Modafinil for narcolepsy: Systematic review and meta-analysis

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Summary

Background: To assess the effectiveness and safety of modafinil vs. no active treatment or other drugs in the treatment of narcolepsy.

Material/Methods: The following electronic databases were searched throughout January 2009: MEDLINE, EMBASE and The Cochrane Library. Additional references were obtained from reviewed articles. Only randomized controlled trials were included.

Results: We included 9 trials involving 1,054 patients in the study. Modafinil in comparison with placebo brings significant benefit in terms of elimination of excessive daytime sleepiness assessed by: ESS scale – weighted mean difference (WMD) –2.73 points (95%CI –3.39, –2.08), MSLT test – WMD 1.11 minutes (95%CI 0.55, 1.66) and MWT test – WMD 2.82 minutes (95%CI 2.40, 3.24), as well as the number and duration of somnolence, sleep attacks and naps per day, but was not different from placebo in the number of attacks of cataplexy per day. Modafinil in comparison with placebo improved quality of life of narcoleptic patients according to SF-36 questionnaire, but was associated with more common nausea. It had similar effect on excessive daytime sleepiness as sodium oxybate and was associated with less common nausea.

Conclusions: In narcoleptic patients, modafinil in comparison with placebo is effective in the treatment of excessive daytime sleepiness, but not cataplexy.

key words: narcolepsy • modafinil • systematic review • meta-analysis

Abbreviations: CGI – Clinical Global Impression Scale; CI – Confidence Interval; EDS – excessive daytime sleepiness; EMEA – European Medicine Agency; ESS – Epworth sleepiness scale; FCRTT – Four-Choice Reaction Time Test; FDA – Food and Drug Administration; ITT – intention to treat; MSLT – Multiple Sleep Latency Test; MWT – Maintenance of Wakefulness Test; RCT – randomized controlled trial; RD – risk difference; RR – relative risk; SF-36 – short form 36; SPCT – Steer Clear Performance Test; VAS – visual analogue scale; WMD – weighted mean difference

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BACKGROUND

Narcolepsy is a chronic sleep disorder characterized by overwhelming daytime sleepiness and sudden attacks of sleep, with or without cataplexy. Although there’s no cure for narcolepsy, medications and lifestyle changes can help manage the symptoms [1]. Modafinil pharmacological profile differs from those of amphetamine and methylphenidate, 2 classical psychostimulants. Modafinil, like other stimulants, increases the release of monoamines, but also elevates hypothalamic histamine levels, leading some researchers to consider modafinil a “wakfulness promoting agent” rather than a classic amphetamine-like stimulant [2]. It is approved for the treatment of the excessive daytime sleepiness associated with narcolepsy and has been used in the treatment of depression, cocaine addiction, Parkinson’s disease, schizophrenia, shift work, attention deficit/hyperactivity disorder, fatigue in multiple sclerosis, residual sleepiness in sleep apnea and morphine-induced sleepiness in cancer [3].

In 2 identified review articles the authors analyzed all possible uses of modafinil [3,4]. They did not pool the data from 4 identified studies on narcolepsy and concluded that modafinil can be effective in many disorders with excessive sleepiness during the day [3,4]. Other review articles analyzed all available methods of treatment of narcolepsy [5] or narcolepsy and other hypersomnias of central origin [6], but the last search was done in July 2007 and was restricted to studies published in English language. All identified review articles and available practice guidelines [7,8] presented the data only descriptively, without meta-analysis. Since no published systematic review with meta-analysis was found, we conducted a systematic review with updated searches to assess the effectiveness and safety of modafinil in comparison with no active treatment or other drugs in the treatment of narcolepsy.

MATERIAL AND METHODS

Criteria for study inclusion in the present review

Types of studies

Prospective parallel or cross-over randomized controlled trials (RCT), single or double blinded, published as full text in peer-reviewed journals. Studies published only as abstracts were excluded.

Types of participants

Participants in included studies were adult narcolepsy patients with or without cataplexy.

Types of intervention

Modafinil in any dose and dosing scheme compared with placebo or other active treatment.

Types of outcome measures

Primary outcomes were: 1) elimination of excessive daytime sleepiness assessed by objective laboratory tests (multiple sleep latency test [MSLT] [9], Maintenance of Wakefulness Test [MWT] [10]) or validated subjective outcome measures (Epworth sleepiness scale [ESS] [11]), number and duration of severe somnolence, sleep attacks and naps, as reported by patients), 2) reduction of cataplexy assessed by simple subjective reporting (no cataplexy, at least 50% decrease).

Secondary outcomes were: 1) quality of life assessed by validated generic questionnaires (Short Form-36) or validated sleep-specific questionnaires [12], 2) disease severity assessed by the Clinical Global Impression scale, 3) performance assessed with the four-choice reaction time test (FCRTT), 4) physician evaluation of alerting effect on VAS scale, 5) adverse events, 6) withdrawals due to adverse events.

Search strategy

The following electronic databases were searched without language restriction from inception until January 2009: MEDLINE via PubMed, EMBASE via Ovid, The Cochrane Central Register of Controlled Trials, The Cochrane Database of Systematic Reviews and BioMed Central. In addition, HTA agencies websites and DARE, NHS EED and HTA databases were searched for review articles. Reference lists of reviews, HTA reports and included studies were checked for additional relevant studies. The EMEA and FDA websites were checked for reported adverse effects and other relevant information concerning clinical trials. Registers of controlled trials (www.controlled-trials.com, www.clinicaltrials.gov) were searched for unpublished or on-going trials. Clinical experts and drug manufacturer were consulted concerning any additional data. In addition, the following conference proceedings were searched: SLEEP 2007 – 21st Annual Meeting of the Associated Professional Sleep Societies (June 9–14, 2007, Minneapolis, Minnesota) and 18th Congress of the European Sleep Research Society (September 12–16, 2006, Innsbruck).

METHODS OF THE REVIEW

The methods of systematic reviews were applied as described in the Cochrane Handbook and the report was prepared according to the QUOROM statement [13,14]. The search was carried out by 2 reviewers independently (M.N., D.G.). Titles and abstracts were independently assessed by 3 reviewers (D.G., M.N., M.M.B.). All potentially relevant articles were retained and their full text was checked to determine whether they met the inclusion criteria.

Data extraction was undertaken by 1 reviewer (D.G.) using a standard data extraction form and checked by 2 other reviewers (M.N., M.M.B.). Discrepancies were resolved by discussion and consultation with a fourth reviewer. A.W. participated in all the stages of the review process as a clinical consultant. For the included studies, information was extracted on study design, participants, intervention, number of patients lost to follow-up, and primary and secondary outcomes. The methodological quality of each included trial was assessed independently by 3 reviewers (D.G., M.N., M.M.B.) according to the Jadad scale [15], and the allocation concealment and intention to treat analysis were evaluated (Table 1).

For dichotomous data, the impact of the intervention was expressed as relative risk (RR) with 95% confidence intervals (CI) and risk difference (RD) with 95% CI using the Mantel-Haenszel method. For continuous data the difference
between the groups was expressed as mean differences with 95% CI (if the same scale was used in all studies) or standardized mean differences with 95% CI (when different scales were used), using inverse variance method otherwise. Heterogeneity among the results of the trials was assessed by Chi-square and I-square tests. Fixed effect model was used by default, but if heterogeneity was detected, a random effects model was used. In all analyses RevMan 5.0.0 was used.

Results

The initial search identified 216 studies from MEDLINE, 110 from EMBASE, 47 from the Cochrane Central Register of Controlled Trials (Figure 1). After initial screening of titles and abstracts (where available), 29 potentially relevant journal articles were retrieved. Of those, 19 papers were excluded either because they: were nonrandomized studies (5), did not include patients with narcolepsy (3), did not assess efficacy of modafinil (4), were a retrospective study (1), represented a report on the open phase of an included study (1), or compared different doses of modafinil (4). Nine RCTs published in 10 articles met our predefined inclusion criteria [16–25]. Additionally, 1 study was found by hand searching of reference lists [26]; however, it was only published in conference abstract form, and as no response from the author was received, it was therefore excluded from the systematic review. Four additional studies were identified in conference proceedings [27–30]. All of them were excluded from the systematic review: 1 was a retrospective analysis of studies conducted in mixed population [27], 1 included children [28], 1 included mixed population [29] and 1 was duplicate publication [30] of a study already excluded from the review [31].

Three included studies were conducted at a single centre, 4 in multiple centres in 1 country, and 2 in multiple centres in more than 1 country. Sample size varied between 10 [20] and 283 [24], however only 3 studies included more than 100 patients [19,24,25]. All studies were double blind; 5 were of cross-over design. US 1998 [24] and US 2000 [25] were twin studies with similar sample size, arms, inclusion and exclusion criteria and outcome measures. Moldofsky et al. [22] was an extension of Broughton et al. [21] – after 6 weeks of cross-over double blind RCT and 16 weeks of open label phase, patients still in the study were randomized into a 2-week double blind parallel study. The characteristics of all included studies are described in Table 2.

Participants in the studies were patients with narcolepsy, and over 17 years old. The percentage of women was from 34% [18] to 66.7% [22], a d mean or median age was between 39 [19,23] and 53 years [16]. Time from the first symptoms of narcolepsy was between 14.5 years [22] to 24.8 years (placebo group in US 2000 study [25]), and the time from the diagnosis of narcolepsy was between 6.6 years [25] to 9.7 years [24].

All studies except 1 [19] assessed efficacy of modafinil in comparison with placebo. Black and Houghton [19] compared modafinil with sodium oxybate in patients with narcolepsy perviously treated with modafinil in fixed doses for 4 weeks. Modafinil was used in the dose of 300 mg/d...
Table 2. Study characteristics.

<table>
<thead>
<tr>
<th>Study author and year of publication; design; country</th>
<th>N</th>
<th>Population</th>
<th>Age, gender, other</th>
<th>Intervention</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besset 1993 [16]; RCT, DB, cross-over; France</td>
<td>16</td>
<td>Narcolepsy for a mean of 21.12 yrs +/-4.23, range 3–48; cataplexy 87.5%</td>
<td>18–64 yrs (median 53); F 44%</td>
<td>Modafinil 300 mg/d vs. placebo</td>
<td>2×4 weeks with 2 weeks run in period and 2 weeks wash out periods between treatments</td>
</tr>
<tr>
<td>Besset 1993 [16]; RCT, DB, cross-over; France</td>
<td></td>
<td>Narcolepsy with cataplexy, mean 14.51±13.98 yrs since first symptoms</td>
<td>40.88 yrs ±13.27; F 34%</td>
<td>Modafinil 300 mg/d vs. placebo</td>
<td>2×4 weeks with 2 weeks run in period and 2 weeks wash out periods between treatments</td>
</tr>
<tr>
<td>Billiard 1994 [18], 1994, RCT, multicentre, DB, cross-over; France</td>
<td>50</td>
<td>Narcolepsy with cataplexy, mean 14.51±13.98 yrs since first symptoms</td>
<td>87.5%</td>
<td>Modafinil 300 mg/d vs. placebo</td>
<td>2×4 weeks with 2 weeks run in period and 2 weeks wash out periods between treatments</td>
</tr>
<tr>
<td>Black 2006 [19]; RCT, multicentre, DB, parallel; North America, Europe</td>
<td>231</td>
<td>Narcolepsy</td>
<td>81.6±17.4 kg</td>
<td>Sodium oxybate (6–9 g), sodium oxybate + modafinil (200–600 mg/d), modafinil (200–600 mg/d) vs. placebo</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Boivin 1993 [20]; RCT, DB, cross-over; Canada</td>
<td>75</td>
<td>Narcolepsy with cataplexy</td>
<td>43±16 yrs; F 63%</td>
<td>Modafinil 200 mg/d, modafinil 400 mg/d vs. placebo</td>
<td>2×4 weeks with 2 weeks run in period and 2 weeks wash out periods between treatments</td>
</tr>
<tr>
<td>Broughton 1997 [21]; RCT, multicentre, DB, cross-over; Canada</td>
<td>75</td>
<td>Narcolepsy; 23±16 yrs since first symptoms and 7 yrs since diagnosis; daytime sleep attacks 100%, cataplexy 80%*</td>
<td>45±16 yrs; F 66.7%</td>
<td>Modafinil (mean dose 329±61 mg) vs. placebo</td>
<td>2 weeks of blinded treatment</td>
</tr>
<tr>
<td>Moldofsky 2000 [22]; RCT, multicentre, DB, parallel; Canada</td>
<td>63</td>
<td>Narcolepsy (participants of Broughton et al. [19] study); mean of 24±15 yrs since first symptoms and 7 years since diagnosis</td>
<td>Modafinil (mean dose 329±61 mg) vs. placebo</td>
<td>2 weeks of blinded treatment</td>
<td></td>
</tr>
<tr>
<td>Saletu 2008 [23]; RCT, DB, cross-over; Austria</td>
<td>16</td>
<td>Narcolepsy</td>
<td>Modafinil 400 mg/d vs. placebo</td>
<td>9 weeks, + open label phase preceded by 2 weeks wash-out period</td>
<td></td>
</tr>
<tr>
<td>US Modafinil in Narcolepsy Multicenter Study Group 1998 [24]; RCT, multicentre, DB, parallel; USA</td>
<td>283</td>
<td>Narcolepsy; from 21±14.6 to 23.2±15.4 yrs since first symptoms and from 7.3±9.6 to 9.7±11.5 yrs since diagnosis; daytime sleep attacks 95%, cataplexy 88%, interrupted nighttime sleep 71%, hypnagogic hallucinations 69%, sleep paralysis 64%</td>
<td>42 yrs, range 18–68 yrs; F 54%; weight 86.7±20 kg, height 172±10 cm</td>
<td>Modafinil 200 mg/d, modafinil 400 mg/d vs. placebo</td>
<td>9 weeks, + 2-weeks cessation of treatment</td>
</tr>
<tr>
<td>US Modafinil in Narcolepsy Multicenter Study Group 2000 [25]; RCT, multicentre, DB, parallel; USA</td>
<td>271</td>
<td>Narcolepsy; from 21.8 to 24.8 yrs since first symptoms and from 6.6 to 8.1 yrs since diagnosis; daytime sleep attacks 94%, cataplexy 72%, interrupted nighttime sleep 71%, hypnagogic hallucinations 61%, sleep paralysis 53%</td>
<td>42 yrs, range 17–67 yrs; F 54%; weight from 79.2±20.1 to 82.5±17.8 kg; height from 171.3±10.8 to 172.6±11</td>
<td>Modafinil 200 mg/d, modafinil 400 mg/d vs. placebo</td>
<td>9 weeks, + 2-weeks cessation of treatment</td>
</tr>
</tbody>
</table>

* Some patients had their cataplexy symptoms relieved with amitriptiline (1 patient), clomipramine (5), fluoxetine (5), imipramine (2), paroxetine (2), protriptyline (8), sertraline (1) or gamma hydroxybutyrate (5). DB – double blind; F – female; RCT – randomized controlled trial.
[16,18,20], 400 mg/d [23], in 2 doses of 200 mg/d or 400 mg/d [21,24,25], or in flexible doses of mean 329 mg [22] and from 200 to 600 mg/d [19]. Sodium oxybate was used in the dose of 6 g per night for 4 weeks, and then for the rest of the study in the dose of 9 g per night.

Most studies were of good quality (≥3 points in Jadad scale), 1 study was of poor quality (2 points in Jadad scale), 5 studies did not provide information on allocation concealment, and 4 had adequate allocation concealment. None of the studies reported proper intention to treat analysis, in 2 studies it was unclear and in 3 studies the authors provided analysis for all randomized patients who received study medication and had at least 1 post-baseline measure for efficacy (modified ITT). Follow-up ranged from 2 to 9 weeks. Quality of included studies is described in Table 1.

**Efficacy**

**Modafinil vs. placebo**

1. **Elimination of excessive sleepiness during the day**

   1.1. Number of severe somnolence, sleep attacks and naps per day

   This outcome measure was used in 4 studies [18,20–22]; 3 were cross-over studies and during modafinil treatment phase showed benefit as compared with placebo treatment phase, and 1 study was parallel and the observed effect of modafinil was similar (Figure 2).

   1.2. Duration of somnolence, sleep attacks and naps per day

   This outcome measure was used in 2 cross-over studies [18,20]. In both studies benefit in the modafinil treatment phase compared with placebo treatment phase was observed (Figure 3).

   1.3 Multiple Sleep Latency Test

   This outcome measure was used in 3 studies [23–25]. In 2 parallel studies the increase in mean sleep latency was observed in modafinil as compared with placebo group (Figure 4) [24,25]. The cross-over study presented median values, which were higher in the modafinil treatment phase compared with the placebo treatment phase (6.6 min vs. 3.2 min; p<0.05) [23].

   1.4. Maintenance of wakefulness test

   This outcome measure was used in 6 studies [16,19,21,22,24,25]. In 4 parallel studies the increase in mean sleep latency was observed in modafinil in comparison with placebo group (Figure 5) [19,22,24,25]. Similar increase in mean sleep latency was also observed in cross-over studies (Figure 5) [16,21].

   In Moldofsky et al. [22], after 2 weeks of blinded phase, in patients who were given placebo while previously on modafinil, significant reduction in sleep latency was observed (by 37%; p=0.006) compared with nonsignificant reduction in patients still on modafinil (by 7%; p=0.35). Significantly more MWT testing sessions were finished without falling
asleep by patients on modafinil compared with patients on placebo (24.3% vs. 6.1%; p<0.001).

In Black and Houghton [19], patients on placebo had significant reduction in daytime sleep latency from the beginning of the baseline period to the end of double-blind treatment phase (~2.72 min; p<0.001), which was a consequence of withdrawal from modafinil. In the modafinil group the reduction in daytime sleep latency was significantly smaller (~0.53 min; p=0.006).

1.5. Epworth sleepiness scale (ESS)

This subjective outcome measure was used in 6 studies [19,21,22–25]. In cross-over study modafinil reduced the likelihood of falling asleep assessed in ESS in comparison with placebo group [21]. The score in ESS scale was also lower in patients receiving modafinil compared with patients on placebo in parallel studies (Figure 6) [22,24,25].

In Molsloski et al. [22], likelihood of falling asleep increased in patients withdrawn from modafinil and receiving placebo (by 19%, p=0.007), compared with patients continuing on modafinil (+1%; p=0.57).

In Saelubu et al. [23], cross-over study median score on ESS scale decreased from 14.5 point during placebo treatment to 12.5 points after 3 weeks of modafinil treatment (p<0.05).

In Black and Houghton [19] no significant change in median average ESS score in modafinil group was seen as compared with placebo group (from 14 points to 15 points vs. from 16 points to 16 points; p=0.77)
2. Elimination of cataplexy

This outcome was measured in 4 studies [18,20-22]. There was no significant effect of modafinil as compared with placebo in 3 cross over studies [18,20,21], as well as in one parallel study [22] (Figure 7).

![Figure 8. The effect of modafinil (all doses) compared with placebo on study discontinuation due to adverse events. CI – confidence interval, M-H – Mantel-Haenszel method.]

| Table 3. Summary of the meta-analysis of the adverse reactions: modafinil vs placebo. |
|---|---|---|---|---|---|---|
| **Adverse effect** | **Number of studies** | **Number of participants (modafinil/placebo)** | **Effect size (95% CI)** | **Analysis model** | **Heterogeneity test** |
| Discontinuation due to adverse events | 6 | 555/366 | RR 2.06 (0.84, 5.10) | F | 15 |
| | | | RD 0.02 (0.00, 0.04) | F | 37 |
| Headache | 5 | 478/290 | RR 1.16 (0.95, 1.40) | F | 26 |
| | | | RD 0.03 (–0.07, 0.13) | F | 37 |
| Infection | 2 | 369/185 | RR 0.88 (0.58, 1.34) | F | 8 |
| | | | RD –0.02 (–0.08, 0.04) | F | 20 |
| Pain | 2 | 369/185 | RR 0.73 (0.43, 1.21) | F | 0 |
| | | | RD –0.03 (–0.09, 0.02) | F | 0 |
| Backpain | 3 | 385/201 | RR 1.06 (0.61, 1.83) | F | 41 |
| | | | RD 0.01 (–0.07, 0.08) | F | 51 |
| Flu syndrome | 2 | 207/108 | RR 1.91 (0.69, 5.25) | F | 0 |
| | | | RD 0.04 (–0.02, 0.09) | F | 0 |
| Nausea | 4 | 448/257 | RR 2.84 (1.44, 5.57) | F | 0 |
| | | | RD 0.07 (0.03, 0.11) | F | 50 |
| Diarrhea | 3 | 432/241 | RR 2.01 (0.96, 4.17) | F | 0 |
| | | | RD 0.04 (0.00, 0.07) | F | 0 |
| Dyspepsia | 2 | 369/185 | RR 0.94 (0.50, 1.75) | F | 40 |
| | | | RD –0.00 (–0.05, 0.04) | F | 38 |
| Dry mouth | 3 | 270/164 | RR 1.35 (0.14, 13.47) | R | 71 |
| | | | RD 0.01 (–0.08, 0.10) | R | 82 |
| Nervousness | 3 | 399/218 | RR 1.37 (0.73, 2.57) | F | 0 |
| | | | RD 0.02 (–0.02, 0.06) | F | 0 |
| Dizziness | 2 | 79/72 | RR 0.64 (0.26, 1.60) | F | 0 |
| | | | RD –0.04 (–0.13, 0.05) | F | 0 |
| Rhinitis | 2 | 369/185 | RR 1.54 (0.46, 5.16) | R | 68 |
| | | | RD 0.03 (–0.05, 0.12) | R | 64 |
| Pharyngitis | 2 | 254/148 | RR 0.89 (0.34, 2.35) | F | 0 |
| | | | RD –0.00 (–0.05, 0.04) | F | 0 |
| Dysmenorrhea | 2 | 207/108 | RR 0.82 (0.33, 2.07) | F | 0 |
| | | | RD –0.01 (–0.07, 0.04) | F | 0 |

F – fixed effects model; R - random effects model; RD – risk difference; RR – relative risk.

3. Quality of life

3.1. SF-36 and disease specific supplementary scales

Quality of life was measured in US 1998 [24] and US 2000 [25] studies according to SF-36 and validated narcolepsy-specific questionnaire [12] and analyzed in Beusterien et al. [17]. At the end of a 9-week treatment period patients receiving...
modafinil compared with those receiving placebo had significantly higher scores in 5 out of 7 narcolepsy-specific domains, SF-36 mental health summary scale and 4 (modafinil 200 mg/d) or 5 (modafinil 400 mg/d) SF-36 domains.

In both modafinil dose groups patients had fewer limitations in everyday activities due to physical problems, more energy, better scores in mental health summary, fewer narcolepsy symptoms, and had higher attention/concentration and productivity and self-esteem. Patients in the higher modafinil dose group also had fewer limitations in everyday activities due to emotional problems, and had better social functioning and overall health perceptions, while patients in lower modafinil dose group had better physical functioning and less driving limitation.

4. Other endpoints

4.1. Disease severity assessed by Clinical Global Impression scale

This outcome was measured in 4 studies [18,19,24,25]. In cross-over study CGI test score was nonsignificantly higher during a 4-week modafinil treatment period compared with placebo phase (2.29 vs. 2.0; p=0.19) [18]. Two out of 3 parallel studies showed significantly larger numbers of patients who improved according to physician assessment as compared with placebo groups [24,25]. One study [19] did not show significant effect. The pooled effect estimate was significant (RR 1.6, 95% CI 1.32 to 1.95), however there was moderate heterogeneity (I²=46%), introduced by Black and Houghton [19], which enrolled patients already treated with modafinil and used different doses of the drug. Pooled CGI data from 2 studies showed significant improvement with no corresponding heterogeneity (RR 2.83, 95% CI 1.90 to 4.20; I²=0%) [24,25].

4.2. Performance assessed with the four-choice reaction time test (FCRTT)

This outcome measure was used in 3 studies [20–22]. In 1 cross-over study, modafinil treatment phase compared with placebo treatment phase was associated with significant reductions in the number of gaps and the percentage of errors, and nonsignificant reduction of the mean reaction time [20]. In another cross-over study [21] and parallel study [22], no significant difference between modafinil and placebo groups were observed.

4.3. Steer Clear Performance Test (SPCT)

This outcome measure was used in 2 studies [24,25]. Significant improvement in driving vehicle ability was observed in the modafinil group as compared with the placebo group (WMD –2.54, 95% CI from –4.24 to –0.85).

4.4. VAS scale physician evaluation of alerting effect

This outcome measure was used in 1 cross-over study [20]. No significant difference between modafinil and placebo treatment phase was seen for alerting effect.

**Modafinil vs. sodium oxybate**

Sodium oxybate is approved as an effective agent for the treatment of all core symptoms of narcolepsy in adult patients with narcolepsy associated with cataplexy. Modafinil was compared with sodium oxybate in 1 study [19]. In this study patients already receiving modafinil were randomized to modafinil continuation or switch to sodium oxybate.

**Elimination of excessive sleepiness during the day**

This outcome was measured by MWT and ESS test. No significant difference was observed between modafinil and sodium oxybate groups in the change of the mean sleep latency (mean difference –1.11 (95% CI from –3.02 to 0.8)). ESS score decreased in sodium oxybate group from 15 to 12 points and increased in modafinil group from 14 to 15 points.

**SAFETY**

Modafinil was associated with more patient withdrawals from treatment due to adverse events – 4% of patients in modafinil group were withdrawn from the studies due to adverse events and 1.6% in placebo group; however, pooled risk ratio was not significant (Figure 8; Table 3).

Rates of adverse events reported in included studies were pooled and the results are presented in Table 3. Significantly more patients reported nausea in the modafinil group as compared with placebo group. Other reported adverse events rates were similar between the groups (Table 3).

In the study comparing modafinil with sodium oxybate, nonsignificantly fewer patients in modafinil group compared to sodium oxybate group discontinued treatment due to adverse events (3.2% vs. 7.3%). Any adverse event rate was also similar in modafinil and sodium oxybate groups (54% vs. 60%). The most commonly reported adverse event was nausea, which was rare in modafinil compared to sodium oxybate group (3.2% vs. 22%; RR 0.15, 95% CI 0.03 to 0.62). Other adverse events rates were similar in modafinil and sodium oxybate groups.

FDA websites included 1 warning of adverse reactions not observed in clinical trials, but noted in their postmarketing surveillance. The FDA issued a warning of serious skin reactions, which may occur during modafinil treatment [32,33], as between December 1998 and January 2007 6 such cases were noted. Those included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms occurring in 4 females and 2 males aged 49, 42, 17, 27, 15 and 7 years respectively. None of the patients died.

**DISCUSSION**

This systematic review assessing effectiveness and safety of modafinil in comparison with no active treatment or other drugs in the treatment of narcolepsy found 9 studies published in 10 articles. These studies enrolled 1,054 patients; among them 629 were receiving modafinil. All studies compared modafinil with placebo, 1 of them also with sodium oxybate [19]. No other published studies assessing the effect of modafinil in comparison with other active treatment, especially methylphenidate, were found.

We found that treatment with modafinil in comparison with placebo is associated with significant benefit in terms...
of the number and duration of somnolence, sleep attacks and naps, increase in mean sleep latency, and reduction in the likelihood of falling asleep as assessed in ESS. No benefit though was associated with modafinil in elimination of cataplexy as measured by the number of attacks per day. However, modafinil compared with placebo improved quality of life of patients with narcolepsy [17], measured by generic instruments such as SF-36, as well as validated narcolepsy-specific questionnaire [12]. In addition, when we pooled the results from 3 studies [19,24,25], patients receiving modafinil were more likely to improve according to physician assessment in Clinical Global Impression Scale as compared with placebo group.

As in every systematic review publication, bias might also be an issue here; however, several databases were searched together with hand searching of the reference lists of included studies and review articles and conference proceedings, checking the registers of controlled trials, contacting drug manufacturers and clinical experts. Due to the small number of trials it was not possible to formally assess the presence of publication bias.

One of the limitations of our review is the length of follow-up of identified studies: 2 to 9 weeks. When compared with the follow-up of clinical studies in other chronic diseases, it seems to be quite short. Nevertheless, the effect of modafinil is already seen after the first dose of the drug, while the effect of some of the disease-modifying drugs used in rheumatoid arthritis is visible only after 3 months of treatment. It seems that such a short follow-up is specific for narcolepsy clinical trials, as in identified Cochrane reviews or protocols less than 30 days follow-up is considered to be short, and over 30 days follow-up is considered to be long [34,35]. If those criteria are applied to included studies, 3 (n=824) [19,24,25] out of 9 (n=1,054) are considered to have long-term follow-up.

More than half of the included studies were of cross-over design. Pooling the data of cross-over and parallel studies together is considered controversial by some researchers. In our analysis results of cross-over and parallel studies were pooled separately in subgroups, and then all together, and are presented in 1 graph where it can easily be seen that the treatment effect of modafinil was similar in those 2 types of study designs.

We identified 2 review articles assessing all possible uses of modafinil [3,4] and 2 reviews analyzing all available methods of treatment of narcolepsy [5] or narcolepsy and other hypersomnias of central origin [6]. All of the identified reviews searched only Medline database or included only English language publications; 1 of them also reviewed reference lists of the studies and abstract of scientific conferences [4]. Two reviews [3,4] included only 4 RCTs, 1 included only three RCTs [5], and 1 other included only 2 RCTs, all of them included in our review [6]. None of the identified review articles pooled the data from identified RCT, and all of them were presented in narrative form. On the basis of 1 of the review articles [6], evidence-based practice parameters of the American Academy of Sleep Medicine were prepared [7]. They recommend modafinil for the treatment of daytime sleepiness due to narcolepsy as generally accepted patient care with a high degree of clinical certainty.

European guidelines published by European Federation of Neurological Societies also recommend modafinil as first line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep [8].

In view of the limitations of previous review studies, our systematic review is the most up-to-date systematic review on the effect of modafinil in narcolepsy, which in its methodology followed the methods described in the Cochrane Handbook, and the report was prepared according to the QUOROM statement [13,14]. Moreover, it contains the largest number of RCTs, the most extensive search of literature, structured assessment of study quality and pooled assessment of the modafinil treatment effect.

**Conclusions**

On the basis of 9 included studies it can be concluded that in patients with narcolepsy modafinil in comparison with placebo was associated with significant benefit in terms of elimination of excessive daytime sleepiness assessed by objective laboratory tests or validated subjective outcome measures, but was not different from placebo in elimination of cataplexy as measured by the number of attacks per day. In addition, modafinil improved quality of life of narcolepsy patients measured both by generic and a narcolepsy-specific questionnaire, and was associated with greater likelihood of improvement according to physician assessment.

On the basis of 1 study it can be concluded that modafinil had similar effect on excessive daytime sleepiness as does sodium oxybate. Modafinil has not been compared directly to methylphenidate, a common treatment of excessive daytime sleepiness, in terms of randomized controlled trial.

**References:**