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Modafinil in the treatment of excessive daytime sleepiness

ABSTRACT

Modafinil (Provigil) is approved for treating excessive daytime sleepiness associated with narcolepsy, for shift-work sleep disorder, and as an adjunctive treatment in patients with obstructive sleep apnea syndrome who have residual daytime sleepiness despite optimal treatment with continuous positive airway pressure. Although modafinil improves measures of sleepiness, it does not generally normalize them, and it may be less effective than other stimulants for some narcoleptic patients. We need head-to-head comparisons of modafinil with traditional stimulants in humans to better define its role. We review the current approved and off-label uses of this drug and the evidence behind them.

KEY POINTS

Modafinil is metabolized in the liver and so may interact with other drugs metabolized by the P450 system, such as oral contraceptives, carbamazepine (Tegretol), propranolol (Inderal), and phenytoin (Dilantin).

The Maintenance of Wakefulness Test is the standard objective measure of the ability to stay awake for a defined time. It is not as useful as the Multiple Sleep Latency Test for diagnostic purposes, but it is often used as an objective measure of treatment response in patients with narcolepsy.

Although modafinil has been used off-label for the treatment of sleepiness and fatigue in other medical conditions, no blinded studies are available supporting its efficacy in these areas specifically.

MODAFINIL (PROVIGIL) HAS BECOME a first-line therapy for a variety of sleep disorders characterized by excessive daytime sleepiness, with more than 2 million new prescriptions written for it annually.[1] As a selective wakefulness-promoting agent with limited potential for abuse, it is generally well tolerated.

However, modafinil's role with respect to traditional stimulants is still evolving. Hopefully, studies in humans that compare modafinil head-to-head with other stimulants will better define its role.

We review here the pharmacology, current approved and off-label uses, and side effects of this commonly prescribed wakefulness-promoting agent.

CURRENTLY APPROVED INDICATIONS

Modafinil is approved by the US Food and Drug Administration (FDA) for:

- Excessive daytime sleepiness associated with narcolepsy
- Residual excessive sleepiness in patients with obstructive sleep apnea syndrome after the continuous positive airway pressure (CPAP) regimen is optimized
- Shift-work sleep disorder.

ACTS MORE SELECTIVELY THAN AMPHETAMINES

Although its precise mechanism of action is unknown, modafinil seems to act selectively in the hypothalamus[2–4] by stimulating wake-promoting centers or by inhibiting sleep-promoting centers, or both. In contrast, traditional stimulants produce widespread central nervous system activation via direct dopaminergic pathways.

TABLE 1

The Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you have not done some of the things recently, try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

0 = would **never** doze
1 = **slight** chance of dozing
2 = **moderate** chance of dozing
3 = **high** chance of dozing

SITUATION	CHANCE OF DOZING
Sitting and reading	_____
Watching TV	_____
Sitting inactive, in a public place (eg, a theater or meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____
TOTAL SCORE[a]	_____

[a]Normal range 0–10, borderline 10–12, abnormal 12–24

JOHNS MW. A NEW METHOD FOR MEASURING DAYTIME SLEEPINESS: THE EPWORTH SLEEPINESS SCALE. SLEEP 1991; 14:540–545.

Modafinil does not appear to interact significantly with other stimulants

Although modafinil does not bind directly to dopamine receptors, it may still affect the dopaminergic system by inhibiting the dopamine transporter.[5] In animal studies, infusion of modafinil, like amphetamine, produced an increase in extracellular brain dopamine.[6] Furthermore, modafinil required the presence of the dopamine transporter for wake-promoting effects. These data suggest that both modafinil and traditional stimulants use dopaminergic pathways to some extent.

Metabolized in the liver

Modafinil is rapidly absorbed, reaching peak plasma concentrations in approximately 2 hours. It is metabolized in the liver, in part by the cytochrome P450 system. Less than 10% is excreted unchanged in the urine. The elimination half-life is 12 to 15 hours.

Potential P450 drug interactions

Modafinil induces several cytochrome P450 enzymes, such as CYP3A4, CYP1A2, and CYP2B6. Consequently, it can reduce concentrations of oral contraceptives, cyclosporine (Neoral), carbamazepine (Tegretol), and clomipramine (Anafranil). Women taking oral contraceptives should therefore use alternative or concomitant methods of contraception if they are taking modafinil.

Modafinil inhibits other enzymes, such as CYP2C19, which can increase the concentrations of diazepam (Valium), propranolol (Inderal), and phenytoin (Dilantin). Patients taking modafinil and phenytoin should be monitored for signs of phenytoin toxicity. In vitro studies have also shown inhibition of CYP2C9, the predominant pathway for warfarin (Coumadin) metabolism. However, in human clinical studies, no significant interactions between modafinil and warfarin have been noted.

Importantly, modafinil does not appear to have any significant interactions with other stimulant drugs.[7] In contrast to modafinil, the traditional stimulant medications have no known effect on the cytochrome P450 system.

MEASURING DAYTIME SLEEPINESS

The Epworth Sleepiness Scale (TABLE 1) is used routinely in sleep centers around the world as a simple measure of excessive daytime sleepiness. It has a high test-retest reliability and a high level of internal consistency.

In this self-administered test, the patient estimates how likely he or she is to is to doze off or fall asleep in eight situations, such as watching television or riding in a car.[8] The scoring is from 0 (never) to 3 (high chance), with total scores ranging from 0 to 24. A score over 10 indicates excessive daytime sleepiness. In various studies, modafinil lowered Epworth scores by 4 to 6 points—but not always into the normal range.

The Multiple Sleep Latency Test is the gold-standard objective assessment of daytime sleepiness. It is done in the sleep laboratory the day after overnight polysomnography.[9] The test consists of five nap trials offered in a standardized sleep-promoting setting at 2-hour intervals over the course of the day.

The time to sleep onset (sleep latency) is measured for each trial, and the mean sleep latency is calculated. Pathologic sleepiness is suggested by a mean sleep latency of 8 minutes or less (84% of patients with narcolepsy have a mean sleep latency of less than 5 minutes), while normal subjects have average latencies of 10 minutes or greater. In various studies, modafinil increased the sleep latency times by about 3 minutes, which was again not always into the normal range.

Another observation during this test is whether the patient enters rapid-eye-movement (REM) sleep soon after falling asleep, which is abnormal: the finding of two or more nap trials with REM sleep has a sensitivity of 80% and a specificity of 93% for the diagnosis of narcolepsy.[10] However, it is important to rule out other causes of daytime sleepiness before diagnosing narcolepsy on the basis of the results of the Multiple Sleep Latency Test, since sleep-onset REM periods may be seen in other conditions, including sleep apnea or withdrawal of REM-suppressing agents.

The Maintenance of Wakefulness Test is the standard objective measure of the ability to stay awake for a defined time. It is not as useful as the Multiple Sleep Latency Test for

diagnostic purposes, but it is often used as an objective measure of treatment response in patients with narcolepsy. It is also used to document the ability to stay awake in people who must stay awake for reasons of personal or public safety (eg, pilots or truck drivers).

In this test, patients are given four trials during which they are seated in a dimly lit room and told to stay awake. As in the Multiple Sleep Latency Test, sleep latency is measured and a mean is calculated.[9]

Although the Maintenance of Wakefulness Test has been used in research studies to assess the effect of treatment, there are no standards as to how great an increase in mean sleep latency constitutes a significant effect.

TREATMENT OF NARCOLEPSY

Narcolepsy is a disorder of sleep-wake dysregulation characterized by excessive daytime sleepiness. It is typically associated with cataplexy and other REM-sleep phenomena.[11] Excessive daytime sleepiness is usually the presenting symptom and may take the form of "sleep attacks," which are short, difficult-to-resist lapses into sleep, often with intrusion of REM sleep. Other symptoms include hypnogogic or hypnopompic hallucinations and sleep paralysis.

Before prescribing modafinil for daytime sleepiness, find the underlying cause

For many years, the mainstays of treatment for narcolepsy were amphetamine-like stimulants such as methylphenidate (Ritalin) and dextroamphetamine (Dexadrine), which are FDA-approved for this indication. However, these are schedule II controlled substances and may be associated with tachyphylaxis and an amphetamine withdrawal syndrome.

Placebo-controlled studies of modafinil in narcolepsy

The US Modafinil in Narcolepsy Multicenter Study Group conducted two large placebo-controlled randomized studies, one with 283 patients[12] and the other with 271 patients.[13] Each study compared modafinil 200 mg per day, 400 mg per day, and placebo for 9 weeks. The second study also looked at withdrawal effects after modafinil treatment. In both studies, patients were subjectively and objectively less sleepy if they were taking modafinil, and the differences were statistically significant.

At 9 weeks in the second study,[13] patients receiving modafinil 200 mg/day scored 13.0 on the Epworth Sleepiness Scale compared with 15.8 in the placebo group ($P < .03$) and 12.3 in the modafinil 400 mg group (P not significant). The pattern was similar on the Maintenance of Wakefulness Test: 4.9 minutes in the modafinil 200 mg group, 3.5 in the placebo group, and 5.1 in the modafinil 400 mg group. In the active treatment groups, all these numbers were significantly different from those at baseline. On the Multiple Sleep Latency Test, the group receiving 400 mg/day showed a significant increase in mean sleep latency whereas the group receiving 200 mg/day did not. No withdrawal syndrome was noted.

Give another dose at noon?

The usual starting dose in patients with narcolepsy is 200 to 400 mg every morning, titrated upward on the basis of clinical response.

Schwartz et al[14] performed a randomized, double-blind study in 24 patients receiving modafinil 400 mg every morning who were still experiencing late-day sleepiness; some received an additional dose of 200 mg at noon, and the rest received placebo. The group receiving active drug at noon had a statistically greater improvement on the evening trials of the Maintenance of Wakefulness Test; however, the overall test results were not statistically different between groups. The Clinical Global Impression of Change Scale revealed greater subjective improvement in the group receiving the noontime dose.

The total daily dose and timing of modafinil should be individualized. In our practice, some patients with refractory excessive daytime sleepiness have benefitted from increasing the dose to 800 mg/day in divided doses, although this is often in combination with other wake-promoting agents. While dosing later than noon is rarely recommended, dosing at noon does not adversely affect sleep architecture.[15]

How does modafinil compare with other stimulants?

To date, no head-to-head studies comparing modafinil and traditional stimulants for narcolepsy have been conducted in humans. In narcoleptic dogs, modafinil 5 mg/kg and amphetamine 0.1 mg/kg are equivalent in

their wake-promoting effect.[6]

Mitler and Hajdukovic[16] reviewed the literature and calculated that the Maintenance of Wakefulness Test score normalized in 55.3% of patients treated with modafinil, 80% with dextroamphetamine, and 70% with methylphenidate. In view of these comparisons, some consider modafinil to be relatively weak.

Modafinil vs sodium oxybate

Sodium oxybate (Xyrem) is not a stimulant, but rather a central nervous system depressant. It is taken in the evening immediately before bed and again 4 hours later. It is FDA-approved for the treatment of cataplexy associated with narcolepsy and also for treatment of excessive daytime sleepiness in narcolepsy.

Most trials of sodium oxybate in narcolepsy have compared it with placebo in patients already taking a stimulant as maintenance therapy.[16–18] However, one trial of patients previously treated with a stable dose of modafinil randomized them to one of four treatments: placebo, sodium oxybate, modafinil, or sodium oxybate plus modafinil.[19] Those in the modafinil group continued with their previous dose (200–600 mg/day), and this was not titrated during the study. Sodium oxybate was started at 6 g per night, then increased to 9 g per night. Sodium oxybate had an alerting effect equal to that of modafinil as measured by the Maintenance of Wakefulness Test.

However, since the dose of modafinil was not titrated to the highest or maximum effective dose, it is hard to say definitively that monotherapy with one agent is clearly better than monotherapy with the other. The group that received sodium oxybate plus modafinil had the largest increase in mean sleep latency as measured by the Maintenance of Wakefulness Test, and this was statistically significant compared with placebo.

The drugs have different mechanisms of action and can be used in combination.[19]

OBSTRUCTIVE SLEEP APNEA SYNDROME

Most patients with obstructive sleep apnea report excessive daytime sleepiness and unrefreshing sleep.[14] CPAP is the gold-standard treatment, although weight loss, positional ther-

apy, oral appliances, and upper airway surgery are effective in some cases. Nightly use of CPAP abolishes obstructive events in many cases and significantly reduces daytime sleepiness.

Modafinil added to CPAP

In a multicenter, double-blind, placebo-controlled study of 157 patients with obstructive sleep apnea and residual excessive daytime sleepiness after treatment with nasal CPAP,[20] the group receiving modafinil 400 mg per day as adjunctive therapy started with an Epworth score of 14.2 and reduced it to 9.6 ($P < .001$); the group receiving placebo started with an Epworth score of 14.4 and reduced it to 12.4 (P not significant). On the Multiple Sleep Latency Test, the modafinil group started at 7.4 minutes and increased it to 8.6 ($P < .05$, but still abnormal), while the placebo group started at 7.5 minutes and decreased it to 7.2.

In a 12-week multicenter, randomized, double-blind, placebo-controlled study of 305 patients treated with nasal CPAP and experiencing residual daytime sleepiness,[21] the mean sleep latency by the Maintenance of Wakefulness Test increased with adjunctive modafinil 200 to 400 mg/day. Again, however, the mean values did not fall into the normal range.

Sodium oxybate and modafinil can be used in combination

In January 2004, the FDA approved modafinil as adjunctive therapy for residual sleepiness despite optimal CPAP therapy in obstructive sleep apnea. However, insufficient sleep and CPAP noncompliance are common causes of sleepiness in patients with sleep apnea and therefore should be addressed before prescribing wake-promoting agents.

In an open-label study of patients with sleep apnea treated with CPAP plus modafinil, mean CPAP use declined significantly from 6.3 hours per night to 5.9 hours per night over the course of 12 weeks.[22] This reduction in CPAP use was not observed in the blinded study discussed above, in which CPAP compliance was monitored.[20]

Urge patients to keep using CPAP

Because wake-promoting agents neither treat upper airway obstruction nor reduce long-term morbidity associated with obstructive sleep apnea, clinicians must counsel patients about the importance of long-term compliance with CPAP and about good sleep hygiene. Also, many patients with sleep apnea have cardiovascular disease, including hypertension, so anyone treated with modafinil should be monitored closely for changes in cardiovascular status.

SHIFT-WORK SLEEP DISORDER

An estimated 6% of full-time workers in the United States work nights or rotating shifts.[23] These people are at risk of shift-work sleep disorder due to desynchrony of the circadian rhythm and the environment.

In general, people with this disorder sleep 1 to 4 hours less per day than other people. The cumulative sleep deprivation can result in impaired alertness during waking hours, decreased work performance, and an increased rate of work-related accidents. In fact, a study using ambulatory electroencephalography found that about 20% of shift workers fell asleep during a single night shift.[24]

In January 2004, the FDA approved modafinil for treating excessive daytime sleepiness associated with shift-work sleep disorder. This indication was based on a 12-week double-blind study in which 209 patients were randomized to receive either modafinil 200 mg or placebo 30 to 60 minutes before the start of each night shift.[25] All patients had severe daytime sleepiness, with a baseline mean sleep latency on the Multiple Sleep Latency Test of less than 6 minutes.

The modafinil group had a statistically significant 1.7-minute increase in mean sleep latency compared with the placebo group, but not enough to get into the normal range. Patients taking modafinil also had a significant improvement in performance on a vigilance test performed at 2-hour intervals during a simulated night shift. According to their sleep diaries, however, there was no significant effect on the number of sleep episodes or near accidents or on caffeine consumption.

A randomized study with 32 patients showed significant improvement on vigilance testing and the Maintenance of Wakefulness Test during a simulated night shift, although values were mostly in the normal range in the placebo group as well.[26] Neither study found modafinil to have any significant adverse

polysomnographic effects on recovery sleep after the night shift.

OFF-LABEL USES OF MODAFINIL

Modafinil has been used off-label in many other clinical conditions, including multiple sclerosis, attention-deficit hyperactivity disorder (ADHD), Parkinson disease, mood disorders, traumatic brain injury, chronic fatigue syndrome, opiate intoxication, and recovery from general anesthesia.

In multiple sclerosis

Fatigue is very common and potentially disabling in patients with multiple sclerosis. In one study, 28% of multiple sclerosis patients reported fatigue to be their most troublesome symptom.[27] In clinical trials, fatigue is often measured by the Fatigue Severity Scale, a nine-item questionnaire that has been validated for distinguishing fatigue in patients with medical illness from that experienced by healthy controls.[28]

Historically, fatigue associated with multiple sclerosis has been treated with amantadine (Symmetrel) or pemoline (Cylert).[29] However, both of these agents can have significant adverse effects. Pemoline use declined due to the potential for hepatotoxicity, and it was pulled from the market in 2005.

Modafinil is an alterative to traditional stimulants for adult ADHD

Modafinil has been used with varying success for the symptomatic treatment of fatigue in multiple sclerosis. In a single-blind study, 72 patients received placebo for weeks 1 to 2, modafinil 200 mg per day for weeks 3 to 4, modafinil 400 mg per day for weeks 5 to 6, and placebo for weeks 7 to 9.[30] Significant improvements on fatigue measures were found for modafinil 200 mg per day over placebo, whereas no differences were found with the higher dose. Mean Epworth Sleepiness Scale scores declined significantly with both doses; however, the baseline Epworth score was already in the normal range.

In contrast, two double-blind, placebo-controlled studies showed no statistically significant improvement in fatigue with modafinil.[31,32] The larger of these studies included 115 patients, in whom modafinil was titrated up to 400 mg per day, as tolerated, over 4 weeks.[31]

In ADHD

Modafinil has been studied in both adult and pediatric ADHD, and it is currently accepted as an alternative to traditional stimulants for adult ADHD.[33]

A double-blind, placebo-controlled, crossover study in 22 adults with ADHD compared modafinil, dextroamphetamine, and placebo.[34] The mean daily modafinil dose was 207 mg, and the mean daily dextroamphetamine dose was 22 mg. Both modafinil and dextroamphetamine produced significant improvements over placebo in five outcome measures, including subjective rating scales and tests of word association and digit span. In another double-blind, placebo-controlled, crossover study, 20 adult ADHD patients treated with modafinil 200 mg per day showed decreased impulsivity on neuropsychiatric testing.[35] Larger studies involving modafinil in adult ADHD patients are needed before reliable conclusions about its efficacy can be drawn.

No large double-blind studies of modafinil in children with ADHD have been published. In a 6-week double-blind study of 24 children with ADHD (ages 5 to 15), modafinil 200 to 300 mg per day produced significantly better results than placebo on a computerized test of performance known as the Test of Variables of Attention. However, no significant improvement was seen in the ADHD Rating Scale.[36]

Importantly, modafinil does not appear to cause significant appetite suppression or weight loss, both of which are common adverse effects of traditional stimulants in children. Therefore, modafinil may be more favorable in this setting.

In Parkinson disease

Many patients with Parkinson disease have sleep disorders: an estimated 60% report nocturnal sleep problems, and up to 50% report excessive daytime sleepiness.[37,38]

Modafinil has been studied in Parkinson patients with excessive daytime sleepiness, but sample sizes were small. The largest randomized, double-blind, placebo-controlled study involved 21 patients treated with modafinil 200 mg daily or placebo.[39] In the modafinil group, the Epworth score decreased from 17.8 at baseline to 14.4 with treatment,

which was statistically significant but still not in the normal range. Also, no significant improvements were seen in fatigue or motor symptoms (measured by the Hoehn and Yahr Scale and the Unified Parkinson Disease Rating Scale).

Larger studies of modafinil in Parkinson disease are needed, and these should measure quality of life as an outcome.

In depression

Fatigue and sleep disturbances are extremely common in depression, and these symptoms may persist even after effective treatment with antidepressant medications. Nierenberg et al found that 44% of patients who responded well to fluoxetine (Prozac) reported residual sleep disturbances and 38% reported residual fatigue.[40]

The Modafinil in Depression Study Group[41] evaluated modafinil in the treatment of residual vegetative symptoms in 136 patients with partially treated major depressive disorder. All patients received at least 5 weeks of antidepressant therapy. Those randomized to receive modafinil received 100 mg/day, titrated to a maximal daily dose of 400 mg based on clinical response. After 2 weeks, the modafinil group felt significantly less tired, but the difference between the modafinil group and the placebo group was no longer significant after 6 weeks. No differences in mood were observed.[41]

A recent open-label study evaluated modafinil 200 mg per day in combination with either fluoxetine or paroxetine (Paxil) as initial therapy for major depressive disorder.[42] Combination therapy significantly improved scores on the Hamilton Rating Scale, Fatigue Severity Scale, and Epworth Sleepiness Scale compared with baseline values; however, there was no placebo comparison.

Currently, there is no consensus regarding the use of modafinil as adjunctive therapy in depression, and more research is needed to determine its role in this setting.

In chronic fatigue syndrome

Randall et al[43] treated chronic fatigue patients with modafinil 200 mg/day, modafinil 400 mg/day, or placebo in a double-blind crossover trial; 17 patients were enrolled, but only 14 completed the protocol. No significant difference was seen in self-ratings of fatigue or quality of life. Larger studies are needed in this area.

ADVERSE EVENTS AND SAFETY ISSUES

Modafinil is usually started at 200 mg/day and increased to 400 mg/day, with higher doses sometimes given in divided doses. The starting dose should be 100 mg in the elderly and in patients with hepatic dysfunction.

The most commonly reported adverse events with modafinil in narcolepsy patients in placebo-controlled trials include headache, nausea, and nervousness. In most of the double-blind placebo-controlled trials of modafinil for approved indications, the drop-out rate in the modafinil group was 5% to 14% compared with 4% to 11% in the placebo group.[13,14,21,44,45]

Headache is the most common adverse effect but is often transient, resolving after about 3 days of treatment.

Although the drug has not been shown to adversely affect sleep architecture on polysomnography, 5% of patients experience insomnia.

Nervousness, anxiety, and stereotypy (repetitive motor behaviors) have been reported, but these symptoms seem to occur less frequently than with the traditional stimulants when the recommended human doses are used.

Modafinil as an adjunctive therapy in depression? More research needed

Cardiovascular effects

Animal studies suggest that there may not be significant differences between modafinil and traditional stimulants in cardiovascular side effects when equipotent doses for alerting effect are used. Shelton et al[46] observed no significant increase in heart rate or blood pressure in dogs receiving modafinil or amphetamine.[46] There was an increase in the motor activity, as measured by number of limb crossings per minute, in dogs treated with amphetamine compared with those treated with modafinil. However, comparative studies in humans with equipotent doses have not been performed.

Modafinil does not increase the heart rate in humans. It was initially thought to have no effect on blood pressure, but a retrospective analysis of several clinical trials showed that

2.4% of patients treated with modafinil required new or higher doses of antihypertensive medications compared with 0.7% with placebo.[47]

Low abuse potential

Modafinil is a schedule IV medication. Its abuse potential has been extensively studied in animals and humans, including patients with a history of substance abuse. These studies have included operant conditioning models, comparative models of amphetamine-like effects, and "willingness to pay" models to determine its approximate street value. All of these studies indicate that modafinil has a low potential for abuse, even at doses as high as 800 mg per day.[48,49]

These findings have several potential explanations. First, unlike modafinil, traditional stimulants and cocaine have dopaminergic receptors in the nucleus accumbens, an area that plays a central role in the behavioral reward circuit. Secondly, modafinil is not very water-soluble and is unstable at high temperatures, so it cannot easily be injected or smoked.[50] There is no known modafinil withdrawal syndrome.

Pregnancy and lactation

Modafinil, like the amphetamines, is in FDA pregnancy category C: ie, animal studies have shown an adverse effect on the fetus, no adequate and well-controlled studies have been done in humans, but the benefits of the drug in pregnant women may justify the potential risks. Sodium oxybate is in category B: ie, animal studies have not demonstrated a risk to the fetus, and no adequate and well-controlled studies have been done in pregnant women.

Embryo toxicity was seen in rats exposed to doses of modafinil approximately 5 to 10 times the maximum recommended human dose.[36] The amount of modafinil excreted in breast milk is unknown.

All women of child-bearing potential should be counseled about the risk of teratogenicity associated with stimulant drugs. In general, they should stop taking these drugs before they conceive, unless the risks of stopping the drug outweigh the benefits (eg, severe narcolepsy in a woman who needs to drive).

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