Part III
Drugs to Treat Excessive Daytime Sleepiness

Modafinil and Armodafinil

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1 Introduction

1.1 Excessive Daytime Sleepiness

Wakefulness of adequately long duration and quality is in every respect essential for good quality of life. Inadequately low wakefulness named excessive daytime sleepiness (EDS) is defined as a reduced ability to maintain continuous wakefulness during the day. EDS may take the form of lapses into sleep or as periods of somnolence leading to sleep onset in favorable circumstances and longer total duration of sleep within 24 h. EDS lowers the quality of life and complicates or disallows many regular activities.

Treatment of EDS starts with the identification of its cause and correction of all behavior bugs including avoidance of inappropriate drugs and substances. In case of a primary form of EDS a symptomatic therapy is the only option. The objective of any treatment is to eliminate EDS and to produce the best possible normal function for patients at workplace, school, at home, and society in general.

Historically, the most widely used and the most effective compounds to treat EDS were the amphetamine-like CNS stimulants (methamphetamine, dexamphetamine, and methylphenidate). Some of these drugs were withdrawn from markets in certain countries because of the risk of misuse and dependence. However, the use of

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the modafinil has considerably increased over the last years because of its favorable side-effect profile and several large controlled trials. Nowadays modafinil is the most frequently used drug for the treatment of EDS in narcolepsy.

1.2 History of Modafinil and Armodafinil

The story of modafinil started in 1974 in France. Two chemists—Assous and Gombert from Laboratoires Lafon—screened molecules in search of analgesics and discovered a new molecule, *adrafinil* [(diphenylmethyl)sulfinyl-2acetohydroxamic acid]. The pharmacological testing of adrafinil was performed later by pharmacologists from Laboratoires Lafon Duteil and Rambert who found out that mice treated with adrafinil exhibited hyperactivity (Duteil et al. 1979). Adrafinil was then tested by Michel Jouvet and coworkers on cats and later on by Milhaud and Klein on monkeys. An increase of electroencephalographic wakefulness was found by the first group and an increase of the nocturnal activity by the second one. In 1977–1978, Jouvet prescribed adrafinil to narcoleptic patients with inconsistent results (Billiard et al. 2007).

Meanwhile, in 1976, an active metabolite of adrafinil, modafinil [2-(diphenylmethyl)sulfinylacetamide] (Fig. 1), was discovered and this new molecule appeared more efficient than adrafinil. Modafinil went through the same steps of development leading to the demonstration of a dose-dependent increase in locomotor activity in mice (Duteil et al. 1990), an increase of electroencephalographic wakefulness in cats (Lin et al. 1992), an increase of electroencephalographic wakefulness (Lagarde and Milhaud 1990), and an increase in nocturnal activity and in behavioral arousal without stereotyped behavior (Hermant et al. 1991) in rhesus monkeys. As soon as early 1983 Jouvet prescribed modafinil to narcoleptic and idiopathic hypersomnia patients. The results surpassed expectations. In 1984 Laboratoire Lafon decided to start clinical trials in both healthy volunteers and narcoleptics. First studies of modafinil on night sleep and daytime sleepiness in healthy volunteers were conducted by Goldenberg et al. (1987) and Saletu et al. (1989). Goldenberg and her colleagues found decreased total sleep time, decreased NREM stages 3 and 4, no modification of REM sleep, and no rebound phenomenon after a single evening dose of modafinil 200 mg or placebo in parallel groups. In addition, sleep latency on the multiple sleep latency test (MSLT) increased in every single session following a single dose of modafinil, 200 mg at

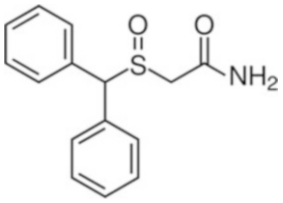

Fig. 1 Chemical structure of modafinil

10 a.m. Saletu with his coworkers compared the effect of modafinil on nocturnal sleep in 100 and 200 mg dosage with D-amphetamine 10 and 20 mg and placebo. Drop in sleep efficiency was much smaller in modafinil compared to amphetamines. Studies in healthy volunteers were accompanied by open-label trials in subjects with narcolepsy and idiopathic hypersomnia performed in different research centers—the first study and the first clinical publication on modafinil came from Jouvet's center in Lyon (Bastuji and Jouvet 1988). These studies and the first multicenter, randomized, placebo-controlled study (Billiard et al. 1994) led to the official registration of modafinil in France in June 1992 followed by its commercial availability there, from September 1994 (Billiard et al. 2007).

Further research including preclinical, phase I trials and multicenter, randomized, placebo-controlled studies were conducted by Cephalon who originally leased the rights from Lafon in 1993, but eventually purchased the company in 2001. Modafinil received orphan drug status in the USA in 1993 and became there commercially available in 1998 (Thorpy 2007). Other European countries made modafinil available in late 1990s. In 2007, Cephalon began to market the R-enantiomer of modafinil called armodafinil in the USA. After protracted patent litigation and negotiations, generic versions of modafinil became available in the USA in 2012. In 2011 Teva took over the Cephalon Company with all products including modafinil and armodafinil.

2 Modafinil Pharmacology and Mode of Action

2.1 Pharmacology

Classical central nervous stimulants (wake-promoting agents) are based on amphetamine. Amphetamine has a simple chemical structure resembling endogenous catecholamines and its major mode of action is an increase of catecholamine (dopamine and norepinephrine but also to a lesser extent serotonin) release and inhibition of catecholamine reuptake. This results in an increase in catecholamine concentration in the synaptic cleft and enhances postsynaptic stimulation. The presynaptic modulations by amphetamines are mediated by specific catecholamine transporters. These transporters—the dopamine transporter (DAT) and the norepinephrine transporter (NET)—move normally dopamine and norepinephrine from the outside to the inside of the cell and amphetamines can reverse the direction of this transport. The side effect of amphetamines is mediated mostly by release of norepinephrine, which stimulates indirectly alpha- and beta-adrenergic receptors. Alpha-adrenergic stimulation produces vasoconstriction, increasing thereby systolic and diastolic blood pressure. In large doses tachycardia and cardiac arrhythmia may occur. Other side effects include mild gastrointestinal disturbances, anorexia, dryness of the mouth, insomnia and restlessness, headache, palpitations, anxiety, and vasomotor disturbances. D-amphetamine isomers are more active than isomers

of the L-type, and have more effects on dopaminergic synapses than on other monoaminergic synapses (Nishino and Mignot 2011; Mignot 2012).

2.2 Mechanism of Action

The precise mechanism of modafinil wakefulness promotion is unknown. Modafinil has weak to negligible interactions with receptors for norepinephrine, serotonin, dopamine, GABA, adenosine, histamine-3, melatonin, and benzodiazepines. Modafinil also does not inhibit activity of MAO-B or phosphodiesterases II–V. Modafinil is not a direct- or indirect-acting dopamine receptor agonist. However, in vitro, modafinil binds to the DAT and inhibits dopamine reuptake. This activity has been associated in vivo with increased extracellular dopamine levels in some brain regions of animals. In genetically engineered mice lacking the DAT, modafinil lacked wake-promoting activity, suggesting that this activity is DAT dependent. Modafinil appears to reduce GABA levels and increase glutamate and serotonin levels in the cortex indirectly, but these activities do not appear to be involved in the clinical effect of modafinil. Modafinil administration increases C-fos activity in the wake-promoting hypothalamic brain regions including hypocretin neurons, in tuberomammillary and suprachiasmatic nuclei, and at higher doses in the striatum and cingulate cortex. Optical enantiomers of modafinil have similar pharmacological actions in animals (FDA 2007; Monderer and Thorpy 2011).

2.3 Pharmacokinetics and Metabolism

Modafinil is a *racemic compound*, whose enantiomers have different pharmacokinetics.

Modafinil is rapidly absorbed (plasma concentrations peaking in 2–4 h) and slowly cleared. It bounds to plasma proteins at 60 % and its volume distribution is 0.8–0.9 l/kg, suggesting that the compound is readily able to penetrate into tissues. Its half-life ranges from 9 to 14 h. The *R enantiomer* of modafinil (armodafinil) has a longer half-life (10–15 h) than S enantiomer (3–4 h).

60–90 % of modafinil is converted in liver to inactive metabolites with subsequent renal elimination. Metabolism primarily utilizes cytochrome P-450 3A4/5. Induction of metabolizing enzymes, most importantly P-450 (CYP) 3A4, has been observed in vitro and in vivo after extended administration of modafinil at 400 mg/day.

Modafinil exhibit linear kinetics upon multiple dosing of 200–600 mg/day once daily in healthy volunteers. Apparent steady states of racemic modafinil are reached after 2–4 days of dosing (Nishino and Mignot 2011; FDA 2007).

3 Clinical Involvement of Modafinil and Armodafinil

EDS is a symptom and can be related to many conditions, but only some of these can be treated symptomatically by modafinil. The following diseases will be mentioned in detail below: narcolepsy type 1 and 2, idiopathic hypersomnia, residual hypersomnia in patients with adequately treated obstructive sleep apnea (OSA), hypersomnia associated with Parkinson's disease (PD), multiple sclerosis (MS), posttraumatic hypersomnia, and shift work disorder.

Armodafinil is targeting the same indications as the racemic form of the drug—modafinil.

3.1 Narcolepsy

Narcolepsy is a disabling lifelong sleep disorder with EDS as the main symptom. There are two forms (independent nosological entities with different pathophysiology) of narcolepsy. Narcolepsy type 1 (narcolepsy with cataplexy) and narcolepsy type 2 (narcolepsy without cataplexy) with the same clinical manifestation of EDS. Narcolepsy type 1 symptoms include not only sleepiness but also abnormal rapid-eye movement (REM) sleep manifestations, including cataplexy (short-lasting symmetrical loss of muscle strength caused by emotional trigger), sleep paralysis, and hypnagogic hallucinations. The disappearance of hypothalamic hypocretin-producing neurons at the disease onset is the main etiopathogenic factor of narcolepsy type 1. Narcolepsy type 2 is clinically characterized by sleepiness, and absence of cataplexies. Its etiopathogenesis is unknown. Narcolepsy type 1 and type 2 belong to the group of central disorders of hypersomnolence according to the International Classification of Sleep Disorders, third edition (American Academy of Sleep Medicine 2014).

EDS is the most inconveniencing symptom in narcolepsy. Both forms of narcolepsy share the same objective criteria of EDS in MSLT: mean sleep latency <8 min and the presence of REM sleep in two or more measurements within MSLT, REM sleep episode within 15 minutes of sleep onset on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT (American Academy of Sleep Medicine 2014). MSLT consists of five 20 min long opportunities to sleep for 15 min. Clinical picture of EDS in both types includes episodes of sleepiness followed by sleep in conditions favorable or even unfavorable for sleeping, sleep attacks with and without preceding sleepiness, and automatic behavior. Naps are usually of short duration and the patient wakes up feeling refreshed. There is no causal treatment of sleepiness and of REM sleep manifestations in narcolepsy.

3.1.1 Modafinil in Narcolepsy

The first multicenter, randomized, placebo-controlled trial of modafinil was performed in patients suffering from narcolepsy type 1 in four research centers in France and Canada. Subjects were either drug naive or had discontinued psychostimulant medication for at least 14 days prior to the study. Modafinil was administered in a double-blind crossover design, at a dosage of 300 mg versus placebo. The duration of the study was 12 weeks with the 4-week treatment/placebo periods. Sleep logs did not show any modification of night sleep, but a reduction of both daytime sleepiness and overwhelming episodes of sleep. Cataplexy remained unchanged. There was a significant improvement of the sleep latencies measured by maintenance of wakefulness test (MWT) in modafinil compared to placebo (Billiard et al. 1994).

Subsequently in Canada, 75 patients with narcolepsy enrolled into a 6-week, three-period, randomized, crossover, placebo-controlled trial. Patients received placebo, modafinil 200 mg, or modafinil 400 mg in divided doses (morning and noon). Evaluations occurred at baseline and at the end of each 2-week period. Compared with placebo, modafinil 200 and 400 mg significantly increased the mean sleep latency on the MWT by 40 and 54 %, with no significant difference between the two doses. Modafinil, 200 and 400 mg, also reduced the combined number of daytime sleep episodes and periods of severe sleepiness noted in sleep logs. The likelihood of falling asleep as measured by the Epworth Sleepiness Scale (ESS) was equally reduced by both modafinil dose levels. There was no effect on nocturnal sleep. Neither dose interfered with the patients' ability to nap voluntarily during the day or with nocturnal sleep quantity or quality. Modafinil caused no changes in blood pressure or heart rate in either normotensive or hypertensive patients. The only significant adverse effects were observed at the 400 mg dose associated with more frequent nausea and nervousness than either placebo or the 200 mg dose (Broughton et al. 1997).

The U.S. Modafinil in Narcolepsy Multicenter Study Group conducted two double-blind, placebo-controlled studies in narcolepsy (U.S. Modafinil in Narcolepsy Multicenter Study Group 1998, 2000); they were similarly designed, with identical end points that measured both objective and subjective sleepiness, as well as overall clinical condition. Each trial (one conducted in 18 research centers and one in 21 centers) used as primary end points the MWT and the Clinical Global Impression of Change (CGI-C). MSLT and ESS were the secondary end points. The duration of each U.S. narcolepsy trial lasted for 9 weeks with visits scheduled every 3 weeks. A total of 558 patients were included in the efficacy analyses of these trials, and randomized to placebo, modafinil 200 mg, or modafinil 400 mg. Eighty-one percent of patients had also cataplexy, but only patients without anticataplectic treatment were included. Combined results of these two studies showed that mean sleep latency on the MWT increased by more than 2 min in each treatment group, compared with a decrease of 0.7 min in the placebo group. A significantly higher percentage of modafinil patients showed improvement in overall clinical condition

in the CGI-C (61–66 % vs. 37 % for placebo). The 18-center study used only a 1-day titration period for the 400 mg group and a higher percentage of patients in the 400 mg group withdrew due to adverse events compared with the 200 mg and placebo groups (12 % vs. 1 % and 0 %, respectively). A more refined step-up protocol lasting 9 days was planned in the subsequent study and only 1 % of the 400 mg group withdrew due to adverse effects. Similar objective improvements were seen on the MSLT and on the ESS. No dose–response effect was seen for the 400 mg dose compared with the 200 mg dose in either study. There were no significant changes in nocturnal sleep parameters. The 21-center study included a 2-week treatment discontinuation phase to determine the effect of withdrawal from modafinil. During the discontinuation period, subjects experienced a loss of improvement in wakefulness that had been seen over the course of the study. No symptoms of tolerance or abrupt withdrawal were reported. The consistency of response on the same measures between trial and improvement across variety of measures within each trial were significant. Absolute changes from baseline on the MWT and MSLT may appear small; however, these tests are done in settings designed to maximize the likelihood of sleep onset. Under these conditions, small increases in sleep latency can represent clinically significant improvements in wakefulness (U.S. Modafinil in Narcolepsy Multicenter Study Group 1998, 2000; Monderer and Thorpy 2011).

The results of the U.S. modafinil trials corroborate those by a group of Canadian investigators in a randomized, double-blind, placebo-controlled, 6-week trial. In this trial, consisting of three 2-week crossover phases, significant improvements were seen on the MWT and ESS at 200 and 400 mg doses, given twice daily in the morning and at noon. This trial also failed to show dose-dependent therapeutic effect (Moldofsky et al. 2000).

Further studies were performed to determinate the optimal dosing protocols for modafinil in narcolepsy (Monderer and Thorpy 2011). While the original US placebo-controlled studies showed no dose–response effect for 400 mg compared to 200 mg, a later study, using a modified version of the MWT that included an evening test session, demonstrated significantly improved evening wakefulness with the 400 mg dose (whether in a single dose or divided dose) compared to the 200 mg dose. The greatest improvement in evening wakefulness was seen with the 400 mg split-dose regimen, as compared to the 200 and 400 mg once-daily regimen (Schwartz et al. 2003a). Next study looking at dosing effects of 600 mg split-dose regimen (400 mg in the morning and 200 mg in the early afternoon) was found to achieve more sustained wakefulness throughout the day compared to 400 mg once daily (Schwartz et al. 2004). A third study showed that split-dose regimens of either 400 mg in the morning and 200 mg at noon or 200 mg both in the morning and at noon were superior to a single dose of 200 mg in the morning (Schwartz et al. 2005).

A small double-blind crossover study with 300 mg modafinil showed a decrease of EDS measured by MWT and also improvement of psychomotor performances involving attention (Besset et al. 1993). This result is in line with new finding of

improvement of driving abilities in patients suffering from narcolepsy and idiopathic hypersomnia (Philip et al. 2014).

3.1.2 Armodafinil in Narcolepsy

Patients receiving armodafinil 150 and 250 mg/day in a large randomized, placebo-controlled study of 196 patients with narcolepsy experienced increased MWT mean sleep latency compared to placebo. These changes were seen at all time points for the 150 mg dose, but statistical significance was not reached at weeks 8 and 12 for the 250 mg group. The CGI-S showed improvement at the final visit in both armodafinil groups as well as the ESS scores. Memory, attention, and fatigue showed statistically significant improvement with both doses of armodafinil (Harsh et al. 2006). Armodafinil administered for 12 months or more was generally well tolerated and improved wakefulness and the overall clinical condition in patients with narcolepsy (Schwartz et al. 2010).

Long-term efficacy of modafinil and armodafinil in narcolepsy was well documented by open-label studies (Besset et al. 1996; Black et al. 2010).

Modafinil and armodafinil are recommended as EDS treatment in narcolepsy by the American Academy of Sleep Medicine (AASM) (Morgenthaler et al. 2007). Modafinil is recommended as EDS treatment in narcolepsy by European Federation of Neurological Societies (Billiard et al. 2006).

3.2 Idiopathic Hypersomnia

Idiopathic hypersomnia (IH) is also a primary disorder of hypersomnolence differing from narcolepsy by the lack of REM sleep disturbances, but the MSLT criterion of mean sleep latency <8 min remains the same (American Academy of Sleep Medicine 2014). IH is a rare lifelong sleep disorder. Persisting EDS cannot be compensated by sleep. IH patients suffer from the impaired quality of life and psychosocial consequences as narcolepsy patients (Ozaki et al. 2012). However, some studies in IH patients used criteria that did not include MSLT tests. The first trial with modafinil in IH was performed as an open-label study in Lyon, France (Bastuji and Jouvet 1988). 18 patients participated in the study and modafinil was administered in the morning and at noon. The dose varied from 200 to 500 mg/day according to the patient's weight and the severity of the symptoms. The number of drowsiness and sleep episodes during daytime was significantly reduced in 15 patients. It took 25 years to have next prospective trials in IH.

Recently, a multicenter study has been performed in 31 adult patients with idiopathic hypersomnia without long sleep time, 14 on modafinil and 17 on placebo. Modafinil 200 mg given in the morning improved ESS and CGI-C compared to placebo and led to a nonsignificant increase in the mean sleep latency on the MWT (Mayer et al. 2013).

There are two large observational studies available (Anderson et al. 2007; Ali et al. 2009). Both studies show the good response rate between 60 and 70 %. Recent French study compared benefits and risks of modafinil in consecutive patients suffering from IH and narcolepsy with cataplexy. The improvement of ESS was similar and sudden loss of efficacy and habituation were rare in both. Patients with IH reported similar but more frequent adverse effects with modafinil than narcolepsy patients: nervousness (14 %), palpitations (13 %), and headache (11 %) (Lavault et al. 2011).

Modafinil is mentioned in AASM practice parameters for the treatment of narcolepsy and hypersomnias of central origin as an optional therapy for treatment of daytime sleepiness due to IH (Morgenthaler et al. 2007).

A randomized, crossover, double-blind placebo-controlled trial has been conducted among 13 patients with narcolepsy and 14 patients with IH. Patients were randomly assigned to receive modafinil (400 mg) or placebo for 5 days prior to the driving test. Each treatment period was separated by at least 3 weeks of washout. Modafinil improved driving performance judged on the number of Inappropriate Line Crossings and Standard Deviation of Lateral Position of the vehicle as well as the mean sleep latency on the MWT. MWT mean sleep latency correlated with the mean number of Inappropriate Line Crossings (Philip et al. 2014). This finding is very important because patients with EDS are at high risk for driving accidents, and physicians are concerned by the effect of alerting drugs on driving skills of sleepy patients.

3.3 Residual Hypersomnia in Patients with Adequately Treated Obstructive Sleep Apnea (OSA)

Some patients with OSA report persistent sleepiness despite optimal treatment of their sleep apnea (usually continuous positive airway pressure—CPAP) (Sforza and Krieger 1992). Modafinil and armodafinil are the only drugs successfully studied in alleviating EDS in OSA.

A 4-week randomized, double-blind, placebo-controlled, parallel group study evaluated the efficacy of modafinil (the first week 200 mg/day, the second to fourth week 400 mg/day) in patients with OSA (respiratory disturbances index—RDI $\geq$15) and residual EDS while compliant with CPAP therapy (CPAP usage $\geq$4 h per night on 70 % of nights). Mean changes from baseline in ESS at weeks 1 and 4 displayed a greater improvement in EDS in patients on modafinil compared to those on placebo. At week 4, 51 % of subjects on modafinil had an ESS within normal range ($<$10) as compared to 27 % in the placebo group. Furthermore, at week 4, the mean sleep latency on MSLT improved from a baseline of 7.4–8.6 min in modafinil group as compared to a decrease from 7.5 to 7.2 min in placebo group. CGI-C ratings were significantly more improved in the modafinil group as compared with the placebo group. There was a small increase in the arousal index in

patients receiving modafinil compared to controls, but no change in either group in the number of hours of CPAP use (Pack et al. 2001). During the follow-up 12-week open-label study the significant improvement seen on the ESS during the 4-week study was maintained and more than 93 % of patients clinically improved on the CGI-C from weeks 2–12 of the open-label study. However, unlike the previous study, there was a small but significant drop in the mean nightly CPAP use (from 6.3 to 5.9 h) (Schwartz et al. 2003c).

A smaller and shorter randomized, double-blind, placebo-controlled crossover study in subjects suffering from OSA compliant with CPAP with 400 mg of modafinil and placebo showed only improvement on MWT and no effect on either the MSLT or ESS and on quality of life (SF-36) or Functional Outcomes of Sleep Questionnaire (FOSQ) or cognitive performance. Patients on modafinil again mildly reduced the CPAP use (Kingshott et al. 2001).

A more recent, 12-week double-blind, placebo-controlled study was conducted with 309 OSA patients compliant with CPAP who were randomized to receive either 400 or 200 mg of modafinil or placebo. Wakefulness was significantly improved on the MSLT with both the 400 and 200 mg of modafinil as compared to control on weeks 4, 8, and 12. The ESS scores decreased by 4.5 in both modafinil groups in contrast to the placebo group, which had a 1.8-point decrease. CGI-C improved in 61 and 68 % of patients on modafinil, respectively, as compared with 37 % on placebo. Vigilance, general productivity, and activity level subscale scores on FOSQ improved with modafinil. The therapy did not change hours of nightly CPAP use (Black and Hirshkowitz 2005).

Two large 12-week randomized, double-blind, placebo-controlled studies evaluated armodafinil in the treatment of residual EDS in patients with OSA on CPAP. Patients had ESS score $\geq$10 and apnea/hypopnea index $\leq$10 in polysomnogram with CPAP and sufficient regular CPAP use (Roth et al. 2006; Hirshkowitz et al. 2007). The results of these two studies (651 patients) were analyzed together in the subsequent paper (Roth et al. 2008). Armodafinil improved wakefulness as measured by mean sleep latency on MWT at week 4, 8, and 12. Armodafinil also improved late-day (afternoon) wakefulness on MWT at the final visit. ESS was improved at all visits in the armodafinil group and at week 12, 49 % of patients in armodafinil group had an ESS $\leq$ 10 compared to 26 % in the placebo group. The quality (not the speed) of long-term memory was improved compared to placebo; however, the power of attention and continuity of attention between treatment groups were not significantly different. Global fatigue scores were improved in both armodafinil groups. However a significant reduction of hours of nightly CPAP use in the armodafinil group was observed. The night sleep variables were in both groups the same (Roth et al. 2008).

A long-term open-label study with armodafinil (50–250 mg/day) in OSA patients showed permanent efficacy and adverse effect of mild-to-moderate intensity (Black et al. 2010).

A recent randomized placebo-controlled crossover trial showed in patients with untreated mild-to-moderate OSA that modafinil significantly improved subjective sleepiness. The size of this effect is clinically relevant at 3–4 ESS points of

improvement. Driving simulator performance and reaction time also improved on modafinil (Chapman et al. 2014).

One must take into account that modafinil does not treat the primary disease and that the improvement of residual sleepiness may diminish compliance to the positive airway pressure therapy and patients need usual regular supervision. Modafinil is recommended as the treatment of residual EDS in OSA by AASM (Morgenthaler et al. 2006); in the USA modafinil is registered for this indication, but not in European Community (EU).

3.4 Hypersomnia Secondary to Parkinson's Disease (PD)

Significant hypersomnolence documented by MSLT has been reported in some cases of PD.

Modafinil was found to be effective in the treatment of EDS in PD (ESS and CGI-C) by two double-blind studies with doses of 100–200 mg/day (Hogl et al. 2002; Adler et al. 2003), but a larger double-blind placebo-controlled study failed to find significant improvement of ESS or MSLT with modafinil 200–400 mg/day (Ondo et al. 2005).

Later a small randomized, open-label 8-week study of 19 subjects with PD demonstrated that although modafinil may be effective in reducing physical fatigability, it did not improve fatigue symptoms and did not change ESS (Lou et al. 2009).

Modafinil 100 mg twice a day was safe and modestly effective for the treatment of EDS in the elderly according to naturalistic open-label 3 weeks study in 10 PD patients (Lokk 2010). This result is not congruent with other open-label studies showing the lack of the effect of modafinil on EDS in PD (Nieves and Lang 2002).

Due to inconsistent results modafinil cannot be recommended generally for the treatment of EDS and fatigue in PD (Sheng et al. 2013). Nevertheless, modafinil has mild side effects, does not modify PD course, and thus can be taken in consideration as off-label therapy in PD subjects handicapped by EDS.

3.5 Posttraumatic Hypersomnia

Hypersomnolence appears to be common consequence of traumatic brain injury (TBI), with one meta-analysis suggesting a frequency of 28 % of TBI patients. In some cases this may be caused by injury to the hypocretin/orexin neurons or other wake-promoting neural systems.

A double-blind, placebo-controlled crossover trial, where 53 participants with TBI were randomly assigned to receive up to 400 mg of modafinil or placebo, showed sporadic statistically significant differences, but there was no clear beneficial pattern from modafinil for any of the 12 outcomes (Jha et al. 2008). Another

prospective, double-blind, randomized, placebo-controlled study with 100 and 200 mg of modafinil in 20 patients with TBI who had fatigue or EDS or both included the ESS, the Fatigue Severity Scale, actigraphy, polysomnography, MWT, and Psychomotor Vigilance Test (PVT). The results indicate that modafinil is effective and well tolerated in the treatment of posttraumatic EDS but not the fatigue (Kaiser et al. 2010).

More studies are needed to elucidate the effectiveness of modafinil in traumatic brain injury.

3.6 Multiple Sclerosis (MS)

Fatigue is a common and disabling feature of multiple sclerosis and anecdotally patients with MS suffer from EDS.

A single-blind study with 72 patients found improvement on fatigue measures with 200 mg of modafinil compared to placebo, but not with the 400 mg dose. ESS was reduced in both 200 and 400 mg arms, but ESS was already in normal range (Rammohan et al. 2002). This result is supported by another small study (Brioschi et al. 2009) but not by another one (Ledinek et al. 2013). A recent retrospective study displayed that modafinil was most effective for patients with fatigue and also EDS (Littleton et al. 2010). Nevertheless, randomized placebo-controlled studies failed to demonstrate the effect of modafinil on fatigue in MS (Moller et al. 2011; Stankoff et al. 2005). Niepel and coworkers speculate that the anti-fatigue effect of modafinil may reflect the activation of the noradrenergic locus coeruleus, since this wakefulness-promoting nucleus is damaged in MS (Niepel et al. 2013).

The evidence of effectiveness of modafinil on fatigue and EDS in MS is not yet sufficient for modafinil to be recommended (Sheng et al. 2013), but in selected patients suffering from EDS in MS modafinil may be taken in consideration as an off-label therapy.

Two double-blind, placebo-controlled studies showed the effect of either 8 weeks of modafinil or 1 week of armodafinil on cognitive performance in patients with MS (Bruce et al. 2012; Lange et al. 2009). The effect of modafinil and armodafinil on cognitive functions in MS merits future research.

3.7 Shift Work Disorder

Shift work disorder is characterized by complaints of insomnia or excessive sleepiness during work hours that take place, at least in part, during the usual sleep time.

Three randomized, double-blind, placebo controlled trials were conducted to evaluate the effect of 200–300 mg of modafinil given prior to their night shift. The first study was short-lasting and simulated the real life in laboratory conditions and two remaining were 12-week studies in real conditions. These studies showed

improvement in vigilance measured by modified MWT, by PVT and CGI-C, and improvement in both the quality of life and FOSQ (Walsh et al. 2004; Czeisler et al. 2005; Erman et al. 2007).

Armodafinil studied in similar 12-week randomized controlled study confirmed similarly beneficial effect and EDS reduction on the way home after night shift. The study also showed improvement of long-term memory and attention (Czeisler et al. 2009).

The improvements from baseline in efficacy assessments started at month 1 and were maintained throughout the open-label study lasting 12 months and more (Black et al. 2010).

Modafinil is registered as the treatment of shift work disorder in the USA but not in the EU. It should be pointed out that the best treatment of the shift work disorder is to quit such job.

3.8 Depression

Sleep disturbances including EDS and fatigue are common symptoms of depression which may persist despite treatment with antidepressant medication.

Modafinil is an effective augmentation strategy for acute depressive episodes, including for symptoms of fatigue, in both unipolar and bipolar affective disorders. The meta-analysis of 6 randomized controlled studies, with a total of 910 patients with major depressive disorder or bipolar depression, revealed effects of modafinil on improvements in overall depression scores and remission rates. The treatment effects were evident in both major depressive disorder and bipolar depression, with no difference between both disorders. Modafinil showed a significant positive effect on fatigue symptoms. The adverse events were no different from placebo (Goss et al. 2013).

3.9 Other Indications

Myotonic dystrophy is frequently associated with severe EDS and two studies noted some improvement, but recently published randomized, double-blind, placebo-controlled study reported no significant effect measured by MWT (Orlikowski et al. 2009).

Although there have been some clinical trials on the effect of modafinil on fatigue and EDS associated with post-polio syndrome, attention deficit hyperactivity disorder, schizophrenia, and cocaine addiction, they are beyond the scope of this chapter.

Modafinil had no effect on fatigue related to cancer and primary brain tumors and should not be prescribed outside a clinical trial setting (Spathis et al. 2014; Boele et al. 2013).

4 Safety

Modafinil and armodafinil are generally well tolerated, with side effects mostly mild-to-moderate intensity. The most frequent undesirable effects are headache, nausea, insomnia and loss of appetite, and nervousness. Some studies in OSA subjects reported mild elevation of blood pressure and more patients taking modafinil have required antihypertensive drugs. Likewise small but consistent increase in blood pressure has been seen in armodafinil. Most studies have not reported any ECG changes with modafinil and armodafinil. It is recommended that both drugs should not be used in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants. Overall, the cardiovascular profile of modafinil and armodafinil is more favorable than with other stimulants available.

Psychiatric symptoms, including mania, delusions, hallucinations, and suicidal ideation, have been experienced in association with modafinil and armodafinil use.

In clinical trials no serious cases of skin rash were reported. Nevertheless rare cases of serious or life-threatening rash such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms have been reported in children and adults taking modafinil. Since it is not possible to predict whether a rash will become serious, ar/modafinil must be discontinued with the first sign of rash (Monderer and Thorpy 2011; FDA 2007).

It is considered that modafinil and armodafinil have low potential of abuse even in high dosage and long-term experience of administration of modafinil is encouraging (Monderer and Thorpy 2011).

There are no important interactions with other drugs. Patients on other psychostimulants can be safely diverted to modafinil (Schwartz et al. 2003b).

Modafinil and armodafinil are category C drugs for pregnancy. It is recommended that pregnant women avoid taking this medication. The amount of modafinil/armodafinil excreted in mother's milk is unknown (Monderer and Thorpy 2011; FDA 2007).

Safety and effectiveness in pediatric patients, below age 16, have not been established. In a controlled 6-week study, 165 pediatric patients (aged 5–17 years) with narcolepsy were treated with modafinil ($n = 123$) or placebo ($n = 42$). There were no statistically significant differences favoring modafinil over placebo in prolonging sleep latency as measured by MSLT or in perceptions of sleepiness as determined by the CGI-C (FDA 2007). Modafinil and armodafinil are not registered for pediatric population in the USA nor in Europe. The age limitation has been criticized by expert group based on their own experience (Lecendreux et al. 2012). This criticism is, among other reasons, caused by the fact that drugs against EDS allowed for children are only amphetamines and their derivatives with well-known elevated risk of abuse.

In terms of overdose, modafinil seems to be a safe drug. In clinical trials, a total of 151 protocol-specified doses ranging from 1,000 to 1,600 mg/day have been

administered to 32 subjects, including 13 subjects who received doses of 1,000 or 1,200 mg/day for 7–21 consecutive days. In addition, several intentional acute overdoses occurred; the two largest being 4,500 and 4,000 mg taken by two subjects participating in foreign depression studies. None of these study subjects experienced any unexpected or life-threatening effects. Adverse events that were reported at these doses included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. From post-marketing experience, there have been no reports of fatal overdoses involving modafinil alone (doses up to 12 g).

5 Nonmedical Use of Modafinil

Modafinil is used by special forces (e.g., army), by solitary sailors in the race, etc., for improving and prolonging the ability to stay awake.

Conclusion
Modafinil and its R-enantiomer armodafinil are wakefulness and alertness enhancing agents frequently used in modern sleep medicine and seems to be the best medication of its kind available for treatment of EDS due to narcolepsy. Both have good safety profile, but they are approved only for the use in adults and in women using birth control means. Modafinil is approved in the USA for the treatment of EDS associated with narcolepsy and with treated OSA and shift work disease but in Europe for narcolepsy only. The therapeutic potential of modafinil and armodafinil seems to be larger than indicated by the label.

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