

## Effects of Modafinil on Sleep Pattern during Methamphetamine Withdrawal: A Double-blind Randomized Controlled Trial

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### Original Article

#### Abstract

**Background:** Methamphetamine (MA) abuse is a serious and costly public health problem worldwide; It also commonly affects the sleep quality. The present study was carried out aiming to evaluate the effectiveness of modafinil versus placebo on sleep pattern in MA withdrawal during an eight-week period.

**Methods:** In a double-blind randomized controlled study, a total of 80 patients with a confirmed diagnosis MA withdrawal were treated with modafinil (200 mg/day). Pittsburgh Sleep Quality Index (PSQI) and Epworth sleepiness scale (ESS) were used to assess sleep pattern in the 1<sup>th</sup> and 56<sup>th</sup> days of the study. Analysis of covariance (ANCOVA) was applied to compare the groups. All analyses were performed by using SPSS software with a 5% significance level.

**Findings:** The mean age of the people in the intervention and placebo groups was  $32.92 \pm 2.06$  and  $34.08 \pm 2.13$  years, respectively. The mean scores of ESS decreased from  $16.15 \pm 4.50$  to  $9.15 \pm 3.34$  after the intervention in the modafinil group ( $P < 0.001$ ), with no significant reduction in the placebo group ( $P = 0.990$ ). The mean scores of PSQI decreased from  $13.88 \pm 3.40$  to  $9.92 \pm 3.10$  after the intervention in the modafinil group ( $P < 0.001$ ), however there was no significant reduction in the placebo group ( $P = 0.980$ ). The value of the Eta effect size of the PSQI and ESS questionnaires was 0.52 and 0.72, respectively. Modafinil was superior to placebo in improving the PSQI and ESS scales in the 56<sup>th</sup> day of assessment ( $P < 0.050$ ).

**Conclusion:** Modafinil improves the sleep quality in patients with MA withdrawal.

**Keywords:** Methamphetamine; Modafinil; Placebo; Sleep

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## Introduction

Methamphetamine (MA) is one of the most addictive stimulants with severe short-term and long term effects on monoamine neurotransmitter system,<sup>1</sup> including increase in the dopamine level and hence consciousness.<sup>2</sup> In addition, it is the cause of admission in an overall 8% of all patients admitted for MA addiction treatment,<sup>3</sup> second to marijuana, the world's most popular illegal substance. The rate of MA use is also increasing in Iran.<sup>4</sup> In Iran, about 50% of admission in psychiatric hospitals is associated with MA addiction.<sup>3</sup> MA has also severe withdrawal symptoms and complications including sleep disorders.<sup>5,6</sup>

While there is no approved medically assisted therapy for MA,<sup>3,7</sup> recent studies showed controversial results for the effect of Modafinil on the amphetamine and MA dependency.<sup>7-11</sup> Modafinil is an unrivaled wakefulness-promoting medication and not addictive with an excellent safety profile. Its mechanism of effect is not clearly known,<sup>12,13</sup> but it acts on brain pathways particular subsets that adjust sleep and wakefulness. Not only it does not connect to many sleep/wake regulation receptors, including dopamine, serotonin, norepinephrine, and  $\gamma$ -aminobutyric acid (GABA), but it also does not affect the extrapyramidal motor system exhibited by both stimulants, such as hyperactivity, restlessness, and irritability. This suggests that modafinil has the potential to increase wakefulness without the accompanying side effects possessed by other wakefulness-promoting agents.<sup>14</sup>

There are several reasons which make modafinil a great choice for treating MA dependence. These reasons include stimulant properties of modafinil that alleviates some drug withdrawal symptoms, attenuate reinstatement of MA self-administration in animal testing, has lower abuse potential than methylphenidate or amphetamine, ameliorates cognition and mood, and is used in trials of treatment for cocaine dependence, and is proved to be safe and well-tolerated in almost all studies.<sup>8</sup> Modafinil also has fewer side effects such as headache, vomiting, anger, anxiety, insomnia, nasal allergic inflammation, diarrhea, backache, dizziness, indigestion, flu, dry mouth, and anorexia; most of the patients use it with no problems.<sup>8,10</sup>

Modafinil promotes the performance of healthy volunteers deprived of sleep,<sup>15,16</sup> and studies showed that after a long period of sleep deprivation using the drug, there was a trend to wake up earlier, hence reducing the duration of the recovery sleep period.<sup>17</sup> Based on these studies, after sleep deprivation concerning substance use, the need for sleep is decreased.<sup>17,18</sup> Because of the significant features of MA withdrawal such as excessive pressure and fatigue, the wake-raising features of Modafinil make it a great candidate for withdrawal pharmacotherapy.<sup>19</sup> Some new studies concerning the efficacy of Modafinil showed its effectiveness to treat amphetamine and MA addiction.<sup>8-11</sup> As assessed in other studies, 400 mg of Modafinil daily was more than the 200 mg dose recommended for the treatment of excessive daytime sleepiness disorders.<sup>9</sup> Moreover, the previous clinical trial for the efficacy of Modafinil on MA dependence also examined 200 mg daily and there was no significant effect for Modafinil relative to placebo.<sup>10</sup> It was found in the present study that the studies appear to be in contradiction with each other. Therefore, the aim in this study was to measure the effect of 200 mg daily dose of Modafinil (versus placebo) on sleep pattern during an eight-week period after the MA withdrawal.

## Methods

This was a double-blind randomized controlled trial. 80 adult men with a confirmed diagnosis of MA withdrawal (negative urine test for MA) were selected from outpatients in the psychiatry hospital, Sari, Iran. By random permuted blocks, the participants were assigned either to modafinil or placebo medication groups. They were treated with modafinil (200 mg/day) or placebo for 8 weeks. Then, sleep patterns and quality were measured by the Pittsburgh Sleep Quality Index (PSQI) and Epworth sleepiness scale (ESS). All participants provided a written consent as approved by IRB prior to the data collection [Iranian Registry of Clinical Trials (IRCT) Code: IRCT20181218042036N1]. Consort pattern of this double-blind randomized controlled study is demonstrated in figure 1.

Inclusion criteria were recent MA dependency based on Diagnostic and Statistical Manual of Mental Disorders-5<sup>th</sup> Edition-Text Revision (DSM-V-TR) and Structured Clinical Interview (SCID)

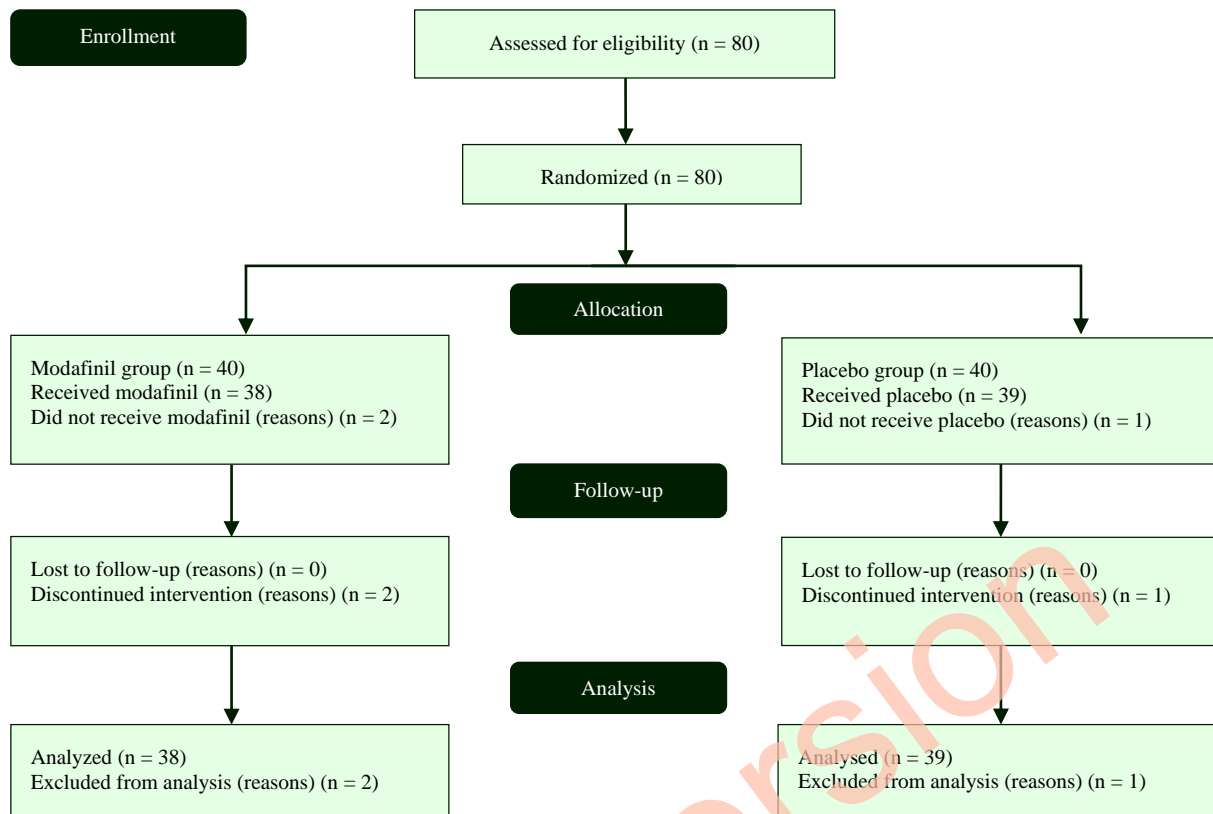


Figure 1. Consort pattern of the double-blind randomized controlled study

for DSM-V criteria, provided consent to participate in the study, willingness to attend the study until the end, men aged 18 to 65 years old, negative urine test for MA, and no contraindication for the use of modafinil. Exclusion criteria included using any other drugs than MA as verified by SCID and laboratory tests, holding co-morbidities such as serious coronary, liver, neurologic, or psychiatric illnesses, uncontrolled diabetes mellitus (DM) or hypertension, and any contraindication to use medicines, having suicidal thoughts and aggression, or participating in another trial at the same time.

The Excel software was employed in this study to generate the randomization codes in permuted randomization blocks. The block size was 4 with 6 combinations of sequences: AABB, ABAB, ABBA, BAAB, BABA, and BBAA. Randomization and allocation were performed by a trained person who was not involved in baseline and follow-up measurement. The sealed envelopes were used to conceal the allocation. It was a triple-blind design and the research investigators, data collectors, and trial participants were all blinded to the treatment allocation. Modafinil and placebo were similar in their size, color, shape, texture, and odor.

After random allocation, the patients visited each other every two weeks in order to check possible changes in the medications, each other's health, and completion of evaluations. The participants started 100 mg of modafinil or the placebo daily, and after 3 days, the dosage increased to 200 mg of modafinil or placebo daily until the end of week 8. Urine screening for MA was conducted every two. The modafinil used for this trial was manufactured by the Sobhan pharmaceuticals company in Iran.

At baseline, complete blood count (CBC), fasting blood sugar (FBS), blood urea nitrogen (BUN), Creatinine (Cr), aspartate aminotransferase (AST), U/N, and electrocardiogram (ECG) were measured. Psychiatric interview was conducted for all patients according to DSM-5 and SCID. Clinical effects of the prescribed medicine and also its side effects were assessed according to the checklist in the first and eighth weeks. The patients were not aware of the type of drug (Modafinil-placebo), and in order to eliminate any bias in assessing and scoring criteria, the assessor was not informed about the type of the drug used.

The sleep pattern and quality were measured at baseline and at eight weeks by two standardized valid scales, the ESS and PSQI. The ESS measures a participant’s habitual “likelihood of dozing off or falling asleep”. It has 8 self-administrated items, each scored from 0-3, with a total score ranged from 0 to 24. The total score of 10 or higher is considered significant sleepiness disorder.<sup>20</sup> ESS was translated to Farsi and the ESS-IR (Iranian version of ESS) showed to have a Cronbach’s alpha coefficient of 0.82.<sup>21</sup> The PSQI scale consists of 19 items in 7 dimensions, is self-administrated, and measures sleep habits during the last month. Its final score ranges from 0 to 21, and numbers greater than 5 are considered as impaired sleep quality.<sup>22</sup> This scale was also translated to Farsi and its Cronbach’s alpha coefficient was 0.77.<sup>23</sup>

At baseline, the current and lifetime mental disorders were also measured by a structured clinical interview for the DSM-IV axis 1 (SCID) disorder.<sup>24</sup> The SCID reliability was previously assessed by the test-retest method and it was shown to be fair to good for most diagnostic categories, with a weighted Kappa of 0.52 and 0.55 for the current mental disorders and for lifetime diagnoses, respectively.<sup>25</sup> Study participants with synchronic diseases were also assessed by a structured clinical interview for the DSM-IV axis 1 disorder and those suffering from such disorders were excluded from the trial.

The data on the quantitative variables collected in the two studied groups was described as mean ± standard deviation (SD). Data analysis was per-protocol. Pearson correlation was employed to determine the multivariate or univariate methods. The independent-samples t-test was utilized to compare the mean values of the two groups before and after the intervention, and the paired t-test was applied to assess changes in the study groups before and after the

intervention. Analysis of covariance (ANCOVA) was applied to compare the groups in order to control the confounding effects of the pretest measurements of the variables studied. SPSS software (version 25, IBM Corporation, Armonk, NY, USA) was employed to analyze the data in 5% significance level.

### Results

The mean age of the subjects in the intervention and placebo groups were 32.92 ± 2.06 and 34.08 ± 2.13 years, respectively.

The mean scores of ESS decreased from 16.15 ± 4.50 to 9.15 ± 3.34 after the intervention in the modafinil group (P < 0.001), but there was no significant difference in the placebo group (P = 0.990) (Table 1).

The mean scores of PSQI decreased from 13.88 ± 3.40 to 9.92 ± 3.10 after the intervention in the modafinil group (P < 0.001), however there was no significant difference in the placebo group (P = 0.980).

At baseline, there was no significant difference between the intervention and control groups regarding the mean score of ESS (P = 0.690), however it was significant after the intervention (P < 0.001). Similarly, at baseline, there was no significant difference between the intervention and control groups regarding the mean score of PSQI (P = 0.830), however it was significant after the intervention (P < 0.001).

### Discussion

It was found in this study that Modafinil improves the sleep pattern and quality in patients with MA withdrawal. The findings of the current study match with previous studies showing the performance-enhancing effect of Modafinil on cognitive function, including problem-solving, working memory, planning problems, decision making, and redirecting attention flexibly.<sup>26</sup>

**Table 1.** Descriptions and comparison of sleep quality and sleepiness in Pittsburgh Sleep Quality Index (PSQI) and Epworth sleepiness scale (ESS) between the two groups and for each group before and after intervention

Group	PSQI score before intervention (mean ± SD)	PSQI score after intervention (mean ± SD)	P	ESS score before intervention (mean ± SD)	ESS score after intervention (mean ± SD)	P
Intervention	13.88 ± 3.40	9.92 ± 3.10	< 0.001	16.15 ± 4.50	9.15 ± 3.34	< 0.001
Control	13.55 ± 3.22	13.54 ± 3.10	0.980	16.38 ± 4.90	16.30 ± 4.40	0.990
P	0.690	< 0.001	-	0.830	< 0.001	-

PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth sleepiness scale; SD: Standard deviation

11 hours after taking the drug, total sleep time was decreased using 300 and 400 mg of modafinil compared with the placebo and the effect of Modafinil on sleep, performance, and its duration of activity was dose-related.

These findings contribute to understanding the use of the drug in sleep disorders and how it works. In another study, sleep electroencephalography was used to investigate how Modafinil works in humans.<sup>27</sup> There was a reduction in rapid eye movement sleep (REM sleep or REMS) with Modafinil to be secondary to the drug's alerting effect and there was no proof of REM sleep direct suppression.<sup>27</sup>

Other studies provided evidence of a long duration of action of modafinil in humans.<sup>28-30</sup> The apparent lack of the need for sleep during the recovery period could have been due to the remaining effect of the drug. Its use in predominant extreme daytime sleepiness or as a means of counteracting the effects of sleep disturbance inherent in some occupations is likely to have less unwanted behavioral effects than amphetamine with its more complex pharmacological profile, especially involving the noradrenergic system.<sup>31</sup> Moreover, treatment with Modafinil increased daytime wakefulness versus baseline irrespective of which psychostimulant was taken previously and Modafinil was an effective and well-tolerated treatment for improving daytime wakefulness in patients with narcolepsy previously treated with psychostimulants.<sup>32</sup>

Modafinil showed to have other positive effects such as increase in wakefulness, reduction in food uptake, and no effect on heart rate.<sup>33,34</sup> A previous study on Modafinil as 400 mg daily (200 mg higher than the rate used in the current trial) showed improvement in severe daytime

sleepiness disorders.<sup>9</sup> In the present trial, similar improvement was found in sleep outcomes with Modafinil as 200 mg daily. The low dosage of Modafinil treatment in this study was tolerated very well, had no significant side effect, and was effective in comparison to the placebo.

Trials of Modafinil on individuals with cocaine dependency indicated equivalent effect when 400 mg or 200 mg daily doses were used.<sup>35-37</sup> In imaging trials, Modafinil's dopaminergic effects were also similar when 400 mg or 200 mg doses were given.<sup>38</sup> Previs trial of Modafinil 200 mg daily failed to show significant effect on MA use and retention.<sup>10</sup> These findings suggested that Modafinil 200 mg daily was only effective when MA dependency was severe, or Modafinil was given at withdrawal phase after MA drug treatment.

As one limitation in this study, two participants in modafinil group were excluded from the study on the third and seventh weeks and one subject in the placebo group was excluded from the study on the sixth week due to simultaneous use of MA. However, these drop-outs are not expected to change the study findings and conclusion.

## Conclusion

The RCT evidence suggests that Modafinil improves the sleep pattern and quality in patients with MA withdrawal.

## Conflict of Interests

The Authors have no conflict of interest.

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## تأثیر مدافینیل بر الگوی خواب هنگام ترک مت‌آفتامین: یک مطالعه کارآزمایی بالینی تصادفی دو سوکور

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### مقاله پژوهشی

### چکیده

**مقدمه:** سوء مصرف مت‌آفتامین و وابستگی به آن، یکی از مشکلات جدی بهداشت عمومی در سراسر جهان محسوب می‌شود که طیف وسیعی از جامعه را در برمی‌گیرد و هزینه‌های سنگین پزشکی و روان‌پزشکی را به جامعه تحمیل می‌کند. هدف از انجام پژوهش حاضر، ارزیابی اثربخشی مدافینیل و دارونما بر الگوی خواب هنگام ترک مت‌آفتامین طی هشت هفته بود.

**روش‌ها:** در این مطالعه کنترل شده تصادفی دو سوکور، ۸۰ بیمار با تشخیص تأیید شده ترک مت‌آفتامین با مدافینیل (۲۰۰ میلی‌گرم در روز) تحت درمان قرار گرفتند. برای ارزیابی الگوی خواب در روزهای اول و ۱۵۶ تحقیق، از شاخص کیفیت خواب Pittsburgh (Pittsburgh Sleep Quality Index یا PSQI) و مقیاس خواب‌آلودگی Epworth (Epworth Sleepiness Scale یا ESS) استفاده گردید. داده‌ها با استفاده از آزمون ANCOVA در نرم‌افزار SPSS مورد تجزیه و تحلیل قرار گرفت.  $P < 0/050$  به عنوان سطح معنی‌داری در نظر گرفته شد.

**یافته‌ها:** میانگین سنی شرکت‌کنندگان گروه‌های مداخله و دارونما به ترتیب  $27/06 \pm 32/92$  و  $24/08 \pm 27/13$  سال بود. میانگین نمرات ESS پس از مداخله در گروه مصرف‌کننده مدافینیل از  $4/50 \pm 16/15$  به  $3/34 \pm 9/15$  کاهش یافت ( $P < 0/001$ )، اما اختلاف معنی‌داری در گروه دریافت‌کننده دارونما وجود نداشت ( $P = 0/990$ ). میانگین نمرات PSQI بعد از مداخله در گروه مصرف‌کننده مدافینیل از  $3/40 \pm 13/88$  به  $3/10 \pm 9/92$  کاهش پیدا کرد ( $P < 0/001$ )، اما تفاوت معنی‌داری در گروه دریافت‌کننده دارونما مشاهده نشد ( $P = 0/980$ ). مقدار اندازه اثر Eta در پرسش‌نامه‌های PSQI و ESS به ترتیب  $0/52$  و  $0/72$  به دست آمد. مدافینیل در بهبود مقیاس‌های PSQI و ESS در روز ۱۵۶ برتر از دارونما عمل کرد ( $P < 0/050$ ).

**نتیجه‌گیری:** دشواری خواب هنگام ترک مت‌آفتامین شایع می‌باشد و ممکن است خطر عود وابستگی را افزایش دهد. پزشکان باید این مشکلات را در نظر بگیرند و سعی کنند آن را مدیریت نمایند.

**واژگان کلیدی:** مت‌آفتامین، مدافینیل، دارونما، خواب

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