWT20, and FOSQ, and as an odds ratio for the proportion achieving at least minimal improvement on the CGI-C and experiencing cumulative or individual TEAEs. The absolute outcome values for all treatments were calculated by combining the ITC-derived treatment effect estimate with the placebo effect (calculated as a weighted average across all placebo arms). Uncertainty around point estimates for relative and absolute change from baseline was measured by the 95% credible interval (CrI). League tables of all pairwise comparisons and ranking probability tables are provided in the supplemental material. Graphical summaries (ie, forest plots) of the ITC results, including the line of no effect of reference, are presented relative to placebo. Statements describing a "greater" improvement for a given treatment as relative to another treatment refer to the 95% CrI of the pairwise comparison not crossing 0 (for mean differences) or 1 (for odds ratios); statements describing improvements as "not greater" refer to the 95% CrI of the pairwise comparison crossing 0 or 1, respectively.

RESULTS

A total of 639 records were initially identified. The majority of the 618 studies excluded at title/abstract review included study designs not of interest (eg, nonsystematic review articles, letters, comments, or editorials) or populations not of interest (eg, healthy controls or patients with sleep disorders other than OSA). Of the 21 citations examined in full-text review, 14 citations were excluded due to wrong study design (n = 3), wrong population size (n = 1), missing outcomes of interest (n = 1), and systematic literature reviews that were used to identify additional references of interest prior to exclusion (n = 9); no additional references were identified. Finally, 7 records were included in the ITC (**Figure S1** in the supplemental material). These 7 records described 6 trials comprising 1,714 participants (**Table 1**).[36–38,44–48] Study inclusion and exclusion criteria were generally similar. Patients were not allowed to have sleep disorders other than OSA. Most trials did not allow use of the study drug within at least 1 month of the study[46] or ever.[38,44,45,48] Excessive caffeine consumption and/or over-the-counter or prescription medications affecting sleepiness/wakefulness were also explicitly excluded. Patients in all trials had either been on stable CPAP therapy for ≥ 2 weeks prior to study start and had an apnea-hypopnea index of ≤ 10 events/h[36–38,45–47] or had current (70%) or prior (30%) attempts to use a primary OSA therapy (positive airway pressure, mandibular advancement device, or surgical intervention).[44,48] Participant demographics were generally similar across the included trials' treatment arms (eg, age, proportion male, and body mass index; **Table 2**). Inoue et al[37] described a higher proportion of male participants (~96% vs ≤ 75%) and a lower body mass index (~27.6 vs ≥ 33 kg/m^2) than comparator trials, but the trial was not deemed sufficiently different to be excluded from the ITC. Baseline ESS values were similar across study arms, indicating similar EDS severity. Heterogeneity testing did not reveal substantial differences in outcomes for trials testing the same comparators. All trials included 1 placebo arm and at least 1 arm including modafinil, armodafinil, or solriamfetol.

Table 1—Trial characteristics and outcomes of interest.

	Schweitzer et al 2018[44,48]	Black and Hirshkowitz 2005[36]	Hirshkowitz et al 2007[46]	Inoue et al 2013[37]	Pack et al 2001[38,45]	Roth et al 2006[47]
ClinicalTrials.gov identifier	NCT02348606	NR	NCT00079677[a]	NR	NR	NCT00078325[a]
Countries	Canada, Germany, Netherlands, United States	United Kingdom, United States	Australia, France, Germany, Russia, United States	Japan	United States	Canada, United States
Total sample size, n	476	309	263	114	157	395
Minimum age, y	18	18	18	20	18	18
Minimum ESS score at enrollment	10	10	10	11	10	10
CPAP prior to trial, %	70[b]	100[c]	100[c]	100[c]	100[c]	100[c]
Trial duration, wk	12	12	12	4	4	12
Treatments	Placebo, solriamfetol 37.5 mg qd,[d] solriamfetol 75 mg qd, solriamfetol 150 mg qd, solriamfetol 300 mg qd	Placebo, modafinil 200 mg qd, modafinil 400 mg qd	Placebo, armodafinil 150 mg qd	Placebo, modafinil 200 mg qd	Placebo, modafinil 200–400 mg qd[e]	Placebo, armodafinil 150 mg qd, armodafinil 250 mg qd
Outcome evaluation timepoints, wk						
ESS	4, 8, 12	4, 8, 12	4, 8, 12	4	4	4, 8, 12
MWT20	4, 12	4, 8, 12	NA	4	NA	NA
MWT30	4, 12	NA	4, 8, 12	NA	NA	4, 8, 12
MWT40	4, 12	NA	NA	NA	NA	NA
FOSQ	4, 8, 12	12	NA	NA	4	NA
PGI-C	4, 8, 12	NA	NA	NA	NA	NA
CGI-C	4, 8, 12	4, 8, 12	12	NA	4	4, 8, 12
EQ-5D	4, 8, 12	NA	NA	NA	NA	NA
SF-36	8	NA	NA	NA	NA	NA
TEAEs reported in ≥ 5% of any trial arm						
Anxiety	✓	✓	✓		✓	✓
Decreased appetite	✓					
Diarrhea	✓	✓	✓			✓
Dry mouth	✓					✓
Headache	✓	✓	✓	✓	✓	✓
Insomnia	✓	✓		✓	✓	✓
Nasopharyngitis[f]	✓		✓			
Nausea	✓	✓	✓		✓	
Feeling jittery	✓					
Irritability	✓					
Pruritus	✓					
Sinusitis	✓					
Others		Infection, accidental injury, hypertension, nervousness, dizziness, rhinitis	Upper respiratory tract infection, dizziness	Upper abdominal pain, palpitation	Nervousness, rhinitis, dizziness	Dizziness, arthralgia

[a]ClinicalTrials.gov entry was required to extract outcomes of interest. [b]Refers to any level of compliance of CPAP, oral pressure therapy, oral appliance, or upper airway stimulator prior to trial start. [c]Refers to ≥ 4 hours CPAP use per night on ≥ 70% of nights for ≥ 2 weeks prior to trial start. [d]Considered a starting dose; not analyzed via indirect treatment comparison. [e]Refers to 1 week at 200 mg qd and 3 weeks at 400 mg qd; standardized to 400 mg qd modafinil. [f]Not considered to be associated with treatment; not analyzed via indirect treatment comparison. CGI-C = Clinical Global Impression of Change, CPAP = continuous positive airway pressure, EQ-5D = EuroQol 5-Dimension Scale, ESS = Epworth Sleepiness Scale, FOSQ = Functional Outcomes of Sleep Questionnaire, MWT = Maintenance of Wakefulness Test performed over 20, 30, or 40 minutes, NA = not applicable, NR = not reported, PGI-C = Patient Global Impression of Change, qd = daily, SF-36 = 36-item Short Form Health Survey, TEAE = treatment-emergent adverse event.

Table 2—Patient characteristics.

	Schweitzer et al 2018[44,48]				Black and Hirshkowitz 2005[36]			Hirshkowitz et al 2007[46]		Inoue et al 2013[37]		Pack et al 2001[38,45]		Roth et al 2006[47]		
	Placebo	Solriamfetol 75 mg qd	Solriamfetol 150 mg qd	Solriamfetol 300 mg qd	Placebo	Modafinil 200 mg qd	Modafinil 400 mg qd	Placebo	Armodafinil 150 mg qd	Placebo	Modafinil 200 mg qd	Placebo	Modafinil 400 mg qd	Placebo	Armodafinil 150 mg qd	Armodafinil 250 mg qd
Number of patients	119	62	117	118	104	104	101	130	129	62	52	80	77	130	131	131
Age, y																
Mean	54	54	53	53	51	48	49	51	51	51	49	50	50	50	49	49
Range	50–74	29–74	21–75	24–72	28–68	24–68	28–70	25–68	27–69	NR		28–72	32–76	NR		
Males, %	65	57	62	63	72	87	68	72	75	98	94	74	79	69	74	68
White, %	73	74	80	76	NR			85	83	NR		NR		87	83	85
BMI, mean, kg/m^2	33.1	33.4	33.3	32.9	37.3	36.2	36.9	30.8	36.3	27.3	27.9	35.0	35.9	37.0	36.6	36.5
Baseline outcomes																
ESS	15.6	15.0	15.1	15.1	14.7	15.8	14.8	16.0	15.6	14.6	14.3	14.4	14.2	15.9	15.4	15.3
MWT20	10.8[a,b]	10.8[a,b]	10.7[a,b]	10.3[a,b]	13.8[b]	13.1[b]	13.5[b]	NA		14.3	14.0	NA		NA		
MWT30[b]	12.0[b,c]	11.9[b,c]	12.0[b,c]	11.5[b,c]	NA			23.3[b]	23.7[b]	NA		NA		23.2[b]	21.5[b]	23.3[b]
MWT40	12.6[b]	12.4[b]	12.5[b]	12.1[b]	NA			NA		NA		NA		NA		

[a]Values were derived by censoring original clinical trial data at 20 minutes to generate the MWT20.[44] [b]Mean of first 4 tests of the testing day. [c]Values were derived by censoring original clinical trial data at 30 minutes to generate MWT30.[44] BMI = body mass index, ESS = Epworth Sleepiness Scale, MWT = Maintenance of Wakefulness Test performed over 20, 30, or 40 minutes, NA = not applicable, NR = not reported, qd = daily.

Overall bias was low across the 6 trials included in the ITC (**Table S5** in the supplemental material), and variables for which bias was "high" or "unclear" were not of substantial concern for inclusion into the analysis, except the standard deviation for the FOSQ outcome reported in Dinges and Weaver,[45] which was substantially higher than those provided in comparator trials.

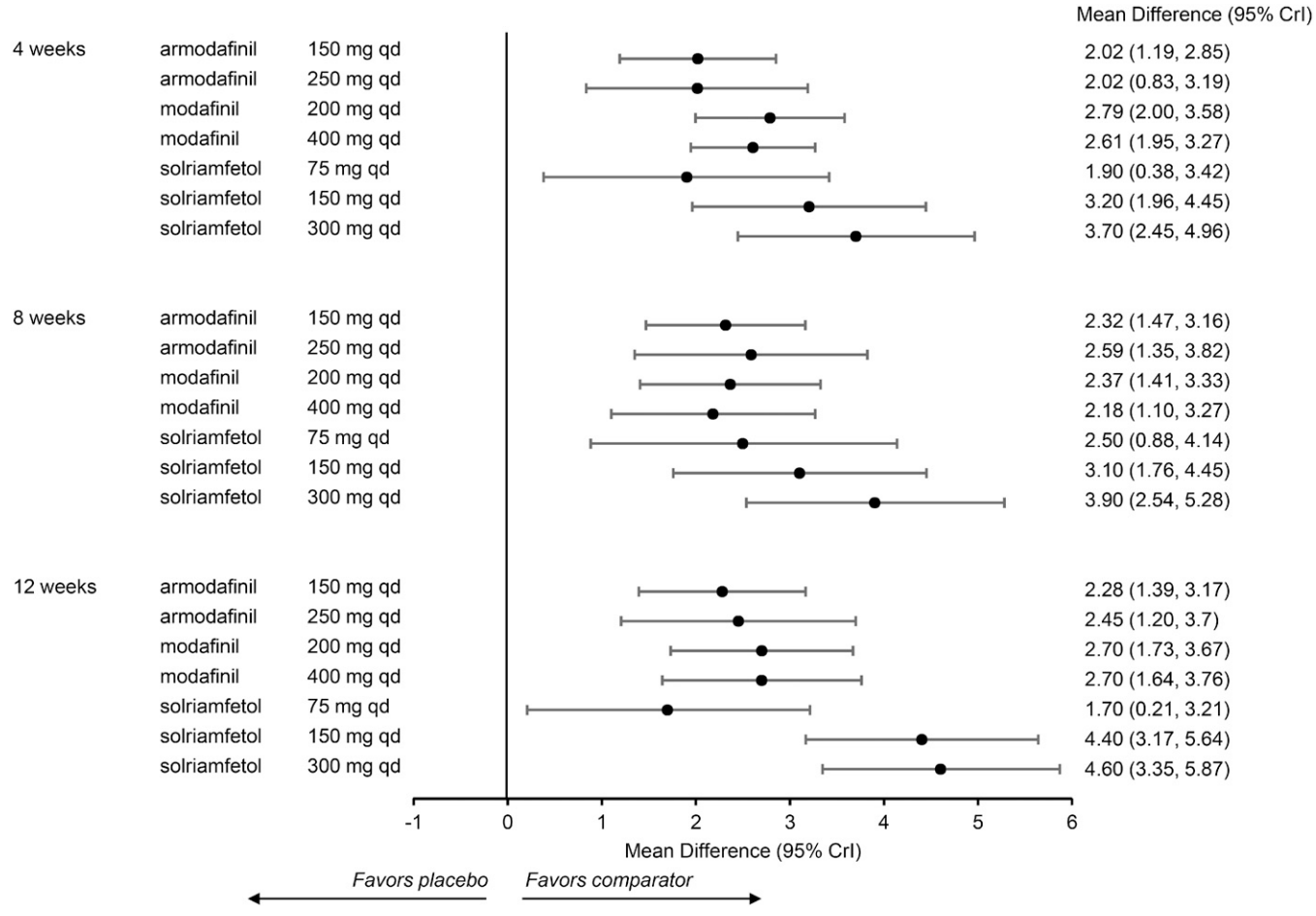
We found that ITC analyses were feasible at 4, 8, and/or 12 weeks for ESS (patient-assessed daytime sleepiness rated on a scale of 0–24), MWT20 (the number of minutes patients stay awake during 20 minutes in a dark, quiet setting), FOSQ (patient-assessed impact of sleepiness on functional outcomes on a scale of 5–20), and CGI-C (a clinician-assessed determination of the proportion of patients who have minimally, much, or very much improved) scores. It was deemed not possible to compare MWT30 due to large differences in baseline values (mean baseline MWT30 across 3 trials ranged from 11.5–23.7; **Table 2**). Other efficacy outcomes of interest (ie, PGI-C, SF-36, and EQ-5D) were not reported in the trials for modafinil or armodafinil and were therefore not possible to analyze. **Figure S2** in the supplemental material shows the network of treatment comparisons for efficacy outcomes of interest included in our analysis.

Safety outcomes analyzed via ITC included incidence of any TEAEs, serious TEAEs, discontinuation due to TEAEs, and individual TEAEs experienced in ≥ 5% of participants in any trial arm (ie, anxiety, diarrhea, dry mouth, headache, nausea, and insomnia).

ESS

All 6 trials included in the ITC provided ESS results at 4 weeks, and 4 trials provided ESS results at 8 and 12 weeks.[36,46–48] These trials enabled a network comparing solriamfetol against modafinil and armodafinil at all 3 time points (**Figure S2**). All comparators showed greater improvement on ESS compared with placebo after just 4 weeks; this trend was maintained at 8 and 12 weeks. At all time points, solriamfetol at 150 mg and 300 mg demonstrated the greatest numerical improvement on ESS vs placebo compared with other WPAs (**Figure 1**). As shown in **Table S6** in the supplemental material, the absolute reductions (calculated from ITC-derived treatment effect estimates) on the ESS from baseline at 12 weeks (mean difference [95% CrI]) for solriamfetol were −4.61 (−6.05, −3.20; 75 mg), −7.31 (−8.45, −6.18; 150 mg), and −7.51 (−8.68, −6.35; 300 mg); the reductions for armodafinil were −5.19 (−5.95, −4.43; 150 mg) and −5.36 (−6.51, −4.21; 250 mg); the reductions for modafinil were −5.61 (−6.62, −4.61; 200 mg) and −5.61 (−6.71, −4.52; 400 mg); and the reduction

Figure 1—Forest plots of ESS outcomes relative to placebo at 4, 8, and 12 weeks.



CrI = credible interval, ESS = Epworth Sleepiness Scale, qd = daily.

for placebo was −2.91 (−3.31, −2.51). Solriamfetol at 150 mg and 300 mg were associated with greater improvements on the ESS at 12 weeks than all doses of armodafinil and modafinil (**Table S7** in the supplemental material). Accordingly, solriamfetol at 150 and 300 mg had the highest probabilities of demonstrating the greatest improvement on the ESS at 12 weeks (**Table S8** in the supplemental material).

MWT20

Three trials provided MWT20 results at 4 weeks,[36,37,48] and 2 trials provided MWT20 results at 12 weeks.[36,48] These trials enabled a network comparing solriamfetol against modafinil only (**Figure S2**). All comparators showed a greater improvement on the MWT20 vs placebo at both 4 and 12 weeks; solriamfetol at 150 mg and 300 mg showed the greatest numerical improvement at both assessment points (**Figure 2**). As shown in **Table S9** in the supplemental material, the absolute increases on the MWT20 from baseline at 12 weeks (mean difference [95% CrI]) for solriamfetol were 3.50 (2.10, 4.88; 75 mg), 4.45 (3.37, 5.52; 150 mg), and 4.98 (3.85, 6.11; 300 mg); the increases for modafinil were 1.84 (0.64, 3.02; 200 mg) and 1.73 (0.42, 3.04; 400 mg), while placebo was associated with a decrease of −0.87 (−1.48, −0.25). Solriamfetol at 150 mg and 300 mg doses were associated with greater improvements on the MWT20 at 12 weeks than modafinil at 200 or 400 mg (**Table S10** in the supplemental material). Accordingly, solriamfetol at 150 mg and 300 mg doses had the highest probabilities of demonstrating the greatest improvement on the MWT20 at 12 weeks (**Table S11** in the supplemental material).

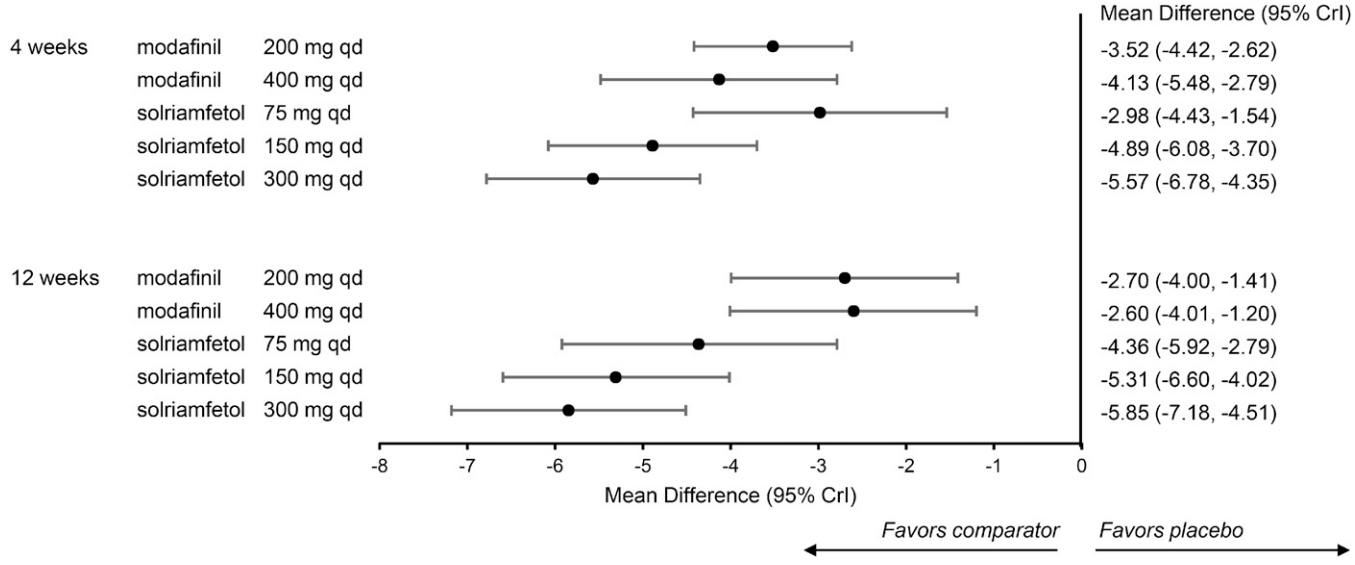
CGI-C

Four trials provided CGI-C results at 4 weeks,[36,38,47,48] 3 trials provided results at 8 weeks,[36,47,48] and 4 trials provided results at 12 weeks.[36,46–48] These trials enabled a network comparing solriamfetol against modafinil and armodafinil at all 3 time points (**Figure S2**). All comparators showed greater odds of improvement on CGI-C vs placebo at 4, 8, and 12 weeks; solriamfetol at 150 mg and 300 mg showed the greatest numerical improvement at 8 and 12 weeks (**Figure 3**). As shown in **Table S12** in the supplemental material, the absolute rates of improvement at 12 weeks (proportion [95% CrI]) for solriamfetol were 67% (52%, 80%; 75 mg), 89% (81%, 95%; 150 mg), and 87% (78%, 93%; 300 mg); the rates for armodafinil were 72% (65%, 78%; 150 mg) and 78% (69%, 85%; 250 mg); the rates for modafinil were 68% (56%, 79%; 200 mg) and 75% (64%, 84%; 400 mg); and the incidence for placebo was 45% (40%, 49%). At 12 weeks, solriamfetol at 150 mg was associated with a greater likelihood of CGI-C improvement than modafinil at 200 or 400 mg and armodafinil at 150 mg; solriamfetol at 300 mg was associated with a greater likelihood of CGI-C improvement than modafinil 200 mg and armodafinil 150 mg (**Table S13** in the supplemental material). Solriamfetol at 150 mg and 300 mg doses had the highest probabilities of CGI-C improvement at 12 weeks (**Table S14** in the supplemental material).

FOSQ

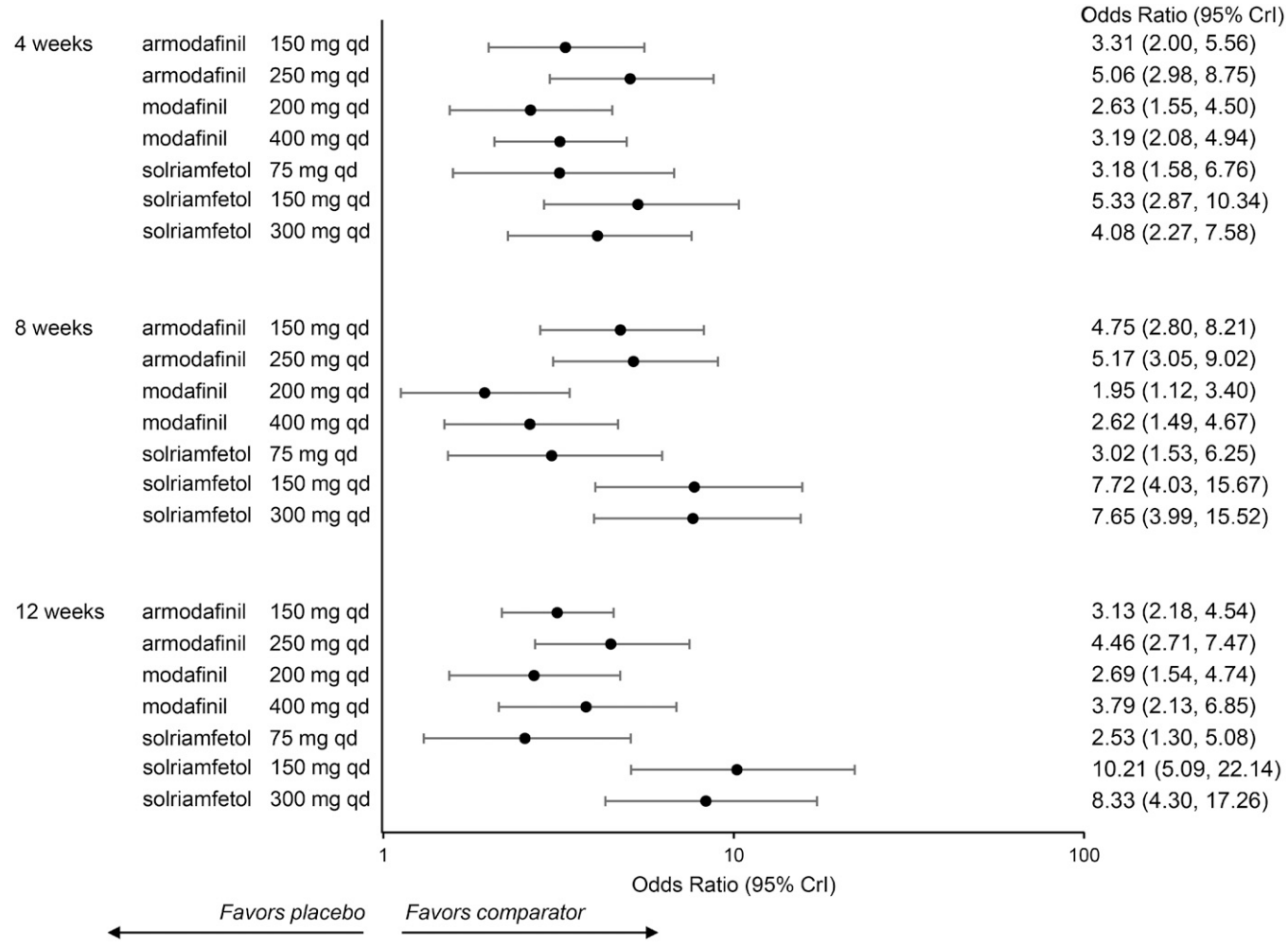
Two trials provided FOSQ results at 4 weeks,[45,48] but that network was not viable due to the large standard deviations for FOSQ results in placebo and modafinil participants in the trial by Dinges and Weaver.[45] Two trials provided FOSQ results at 12 weeks,[36,48] which enabled a network comparing solriamfetol against modafinil (**Figure S2**). At 12 weeks, all comparators except for solriamfetol 75 mg showed a greater improvement on the FOSQ vs placebo (**Figure 4**). As shown in **Table S15** in the supplemental material, the absolute increases on the FOSQ from baseline at 12 weeks (mean difference [95% CrI]) for solriamfetol were 2.05 (1.34, 2.76; 75 mg), 2.53 (1.99, 3.07; 150 mg), and 2.77 (2.21, 3.33; 300 mg); the increases for

Figure 2—Forest plots of MWT20 outcomes relative to placebo at 4 and 12 weeks.



CrI = credible interval, MWT20 = Maintenance of Wakefulness Test at 20 minutes, qd = daily.

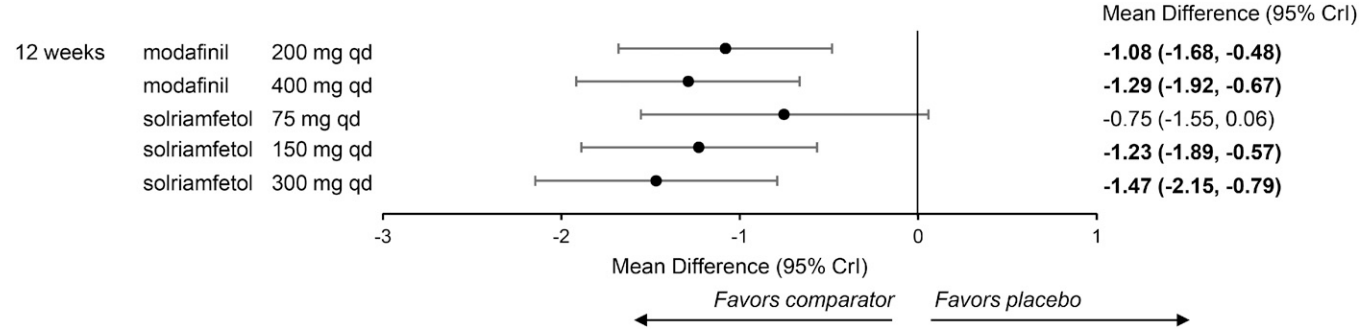
Figure 3—Forest plots of CGI-C outcomes relative to placebo at 4, 8, and 12 weeks.



CGI-C = Clinical Global Impression of Change, CrI = credible interval, qd = daily.

modafinil were 2.38 (1.81, 2.95; 200 mg) and 2.59 (1.99, 3.19; 400 mg); and the increase for placebo was 1.30 (1.00, 1.60). Solriamfetol at 150 or 300 mg did not demonstrate greater improvement in FOSQ than modafinil at 200 or 400 mg (**Table S16** in the supplemental material). Solriamfetol at 300 mg had the highest probability of demonstrating the greatest improvement on the FOSQ, followed by modafinil 400 mg and solriamfetol 150 mg (**Table S17** in the supplemental material).

Figure 4—Forest plots of FOSQ outcomes relative to placebo at 12 weeks.



Bold formatting indicates that the 95% CrI does not cross the line of no effect. CrI = credible interval, FOSQ = Functional Outcomes of Sleep Questionnaire, qd = daily.

Safety

Trials reporting the incidence of any TEAEs, serious TEAEs, and discontinuation due to TEAEs were also examined via ITC. Relative to placebo, the odds of experiencing any TEAE were greater for solriamfetol at 150 and 300 mg, but not for solriamfetol 75 mg or modafinil 200 mg; other WPAs did not report this outcome (**Figure 5**). The absolute rates of any TEAE (proportion [95% CrI]) for solriamfetol were 39% (26%, 52%; 75 mg), 62% (51%, 73%; 150 mg), and 70% (58%, 79%; 300 mg); the incidence for modafinil 200 mg was 55% (37%, 72%); and the incidence for placebo was 38% (31%, 46%; **Table S18** in the supplemental material).

The odds of experiencing serious TEAEs were not greater for any WPAs at any dose compared with placebo (**Figure 5**). Serious TEAEs were relatively rare, with absolute rates of < 2% for all WPAs and placebo (**Table S18**).

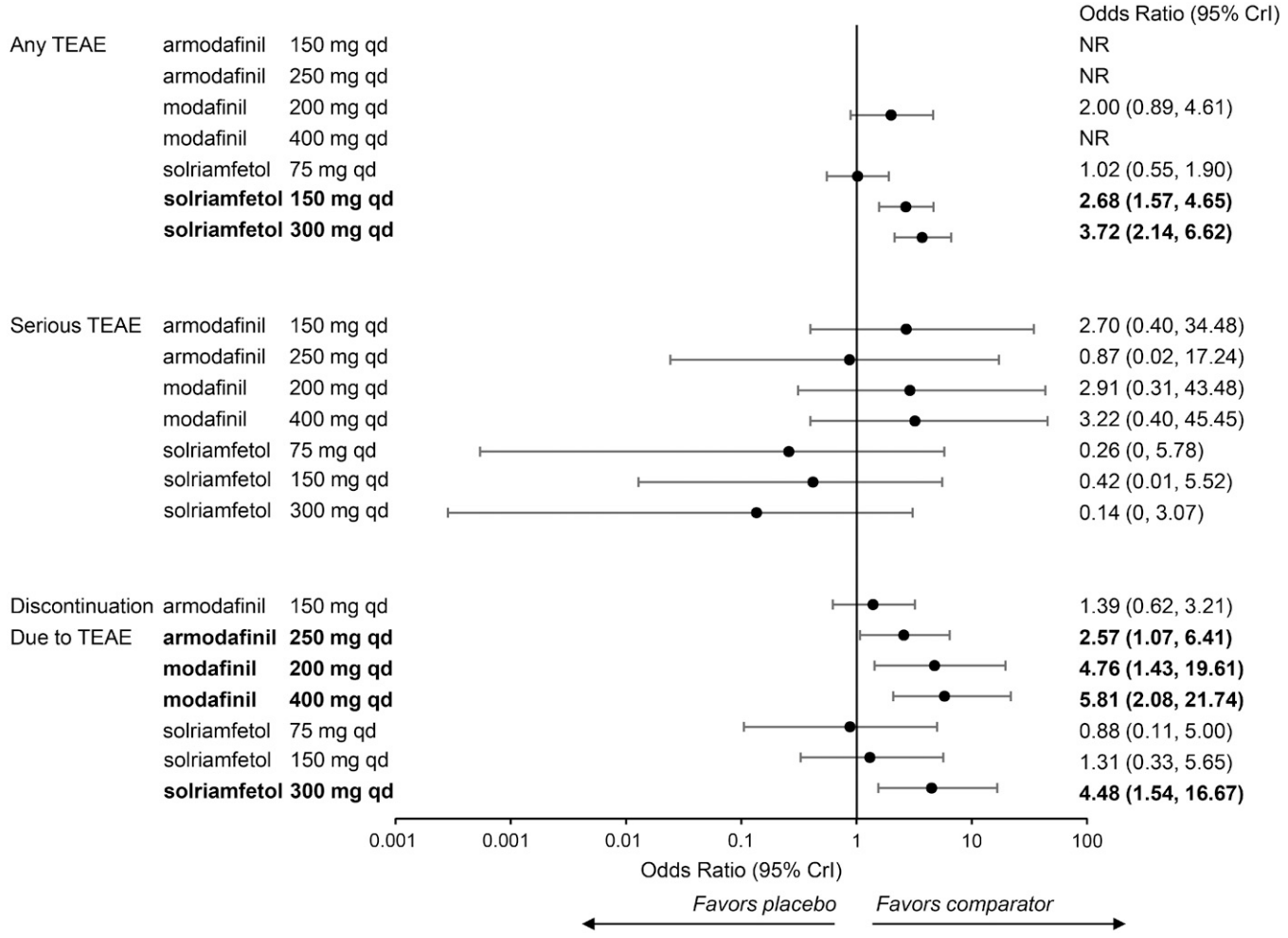
Compared with placebo, the odds of discontinuation due to TEAEs were greater for armodafinil 250 mg, modafinil 200 and 400 mg, and solriamfetol 300 mg, but not for armodafinil 150 mg or solriamfetol 75 or 150 mg (**Figure 5**). The absolute rates of discontinuation due to TEAEs were < 1% for all WPAs and placebo.

The incidence of individual TEAEs reported by trials was also examined in the ITC. Relative to placebo, armodafinil was associated with a greater risk of anxiety, dry mouth (250 mg dose only), headache, insomnia, and nausea (250 mg dose only); modafinil was associated with a higher risk of anxiety (400 mg dose only), headache, insomnia, and nausea; solriamfetol at 150 mg or 300 mg was associated with a higher risk of anxiety, diarrhea (300 mg dose only), dry mouth (300 mg dose only), and insomnia (300 mg dose only); while solriamfetol 75 mg was not associated with an increased risk of any of these TEAEs (**Figure 6**). The absolute risk of experiencing any of these TEAEs was < 20% in most instances (**Table S18**).

DISCUSSION

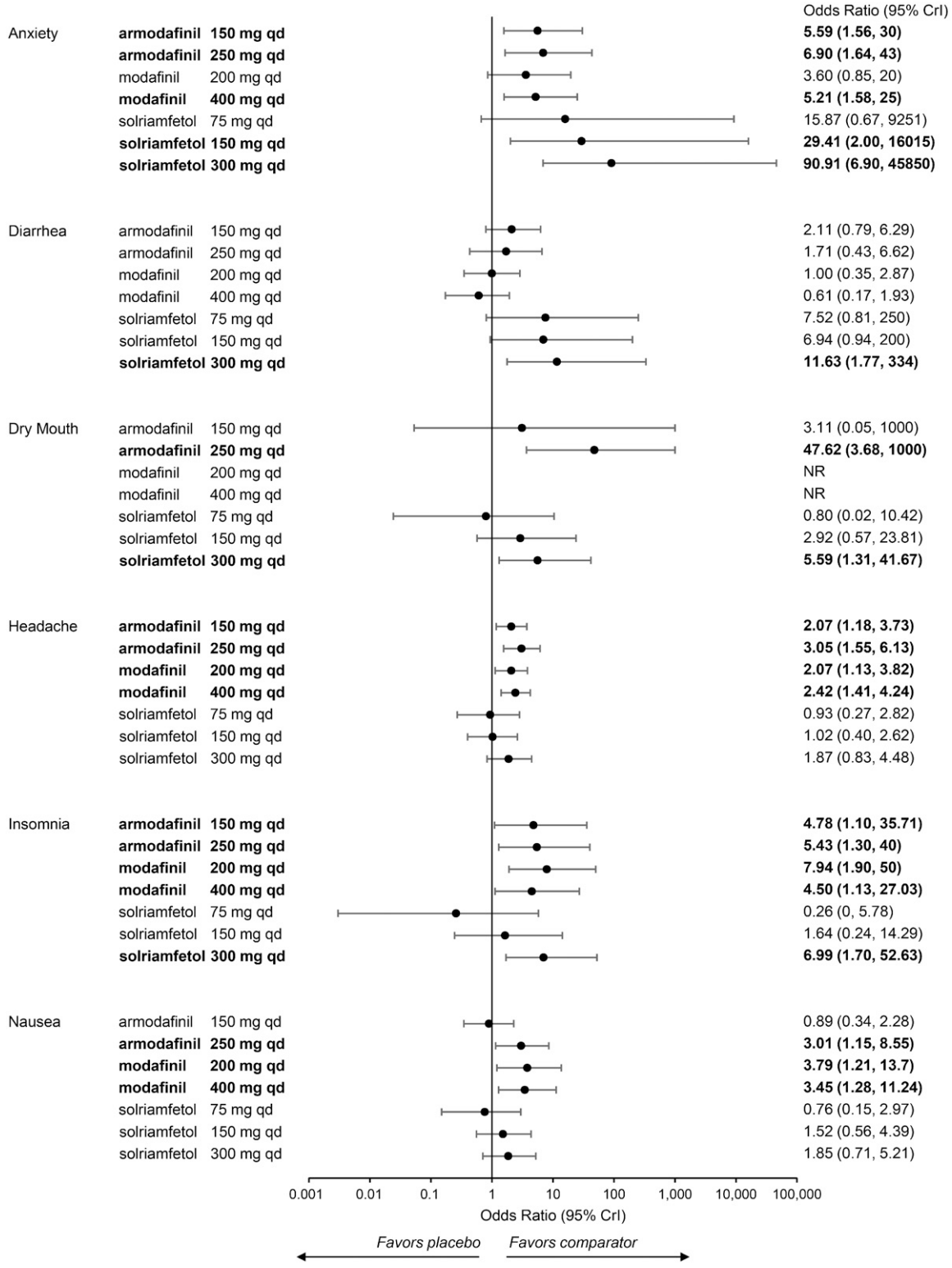
The results of this ITC showed that all WPAs at all doses assessed led to greater improvements than placebo on the ESS

Figure 5—Forest plots of cumulative safety events relative to placebo at end of treatment.



Bold formatting indicates that the 95% CrI does not cross the line of no effect. CrI = credible interval, NR = not reported, qd = daily, TEAE = treatment-emergent adverse event.

Figure 6—Forest plots of individual safety events relative to placebo at end of treatment.



Bold formatting indicates that the 95% CrI does not cross the line of no effect. CrI = credible interval, NR = not reported, qd = daily.

and MWT20 and in odds of improvement in CGI-C after 4 weeks of treatment; these effects were maintained at 12 weeks. Among the WPAs, solriamfetol at 150 mg and 300 mg consistently ranked first or second in probability of the greatest improvement on the ESS and MWT20 and in the likelihood of CGI-C improvement. Furthermore, the risks of serious TEAEs, discontinuation-related TEAEs, and individual TEAEs were relatively low for all WPAs in most instances.

Our ITC is consistent with prior meta-analyses of modafinil and armodafinil in terms of outcomes analyzed (ie, ESS, MWT, and CGI-C are commonly reported). Four pairwise meta-analyses have been conducted for modafinil and armodafinil vs placebo among patients with EDS associated with OSA.[49–52] These previous meta-analyses all demonstrated the efficacy of WPAs over placebo on the ESS, MWT, and CGI-C while maintaining tolerability. However, in some of the previous pairwise meta-analyses, data for modafinil and armodafinil were pooled to create a single point estimate, despite evidence of different pharmacologic properties for these drugs.[53] Other potential confounding factors not accounted for in previous pairwise meta-analyses are different trial, patient, and efficacy test characteristics; some trials included in previous meta-analyses are crossover studies that may not account for carryover effects or may compare MWT tests of different durations. In contrast, the ITC presented here shows the comparability of key trial and participant characteristics from the included studies and provides comparative effectiveness data at specific time points for individual WPA doses, which provides meaningful evidence about the relationships between treatment dose and treatment duration on efficacy outcomes. Furthermore, this ITC analyzes MWT tests based on test duration, ensuring like-for-like comparisons. Notably, this is the first ITC in patients with EDS associated with OSA that includes solriamfetol as a comparator with modafinil and armodafinil.

The primary strength of this ITC study is that it provides important comparative efficacy information about WPAs for patients with EDS associated with OSA in the absence of head-to-head trials by measuring 2 of the most commonly reported clinical efficacy measures (ESS and MWT), while also demonstrating the relative risk of experiencing adverse events. Populations in the included trials were largely homogeneous, and all trials were placebo-controlled and reported outcomes at 4-week intervals. These characteristics ensured generation of unambiguous networks, with separate network nodes for different treatment doses, at discrete time points.

ITC methodology is subject to limitations typical to any meta-analysis, as well as some unique limitations. Notably, the results obtained represent the statistical aggregation of data from the network pool. Thus, meta-analysis results should be consistent with (but are not exactly equal to) any individual RCT. An additional limitation is the limited comparator data available to inform each ITC network, as few trials met the inclusion criteria necessary to enable comparison with the TONES 3 pivotal trial for solriamfetol.[48] In some cases (eg, FOSQ at 12 weeks), only 2 trials informed the network used in an ITC. Since a small number of data points were used in these instances to create the related network and perform the ITC, caution should be exercised in strictly interpreting whether a given comparator led to greater improvement than other comparators.

Another limitation includes the need to censor MWT40 data to mimic an MWT20 test, which may underestimate improvements in wakefulness in the MWT40-tested population.[42,43]

Finally, there were limited efficacy outcomes available for analysis. The TONES 3 trial tested a variety of sleepiness, wakefulness, and patient- and clinician-reported outcomes,[48] but most comparable trials were limited to reporting ESS, MWT, and/or CGI-C. It is possible that comparative efficacy is not fully realized when limited to these 3 outcomes; in other words, a patient may prefer a particular intervention for a reason not fully captured within these outcomes. Patient- and physician-reported outcomes do merit further evaluation, as they may be important in understanding the best option for each patient with EDS. Furthermore, trials assessing armodafinil at 150 or 250 mg and modafinil at 400 mg did not report incidence of any TEAEs. The rates of serious, discontinuation-related, and individual adverse events were relatively rare across all trials, and analyses were limited by the sparsity of the network and low event rates. As noted in the Methods section, imputations were used to analyze outcomes with missing errors and rare TEAEs; the accepted approaches used here were robust, based on sensitivity testing, but we acknowledge that these methods may introduce bias. No statistically significant heterogeneity was identified for the available comparisons (as defined by I^2 statistic values), although it must be noted that heterogeneity tests are known to have low power to detect differences when informed by a small sample of studies.[54] Consistency testing was not possible because direct and indirect RCT comparisons were not available for any treatment pairs.

Despite the prevalence of EDS associated with OSA,[5,6] there are few treatment options approved to treat this condition, particularly outside the United States.[15] Furthermore, approximately half of all patients with EDS associated with OSA may not respond to modafinil or armodafinil therapy.[38,55] A recent review of over 12 million patients with OSA found that only 5% had been prescribed 1 or more pharmacotherapies,[16] despite estimates that 2 to 4 times as many patients with OSA experience EDS.[5,6] Low drug-treatment rates in this population may reflect limited consideration for pharmacotherapy as a treatment option by physicians. Clear evidence of efficacy across sleepiness, wakefulness, and functional outcomes and limited potential for adverse events may improve treatment rates in the OSA patient population.

In summary, this is the first ITC to compare solriamfetol, modafinil, and armodafinil across wakefulness and sleepiness outcomes in patients with EDS associated with OSA. Compared with placebo, all 3 agents improved wakefulness and sleepiness outcomes and were associated with a low risk of serious or discontinuation-causing TEAEs. Solriamfetol at 150 and 300 mg was associated with the greatest improvements or likelihood of achieving efficacy outcomes.

ABBREVIATIONS

CGI-C, Clinical Global Impression of Change

CPAP, continuous positive airway pressure
CrI, credible interval
EDS, excessive daytime sleepiness
ESS, Epworth Sleepiness Scale
EQ-5D, EuroQol 5-Dimension Scale
FOSQ, Functional Outcomes of Sleep Questionnaire
ITC, indirect treatment comparison
MWT, Maintenance of Wakefulness Test
NA, not applicable
NR, not reported
OSA, obstructive sleep apnea
PGI-C, Patient Global Impression of Change
qd, daily
SF-36, 36-item Short Form Health Survey
TEAE, treatment-emergent adverse event
TONES 3, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness
WPA, wake-promoting agent

REFERENCES

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders.* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
2. National Institute for Health and Care Excellence (NICE). Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome. https://www.nice.org.uk/guidance/ta139. Accessed November 18, 2020.
3. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2019; 15(2):335–343.
4. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population—a review on the epidemiology of sleep apnea. *J Thorac Dis.* 2015;7 (8):1311–1322.
5. Gasa M, Tamisier R, Launois SH, et al; Scientific Council of the Sleep Registry of the French Federation of Pneumology-FFP. Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure. *J Sleep Res.* 2013;22(4): 389–397.
6. Pépin JL, Viot-Blanc V, Escourrou P, et al. Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study. *Eur Respir J.* 2009;33(5):1062–1067.
7. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol.* 2013;177(9): 1006–1014.
8. Dean B, Aguilar D, Shapiro C, et al. Impaired health status, daily functioning, and work productivity in adults with excessive sleepiness. *J Occup Environ Med.* 2010; 52(2):144–149.
9. Omachi TA, Claman DM, Blanc PD, Eisner MD. Obstructive sleep apnea: a risk factor for work disability. *Sleep.* 2009;32(6):791–798.
10. Ronksley PE, Hemmelgarn BR, Heitman SJ, et al. Excessive daytime sleepiness is associated with increased health care utilization among patients referred for assessment of OSA. *Sleep.* 2011;34(3):363–370.
11. Stepnowsky C, Sarmiento KF, Bujanover S, Villa KF, Li VW, Flores NM. Comorbidities, health-related quality of life, and work productivity among people with obstructive sleep apnea with excessive sleepiness: findings from the 2016 US National Health and Wellness Survey. *J Clin Sleep Med.* 2019;15(2):235–243.
12. Tregear S, Reston J, Schoelles K, Phillips B. Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. *J Clin Sleep Med.* 2009;5(6):573–581.
13. Garbarino S, Guglielmi O, Sanna A, Mancardi GL, Magnavita N. Risk of occupational accidents in workers with obstructive sleep apnea: systematic review and meta-analysis. *Sleep.* 2016;39(6):1211–1218.
14. Epstein LJ, Kristo D, Strollo PJ Jr, et al; Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med.* 2009;5(3):263–276.
15. Abad VC, Guilleminault C. Solriamfetol for the treatment of daytime sleepiness in obstructive sleep apnea. *Expert Rev Respir Med.* 2018;12(12):1007–1019.
16. Ohayon MPJ, Gibson SP, Scheckner B, Milesi C. The use of stimulants, sedative-hypnotics, and antidepressants in patients with obstructive sleep apnea in the United States. *Ann Neurol Suppl.* 2018;22(84):S130.
17. Auger RR, Goodman SH, Silber MH, Krahn LE, Pankratz VS, Slocumb NL. Risks of high-dose stimulants in the treatment of disorders of excessive somnolence: a case-control study. *Sleep.* 2005;28(6):667–672.
18. Takenoshita S, Nishino S. Pharmacologic management of excessive daytime sleepiness. *Sleep Med Clin.* 2017;12(3):461–478.
19. U.S. Food & Drug Administration. NDA Approval for Sunosi (solriamfetol) in Narcolepsy and Obstructive Sleep Apnea, March 20, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/211230Orig1s000,%20Orig2s000ltr.pdf. Accessed November 18, 2020.
20. U.S. Food & Drug Administration. Supplemental NDA Approval for Provigil (Modafinil) Tablets in Obstructive Sleep Apnea/Hypopnea Syndrome and Shift Work Sleep Disorder, January 23, 2004. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2004/20717se1-008ltr.pdf. Accessed November 18, 2020.
21. U.S. Food & Drug Administration. NDA Approval for Nuvigil (Armodafinil) in Obstructive Sleep Apnea/Hypopnea Syndrome, Narcolepsy, and Shift Work Sleep Disorder, June 15, 2007. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/021875s000ltr.pdf. Accessed November 18, 2020.
22. Sunosi™ (solriamfetol) tablets Summary of Product Characteristics. Dublin, Ireland: Jazz Pharmaceuticals Ireland Ltd; 2020.
23. European Medicines Agency. Questions and Answers on the Review of Medicines Containing Modafinil [EMEA/H/A-31/1186]. https://www.ema.europa.eu/en/documents/referral/questions-answers-review-medicines-containing-modafinil-re-examination_en.pdf. Accessed November 18, 2020.
24. Sunosi. Package insert. Jazz Pharmaceuticals, Inc; 2019.
25. Provigil. Package insert. Teva Pharmaceuticals USA, Inc; 2019.
26. Nuvigil. Package insert. Teva Pharmaceuticals USA, Inc; 2019.
27. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.
28. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med.* 2015;162(11):777–784.
29. Ades AE, Caldwell DM, Reken S, Welton NJ, Sutton AJ, Dias S. Evidence Synthesis of Treatment Efficacy in Decision Making: A Reviewer's Checklist. NICE Decision Support Unit Technical Support Document No. 7. https://www.ncbi.nlm.nih.gov/books/NBK395872/. Accessed August 25, 2021.
30. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal: User Guide for Company Evidence Submission Template. https://www.nice.org.uk/process/pmg24/resources/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf-72286715419333. Accessed November 18, 2020.
31. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health.* 2011;14(4):429–437.
32. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health.* 2011;14(4):417–428.
33. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health.* 2014;17(2):157–173.
34. Cochrane Handbook version 5.1.0. Risk of Bias Tool. http://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm. Accessed November 18, 2020.

35. Lunn D, Thomas A, Best N, Spiegelhalter D. WinBUGS—a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput.* 2000;10(4):325–337.
36. Black JE, Hirshkowitz M. Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated obstructive sleep apnea/hypopnea syndrome. *Sleep.* 2005;28(4):464–471.
37. Inoue Y, Takasaki Y, Yamashiro Y. Efficacy and safety of adjunctive modafinil treatment on residual excessive daytime sleepiness among nasal continuous positive airway pressure-treated Japanese patients with obstructive sleep apnea syndrome: a double-blind placebo-controlled study. *J Clin Sleep Med.* 2013;9(8):751–757.
38. Pack AI, Black JE, Schwartz JRL, Matheson JK. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2001;164(9):1675–1681.
39. Balk E, Earley A, Patel K, Trikalinos T, Dahabreh I. Empirical Assessment of Within-Arm Correlation Imputation in Trials of Continuous Outcomes. Agency for Healthcare Research and Quality. https://www.ncbi.nlm.nih.gov/books/NBK115797/. Accessed November 18, 2020.
40. Higgins J, Thomas J, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.0* [updated 2019]. https://www.ncbi.nlm.nih.gov/books/NBK395872/. Accessed August 25, 2021.
41. National Institute for Health and Care Excellence (NICE). NICE Decision Support Unit Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. http://nicedsu.org.uk/wp-content/uploads/2017/05/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf. Accessed November 18, 2020.
42. Arzi L, Shreter R, El-Ad B, Peled R, Pillar G. Forty- versus 20-minute trials of the Maintenance of Wakefulness Test regimen for licensing of drivers. *J Clin Sleep Med.* 2009;5(1):57–62.
43. Shreter R, Peled R, Pillar G. The 20-min trial of the Maintenance of Wakefulness Test is profoundly affected by motivation. *Sleep Breath.* 2006;10(4):173–179.
44. Jazz Pharmaceuticals 14-003/TONES 3 trial data on file (Unpublished data).
45. Dinges DF, Weaver TE. Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with nCPAP. *Sleep Med.* 2003;4(5):393–402.
46. Hirshkowitz M, Black JE, Wesnes K, Niebler G, Arora S, Roth T. Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. *Respir Med.* 2007;101(3):616–627.
47. Roth T, White D, Schmidt-Nowara W, et al. Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP-adherent adults. *Clin Ther.* 2006;28(5):689–706.
48. Schweitzer PK, Rosenberg R, Zammit GK, et al; TONES 3 Study Investigators. Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3): a randomized controlled trial. *Am J Respir Crit Care Med.* 2019;199(11):1421–1431.
49. Avellar AB, Carvalho LB, Prado GF, Prado LB. Pharmacotherapy for residual excessive sleepiness and cognition in CPAP-treated patients with obstructive sleep apnea syndrome: a systematic review and meta-analysis. *Sleep Med Rev.* 2016;30:97–107.
50. Chapman JL, Vakulin A, Hedner J, Yee BJ, Marshall NS. Modafinil/armodafinil in obstructive sleep apnoea: a systematic review and meta-analysis. *Eur Respir J.* 2016;47(5):1420–1428.
51. Kuan YC, Wu D, Huang KW, et al. Effects of modafinil and armodafinil in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. *Clin Ther.* 2016;38(4):874–888.
52. Sukhal S, Khalid M, Tulaimat A. Effect of wakefulness-promoting agents on sleepiness in patients with sleep apnea treated with CPAP: a meta-analysis. *J Clin Sleep Med.* 2015;11(10):1179–1186.
53. Darwish M, Kirby M, Hellriegel ET, Robertson P Jr. Armodafinil and modafinil have substantially different pharmacokinetic profiles despite having the same terminal half-lives: analysis of data from three randomized, single-dose, pharmacokinetic studies. *Clin Drug Investig.* 2009;29(9):613–623.
54. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? *Psychol Methods.* 2006;11(2):193–206.
55. Black JE, Hull SG, Tiller J, Yang R, Harsh JR. The long-term tolerability and efficacy of armodafinil in patients with excessive sleepiness associated with treated obstructive sleep apnea, shift work disorder, or narcolepsy: an open-label extension study. *J Clin Sleep Med.* 2010;6(5):458–466.

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