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Assessing Condition-Specific Adverse Event Profiles of Modafinil for Labelled and Off-Label Uses: A Systematic Review and Meta-Analysis

Jaehee Jung[1] | Jaeyoon Youm[2] | Jihyun Kang[3] | Ah-Young Kim[4] | Jae Kyung Suh[5] | Hye-Young Kang[1]

[1]College of Pharmacy, Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon, South Korea | [2]Department of Pharmaceutical Medicine & Regulatory Sciences, College of Medicine and College of Pharmacy, Yonsei University, Incheon, South Korea | [3]Graduate Program of Industrial Pharmaceutical Science, Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon, South Korea | [4]College of Pharmacy, Ewha Womans University, Seoul, South Korea | [5]National Evidence-based Healthcare Collaborating Agency (NECA), Seoul, South Korea

Correspondence: Hye-Young Kang (hykang2@yonsei.ac.kr)

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ABSTRACT

Modafinil is approved for excessive daytime sleepiness in narcolepsy, obstructive sleep apnoea (OSA), and shift work sleep disorder (SWSD), but its widespread off-label use raises safety concerns. We evaluated the risk of adverse events (AEs) associated with both labelled and off-label use of modafinil. A systematic search of PubMed, Embase, and Cochrane identified 54 studies that met the inclusion criteria. In labelled uses, narcolepsy patients had significantly elevated risks of diarrhoea (risk ratio [RR]: 2.16, 95% confidence interval [CI]: 1.06–4.41) and nausea compared to those with placebo (RR: 2.44, 95% CI: 1.05–5.72). OSA/hypopnea syndrome patients had higher risks of insomnia (RR: 5.82), anxiety/nervousness (RR: 3.26), and headache (RR: 1.92). SWSD patients had elevated risks of insomnia (RR: 4.09), anxiety/nervousness (RR: 3.85), and nausea (RR: 2.93). Among off-label users, patients with attention deficit hyperactivity disorder had higher risks of insomnia (RR: 4.97) and decreased appetite (RR: 4.21). Patients with major depressive disorder showed higher risks of anxiety/nervousness (RR: 1.95). While modafinil users share common AEs, specific risks vary across patient groups. Our findings on condition-specific AE profiles would support cautious prescribing of modafinil and careful consideration of alternative treatments.

1 | Introduction

Modafinil is approved for treating excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnoea (OSA), and shift work sleep disorder (SWSD) [1]. Although the exact mechanism remains unclear, it is hypothesised that modafinil promotes wakefulness through weakly inhibiting the dopamine transporter and reducing dopamine reuptake, according to the Guide-to-Pharmacology [2]. In addition to its approved use, modafinil has been widely utilised off-label to treat attention-deficit/hyperactivity disorder (ADHD) [3], depression [4] and substance use disorder [5]. Moreover, there have been ongoing studies exploring its potential applications in healthy individuals who require sustained concentration despite fatigue, such as pilots [6], healthcare professionals working in rotating shifts [7] and chess players [8].

According to the Medication Guide issued by the Ministry of Food and Drug Safety (MFDS) in South Korea [9], common adverse events (AEs) (1%–<10%) associated with modafinil use in adults experiencing somnolence related to narcolepsy include nervousness, insomnia, anxiety, depression, abdominal pain, nausea, dry mouth, diarrhoea, blurred vision, anorexia and back pain. Similarly, the US Food and Drug Administration (FDA)

Plain Language Summary

Modafinil is a medication used to help people stay awake, especially those with sleep disorders. However, it is also widely used for other conditions, such as ADHD or depression, where it is not officially approved. We reviewed data from 54 research papers to understand the adverse events of modafinil. We found that while users share some common adverse events, specific risks vary depending on why the drug is being used. These findings suggest that doctors should consider the patient's specific condition when prescribing modafinil.

prescribing information for modafinil reveals that the most frequently reported AEs (≥ 5%) when used to treat narcolepsy, OSA and SWSD include headache, nausea, nervousness, rhinitis, back pain, anxiety, insomnia, dizziness and dyspepsia [10].

The widespread use of modafinil and its frequent AEs have prompted several systematic reviews and meta-analyses compiling AE data from randomised controlled trials (RCTs) for both labelled indications, such as narcolepsy and OSA, and off-label uses, including ADHD [11] and poststroke care [12]. However, the available safety information from official sources primarily relates to studies examining labelled indications, with a lack of comprehensive analyses of AEs in the use of off-label indications.

Therefore, this study aims to conduct a comprehensive and systematic review of the literature to identify the AE profiles of modafinil in both labelled and off-label use. Additionally, we performed subgroup analyses based on the underlying medical conditions to investigate potential variations in the types and frequencies of AEs across different patient populations. Through these analyses, we expect to provide a clearer understanding of modafinil's safety profile, highlighting specific AEs associated with distinct clinical groups and emphasizing the need for close monitoring when prescribing modafinil.

2 | Material and Methods

The systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [13] (Supplementary Table 1). The study was registered in PROSPERO (CRD42024628988), which is available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024628988.

2.1 | Literature Search

The literature search was conducted using three databases (i.e., PubMed, Embase, and Cochrane) to identify articles published up to January 6, 2025. Key search terms were employed, utilizing logical combinations of MeSH and Emtree terms. To ensure comprehensive inclusions, no restrictions were placed on the study population (patients). Modafinil was designated as the intervention (intervention), placebo as the control (comparison), and 12 specific AEs as the outcomes (outcome): headache, decreased appetite, abdominal pain, nausea, anxiety/nervousness, dizziness, insomnia, weight loss, diarrhoea, dyspepsia, back pain, and rhinitis. These AEs, each reported with a frequency of 5% or higher, were sourced from Lexicomp online (https://online.lexi.com/lco/action/home), a reputable and up-to-date medical information resource. This approach ensures the inclusion of the most current and clinically relevant AE data associated with modafinil. The search process involved all synonyms and equivalents of the intervention and outcome terms using the OR operator, and these groups were then combined by the AND operator. Detailed search terms for each database are presented in Supplementary Table 2–4.

2.2 | Literature Selection and Exclusion

Three researchers (JJ, JY and JK) independently selected and excluded articles based on predetermined criteria. Disagreements were resolved through discussion. All RCTs and crossover studies involving modafinil and placebo groups were included, while systematic reviews, meta-analyses and case reports were excluded. Initially, studies reporting AEs related to modafinil, following 'patients,' 'intervention,' 'comparator,' and 'outcome' (PICO) search formula, were selected for comprehensive coverage. A final selection process was then applied based on primary and secondary exclusion criteria. Duplicated articles were removed, and primary exclusions were made based on title and abstracts, eliminating studies that were unrelated to modafinil; did not involve human subjects; were incomplete publications (e.g., posters, abstracts); were review articles or case reports; lacked full-text availability; and were duplicates. In the secondary exclusion stage, full-text articles were reviewed and excluded if they lacked an RCT design; had no placebo control group; did not report AEs; reported AEs but without the exact number of subjects; were incomplete publications; involved nonhuman studies; and were duplicates.

2.3 | Data Extraction and Quality Assessment

Key information from selected articles, including the first author, publication year, study design, drug dosage, indication, number of patients with AEs, and specific AE types, was extracted and presented in Table 1. Study quality was assessed using the Cochrane Risk of Bias 2.0 tool [63], which evaluates bias in RCTs across multiple domains, assigning ratings of high, low or unclear risk of bias. Two researchers independently performed the quality assessments, resolving disagreements through discussion.

2.4 | Statistical Analysis

For conducting the meta-analysis, we employed the Mantel–Haenszel method utilising a random effects model [64]. The risk ratio (RR) of modafinil's association with each AE was calculated using the equation below. To assess the heterogeneity among the included literature, I^2 values were computed. All statistical analyses were conducted using Review Manager ver. 5.3 software and the findings were visually represented using forest plots

TABLE 1 | Characteristics of the included studies for systematic literature review and meta-analysis.

No	Author(s), year	Study design	Intervention (unit: mg)	Underlying disease	Total number of patients for AE evaluation	Number of patients experiencing each type[a] of AE											
						1	2	3	4	5	6	7	8	9	10	11	12
1	Abolfazli et al., 2011 [4]	RCT	–Fluoxetine + modafinil 200/200 –Fluoxetine + placebo	MDD	M: 23 P: 23	M: 5 P: 5	M: 6 P: 4		M: 4 P: 4	M: 7 P: 5		M: 7 P: 5					
2	Adler et al., 2003 [14]	Cross-over RCT	–Placebo→modafinil 200 –Modafinil 200→placebo	Parkinson's disease	M: 10 P: 10	M: 0 P: 1				M: 0 P: 1		M: 1 P: 0				M: 0 P: 1	
3	Arbabi et al., 2012 [15]	RCT	–Risperidone + modafinil 100 –Risperidone + placebo	Schizophrenia	M: 23 P:23	M: 5 P: 3			M: 6 P: 4		M: 5 P: 3	M: 4 P: 3					
4	Baakman et al., 2019 [16]	Cross-over RCT	–Modafinil 200 –Placebo	Healthy	M: 13 P: 36	M: 5 P: 6		M: 1 P: 1	M: 1 P: 1	M: 3 P: 1	M: 0 P: 3						M: 2 P: 3
5	Biederman et al., 2005 [17]	RCT	–Modafinil 170–425 –Placebo	Children and adolescents with ADHD	M: 164 P: 82	M: 32 P: 12	M: 26 P: 3	M: 12 P: 9		M: 7 P: 5		M: 48 P: 3					M: 16 P: 9
6	Biederman et al., 2006 [18]	RCT	–Modafinil 200/200 –Modafinil 200/100 –Modafinil 100/200 –Modafinil 300/0 –Placebo	Children and adolescents with ADHD	M 200/200: 50 M 200/100: 49 M 100/200: 48 M 300/0: 50 P: 51	M: 26 P: 11	M: 14 P: 1	M: 18 P: 4				M: 23 P: 1					M: 9 P: 2
7	Black and Hirshkowitz, 2005 [19]	RCT	–Modafinil 400 –Modafinil 200 –Placebo	OSA/HS	M 400: 99 M 200: 103 P: 103	M: 50 P: 13			M: 20 P: 23	M: 26 P: 4	M: 11 P: 3	M: 11 P: 1		M: 13 P: 8			M: 11 P: 8
8	Black and Houghton, 2006 [20]	RCT	–Placebo –Modafinil 200~600	Narcolepsy	M: 63 P: 56	M: 7 P: 12			M: 2 P: 1	M:1 P: 2	M: 2 P: 3			M: 2 P: 0			M: 3 P: 4
9	Chapman et al., 2014 [21]	Cross-over RCT	–Modafinil 200 –Placebo	OSA	26 Crossover	M: 0 P: 1			M: 2 P: 1	M: 0 P: 1		M: 5 P: 0					
10	Chitsaz et al., 2024 [22]	RCT	–Modafinil 200 –Placebo	Parkinson's disease	M: 22 P: 11	M: 1 P: 1			M: 1 P: 0								

(Continues)

TABLE 1 | (Continued)

No	Author(s), year	Study design	Intervention (unit: mg)	Underlying disease	Total number of patients for AE evaluation	Number of patients experiencing each type[a] of AE											
						1	2	3	4	5	6	7	8	9	10	11	12
11	Czeisler et al., 2005 [23]	RCT	–Modafinil 200 –Placebo	SWSD	M: 96 P: 108	M: 25 P: 21		M: 6 P: 2	M: 9 P: 3	M: 6 P: 1		M: 6 P: 0					M: 3 P: 7
12	Dauvilliers et al., 2013 [24]	RCT	–Placebo –Modafinil 100~400	Narcolepsy	M: 33 P: 30	M: 6 P: 6		M: 7 P: 0	M:1 P: 2	M: 2 P: 0	M:4 P: 0			M: 4 P: 0			
13	DeBattista et al., 2003 [25]	RCT	–Antidepressants + modafinil ~400 –Antidepressants + placebo	MDD	M: 69 P: 67	M: 15 P: 8			M: 3 P: 5	M: 19 P: 7		M: 13 P: 9		M: 5 P: 5			M: 5 P: 4
14	DeVito et al., 2022 [26]	RCT	–Modafinil ~400 + CM –Modafinil ~400 + YC –Placebo+CM –Placebo+YC	Substance use disorder	M: 42 P: 43	M: 10 P: 9	M: 5 P: 3			M: 13 P: 6		M: 13 P: 7					
15	Dunlop et al., 2007 [27]	RCT	–Modafinil 100~200 –Placebo	MDD	M: 34 P: 31	M: 11 P: 6	M: 4 P: 2		M: 6 P: 8	M: 5 P: 3		M: 3 P: 6		M: 7 P: 8			
16	Erman and Rosenberg, 2007 [28]	RCT	–Modafinil 300 –Modafinil 200 –Placebo	SWSD	M 300: 90 M 200: 87 P: 86	M: 38 P: 16	M: 8 P: 0		M: 22 P: 4	M: 12 P: 2		M: 12 P: 2					
17	Evans et al., 2023 [29]	Cross-over RCT	–Modafinil 300 –Placebo	Healthy	M: 19 P: 20	M: 1 P: 0		M: 1 P: 0	M: 3 P: 0	M: 0 P: 1		M: 1 P: 0		M: 1 P: 0			
18	Fava et al., 2005 [30]	RCT	–SSRI + modafinil 100~200 –SSRI + placebo	MDD	M: 158 P: 153	M: 21 P: 24			M: 15 P: 3		M: 11 P:3	M: 7 P: 7		M: 6 P: 10			M: 9 P: 5
19	Franke et al., 2017 [8]	Cross-over RCT	–Modafinil 400 –Placebo	Healthy	39 Crossover	M: 7 P: 1						M: 9 P: 1					
20	Freudenreich et al., 2009 [31]	RCT	–Modafinil 300 –Placebo	Schizophrenia	M: 19 P: 16	M: 2 P: 0		M: 1 P: 2			M: 2 P: 2						
21	Fry et al., 1998 [32]	RCT	–Modafinil 400 –Modafinil 200 –Placebo	Narcolepsy	M 400: 95 M 200: 96 P: 92	M: 98 P: 33	M: 9 P: 1		M: 24 P: 5	M: 18 P: 5		M: 3 P: 1		M: 14 P: 4	M: 10 P: 8	M:16 P: 3	M: 21 P: 11

(Continues)

TABLE 1 | (Continued)

No	Author(s), year	Study design	Intervention (unit: mg)	Underlying disease	Total number of patients for AE evaluation	Number of patients experiencing each type[a] of AE											
						1	2	3	4	5	6	7	8	9	10	11	12
22	Gill et al., 2006 [33]	Cross-over RCT	–Modafinil 200 → placebo –Placebo → modafinil 200	Healthy	25 Crossover	M: 2 P: 0			M: 1 P: 0	M: 4 P: 0	M: 1 P: 0			M: 0 P: 1			
23	Greenhill et al., 2006 [3]	RCT	–Modafinil 170–425 –Placebo	Children and adolescents with ADHD	M: 131 P: 67	M: 29 P: 6	M: 23 P: 2	M: 16 P: 3	M: 6 P: 2	M: 7 P: 3		M: 37 P: 5	M: 7 P: 0				M: 10 P: 7
24	US Modafinil in Narcolepsy Multicenter Study Group, 2000 [34]	RCT	–Modafinil 400 –Modafinil 200 –Placebo	Narcolepsy	M 400: 89 M 200: 89 P: 93	M: 85 P: 41			M: 23 P: 2	M: 12 P: 7				M: 16 P: 4	M: 16 P: 6	M: 19 P: 13	M: 18 P: 3
25	Gurtman et al., 2008 [35]	Cross-over RCT	–Modafinil 300 –Placebo	Healthy	16 Crossover	M: 4 P: 6		M: 2 P: 1	M: 0 P: 1		M: 1 P: 1						
26	Heinzerlinget al., 2010 [5]	RCT	–Modafinil 400 –Placebo	Substance use disorder	M: 34 P: 37	M: 11 P: 7			M: 7 P: 4			M: 10 P: 7					
27	Högl et al., 2002 [36]	Cross-over RCT	–Modafinil 100~200 –Placebo	Parkinson's disease	15 Crossover						M: 1 P: 0	M: 1 P: 1		M: 2 P: 1			
28	Inoue et al., 2013 [37]	RCT	–nCPAP + modafinil 200 –nCPAP + placebo	OSA	M: 52 P: 62	M: 6 P: 4		M: 0 P: 2				M: 2 P: 0					
29	Inoue et al., 2021 [38]	RCT	–Modafinil 200 –Placebo	Idiopathic hypersomnia without long sleep time	M: 34 P: 37	M: 6 P: 3	M: 2 P: 0		M:3 P: 0				M: 2 P: 0	M: 2 P: 0			
30	Jha et al., 2008 [39]	Cross-over RCT	–Modafinil ~400 –Placebo	Traumatic brain injury	51 Crossover	M: 15 P: 10			M: 3 P: 1		M: 4 P: 2	M: 10 P: 2					M: 1 P: 3
31	Kahbazi et al., 2009 [40]	RCT	–Modafinil 200–300 –Placebo	Children and adolescents with ADHD	M: 23 P: 23	M: 2 P: 1	M: 7 P: 2	M: 2 P: 1	M: 2 P: 2	M: 2 P: 2		M: 4 P: 2	M: 2 P: 1				

(Continues)

TABLE 1 | (Continued)

No	Author(s), year	Study design	Intervention (unit: mg)	Underlying disease	Total number of patients for AE evaluation	Number of patients experiencing each type[a] of AE											
						1	2	3	4	5	6	7	8	9	10	11	12
32	Kaiser et al., 2010 [41]	RCT	-Modafinil 100–200 –Placebo	Traumatic brain injury	M:10 P:10		M: 0 P: 1	M: 1 P: 0									
33	Kampman et al., 2015 [42]	RCT	–Modafinil 300 –Placebo	Substance use disorder	M: 47 P: 47	M: 6 P: 7				M: 7 P: 2		M: 10 P: 3					
34	Lundorff et al., 2009 [43]	Cross-over RCT	–Modafinil 200 –Placebo	Advanced cancer	M: 26 P: 28 Crossover	M: 6 P: 4			M: 8 P: 12	M: 3 P: 9				M: 3 P: 4			
35	Mayer et al., 2015 [44]	RCT	–Modafinil 100 –Placebo	Idiopathic hypersomnia without long sleep time	M: 17 P: 14	M: 8 P: 1					M: 1 P: 0					M: 1 P: 0	
36	Müller et al., 2013 [45]	RCT	–Modafinil 200 –Placebo	Healthy	M: 32 P: 32	M: 1 P: 0											
37	Murphy et al., 2008 [46]	Cross-over RCT	–Modafinil 50~100 –Placebo	Children with cerebral palsy	9 Crossover	M: 0 P: 1	M: 1 P: 0					M: 1 P: 0					
38	Ondo et al., 2005 [47]	RCT	–Modafinil 200–400 –Placebo	Parkinson's disease	M: 20 P: 20				M: 1 P: 0	M: 1 P: 0	M: 1 P: 0					M: 1 P: 0	
39	Orlikowski et al., 2009 [48]	RCT	–Modafinil 300 –Placebo	Myotonic muscular dystrophy in adults	M: 13 P: 15	M: 0 P: 1			M: 0 P: 2		M: 0 P: 1	M: 1 P: 0	M: 1 P: 0	M: 1 P: 0			
40	Pack et al., 2001 [49]	RCT	–Modafinil 200~400 –Placebo	OSA/HS	M: 77 P: 80	M: 18 P: 9			M: 5 P: 3	M: 14 P: 3	M: 5 P: 2	M: 4 P: 1					M: 6 P:2
41	Poulsen et al., 2015 [50]	RCT	–Modafinil ~400 –Placebo	Poststroke	M: 20 P: 20	M: 0 P: 2					M: 5 P: 0	M: 4 P: 3					
42	Rabkin et al., 2010 [51]	RCT	–Modafinil 50~200 –Placebo	HIV/AIDS	M: 62 P: 53	M: 4 P: 3			M: 2 P: 0	M: 1 P: 0		M: 3 P: 1					
43	Roerig et al., 2009 [52]	RCT	–Olanzapine + modafinil 200 –Olanzapine + placebo	Healthy	M: 22 P: 28	M: 8 P: 9											

(Continues)

TABLE 1 | (Continued)

No	Author(s), year	Study design	Intervention (unit: mg)	Underlying disease	Total number of patients for AE evaluation	Number of patients experiencing each type[a] of AE											
						1	2	3	4	5	6	7	8	9	10	11	12
44	Rugino and Samsock, 2003 [53]	RCT	–Modafinil 100 –Placebo	Children and adolescents with ADHD	M: 11 P: 11	M: 1 P: 0	M: 0 P: 1	M: 2 P: 0									
45	Saletu et al., 2005 [54]	Cross-over RCT	–Modafinil 200~400 –Placebo	Narcolepsy	16 Crossover	M: 8 P: 7			M: 2 P: 2		M: 4 P: 6					M: 1 P: 2	
46	Schmitz et al., 2012 [55]	RCT	–Modafinil 400 –Placebo	Substance use disorder	M: 20 P: 16					M: 9 P: 8							
47	Shearer et al., 2009 [56]	RCT	–Modafinil 200 –Placebo	Substance use disorder	M: 38 P: 42	M: 9 P: 6		M: 5 P: 3	M: 5 P: 6	M: 3 P: 0		M: 12 P: 17	M: 2 P: 8				
48	Silveira et al., 2017 [57]	RCT	–Modafinil 200~500 –Placebo	Primary biliary cirrhosis	M: 17 P: 19	M: 1 P: 3			M: 0 P: 1			M: 0 P: 1		M: 1 P: 1			
49	Spathis et al., 2014 [58]	RCT	–Modafinil 100~200 –Placebo	Lung cancer	M: 104 P: 103	M: 23 P: 25			M: 16 P: 20	M: 9 P: 10							
50	Sugden et al., 2012 [7]	RCT	–Modafinil 200 –Placebo	Healthy	M: 20 P: 19	M: 2 P: 1			M: 2 P: 1		M: 0 P: 1			M: 1 P: 0			
51	Swanson et al., 2006 [59]	RCT	–Modafinil 340~425 –Placebo	Children and adolescents with ADHD	M: 125 P: 64	M: 21 P: 9	M: 18 P: 1	M: 12 P: 5				M: 30 P: 0					M: 5 P: 5
52	Tyne et al., 2010 [60]	RCT	–Modafinil ~400 –Placebo	Parkinson's disease	M: 6 P: 7	M: 1 P: 2			M: 0 P: 1	M: 1 P: 0	M: 0 P: 1				M: 0 P: 1	M: 1 P: 1	
53	Vasconcelos et al., 2007 [61]	Cross-over RCT	–Modafinil 400 –Placebo	Postpolio syndrome	M: 36 P: 36	M: 2 P: 1	M: 2 P: 0	M: 3 P: 0		M: 4 P: 0		M: 4 P: 1		M: 0 P: 1			
54	Wintzen et al., 2007 [62]	Cross-over RCT	–Modafinil 400 –Placebo	Myotonic dystrophy	13 Crossover	M: 1 P: 0											

Abbreviations: AE = adverse event, ADHD = attention deficit hyperactivity disorder, CM = contingency management, HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome, HS = hypopnea syndrome, M = modafinil, MDD = major depressive disorder, nCPAP = nasal Continuous Positive Airway Pressure, OSA = obstructive sleep apnoea, P = placebo, RCT = randomised controlled trial, SSRI = Selective Serotonin Reuptake Inhibitor, SWSD = shift work sleep disorder, YC = yoked-control.

[a]1: headache, 2: decreased appetite, 3: abdominal pain, 4: nausea, 5: anxiety/nervousness 6: dizziness, 7: insomnia, 8: weight loss, 9: diarrhoea, 10: dyspepsia, 11: back pain, 12: rhinitis.

Risk ratio = incidence rate of an AE in modafinil group/ incidence rate of an AE in placebo group

Publication bias was assessed using funnel plots and Egger's test. In accordance with the Cochrane Handbook [65], we performed Egger's test only for meta-analyses that included 10 or more results. Funnel plots were generated using Review Manager ver. 5.3 software, and Egger's test was conducted using the metafor package in R studio version 4.4.3.

3 | Results

3.1 | Characteristics of the Included Literature

A comprehensive international literature search was conducted, resulting in 7665 articles identified from three databases: PubMed (534 articles), Embase (6622 articles) and Cochrane (509 articles). After removing duplicated articles, 6937 articles remained. We further excluded 6228 articles during the initial screening of titles and abstracts. A total of 709 articles remained, and 462 duplicated articles were removed. The full texts of the remaining 247 articles were thoroughly examined, resulting in the exclusion of 193 articles. The number of articles excluded for each criterion is shown in Figure 1. Ultimately, 54 articles met the inclusion criteria and were included in the analysis.

3.2 | Results of Quality Assessment and Publication Bias

As all included studies were RCTs, bias related to randomisation or blinding generally showed low risk. Ten studies had a high risk of attrition bias, mostly due to the lack of intention to treat (ITT) analysis (Supplementary Figures 1–25). Funnel plots showed no major asymmetry in the overall analyses. However, Egger's test indicated statistically significant (<0.05) asymmetry in the overall analyses of nausea and insomnia (Supplementary Figures 26–37).

3.3 | Overall Analysis

Among the AEs associated with modafinil treatments, headache was the most frequently studied (50 out of 54 articles), followed by nausea (35 articles), insomnia (32 articles), anxiety/nervousness (29 articles), dizziness (19 articles), diarrhoea (17 articles), decreased appetite (15 articles), abdominal pain (16 articles), rhinitis (14 articles), back pain (7 articles), weight loss (5 articles) and dyspepsia (3 articles). All the studies included in the analysis were RCTs, comprising 14 crossover RCTs and 40 parallel RCTs (Table 1).

When assessing the RR for each AE across all subjects, regardless of labelled or off-label use, patients receiving modafinil were significantly more likely to experience the following AEs compared to the control group (ranked by RR magnitude): decreased appetite (RR: 2.90, 95% confidence interval [CI]: 1.84–4.58), insomnia (RR: 2.19, 95% CI: 1.57–3.07), anxiety/nervousness (RR: 1.60, 95% CI: 1.18–2.17) and headache (RR: 1.24, 95% CI: 1.11–1.39) (Table 2, Supplementary Figures 1–12).

Although RRs for abdominal pain, nausea, dizziness, weight loss, diarrhoea and back pain were ≥1, they did not reach statistical significance. On the other hand, the RRs for dyspepsia and rhinitis were <1, indicating a lower likelihood of recurrence, but these findings were also not statistically significant (Table 2, Supplementary Figures 1–12).

3.4 | Subgroup Analysis

We conducted subgroup analyses based on the underlying condition of the patients included in the RCTs to investigate potential differences in the occurrence of AEs associated with these diseases. When analysing RR for each AE for use in *labelled indications*, the following results were observed: *Narcolepsy* patients exhibited increased risks of nausea (5 articles, RR: 2.44, 95% CI: 1.05–5.72) and diarrhoea (4 articles, RR: 2.16, 95% CI: 1.06–4.41); patients with OSA/hypopnea syndrome (HS) experienced higher risks of insomnia (four articles, RR: 5.82, 95% CI: 1.74–19.44), anxiety/nervousness (3 articles, RR: 3.26, 95% CI: 1.35–7.86), and headache (4 articles, RR: 1.92, 95% CI: 1.26–2.90); patients with *SWSD* encountered higher risks of insomnia (2 articles, RR: 4.09, 95% CI: 1.10–15.16), anxiety/nervousness (2 articles, RR: 3.85, 95% CI: 1.15–12.86), and nausea (2 articles, RR: 2.93, 95% CI: 1.31–6.55) (Table 2, Supplementary Figures 13–24).

For use *in off-label indication*, the following results were observed: *ADHD* patients treated with modafinil had a higher risk of insomnia (5 articles, RR: 4.97, 95% CI: 2.56–9.66) and decreased appetite (6 articles, RR: 4.21, 95% CI: 2.18–8.12) compared to the control group; patients with *major depressive disorder (MDD)* had a higher risk of anxiety/nervousness (3 articles, RR: 1.95, 95% CI: 1.11–3.42); *healthy* individuals were at higher risk of insomnia (2 articles, RR: 6.62, 95% CI: 1.21–36.17) (Table 2, Supplementary Figures 13–24). All of these results are statistically significant. Fixed-effect results for subgroups were also presented in Supplementary Table 5 and showed consistent direction of effect.

In patients with Parkinson's disease, substance use disorder, schizophrenia, traumatic brain injury, idiopathic hypersomnia and myotonic dystrophy, the RRs for all AEs were not statistically significant (Table 2, Supplementary Figures 13–24). For cerebral palsy, poststroke conditions, HIV/AIDS, primary biliary cirrhosis, lung cancer, advanced cancer, and postpolio syndrome, only one article was available, and thus a synthesized value could not be calculated. These single-trial conditions were, however, included in the "total" analysis to broadly synthesize all available evidence.

4 | Discussion

Since its FDA approval in 1998 for the treatment of narcolepsy, modafinil has gained worldwide usage for various off-label purposes, including alleviating fatigue and promoting wakefulness

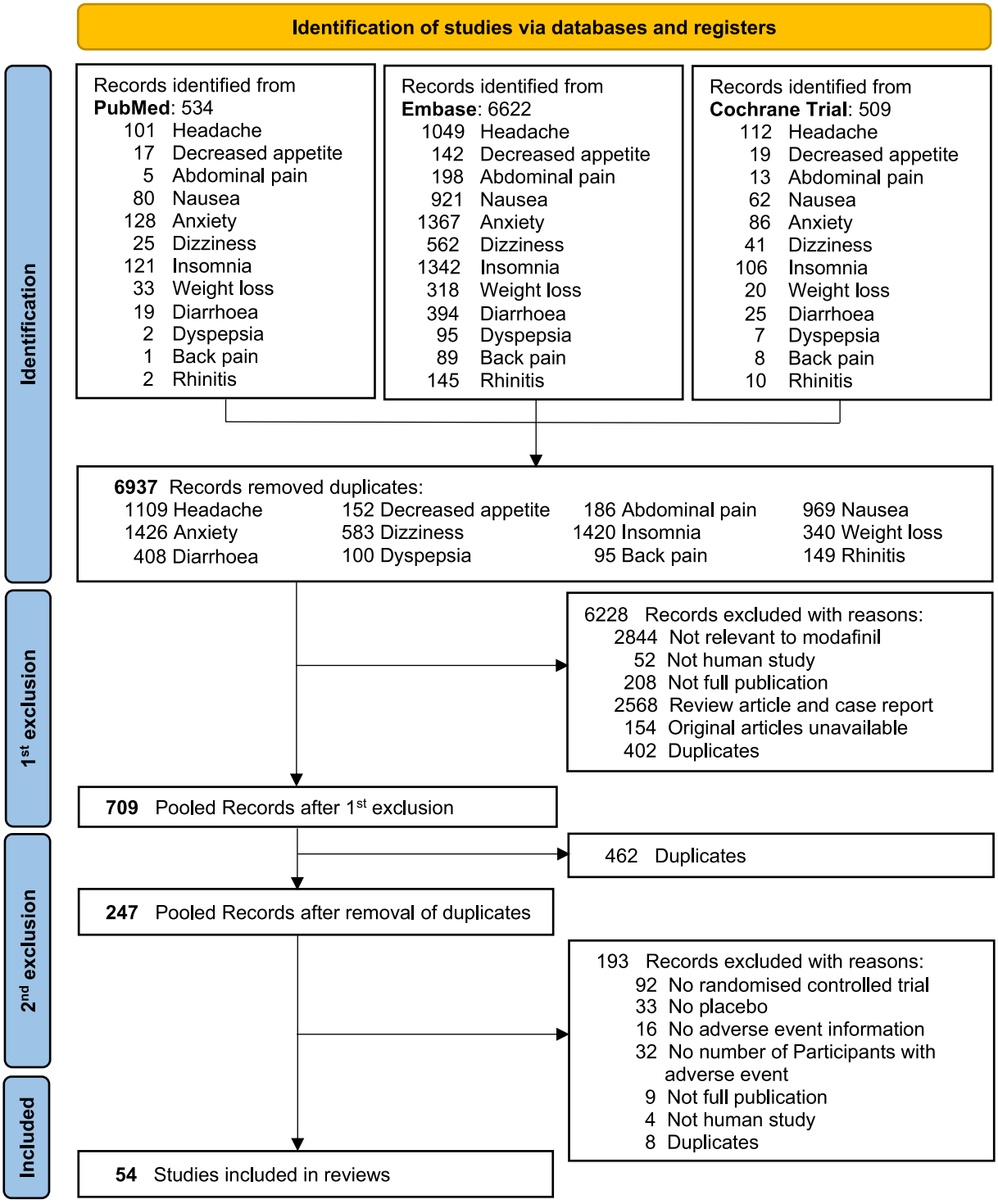

FIGURE 1 | Flowchart for identifying relevant studies.

in individuals with different medical conditions and sleep disorders. It has also been utilised to enhance concentration in patients with ADHD or healthy individuals. Academic consensus holds that modafinil enhances alertness by activating wakefulness-related systems such as hypocretin and dopamine while increasing excitatory glutamatergic neurotransmission in various brain regions [66]. Modafinil is primarily metabolised in the liver, slightly affecting specific cytochrome P450 enzymes. Still, it demonstrates a safe profile, even when used with monoamine oxidase inhibitors like tranylcypromine and phenelzine [1].

Among 12 AEs associated with modafinil, insomnia was observed to have a significantly increased RR in the largest number of underlying disease groups. Of the 12 patient groups analysed, significant positive associations with insomnia were observed in four patient groups, including OSA/HS, SWSD, ADHD and healthy individuals, compared to control groups not receiving modafinil treatment. The RRs were notably high, ranging from 4.09 to 6.62, highlighting the need for careful consideration. Anxiety/nervousness was the second most common significant AE with a positive association with modafinil, observed in

TABLE 2 | Summary of meta-analyses: risk ratio of adverse events for modafinil compared to placebo.

Type of underlying diseases of patients included in the studies	No. articles No. of participants Risk ratio comparing modafinil vs. placebo [95% confidence interval] 1. Headache	2. Decreased appetite	3. Abdominal pain	4. Nausea	5. Anxiety/ nervous-ness	6. Dizziness	7. Insomnia	8. Weight loss	9. Diarrhoea	10. Dyspepsia	11. Back pain	12. Rhinitis
Total of all underlying diseases	***N*=50** ***n*=5044** **1.24** **[1.11, 1.39]**	***N*=15** ***n*=1870** **2.90** **[1.84, 4.58]**	*N*=16 *n*=1657 1.44 [0.97, 2.13]	*N*=35 *n*=3672 1.31 [0.97, 1.76]	***N*=29** ***n*=3408** **1.60** **[1.18, 2.17]**	*N*=19 *n*=1520 1.46 [0.95, 2.25]	***N*=32** ***n*=3811** **2.19** **[1.57, 3.07]**	*N*=5 *n*=423 1.88 [0.36, 9.81]	*N*=17 *n*=1974 1.10 [0.77, 1.57]	*N*=3 *n*=567 0.88 [0.47, 1.64]	*N*=7 *n*=690 1.00 [0.59, 1.69]	*N*=14 *n*=2818 0.97 [0.72, 1.30]
Narcolepsy	*N*=5 *n*=768 1.12 [0.87, 1.45]			***N*=5** ***n*=718** **2.44** **[1.05, 5.72]**	*N*=4 *n*=736 1.20 [0.65, 2.23]	*N*=3 *n*=214 0.93 [0.28, 3.15]			***N*=4** ***n*=736** **2.16** **[1.06, 4.41]**	*N*=2 *n*=554 0.91 [0.40, 2.08]	*N*=3 *n*=586 1.07 [0.43, 2.64]	*N*=3 *n*=673 1.22 [0.52, 2.85]
OSA/HS	***N*=4** ***n*=628** **1.92** **[1.26, 2.90]**			*N*=3 *n*=514 0.86 [0.29, 2.60]	***N*=3** **n=514** **3.26** **[1.35, 7.86]**	*N*=2 *n*=462 2.12 [0.79, 5.69]	***N*=4** **n=628** **5.82** **[1.74, 19.44]**					*N*=2 *n*=462 1.28 [0.30, 5.41]
SWSD	*N*=2 *n*=467 1.25 [0.86, 1.80]			***N*=2** **n=467** **2.93** **[1.31, 6.55]**	***N*=2** **n=467** **3.85** **[1.15, 12.86]**		***N*=2** **n=467** **4.09** **[1.10, 15.16]**					
ADHD	*N*=6 *n*=949 1.24 [0.78, 1.98]	***N*=6** **n=949** **4.21** **[2.18, 8.12]**	*N*=6 *n*=949 1.19 [0.74, 1.92]	*N*=2 *n*=244 1.29 [0.39, 4.29]	*N*=3 *n*=490 0.89 [0.41, 1.94]		***N*=5** ***n*=927** **4.97** **[2.56, 9.66]**	*N*=2 *n*=244 3.44 [0.57, 20.87]				*N*=4 *n*=881 0.79 [0.48, 1.30]

(Continues)

TABLE 2 | (Continued)

Type of underlying diseases of patients included in the studies	No. articles No. of participants Risk ratio comparing modafinil vs. placebo [95% confidence interval] 1. Headache	2. Decreased appetite	3. Abdominal pain	4. Nausea	5. Anxiety/ nervous-ness	6. Dizziness	7. Insomnia	8. Weight loss	9. Diarrhoea	10. Dyspepsia	11. Back pain	12. Rhinitis
MDD	$N=4$ $n=556$ 1.18 [0.79, 1.76]	$N=2$ $n=109$ 1.60 [0.64, 4.01]		$N=4$ $n=556$ 1.17 [0.45, 3.05]	**$N=3$** **$n=245$** **1.95** **[1.11, 3.42]**		$N=4$ $n=556$ 1.10 [0.68, 1.79]		$N=3$ $n=512$ 0.75 [0.42, 1.34]			$N=2$ $n=447$ 1.50 [0.66, 3.40]
Parkinson's disease	$N=3$ $n=66$ 0.49 [0.11, 2.13]			$N=3$ $n=86$ 1.18 [0.20, 7.08]	$N=3$ $n=73$ 1.51 [0.25, 8.99]	$N=3$ $n=83$ 1.46 [0.24, 8.77]	$N=2$ $n=50$ 1.60 [0.21, 12.12]				$N=3$ $n=73$ 1.06 [0.20, 5.59]	
Healthy	$N=8$ $n=403$ 1.47 [0.91, 2.39]		$N=3$ $n=120$ 2.47 [0.54, 11.40]	$N=5$ $n=211$ 2.15 [0.62, 7.48]	$N=3$ $n=140$ 3.64 [0.53, 24.82]	$N=4$ $n=172$ 0.77 [0.18, 3.35]	**$N=2$** **$n=117$** **6.62** **[1.21, 36.17]**		$N=3$ $n=130$ 1.45 [0.24, 8.91]			
Substance use disorder	$N=4$ $n=330$ 1.32 [0.85, 2.04]				$N=4$ $n=295$ 1.84 [0.81, 4.20]		$N=4$ $n=330$ 1.47 [0.81, 2.69]					
Schizophrenia	$N=2$ $n=77$ 1.79 [0.54, 5.87]					$N=2$ $n=67$ 1.87 [0.62, 5.65]						

(Continues)

TABLE 2 | (Continued)

Type of underlying diseases of patients included in the studies	No. articles No. of participants Risk ratio comparing modafinil vs. placebo [95% confidence interval] 1. Headache	2. Decreased appetite	3. Abdominal pain	4. Nausea	5. Anxiety/ nervous-ness	6. Dizziness	7. Insomnia	8. Weight loss	9. Diarrhoea	10. Dyspepsia	11. Back pain	12. Rhinitis
Traumatic brain injury				$N=2$ $n=122$ 3.00 [0.49, 18.29]								
Idiopathic hypersomnia	$N=2$ $n=102$ 2.78 [0.93, 8.30]											
Myotonic dystrophy	$N=2$ $n=54$ 1.07 [0.12, 9.70]											

Note: Only statistically significant RRs are highlighted in bold.
Abbreviations: ADHD = attention deficit hyperactivity disorder, HS = hypopnea syndrome, MDD = major depressive disorder, OSA = obstructive sleep apnoea, SWSD = shift work sleep disorder.

patients with OSA/HS, SWSD and MDD. The RRs ranged from 1.95 to 3.85 (Table 2).

Overall, patients treated with modafinil tend to experience similar types of AEs. However, the specific AEs significantly associated with modafinil varied across certain patient groups. For example, no increased risk of decreased appetite was reported in patients using modafinil for any of the labelled indications (i.e., narcolepsy, OSA/HS and SWSD). In contrast, among off-label uses, ADHD patients showed a significantly higher risk of decreased appetite (RR: 4.21, 95% CI: 2.18–8.12). In addition, the risk of insomnia was highest in healthy individuals. While the highest RR for insomnia in patients was 5.82, it reached 6.62 in healthy individuals, suggesting an even greater susceptibility in this group. However, this finding should be interpreted with caution, as it was based on only two studies, and one of them specifically enrolled sleep-deprived participants, potentially increasing the susceptibility to insomnia.

Our findings suggest that modafinil use may exacerbate complications related to underlying conditions, particularly in patients with ADHD and MDD. For instance, our results showed a significantly higher risk of decreased appetite (RR: 4.21, 95% CI: 2.28–8.12) and insomnia (RR: 4.97, 95% CI: 2.56–9.66) among ADHD patients treated with modafinil, compared to those not receiving it. It is well established that children with ADHD are at a higher risk of experiencing anxiety and depression, which can contribute to an increased likelihood of insomnia. In addition, medications commonly prescribed for ADHD, such as methylphenidate and atomoxetine, are known to cause decreased appetite [67] and insomnia [68]. Our findings indicate that ADHD patients, who are already predisposed to decreased appetite and insomnia due to the nature of the disorder, may face an even greater risk when treated with modafinil. Therefore, careful consideration is required when prescribing modafinil to ADHD patients, including evaluating alternative treatment options.

Similarly, anxiety and nervousness should be closely monitored in patients with MDD. Research indicates that these symptoms are among the most common comorbidities of MDD [69, 70], with approximately 46.0%–53.2% of MDD patients meeting the criteria for anxious depression [71, 72], and 68.9% having comorbid anxiety disorders [73]. Furthermore, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), which are commonly used to treat MDD, have been associated with anxiety and nervousness as potential AEs [74]. Given that MDD patients are already vulnerable to these symptoms, modafinil treatment may further elevate their risk. Therefore, prescribing modafinil to MDD patients should be approached with caution, and alternative treatment options should be carefully considered.

With a growing interest in the off-label use of modafinil, several systematic reviews and meta-analyses, including studies on schizophrenia [75], poststroke care [12], ADHD [76] and neuroenhancement in healthy individuals [77], have been published. However, as of our current knowledge, no literature has systematically demonstrated or compared the risk of AEs associated with modafinil use across different indications. This review offers a comprehensive analysis of the risk of AEs, providing valuable insights for clinicians when prescribing modafinil for both labelled and off-label indications.

Several limitations should be taken into consideration when interpreting the findings of our study. Firstly, the RR for each AE was calculated based solely on the frequency of AEs in the modafinil and placebo groups without considering the severity of these events. Additionally, the estimated RRs were not adjusted for dosage and duration of modafinil therapy. Secondly, because AEs were selected based on a $\geq 5\%$ frequency threshold, clinically important outcomes, such as cardiovascular events, serious psychiatric events, and hepatotoxicity, were not included in our meta-analysis. Cardiovascular events (palpitation 2%, tachycardia 2%, and vasodilation 2%) and hepatotoxicity (hepatic insufficiency 2%) were reported at frequencies below the 5% threshold. Serious psychiatric events (psychosis and suicidal ideation) were primarily reported post marketing or lacked defined frequencies, making them unsuitable for systematic synthesis across the included clinical trials. Although these are critical safety concerns, their exclusion represents an important limitation. Further large-scale real-world studies are warranted to clarify their impact on modafinil's safety profile across different patient populations. Thirdly, all of the primary studies included in our meta-analysis are RCTs, the gold standard for ensuring internal validity. However, they have the limitation of not representing real-world practices and outcomes. To confirm the findings of our meta-analysis in the real world, a future study that synthesises results from observational studies could be beneficial. Fourthly, Egger's test revealed significant asymmetry in the overall analyses of nausea and insomnia. However, when we examined the funnel plots stratified by underlying condition (Supplementary Figures 26–37), the studies clustered clearly according to indication. This indicates that the observed asymmetry may be explained by between-subgroup differences rather than publication bias. Lastly, studies that did not represent the number of AEs were excluded from the analysis. Some studies only provided a list of AEs without specifying the number of patients who experienced them. Since our analysis required the actual number of affected patients, these studies were excluded. As a result, our findings on the risk of AEs may be either underestimated or overestimated.

Despite these limitations, this study offers an updated and comprehensive assessment of the AE risks associated with modafinil. By including only double-blind, placebo-controlled RCTs, our review ensures strong internal validity, enhancing the ability to establish a causal relationship between modafinil use and AEs. It is expected that these findings provide valuable insights for clinicians when prescribing modafinil in clinical practice and serve as a foundation for future research.

5 | Conclusions

In the overall analysis, including both patients and healthy individuals, the risk of experiencing AEs such as headache, decreased appetite, anxiety/nervousness, and insomnia was significantly higher in the modafinil group compared to the placebo group. Regardless of underlying conditions, patients

treated with modafinil generally experience similar types of AEs. However, the specific AEs significantly associated with modafinil varied across certain patient groups. Notably, modafinil use may exacerbate complications in individuals with ADHD and MDD, highlighting the need for cautious prescribing and careful consideration of alternative treatment options in these patient groups.

Author Contributions

Jaehee Jung and Jaeyoon Youm contributed equally to this work. **Jaehee Jung:** conceptualization, methodology, investigation, data curation, writing – original draft, visualization. **Jaeyoon Youm:** methodology, investigation, data curation, writing – original draft. **Jihyun Kang:** investigation, data curation, writing – original draft, visualization. **Ah–Young Kim:** methodology, writing – review and editing. **Jae Kyung Suh:** methodology, writing – review and editing. **Hye-Young Kang:** methodology, writing – review and editing, supervision.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supplementary Table 1:** PRISMA 2020 Checklist Preferred Reporting Items for Systematic Reviews and Meta-analysis checklist. **Supplementary Table 2:** Search term and results from PubMed Database. **Supplementary Table 3:** Search term and results from Embase Database. **Supplementary Table 4:** Search term and results from Cochrane Database. **Supplementary Table 5:** Comparison of random-effects and fixed-effect model results in subgroup analyses. **Supplementary Figure 1:** Meta-analysis results of adverse events for modafinil compared to placebo: headache events. **Supplementary Figure 2:** Meta-analysis results of adverse events for modafinil compared to placebo: decreased appetite events. **Supplementary Figure 3:** Meta-analysis results of adverse events for modafinil compared to placebo: abdominal pain events. **Supplementary Figure 4.** Meta-analysis results of adverse events for modafinil compared to placebo: nausea events. **Supplementary Figure 5:** Meta-analysis results of adverse events for modafinil compared to placebo: anxiety events. **Supplementary Figure 6:** Meta-analysis results of adverse events for modafinil compared to placebo: dizziness events. **Supplementary Figure 7:** Meta-analysis results of adverse events for modafinil compared to placebo: insomnia events. **Supplementary Figure 8:** Meta-analysis results of adverse events for modafinil compared to placebo: weight loss events. **Supplementary Figure 9:** Meta-analysis results of adverse events for modafinil compared to placebo: diarrhoea events. **Supplementary Figure 10:** Meta-analysis results of adverse events for modafinil compared to placebo: dyspepsia events. **Supplementary Figure 11:** Meta-analysis results of adverse events for modafinil compared to placebo: back pain events. **Supplementary Figure 12:** Meta-analysis results of adverse events for modafinil compared to placebo: rhinitis events. **Supplementary Figure 13:** Meta-analysis results of adverse events for modafinil compared to placebo: headache events by underlying diseases. **Supplementary Figure 14:** Meta-analysis results of adverse events for modafinil compared to placebo: decreased appetite events by underlying diseases. **Supplementary Figure 15:** Meta-analysis results of adverse events for modafinil compared to placebo: abdominal pain events by underlying diseases. **Supplementary Figure 16:** Meta-analysis results of adverse events for modafinil compared to placebo: nausea events by underlying diseases. **Supplementary Figure 17:** Meta-analysis results of adverse events for modafinil compared to placebo: anxiety events by underlying diseases. **Supplementary Figure 18:** Meta-analysis results of adverse events for modafinil compared to placebo: dizziness events by underlying diseases. **Supplementary Figure 19:** Meta-analysis results of adverse events for modafinil compared to placebo: insomnia events by underlying diseases. **Supplementary Figure 20:** Meta-analysis results of adverse events for modafinil compared to placebo: weight loss events by underlying diseases. **Supplementary Figure 21:** Meta-analysis results of adverse events for modafinil compared to placebo: diarrhoea events by underlying diseases. **Supplementary Figure 22:** Meta-analysis results of adverse events for modafinil compared to placebo: dyspepsia events by underlying diseases. **Supplementary Figure 23:** Meta-analysis results of adverse events for modafinil compared to placebo: back pain events by underlying diseases. **Supplementary Figure 24:** Meta-analysis results of adverse events for modafinil compared to placebo: rhinitis events by underlying diseases. **Supplementary Figure 25:** Risk of bias

graph. **Supplementary Figure 26:** Funnel plot of studies included in meta-analysis for the adverse events of modafinil compared to placebo: headache events. (A) Overall set of studies, (B) Studies included in the subgroup analysis by underlying diseases. **Supplementary Figure 27:** Funnel plot of studies included in meta-analysis for the adverse events of modafinil compared to placebo: decreased appetite events. (A) Overall set of studies and (B) studies included in the subgroup analysis by underlying diseases. **Supplementary Figure 28:** Funnel plot of studies included in meta-analysis for the adverse events of modafinil compared to placebo: abdominal pain events. (A) Overall set of studies and (B) studies included in the subgroup analysis by underlying diseases. **Supplementary Figure 29:** Funnel plot of studies included in meta-analysis for the adverse events of modafinil compared to placebo: nausea events. (A) Overall set of studies and (B) studies included in the subgroup analysis by underlying diseases. **Supplementary Figure 30:** Funnel plot of studies included in meta-analysis for the adverse events of modafinil compared to placebo: anxiety events. (A) Overall set of studies and (B) studies included in the subgroup analysis by underlying diseases. **Supplementary Figure 31:** Funnel plot of studies included in meta-analysis for the adverse events of modafinil compared to placebo: dizziness events. (A) Overall set of studies and (B) studies included in the subgroup analysis by underlying diseases. **Supplementary Figure 32:** Funnel plot of studies included in meta-analysis for the adverse events of modafinil compared to placebo: insomnia events. (A) Overall set of studies and (B) studies included in the subgroup analysis by underlying diseases. **Supplementary Figure 33:** Funnel plot of studies included in meta-analysis for the adverse events of modafinil compared to placebo: weight loss events. (A) Overall set of studies and (B) studies included in the subgroup analysis by underlying diseases. **Supplementary Figure 34:** Funnel plot of studies included in meta-analysis for the adverse events of modafinil compared to placebo: diarrhoea events. (A) Overall set of studies and (B) studies included in the subgroup analysis by underlying diseases. **Supplementary Figure 35:** Funnel plot of studies included in meta-analysis for the adverse events of modafinil compared to placebo: dyspepsia events. (A) Overall set of studies and (B) studies included in the subgroup analysis by underlying diseases. **Supplementary Figure 36:** Funnel plot of studies included in meta-analysis for the adverse events of modafinil compared to placebo: back pain events. (A) Overall set of studies and (B) studies included in the subgroup analysis by underlying diseases. **Supplementary Figure 37:** Funnel plot of studies included in meta-analysis for the adverse events of modafinil compared to placebo: rhinitis events. (A) Overall set of studies and (B) studies included in the subgroup analysis by underlying diseases.