Adverse Event Profiles of Modafinil Use for Major Depressive Disorder : A Systematic Review and Meta-Analysis

EPH207

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INTRODUCTION

Modafinil is an approved medication primarily used for treating excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder. However, its usage extends beyond approved indications, including off-label use for major depressive disorder (MDD).

OBJECTIVES

This systematic review aims to comprehensively assess adverse events of unapproved application (MDD) of modafinil in MDD patients.

METHODS

An extensive search was conducted across PubMed, Embase, and Cochrane databases using MeSH terms and Emtree terms such as modafinil, headache, nervousness, anxiety, etc. The review focused on 12 adverse events associated with modafinil use compared to a placebo. Statistical analyses were held using Review Manager ver. 5.3 software, and the results were graphically illustrated in forest plots. The quality of the literature was evaluated using Risk of Bias ver. 2.0.

RESULT

A thorough search of PubMed, Embase, and Cochrane databases was conducted to retrieve 7,188 relevant literature: PubMed (499 articles), Embase (6,186 articles), and Cochrane (503 articles). After removing duplicates, 6,528 articles remained and then 5,866 were excluded during the initial screening. And in second examination, 226 articles were reviewed, resulting in the exclusion of 222 articles. Finally, 4 articles were included in the analysis. An analysis of the risk ratio (RR) for each adverse event was conducted to identify high-risk adverse events associated with modafinil usage in MDD patients.

Eventually, anxiety/nervousness (RR: 1.95, 95% CI: 1.11-3.42) was identified as a high-risk adverse event.

Fig 1. Flowchart for identifying relevant studies

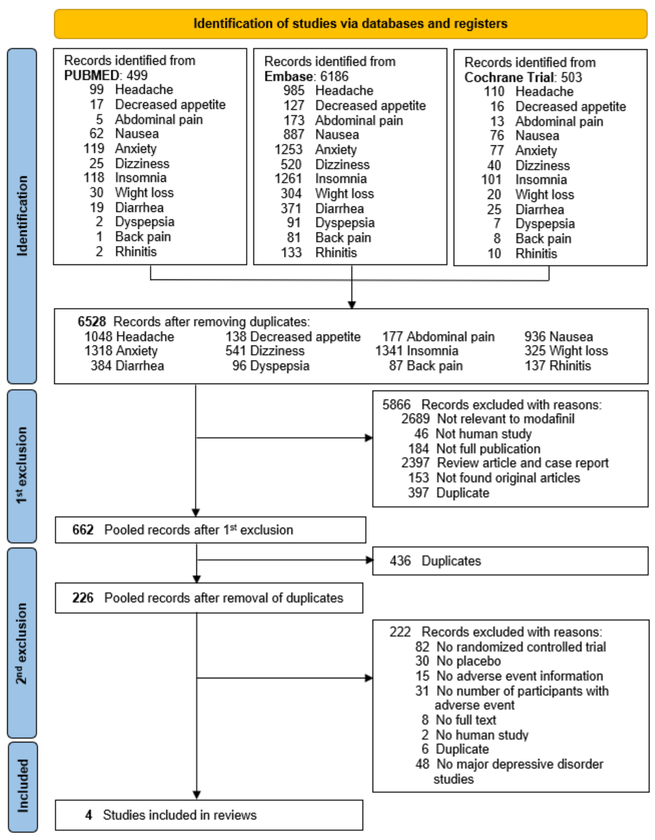


Table 1. Characteristic of the included studies for systematic literature review and meta-analysis

No	First Author (year of publication)	Study design	Intervention (unit: mg)	Total number of patients for adverse event evaluation	Number of patients experiencing each type of adverse events											
					1	2	3	4	5	6	7	8	9	10	11	12
1	DeBattista (2003)	RCT	- antidepressants +modafinil ~400 - antidepressants +placebo	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
2	Fava (2005)	RCT	- SSRI + modafinil 100~200 - SSRI + placebo	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
3	Dunlop (2007)	RCT	- modafinil 100~200 - placebo	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			
4	Abolfazli (2011)	RCT	- fluoxetine +modafinil 200/200 - fluoxetine + placebo	M: 23 P: 23	M: 5 P: 5	M: 6 P: 4		M: 4 P: 4	M: 7 P: 5		M: 7 P: 5					

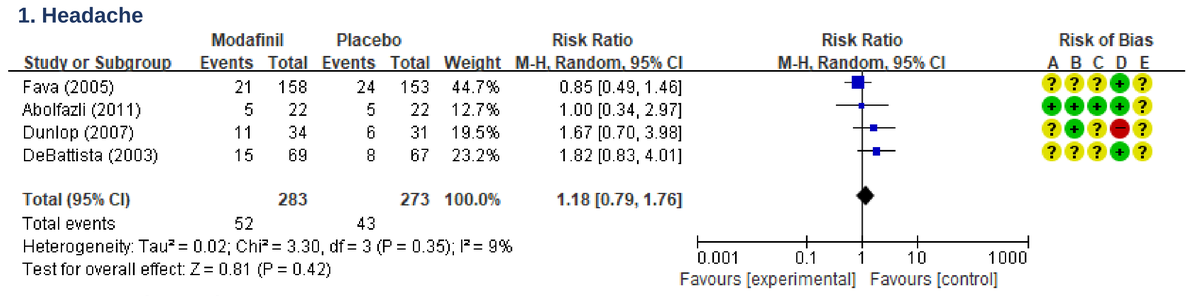
M: modafinil, P: placebo, RCT: randomized controlled trial, SSRI: Selective Serotonin Reuptake Inhibitor

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

Table 2. Summary of meta-analyses: Risk ratio of adverse events in major depressive disorder for modafinil compared to placebo

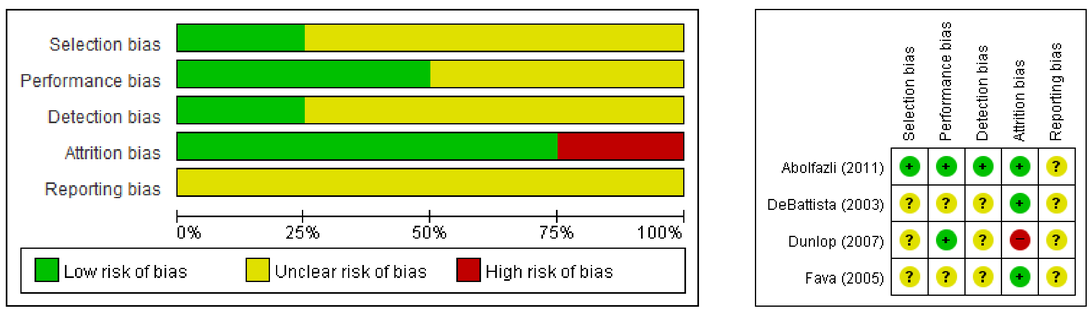
No.	Adverse events	Number of articles	Number of participants	Risk ratio comparing modafinil vs. placebo	95% confidence interval
1	Headache	4	556	1.18	0.79, 1.76
2	Decreased appetite	2	109	2.53	0.76, 8.41
3	Abdominal pain	-	-	-	-
4	Nausea	4	556	1.17	0.45, 3.05
5	Anxiety/ nervousness	3	245	1.95	1.11, 3.42
6	Dizziness	-	-	-	-
7	Insomnia	4	556	1.1	0.68, 1.79
8	Weight loss	-	-	-	-
9	Diarrhea	3	512	0.75	0.42, 1.34
10	Dyspepsia	-	-	-	-
11	Back pain	-	-	-	-
12	Rhinitis	2	447	1.5	0.66, 3.40

Figure 2. Forest plots of each adverse events in major depressive disorder



* Risk of bias legend: (A) Selection bias, (B) Performance bias, (C) Detection bias, (D) Attrition bias, (E) Reporting bias

Figure 3. Risk of Bias



CONCLUSION

Our findings highlight anxiety/nervousness was the only statistically significant adverse event in MDD population when using modafinil and emphasize the need for careful consideration and monitoring when prescribing modafinil in MDD patients.

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