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Modafinil reduces patient-reported tiredness after sedation/analgesia but does not improve patient psychomotor skills

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Background: Early recovery of patients following sedation/analgesia and anesthesia is important in ambulatory practice. The aim of this study was to assess whether modafinil, used for the treatment of narcolepsy, improves recovery following sedation/analgesia.
Methods: Patients scheduled for extracorporeal shock wave lithotripsy were randomly assigned to one of four groups. Two groups received a combination of fentanyl/midazolam with either modafinil or placebo. The remaining groups received remifentanil/propofol with either modafinil or placebo. Modafinil 200 mg was administered to the treatment group patients 1 h before sedation/analgesia. Groups were compared using the digital symbol substitution test (DSST), trail making test (TMT), observer scale of sedation and analgesia (OAA/S) and Aldrete score. Verbal rating scale (VRS) scores for secondary outcome variables e.g. energy, tiredness and dizziness were also recorded before and after treatment.
Results: Sixty-seven patients successfully completed the study. Groups received similar doses of sedation and analgesic drugs. No statistically significant difference was found for DSST between groups. No significant adverse effects occurred in relation to modafinil. No statistically significant difference between groups was identified for TMT, OAA/S and Aldrete scores. The mean VRS score for tiredness was lesser in the modafinil/fentanyl/midazolam group [1.3 (2.0)] compared with the placebo group [3.8 (2.5)], $P = 0.02$. Such a difference was not found between the remifentanil/propofol groups [placebo 2.6 (2.2) vs. modafinil 3.1(2.7)], $p > 0.05$. Dizziness was greater in the modafinil/remifentanil/propofol group 1.7 (2.0) vs. placebo 0.0 (0.5), $p < 0.05$.
Conclusion: Modafinil reduces patient-reported tiredness after sedation/analgesia but does not improve recovery in terms of objective measures of patient psychomotor skills.

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A growing number of patients today undergo ambulatory surgery and anesthesia, where an important focus is on rapid recovery. Developments in both surgery and anesthesia have contributed to the growth of ambulatory care. Anesthesia techniques have been developed that help ensure that patients satisfy the requirements for same-day home discharge.

Modafinil (2-[(diphenylmethyl) sulfinyl]acetamide) is a wake-promoting agent that is increasingly attracting attention for its potential benefits in a wide array of illness, including narcolepsy, obstructive sleep apnea/hypopnea sydrome (OSA/H), shift–work sleep disorder, attention deficit/hyperactivity disorder (ADHD), cocaine dependancy and depression.[1–5] Modafinil has been shown to counter the adverse effects of overnight sleep deprivation on working memory during the performance of moderately difficult tasks.[6] However, despite increasing clinical application of the drug, no broad consensus exists on the underlying mechanisms of modafinil pharmacology. Modafinil may exert its effects through interaction with catecholamine neurotransmitters in the brain[7]; however, there is also some evidence to suggest that modafinil increases wakefulness by promoting glutamate release and inhibiting GABA release.[8] Modafinil does not appear to act via histamine H(3)-receptors unlike other drugs with similar effects.[9] While its 'wakefulness'-promoting effect has been compared with that of amphetamines and caffeine, importantly, modafinil appears to lack a potential for tolerance and withdrawal symptoms on cessation of use.[10]

An earlier study on modafinil use in patients following various forms of general anesthesia[11] reported a beneficial effect in terms of reducing the incidence of 'subjective moderate to severe fatigue' in modafinil-treated patients vs. placebo. In this current study, we hypothesized that the administration of modafinil by improving psychomotor function would improve patient recovery following standardized forms of sedation/analgesia.

Our primary objective was to evaluate the effect of modafinil on the ability of patients to complete the digital symbol substitution test (DSST),[12] a test of psychomotor function following sedation/analgesia. In this study, we hypothesized that modafinil use would improve patients' ability to complete the DSST compared with the placebo-treated groups, by seven symbols during a fixed time period of 2 min. Secondary objectives included evaluation of the effect of modafinil on patients' ability to complete the trail making test (TMT),[13] and its effect on various subjective aspects of recovery such as tiredness and energy levels. An additional goal was to identify the occurrence of specific side effects related to the administration of modafinil in patients receiving sedation/analgesia.

Materials and methods

Following local ethics committee approval, 67 patients scheduled for elective extra corporal shock wave lithotripsy (ESWL) treatment of kidney or ureter stones were enrolled in this study. ESWL was chosen as it is a homogenous procedure in terms of duration and intensity of the pain stimulus; adult patients generally receive a given number of shock waves of a pre-defined intensity according to the guidelines of the ESWL equipment being used. Inclusion criteria were ASA physical status I–II adult patients, aged 18–80 years old. Exclusion criteria included patients of ASA class 3, 4 or 5, visual or motor impairement to a level that made the completion of the DSST and TMT tests impossible, known liver or renal impairment, psychiatric illness, known allergy to any of the medications used in the study, epilepsy, breastfeeding or use of the oral contraceptive pill. The study was approved by the local medical ethics committee. All patients gave written informed consent.

One of two investigators, blinded to patient group allocation, performed baseline tests of psychomotor function, the DSST and TMT, before the start of sedation/analgesia. The DSST assesses cognitive speed and accuracy, and requires the participant to identify nine different symbols by using a pre-defined corresponding number for each symbol, during a fixed time period. The TMT is a test for broad cognitive performance that uses the connect-a-dot concept, requiring the participant to draw lines from circle to circle to consecutively link numbers in the quickest time possible. They also made a score of Observer's Assessment of Alertness and Sedation (OAA/S)[14] at this time. Additionally, all patients were asked to assign a score on an 11-point 0–10 verbal rating scale (VRS) for their feelings of energy, appetite, nausea, restlessness, tiredness, relaxation, dizziness, pain and sleepiness. All questions were asked by one of two investigators, and phrased as follows: e.g. for energy, patients were asked to score their feeling of energy, where 0 indicated a feeling of having no energy and 10 indicated a feeling of having the maximum amount of energy the patient could imagine having.

The randomization process was carried out once patients signed an informed consent form. The randomization process involved removal of a number 1, 2, 3 or 4 from a bag indicating to which study group the patient would belong. Two of the groups received a combination of midazolam and fentanyl, with either placebo (group MFP) or modafinil (group MFM), and the other two groups received a combination of remifentanil and propofol, with either placebo (group RPP) or modafinil (group RPM) (Fig. 1). The placebo was prepared by our institution's pharmacy department and was identical in appearance to the modafinil tablet. Both modafinil 200 mg and the placebo were administered 1 h before the commencement of ESWL therapy to ensure that the time of peak plasma concentration of modafinil, which is 2–4 h after oral administration,[15] coincided with the recovery period following ESWL treatment. Administration times of modafinil/placebo and sedation/analgesia were recorded.

The drug regimen for groups MFP and MFM was midazolam 0.03 mg/kg and fentanyl 1 μg/kg, plus extra boluses of fentanyl 0.5 μg/kg when a patient reported pain, and midazolam 0.15 mg boluses according to the observed level of sedation. For groups RPP and RPM, the dosing regimen was propofol 1–3 mg/kg/h and remifentanil 3–6 μg/kg/h, starting at the lower doses of 1 mg/kg/h for propofol and 3 μg/kg/h for remifentanil and increasing incrementally, e.g. remifentanil was initially increased to 4 μg/kg/h and subsequently

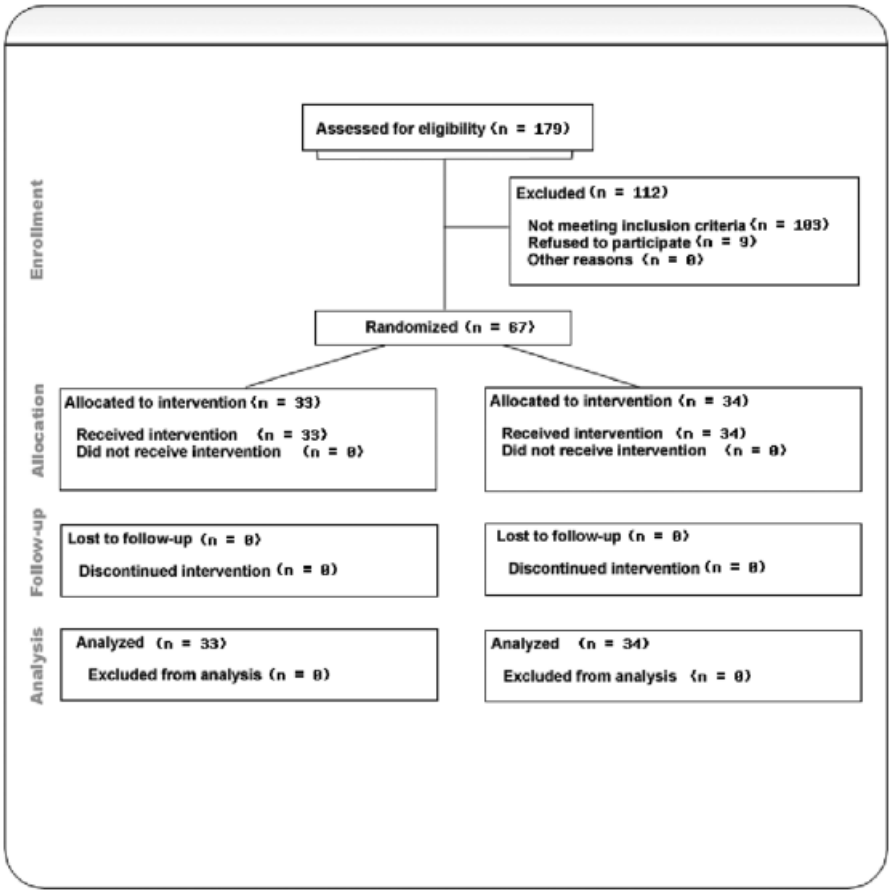

Fig. 1. Consort flow chart. Arm A, placebo; Arm B, modafinil.

5 μg/kg/h according to the patient-reported pain with propofol being increased in 1 mg/kg/h increments according to the observed level of patient sedation. A standard target level of sedation, whereby patients were calm, co-operative and communicative (Ramsay sedation scale 2) or asleep but responded quickly to verbal instruction (Ramsay sedation scale 3) was used.[16,17] The investigators were unaware of the group to which patients were assigned; this information was known only to the anesthesiologist and anesthetic nurse, responsible for a patient's sedation/analgesia. The blinded investigators were only made aware of the group allocation after all data were collected.

During the ESWL therapy and in the recovery room post-treatment, all patients had electrocardiogram, non-invasive blood pressure and peripheral pulse oximetry monitoring. Supplemental oxygen was administered via a face mask at a rate of 6 l/min. Before commencing sedation/analgesia, all patients received granisetron 1 mg and dexamethasone 8 mg intravenously (i.v.) as anti-emetic prophylaxis and diclofenac 75 mg i.v. for post-treatment pain; where diclofenac was contraindicated, paracetamol 1 g was administered i.v. The occurrence of any adverse events such as bradycardia (defined as a >20% decrease in heart rate from baseline), oxygen desaturation (defined as a decrease in saturation to 94% or less) and hypo or hypertension (defined as an alteration of >20% greater or less than baseline recordings) were also recorded.

Once ESWL treatment was complete, sedation/analgesia drugs were discontinued and patients were transferred to the recovery room (phase 1 recovery). Total doses of all drugs administered were noted. Approximately 15 min after ending the ESWL therapy, the TMT and DSST were repeated. A second OAA/S and VRS (0–10) for a number of different variables were also performed in the recovery room. A post-anesthesia recovery score (Aldrete Score) was recorded for the first time. The exact time from the completion of ESWL shocks to the performance of these tests was recorded.

Patients were discharged from the recovery room to the ward (phase 2 recovery) when their

vital signs were normal, pain scores were satisfactory (VRS ≤ 4) and they had no nausea or vomiting. At 1 h after the last ESWL shock, patients completed a third and final DSST, TMT and VRS. A second OAA/S and Aldrete score were recorded at this time. The exact time of these tests was recorded for each patient.

Finally, the day after the ESWL treatment, patients were contacted by telephone and asked to score an 11 point (0–10) VRS, their feeling of sleepiness, agitation, nervousness, excitement, appetite, headache and itchiness.

Power calculations

To calculate the number of patients per group to be enrolled in the study, we used the results from a previous study. We took the outcome of the DSST as our primary outcome variable. With our study, we wanted to be able to show a difference of seven symbols in the DSST between groups. Within-group data from a study by Lichtor et al.[18] showed a standard deviation of six symbols in the DSST. We accepted an α-value of 0.05 (and thus 0.025 for the four-group comparison) and a power of 80%. This results in a minimum study size of 15 per group and 60 for the total study.

Statistical analysis

Intergroup comparisons for age, weight, operative time and VRS scores were conducted using an analysis of variance (ANOVA) with a Student–Newman–Keuls test or a non-parametric Kruskal–Wallis test when appropriate. Intergroup comparisons for ASA class distribution and male/female ratios were analyzed using the Fisher test for independence. Intragroup comparisons of VRS scores over time were performed using a repeated-measures ANOVA with a Student–Newman–Keuls test or a Friedman non-parametric test when appropriate. A Student's *t*-test was used to demonstrate a significant difference between the maximal anticipated VRS score and the maximal real post-operative VRS score. Intergroup comparisons of VRS intensity scores were analyzed using an ANOVA with a Student–

Table 1

Verbal rating scale (VRS) for variables showing a statistically significant difference at different time points.

	Midazolam/ Fentanyl/Placebo ($n = 17$)	Midazolam/ Fentanyl/Modafinil ($n = 16$)	Remifentanil/ Propofol/Placebo ($n = 16$)	Remifentanil/ Propofol/Modafinil ($n = 18$)
Pain				
Pre	1.5 (1.7)	0.1 (0.5)	0.3 (0.9)	1.9 (2.3)*
RR	1.0 (1.3)	0.9 (1.9)	1.3 (1.9)	1.8 (2.1)
Post	0.6 (1.2)	0.6 (1.6)	1.1 (1.7)	2.1 (2.1)
Tiredness				
Pre	3.2 (2.2)†	2.4 (2.5)	1.9 (2.2)	3.6 (2.2)
RR	5.1 (2.6)	3.1 (3.5)	3.5 (2.8)	4.4 (2.7)
Post	3.8 (2.5)‡	1.3 (2.0)	2.6 (2.2)	3.1 (2.7)
Dizziness				
Pre	0.3 (1.0)	0.3 (0.8)	0.06 (0.3)	0.6 (1.1)
RR	1.5 (2.2)	1.5 (2.3)	0.4 (1.1)	2.1 (2.4)
Post	0.7 (1.5)	0.6 (1.4)	0.0 (0.5)	1.7 (2.0)§
Energy				
Pre	7.1 (1.0)¶	6.8 (1.6)	7.1 (1.5)‖	6.2 (1.4)
RR	5.0 (1.6)	5.5 (2.3)	5.4 (1.1)	5.4 (1.7)
Post	6.7 (1.2)¶	6.8 (1.3)	6.7 (1.8)	6.5 (1.0)
Sleepiness				
Pre	2.7 (2.4)**	1.8 (3.0)	2.7 (2.9)	2.5 (2.1)
RR	5.1 (2.8)	3.1 (3.3)	3.7 (2.4)	3.3 (2.7)
Post	4.3 (2.9)	2.6 (3.5)	3.7 (2.4)	3.3 (2.7)

Values are mean (SD). Pre, before ESWL; RR, recovery room; Post, 1h after last ESWL shock.
Statistically significant difference between groups:
*Pain, Pre: group RPM vs. groups MFM and RPP;
‡Tiredness, post: group MFP vs. group MFM;
§Dizziness, post: group RPM vs. group RPP.
¶Statistically significant difference within groups; zEnergy, group MFP, RR vs. pre, and RR vs. post;
†Tiredness, group MFP, Pre versus RR;
**Sleepiness, group MFP, pre vs. RR;
‖Energy, group RPP, pre vs. RR.

Newman–Keuls test, a non-parametric Kruskal–Wallis test, a *t*-test, or a Student–Newman–Keuls test when appropriate. Statistical significance was accepted at a probability value <0.05.

Results

In total, 67 patients completed the study, randomly distributed over four groups. The demographic details of patients who completed the study showed no statistically significant differences for age [which varied from 47.7 (12.1) years in group MFP to 53.0 (12.6) years in group RPM], weight, height and ASA classification. There was a statistically significant difference in the percentage of male patients in group RPM (94%) compared with RRP (63%), $P = 0.05$. There were no statistically significant between-group differences for oxygen desaturation, bradycardia, hyper/hypotension, duration of ESWL treatment, which varied from 32.4 (5.7) min in group RPM to 36.6 (5.9) min in group MFP, the total number of shocks and shock level. Total doses of sedating and analgesic agents administered did not differ between placebo- and modafinil-treated groups. Group MFP received an average dose of 153.7 (45) μg of fentanyl and 4.1 (5.4) mg of midazolam vs. group MFM, who received 151.6 (72.3) μg of fentanyl and 3.2 (0.9) mg of midazolam. Group RPP received remifentanil 246.9 (99.7) μg and propofol 76.4 (24.7) mg, while group RPM received 309.4 (116.5) μg of remifentanil and 76.1 (35.0) mg of propofol.

For DSST, our primary endpoint, no statistically significant difference was shown in the number of digits substituted by symbols in a 2-min period, between modafinil- and placebo-treated groups, as shown in Table 2. Similarly, other objective tests, namely TMT (Table 3), OAA/S and Aldrete scores, revealed no statistically significant between- or within-group differences at the time points measured.

Secondary endpoints of note include VRS (0–10) on the day of treatment pre-ESWL, in the recovery room and at 1 h after ESWL; the following differences were found between groups: pre-ESWL pain scores were statistically significantly greater, $P = 0.002$ in group RPM [1.9 (2.3)] vs. groups MFM [0.1 (0.5)] and RPP [0.3 (0.9)]. The VRS for tiredness 1 h post-ESWL was statistically significantly greater in group MFP [3.8 (2.5)] than in group MFM [1.3 (2.0)], $P = 0.02$. Dizziness scores post-ESWL were statistically significantly greater in group RPM [1.7 (2.0)] than in group RPP [0.0 (0.5)], $P = 0.03$.

In both placebo-treated groups, statistical analysis within each group over time demonstrated statistically significantly lower VRS scores for energy in the recovery room [5.0 (1.6)] vs. pre-ESWL [7.1 (1.0)], $P < 0.0001$ and vs. 1 h post-ESWL [6.7 (1.2)] ($P < 0.01$)

Table 2

Digital symbol substitution test.

	Midazolam/ Fentanyl/Placebo ($n = 17$)	Midazolam/ Fentanyl/Modafinil ($n = 16$)	Remifentanil/ Propofol/Placebo ($n = 16$)	Remifentanil/ Propofol/Modafinil ($n = 18$)
Pre-ESWL	59.3 (13.3)	57.1 (21.2)	65.7 (15.2)	58.2 (14.5)
Recovery room	52.6 (17.7)	53.1 (22.6)	63.8 (15.2)	57.1 (13.8)
1 h post-ESWL	63 (16.2)	58.8 (21.5)	69.1 (18.1)	61.8 (15.6)

Values are mean (SD). Values are number of digits substituted in a 2-min time period. No statistically significant difference was found.

Table 3

Trail making test part A.

	Midazolam/ Fentanyl/Placebo ($n = 17$)	Midazolam/ Fentanyl/Modafinil ($n = 16$)	Remifentanil/ Propofol/Placebo ($n = 16$)	Remifentanil/ Propofol/Modafinil ($n = 18$)
Pre-ESWL	29.9 (10.4)	36.2 (19.9)	33.7 (17.6)	32 (11.5)
Recovery room	32.3 (15.7)	34.7 (15.2)	28.8 (11.4)	30.4 (11.4)
1 h post-ESWL	25.1 (9.8)	34.1 (24.5)	25.2 (9.8)	25.8 (7.9)

Values are mean (SD). Values are seconds taken to complete the trail finding test. No statistically significant difference was found between tests performed at each of three time points.

in group MFP. In the RPP group, there was also a statistically lower energy level reported in the recovery room [5.0 (1.1)] vs. pre-ESWL [7.1 (1.5)], $P = 0.02$. Modafinil-treated groups showed no such within-group statistically significant differences over time.

Within-group MFP, a statistically higher mean VRS (0–10) for tiredness in the recovery room [5.1 (2.6)] vs. pre-ESWL [3.2 (2.2)], was identified, $P = 0.012$. Similarly, for sleepiness, group MFP demonstrated a statistically significantly greater VRS in the recovery room [5.1 (2.8)] vs. pre-ESWL [2.7 (2.4)], $P = 0.02$ (Table 1).

VRS recorded the day after ESWL therapy demonstrated a statistically significantly higher score for appetite in group RPP [8.1 (1.9)] than in group MFP [6.4 (1.9)], $P = 0.038$. No other statistically significant differences were found between groups on the day after therapy.

Discussion

This is the first randomized, double-blind, placebo-controlled study examining the influence of modafinil on the recovery of patients following sedation/analgesia. The primary hypothesis of this study was that administration of modafinil to patients receiving sedation/analgesia improved patient recovery in terms of an objective measurement of psychomotor function. This was primarily assessed using the DSST and failed to show a statistically significant difference between modafinil and placebo groups.

Some secondary endpoints, including subjective patient reporting of tiredness level after sedation/analgesia, revealed reduced tiredness levels in the modafinil-treated group following the use of midazolam/fentanyl but not following the use of remifentanil/propofol. This secondary finding is in keeping with earlier studies, which reported less post-operative 'moderate to severe fatigue' in modafinil vs. placebo-treated patients following non-standardized general anesthesia[11] and an improvement in opioid-induced sedation in modafinil-treated patients with non-malignant pain.[19] However, the value of these subjective findings in light of the absence of an objective improvement in the recovery process must be questioned.

The psychomotor tests used in this study i.e. DSST and TMT are designed to objectively measure a patient's visual–motor co-ordination and speed, and have been used in previous studies on modafinil use.[20,21] The DSST has also been used in studies comparing patient recovery following various forms of sedation,[22,23] while OAA/S and Aldrete scores are objective assessments of a patient's clinical recovery status. As mentioned previously, modafinil has been shown to counter the adverse effects of overnight sleep deprivation on working memory. An implication of this could be that a cognitive task with a stronger working memory component, than what is the case with DSST, might be more sensitive. Another possible limitation of DSST is the time frame; the DSST runs for a 2-min period, which may be a short time span when one considers the importance of tiredness in the context of this study. The DSST has also been used in studies comparing patient recovery following various forms of sedation,[22,23] while OAA/S and Aldrete scores are objective assessments of a patient's clinical recovery status.

Importantly, VRS scores focusing on the potential side effects of modafinil adminstration, demonstrated none, apart from the incidence of dizziness, which was statistically significantly greater in the modafinil- vs. the placebo-treated remifentanil/propofol group at 1 h after the ESWL treatment. Although dizziness is a recognized side effect of remifentanil use,[24] the doses received by both study groups were similar, indicating that the higher incidence of dizziness is likely to be related to modafinil administration. Earlier clinical trials have reported the occurrence of dizziness as a side effect of modafinil use.[15] An important feature of modafinil is its reported lack of interference with recovery sleep.[25] In this current study, recovery sleep was not specifically assessed but there was no difference in the level of sleepiness reported by modafinil and placebo-treated groups on the day after treatment. Of relevance is the absence of side effects on the day after treatment in the modafinil- vs. placebo-treated patients.

In the current study, a relatively uniform, although short duration of sedation/analgesia was administered to patients. It is possible that following a longer duration of sedation/analgesia, an objective difference in the psychomotor measures of recovery between modafinil and placebo groups might become apparent. Also, the possibility that modafinil may provide a beneficial effect in specific subgroups of patients, such as those with obstructive sleep apnea syndrome, may have implications for the treatment of such patients in the ambulatory setting.

An improvement in a patient's subjective feelings of tiredness may contribute to an improvement in a patient's overall satisfaction level. Additionally, patient-reported levels of patient

tiredness may influence the physician's decision when determining suitability for home discharge following ambulatory treatment. However, although scales to measure tiredness have been used in research for some time now,[26,27] unlike in the case of pain, there appears to be no standardized cut-off point on the scale to describe a level of tiredness at which the patient is deemed unfit for discharge home. Investigations of both the most effective dose and the most effective timing of modafinil administration are neccessary.

In conclusion, administration of modafinil to patients receiving longer acting forms of sedation/analgesia does not improve psychomotor function, as measured objectively using the DSST. The value of our secondary finding of a reduction in subjective tiredness experienced during the recovery period requires further evaluation. Whether such a reduction in subjective tiredness allows an earlier return to the activities of daily living needs to be established. Importantly, no major adverse effects of modafinil use were identified in this study.

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