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Modafinil for the treatment of attention-deficit/hyperactivity disorder: A meta-analysis

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common and a debilitating neurobehavior disorder in the pediatric population. Although numerous effective psychostimulants are available, more than 30% of patients still do not show adequate treatment response rendering diverse pharmacological options. We aimed at assessing the efficacy and safety of modafinil in the treatment of children and adolescents with ADHD by conducting a meta-analysis. An extensive search of databases and clinical trial registries resulted in five published short-term randomized, double-blind, placebo-controlled trials. Primary efficacy measures were mean change in ADHD Rating Scale-IV Home (ADHD-RS-IV Home) and School Version (ADHD-RS-IV School) from baseline to study end point. The results showed that modafinil more significantly improved ADHD-RS-IV Home (SMD, −0.77 [95%CI, −1.11 to −0.44]) and School (SMD, −0.71 [95%CI, −0.96 to −0.47]) than placebo. Dropout rate due to adverse event did not significantly differ between two groups. In terms of commonly observed side effects, modafinil showed significantly higher incidence of decreased appetite (RR = 5.02, 95% CIs, 2.55 to 9.89, P < 0.00001) and insomnia (RR = 6.16, 95% CIs, 3.40 to 11.17, P < 0.00001). Modafinil did not cause a clinically significant increase of heart rate, systolic blood pressure, and diastolic blood pressure. Although we found that modafinil may be another treatment option in children and adolescents with ADHD, the results should be interpreted and translated into clinical practice with caution, as the meta-analysis was based on a limited number of clinical trials.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD), the most prevalent neuro-behavior disorder in the pediatric population, affects 8–12% of school-aged children. ADHD is a heterogeneous disorder characterized by symptoms of inattention, hyperactivity, and impulsivity (Thapar and Cooper, 2016). It is a debilitating disorder causing impairments in academic, social, and vocational areas. The pathophysiology of ADHD is yet to be elucidated, but imbalance of noradrenergic and dopamine system especially in the frontal cortex has been suggested as the core neurobiological cause (Sharma and Couture, 2014).

In terms of pharmacological treatments, two classical psychostimulants, methylphenidate and amphetamine, have shown to be effective in ADHD by inhibiting reuptake of norepinephrine and dopamine (Greenhill et al., 2002). Despite the two effective psychostimulants available, more than 30% of patients still do not show adequate treatment response (Biederman et al., 2004). Safety of psychostimulants including cardiovascular effect, worsening of psychiatric comorbidity such as tic and Tourette, gastrointestinal symptoms, abuse potential is another concern (Cohen et al., 2015; Spencer et al., 2009). Therefore, new pharmacologic agents are needed to treat those unresponsive and intolerant to standard ADHD medications.

Modafinil, an attention-promoting agent, is pharmacologically different from those of two classical psychostimulants,

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amphetamine and methylphenidate. It is known to act on multiple areas of the ascending arousal and attention systems to increase frontal cortical activity (Lin et al., 1996). Numerous randomized clinical trials (Biederman et al., 2005; Greenhill et al., 2006) and open label studies (Boellner et al., 2006; Rugino and Copley, 2001) have shown that modafinil could be an effective and safe treatment option in ADHD. A post hoc analysis of data consisted of 3 randomized, double-blind, placebo-controlled trials (RCTs) further demonstrated that modafinil improved symptoms of ADHD compared with placebo (Wigal et al., 2006).

Meta-analysis is important, when investigating effect of a drug other than its approved conditions because it can overcome the limitations of small sample sizes, increase the generalizability of results by including many trials conducted in various populations, increase the statistical power for group comparisons, investigate potential publication biases, and quantify and analyze inconsistencies in results across clinical studies (Cohn and Becker, 2003; Han et al., 2014; Pae et al., 2015a, 2015b). Despite the importance, no meta-analysis was conducted to investigate usage of modafinil in ADHD. Therefore, we aimed to perform a meta-analysis to identify the properties of modafinil by assessing its efficacy, discontinuation rate, and side effects with respect to the treatment of children and adolescents with ADHD.

2. Materials and methods

2.1. Sources of data

PubMed, Embase, Medline, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science and the Cochrane Central Register of Controlled Trials Library, and ClinicalTrials.gov (www.clinicaltrials.gov) were repeatedly searched from March 1st to June 1st, 2016 using MeSH terms: “modafinil,” and “attention deficit disorder.” Reference lists from identified articles and reviews were manually searched to find additional studies. Two authors (S.M.W. and S.J.L.) independently reviewed the abstracts identified from the literature search. Potentially eligible papers were then re-evaluated by two other authors (C.H. and C.U.P.) to determine whether they clearly met the selection criteria. If a disagreement occurred, the article in question was discussed and a consensus was reached by the second set of review authors.

2.2. Inclusion criteria for the meta-analysis

All RCTs investigating the efficacy and safety of modafinil or its derivative armodafinil for ADHD were the primary inclusion criteria. For inclusion in our study, patients needed to meet the criteria for ADHD used in the individual trials. Studies were required to: (1) be in double-blind, randomized, and placebo controlled in design; 2) have clearly described all inclusion and exclusion criteria; 3) compared the outcomes of the use of placebo and either modafinil or armodafinil in patients with ADHD; (4) reported the doses and durations of experimental drug administration. We excluded trials that included patients over 18 years. No restrictions regarding the severity of ADHD, gender, study location, or treatment basis (i.e., inpatient or outpatient), pharmaceutical form or dose regimen were utilized.

2.3. Data extraction and quality assessment

Data-collection form was used to extract data including author's name, year of publication, sample size, patients' characteristics (mean age, gender), duration of treatment, dosage, baseline findings, study location country, and study design. Outcome data pertaining to the characteristics of the individual trial and the reported results were extracted for each trial. In addition, the quality of RCTs was also assessed as recommended by the Cochrane Review (Higgins and Green, 2008).

2.4. Study outcome

In terms of efficacy, the primary outcome measures were change from baseline to study end-point in ADHD Rating Scale-IV (ADHD-RS-IV) Home and School Version. Regarding safety and tolerability, numbers of dropouts for any reason and due to adverse events (AEs) were included. The meta-analysis also included the relationship of modafinil with commonly observed AEs such as headache, insomnia, decreased appetite, and heart rate and blood pressure changes.

2.5. Risk of bias

Two authors (C.U.P. and S.M.W.) independently assessed the risk of bias in individual studies. Any disagreement was resolved by

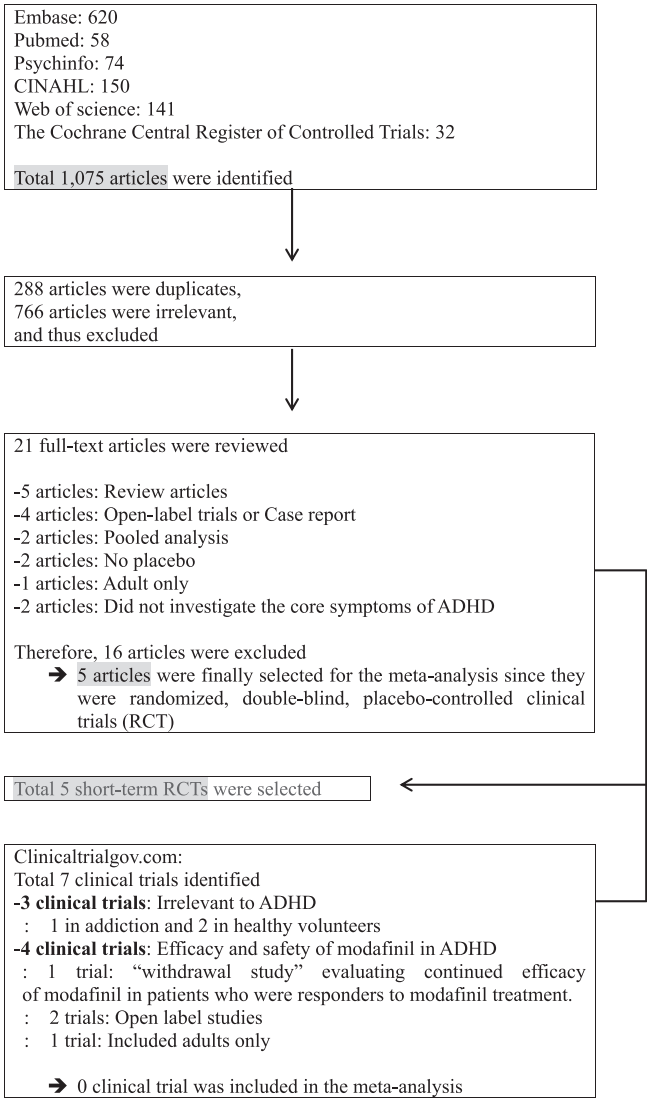

Fig. 1. Schematic presentation of studies selected in the present meta-analysis. ADHD, Attention Deficit Hyperactivity Disorder; RCT, randomized, double-blind, placebo-controlled clinical trial.

Table 1
Summary of currently available randomized, double-blind, placebo-controlled clinical trials of modafinil for the treatment of children and adolescent with attention deficit hyperactivity disorder.

Study	Drugs (mg/d)	Na	Age range	Mean age	Mean weight (kg)	Sex (F,n)	Duration (weeks)	Important inclusion criteria	ADHD-RS-IV School		ADHD- RS-IV Home		Study location
									Baseline	Mean change	Baseline	Mean change	
Biederman et al., 2005	PBO	81	6–17	10.4	41.4	21 (26)	9	IQ > 80	35.3 (8.8)	−7.3 (9.7)	36.8 (9.1)	−7 (10.1)	US
	MODA 170-425	163	6–17	8.9	43.6	51 (31)		IQ > 80	35.7 (9.3)	−15 (11.8)	37.8 (9.5)	−14.3 (12.7)	
Biederman et al., 2006	PBO	51	6–13	8.8	33.6	13 (25)	4	IQ > 80	25.4 (13.8)	−2.33 (11.79)	35.5 (8.9)	−3.45 (8.25)	US
	MODA (morning/ midday) 300/0	50	6–13	8.8	34.8	17 (34)		IQ > 80	27.3 (14.1)	−8.67 (14.14)	36.5 (10.2)	−11.27 (12.87)	
	MODA (morning/ midday) 200/100	49	6–13	9.2	36.9	10 (20)		IQ > 80	27.7 (13.5)	−8 (11.67)	37.6 (9.4)	−8.18 (11.48)	
	MODA (morning/ midday) 100/200	48	6–13	10.5	36.9	10 (21)		IQ > 80	25.5 (14.1)	−5.5 (11.55)	36.8 (9.3)	−8 (10.05)	
	MODA (morning/ midday) 200/200	50	6–13	9.9	42	13 (26)		IQ > 80	23.0 (11.4)	−5.58 (9.69)	34.0 (10.9)	−10.37 (13.08)	
Greenhill et al., 2005	PBO	66	6–17	9.9	40.9	18 (27)	9	IQ > 80	37.9 (9.0)	−9.7 (10.3)	39.3 (9.3)	−7.5 (11.8)	US
	MODA 170-425	128	6–17	9.7	39.7	36 (27)		IQ > 80	38.8 (8.9)	−17.3 (13.1)	39.3 (9.3)	−17.6 (13.3)	
Swanson et al., 2006	PBO	63	6–17	10.1	39.9	22 (34)	7	IQ > 80	36.8 (9.0)	−8.2 (10.3)	38.8 (10.6)	−7.6 (13)	US
	MODA 340-425	120	6–17	8.5	40.5	32 (26)		IQ > 80	37.7 (9.1)	−17.2 (12.8)	38.8 (9.0)	−13.8 (14.3)	
Kahbazi et al., 2009	PBO	23	6–15	9.63	29.04	6 (26)	6	IQ > 70	37.0 (NA)	−7.69 (5.04)	37.5 (NA)	−8.21 (6.15)	Iran
	MODA 200-300	23	6–15	9.63	28.6	5 (22)		IQ > 70	37.5 (NA)	−23.26 (8.15)	36.5 (NA)	−22.47 (8.92)	

MODA: Modafinil, IQ: Intelligent quotient, PBO: Placebo.

consensus among all authors. The risk of bias associated with sequence generation, allocation concealment, the blinding of participants and investigators, the blinding of outcome assessments, incomplete outcome data, selective outcome reporting, and other sources were evaluated according to the Cochrane Review's guidelines (Higgins et al., 2011).

2.6. Statistical analysis

Review Manager Version 5.3 software (Cochrane Collaboration, Oxford, UK) was used to conduct statistical analysis. For continuous measures, difference in change from baseline to follow-up between intervention and control groups are presented as the standardized mean difference (SMD) using the method developed by Hedges (Hedges g) with 95% confidence intervals (95% CIs). Regarding binary measures, the impact of the intervention was expressed as risk ratio (RR) with 95% confidence intervals (CI) using the Mantel-Haenszel method. Heterogeneity between studies was explored by the I^2 statistic. I^2 = 75%–100% indicates considerable heterogeneity, and the heterogeneity threshold was defined as 50% or

Table 2
Safety and tolerability of 5 RCTs of modafinil for the treatment of children and adolescent with attention deficit hyperactivity disorder.

Study	Drugs (mg/d)	Na	AE > 5% subjects (%)	Insomnia subjects (%)	Headache (%)	Decreased appetite (%)	Total dropout rates (%)	Dropout rates due to AE (%)	SAE	
									N	Detail
Biederman et al., 2005	PBO	82	91 (111)	3 (4)	12 (15)	3 (4)	51 (60.71)	3 (4)	1	Headache
	MODA 170-425	164	241	48 (29)	32 (20)	26 (16)	67 (40.85)	5 (3)	2	Steven Johnson, duodenitis,
Biederman et al., 2006	PBO	51	29 (57%)	1 (2)	11 (22)	1 (2)	3 (6)	0 (0)	0	
	MODA total	197	127 (64.80)	23 (11.68)	26 (13.20)	14 (7.11)	22 (11.16)	9 (4.57)	1	Dehydration
	MODA (morning/ midday) 300/0	50	36 (72)	5 (10)	7 (14)	6 (12)	6 (12)	2 (4)	0	
	MODA (morning/ midday) 200/100	49	30 (61.22)	7 (14)	6 (12)	4 (8)	4 (8)	2 (4)	0	
	MODA (morning/ midday) 100/200	48	38 (79.17)	6 (13)	6 (13)	3 (6)	8 (17)	4 (8)	0	
	MODA (morning/ midday) 200/200	50	23 (46)	5 (10)	7 (14)	1 (2)	4 (8)	1 (2)	1	Dehydration
Greenhill et al., 2005	PBO	67	69 (103)	5 (7)	6 (9)	2 (3)	26 (38.81)	4 (5.97)	0	
	MODA 170-425	131	211 (162)	37 (28)	29 (22)	23 (18)	33 (25.19)	6 (4.58)	0	
Swanson et al., 2006	PBO	64	35 (55)	0 (0)	9 (14)	1 (2)	24 (37.5)	0 (0)	0	
	MODA 340-425	125	113 (90)	30 (24)	21 (17)	18 (14)	45 (36)	12 (9.6)	0	
Kahbazi et al., 2009	PBO	23	NA	2 (8.70)	1 (4.34)	2 (8.70)	NA	NA	NA	
	MODA 200-300	23	NA	4 (17.39)	2 (8.70)	7 (30.43)	NA	NA	NA	

AE: Adverse events, MODA: Modafinil, NA: Not available, PBO: Placebo, SAE: Serious adverse events.

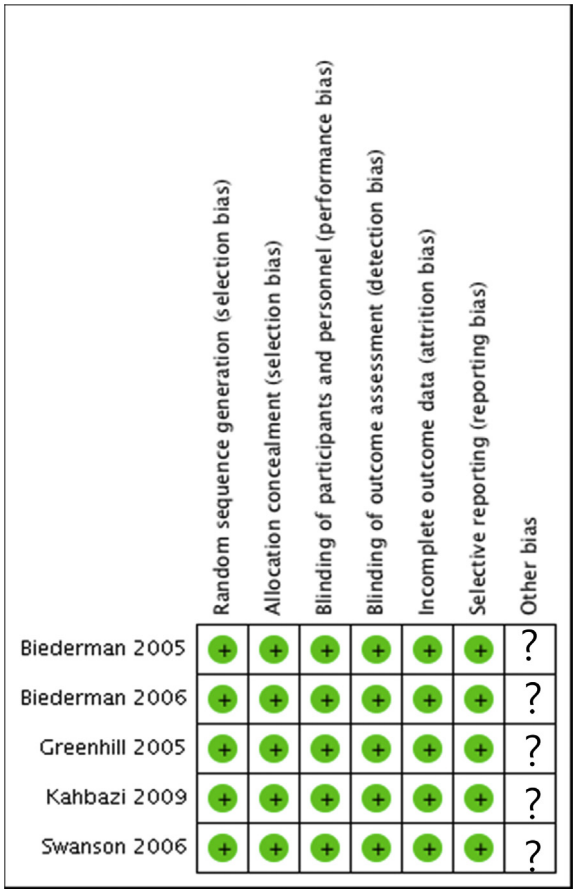

Fig. 2. Risk of bias in individual studies included in the meta-analysis.

more in I^2 value and a $P < 0.10$.

We applied fixed-effects or random-effects models appropriately. A random-effects model was used when the I^2 index reflected significant heterogeneity between the study results ($I^2 > 50\%$ and $P < 0.10$). The random-effects model is more balanced than the fixed-effects model because it allows for sampling variability with and between studies, and smaller studies are weighted more, whereas larger studies are weighted less (Brockwell and Gordon, 2001; Riley et al., 2011).

The sensitivity analyses were carried out by excluding studies successively to test the robustness of the impact of a single study on the overall results.

3. Results

3.1. Study characteristics

A total of 1075 papers were identified from the electronic searches. 1054 were excluded after a preliminary review because they were either irrelevant to our meta-analysis or duplicates. The remaining 21 studies and 7 other clinical trials were retrieved for a more detailed evaluation (Fig. 1). Of 21 studies, 5 were review articles, 4 were either open label or case studies, 2 did not have placebo treatment, 2 did not investigate core symptoms of ADHD, 2 were pooled analysis, and 1 included adults only. Of the 7 records obtained from ClinicalTrials.gov, 3 were irrelevant to the meta-analysis, 1 trial was a "withdrawal study" evaluating continued efficacy of modafinil in patients who were responders to modafinil treatment, 2 trials were open label studies, and 1 trial included adults only (Biederman et al., 2005, 2006; Greenhill et al., 2006; Kahbazi et al., 2009; Swanson et al., 2006).

The main characteristics of these 5 RCTs are presented in Tables 1 and 2. All, but one (Kahbazi et al., 2009), were multicentered studies conducted in the US. Duration of the studies was all short-term trial (≤9 weeks). Total of 927 participants were included. Among them, 287 were on placebo, and 640 were on modafinil. The doses of modafinil varied from 170 to 425 mg/day. One RCT (Biederman et al., 2006) included divided dosing regimen. All 5 studies included female subjects, with proportions ranging from 20% to 34%. Insomnia, headache, and decreased appetite were most commonly observed adverse events. Only 5 cases of serious adverse events were reported (N = 1 for placebo and N = 4 for modafinil).

3.2. Risk of bias

The risk of bias was considered low or unclear in all studies based on evaluations of all domains. In general, all studies included were good in quality in terms of their methodologies (Fig. 2). Publication bias could not be tested because there were too few studies for the various outcomes examined and all RCTs included were published studies.

3.3. Efficacy

3.3.1. ADHD-RS-IV Home and School

The result of the meta-analysis regarding the primary endpoints, ADHD-RS-IV Home and ADHD-RS-IV School, are presented as forest plots (Figs. 3 and 4). Modafinil (SMD, −0.77 [95%CI, −1.11 to −0.44]) more significantly improved ADHD-RS-IV Home scores

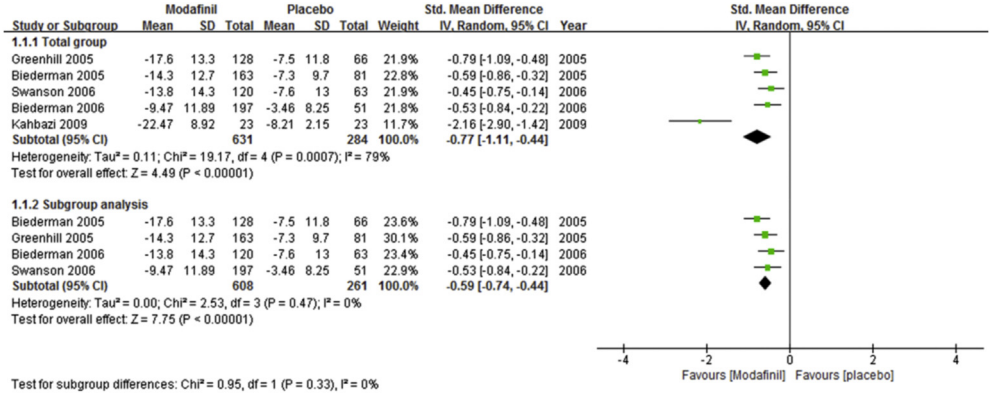

Fig. 3. Mean changes of the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV Home total score from baseline to end point between modafinil and placebo treatment groups. Abbreviations: SD, standard deviation; std, standardized; 95% CI, 95% confidence interval.

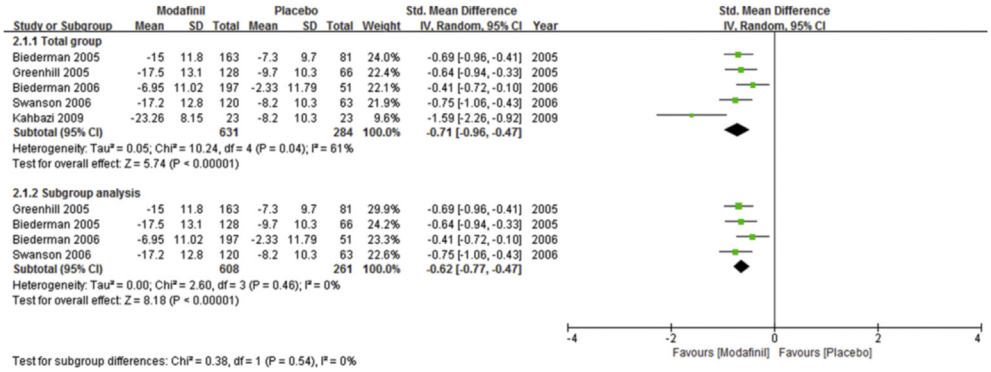

Fig. 4. Mean changes of the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV School total score from baseline to end point between modafinil and placebo treatment groups. Abbreviations: SD, standard deviation; std, standardized; 95% CI, 95% confidence interval.

than placebo. Significant heterogeneity was reported (I^2 = 79%, p = 0.0007), so we used random effects models. In addition, we tried to explain the heterogeneity by conducting a subgroup analysis (Kriston, 2013). From the forest plot, we hypothesized that the heterogeneity occurred due to lack of overlap of confidence interval caused from an outlier (Kahbazi et al., 2009). When excluding Kahbazi et al.'s study, there was no heteriogenity (I^2 = 0%, p = 0.33) while maintaining significant superiority of modafanil over placebo (SMD, −0.59 [95%CI, −0.74 to −0.44]) (Fig. 3).

Same trend was observed with ADHD-RS-IV School. The heterogeneity among studies was significant (I^2 = 61%, p = 0.04), so random effects models were utilized. Extraction of Kahbazi et al.'s study removed heteriogenity (I^2 = 0%, p = 0.46). Modafinil retained superior efficacy over placebo in both total (SMD, −0.71 [95% CI, −0.96 to −0.47]) and subgroup analysis (SMD, −0.62 [95% CI, −0.77 to −0.47]) (Fig. 4).

3.4. Safety and tolerability

One study (Kahbazi et al., 2009) did not provide results regarding discontinuation rate. Total dropout rate was significantly lower in modafinil group than in control group (RR = 0.77, 95% CIs, 0.63 to 0.93, P = 0.006); however, dropout rate due to adverse event did not significantly differ between two groups (Fig. 5). In terms of commonly observed side effects, modafinil showed significantly higher incidence of decreased appetite (RR = 5.02, 95% CIs, 2.55 to 9.89, P < 0.00001) and insomnia (RR = 6.16, 95% CIs, 3.40 to 11.17, P < 0.00001). The rate of headache (RR = 1.26, 95% CIs, 0.90 to 1.75, P = 0.18) did not significantly differ between two groups (Fig. 6). Modafinil did not cause a clinically significant increase of heart rate, systolic blood pressure, and diastolic blood pressure (Fig. 7).

4. Discussion

Despite multiple pharmacological agents available, a large proportion of children and adolescents with ADHD do not gain adequate response (Bond et al., 2012). Modafinil and the classical psychostimulants, methylphenidate and amphetamine, have overlapping mechanism of action; all of them promoting attention (Kumar, 2008). Thus, our primary research question was aimed at assessing the efficacy and safety of modafinil in the treatment of children and adolescents with ADHD. We found 5 RCTs, and the meta-analysis showed statistically superior efficacy of modafinil compared with placebo for the treatment of children and adolescents with ADHD. In terms of primary efficacy measures, mean change in ADHD-RS-IV Home and School, the difference between placebo and modafinil were moderate and very close to large

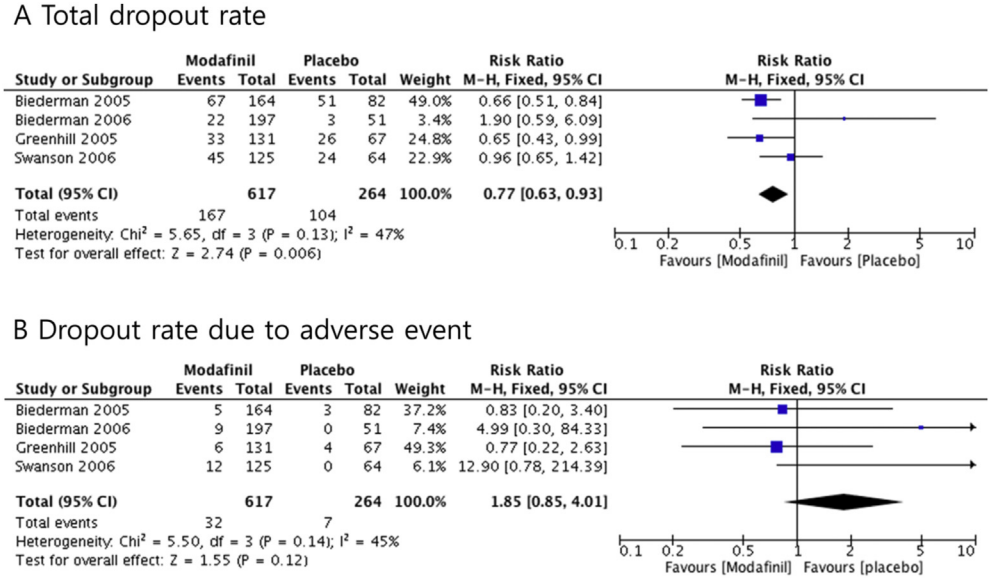

Fig. 5. Effect of modafinil on study discontinuation due to all causes (A) and adverse events (B).

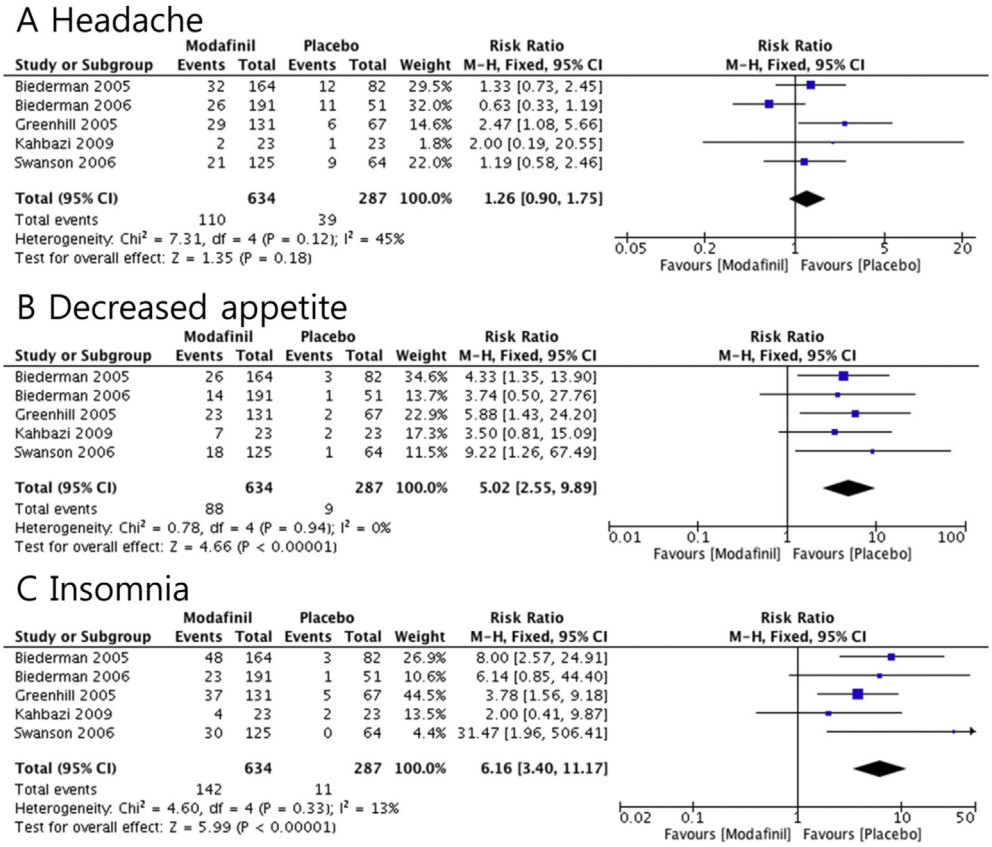

Fig. 6. Effect of modafinil on headache (A), decreased appetite (B), and insomnia (C).

(SMD = −0.77 for ADHD-RS-IV Home and SMD = −0.71 for ADHD-RS-IV School). The effect sizes in the present study were comparable to those from previous meta-analysis investigating multiple drugs, where the effects sizes were found to be varied 0.6 through 0.8 indicating a robust medication effects in the treatment of ADHD despite methodological and medication bias factors (Storebø et al., 2015). Again, such results are quite similar to present meta-analysis indicating a similar efficacy of modafinil compared with different

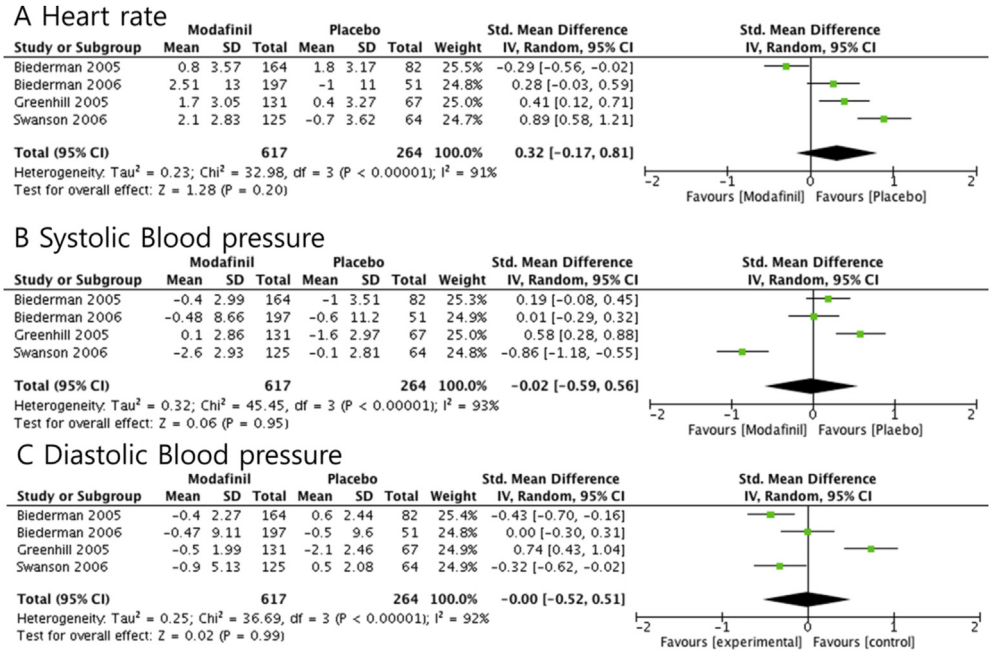

Fig. 7. Effect of modafinil on heart rate (A), systolic blood pressure (B), and diastolic blood pressure (C).

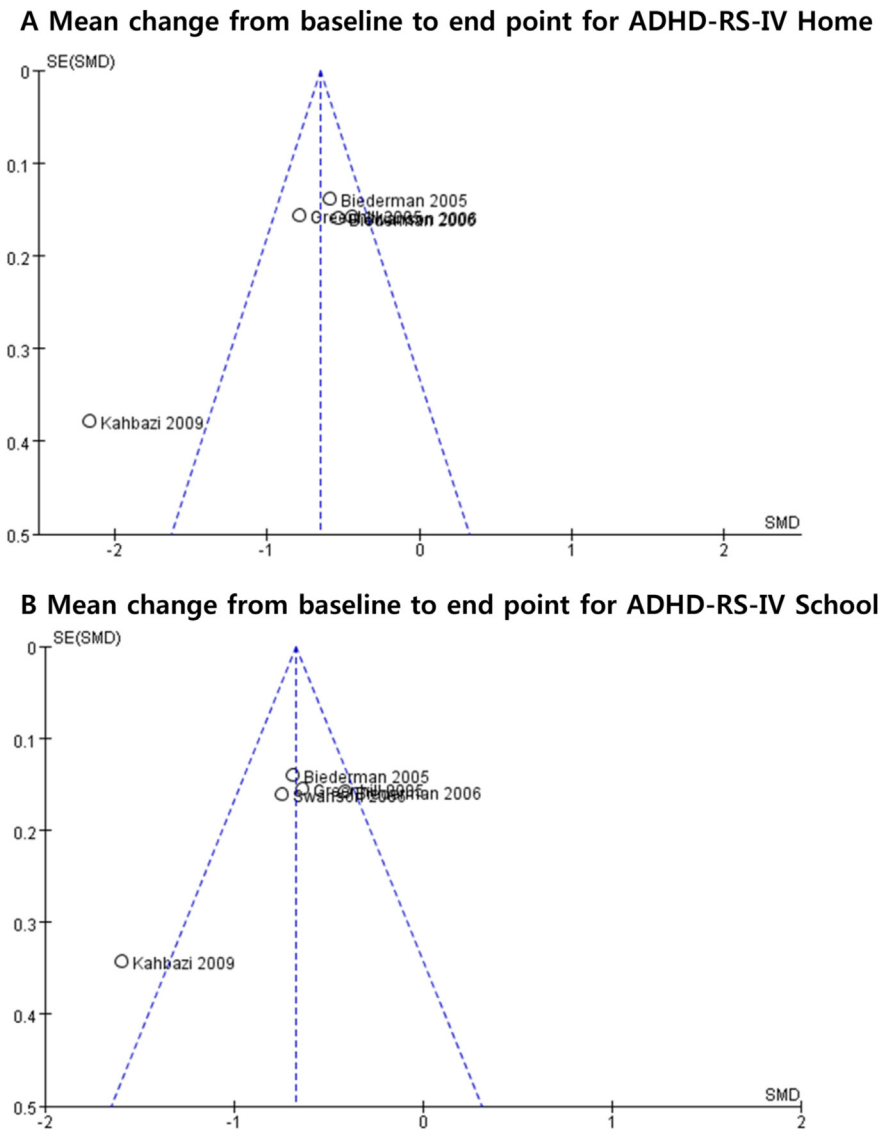

Fig. 8. Funnel plot primary endpoint ADHD-RS-IV Home (A) and ADHD-RS-IV School (B).

ADHD medications for treating ADHD main symptoms. However, we have to note that effect size of medications' efficacy had a trend to be influenced by medication types (i.e., nonstimulant medications < immediate-release/long-acting stimulants) in addition to study design and primary endpoint score (i.e., crossover > parallel designs). Therefore, future controlled clinical trials should bear these potential clinical factors in mind to overcome such methodological issues.

In terms of safety and tolerability, modafinil was generally well tolerated. Interestingly, the total dropout rate of modafinil was significantly lower than that of placebo. However, the results should be interpreted cautiously because the risk ratio (RR = 0.77, 95% CIs, 0.63 to 0.93, P = 0.006) was quite small. Furthermore, such a result was mainly due to a single study by Biederman and colleagues (Biederman et al., 2005). In the other hand, discontinuation due to adverse events did not differ between two groups although favorable trend of placebo over modafinil was observed. Previous meta-analyses, of modafinil in other psychiatric conditions, suggested that modafinil's dropout rate due to all cause and adverse event is either comparable to or worse than placebo (Andrade et al., 2015; Chapman et al., 2016; Kuan et al., 2016). Further studies should be performed to shed light on this important issue.

Above all, most of side effects observed in both groups were mild or moderate in severity. In line with numerous meta-analysis (Andrade et al., 2015; Chapman et al., 2016; Kuan et al., 2016), modafinil showed significantly higher incidence of decreased appetite (OR = 5.87, 95% CIs, 2.86 to 12.04, P < 0.00001) and insomnia (OR = 6.16, 95% CIs, 3.40 to 11.17, P < 0.00001). Although rate of headache did not significantly differ between two groups, a trend favoring placebo over modafinil was noted. Changes in blood pressure and heart rate between the two groups were not statistically different. However, regular monitoring of blood pressure changes in patients treated with modafinil should be considered because multiple studies suggest its cardiovascular risks (Chapman et al., 2016; Sharma and Couture, 2014).

The present study has major strengths. To the best of our knowledge, this is the first meta-analysis to evaluate the benefits and AEs of modafinil in patients with ADHD. All RCTs included were very carefully designed. The demographics of the studies including age range, mean age, gender ratio, and inclusion criteria were comparable reducing clinical heterogeneity among included studies. In addition, all five trials used ADHD-RS-IV Home and

School as their important efficacy measures. Finally, the magnitude of the difference on the primary endpoint between modafinil and placebo treatments was relatively large. Thus, the difference was observed regardless of using fixed or random effect model.

Despite the major strength of this analysis, the present study also has numerous limitations. The main limitations of our study arose from the relatively small studies included. Our results were based on a total of 5 RCTs with a pooled sample size (modafinil and placebo) of only 927 patients. Therefore, we only combined all doses of modafinil and were unable to undertake meta-regression to understand its dose related efficacy and safety. Second, we were not able to find unpublished trials, so all studies included were published studies from major contemporary databases. In addition, funnel plots of the primary endpoints, ADHD-RS-IV Home and ADHD-RS-IV School, showed asymmetrical distribution (Fig. 8). Thus, there is a possibility of publication bias. However, the asymmetry of the funnel plots occurred because of one small study, so more RCTs are needed to properly evaluate publication bias. Third, previous researches have repeatedly shown that pharmaceutical industry sponsorship in drug studies is associated with favorable results to the sponsor's product (Bero, 2013; Lexchin et al., 2003; Lundh et al., 2012). In this perspective, there might have been by industry bias because pharmaceutical company owning Provigil (brand name of modafinil), Cephalon, was involved in 4/5 RCTs. One study was financially sponsored by Cephalon (Biederman et al., 2005), while employees of Cephalon were involved as co-authors in the 3 other trials (Biederman et al., 2006; Greenhill et al., 2005; Swanson et al., 2006). Fourth, the study also lacks long-term data, so we were not able to investigate long-term safety, especially the potential of abuse and addiction. Finally, except for one (Kahbazi et al., 2009), all studies were conducted in the US raising the generalizability issues.

5. Conclusion

We found that modafinil may be another treatment option in children and adolescents with ADHD. However, the present results should be interpreted and translated into clinical practice cautiously because study contained small number of short-term RCTs. Adequately powered, well-designed, head-to-head clinical trials should also more clearly address the comparative efficacy of modafinil and classical psychostimulants before it can be recommended in the clinical practice.

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Conflicts of interest

All authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Contributors

All authors designed the study. C. Pae, S.-M. Wang, C. Han and S.-J. Lee acquired and analyzed the data, which P. Masand, T.Y. Jun and A. Patkar also analyzed. C. Pae, S.-M. Wang, C. Han, S.-J. Lee and A. Patkar wrote the article, which all authors reviewed and approved for publication.

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