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Poised to Challenge Need for Sleep, "Wakefulness Enhancer" Rouses Concerns

Brian Vastag

LAST JANUARY, DRUG MAKER CEPHALON made an unusual request. It wanted the Food and Drug Administration (FDA) to approve a drug not for a condition or a disease, but for a symptom: sleepiness.

Not just routine sleepiness, but excessive, or in the words of one Cephalon advisor, "profound" sleepiness. The kind that makes drivers crash—in both senses.

Marketed as Provigil, modafinil was approved for the treatment of narcolepsy in 1998. Since then, though, the drug has earned a reputation as an all-around pick-me-up, with roughly 90% of prescriptions going for off-label uses, according to Cephalon.

A *Washington Post* article recently recommended it for jet-lag (and complained that it costs more than coffee). A *New Yorker* author found it helpful for late-night writing marathons. In August, world champion sprinter Kelli White took it before a race. Soon after, television news anchor Diane Sawyer popped one. "I feel quite awake," she told the audience of ABC's *Good Morning America*. "I don't feel the heart-racing thing that caffeine sometimes does. A bit jumpy, a little bit extra something going on here."

There is certainly a lot of extra money. In a conference call to investors last November, Cephalon executives said that they would sell \$300 million of modafinil in 2003—more than a million prescriptions, up 31% from 2002. Referring to the company's request for expanded labeling, the company's president enthused, "We're on the brink of a major market opportunity here."

The FDA's central nervous system advisory committee was less enthusiastic. In September, they advised the agency to give Cephalon the go-ahead for broadening modafinil's indications to include two new diagnoses: obstructive sleep apnea and shift work sleep disorder. But the company did not win the endorsement they wanted, to market modafinil for excessive sleepiness from any cause.



Competing with coffee? Sleep experts worry that a drug that improves wakefulness in patients with narcolepsy and a few other disorders will be used off-label by healthy individuals as a means to stint on sleep.

The central dispute revolved around whether narcolepsy, sleep apnea, and shift work sleep disorder typified other causes of sleepiness, a claim made by Cephalon. In supporting materials submitted to the FDA, the company had constructed its own classification of 37 causes of disordered sleep, including alcoholism, menstruation, pregnancy,

and parkinsonism. Most were included in the standard *International Classification of Sleep Disorders*. A few, including "long sleeper" and "subwakefulness syndrome," were not.

The company grouped these disorders into three categories—sleep-wake dysregulation, sleep disruption, and circadian misalignment—and placed narcolepsy, sleep apnea, and shift work sleep disorder, respectively, at the head of each. Because clinical trials showed modafinil promoting alertness in each of the vanguard disorders, it will promote wakefulness in every disorder, the company argued.

The FDA's central nervous system advisory committee was skeptical. Russell Katz, PhD, head of the neuropharmacological drug division at the FDA, repeatedly reminded them that Cephalon had conjured a new taxonomy of sleep disorders to bolster their case.

Committee member Lois Krahn, MD, chair of the department of psychiatry and psychology at the Mayo Clinic, Scottsdale, Ariz, voiced another source of unease during the group's proceedings. "My concern is that patients may . . . view it as a replacement for the normal amount of nighttime sleep," she said. "A person may want to enhance [themselves] and have, let's say, 20 hours of alertness in place of what is more normal."

When talking to the FDA or reporters, the company adamantly rejects such use. "We would never advocate that there is a substitute for sleep," said Jeffry Vaught, PhD, president for research and development at Cephalon, during a phone interview. "The treatment for sleep deprivation is sleep," added company spokeswoman Cheryl Williams.



But at the same time, Cephalon executives have been openly suggesting, at least to investors, that modafinil's off-label use will continue to drive profits. During the November conference call, Robert Roche, PhD, senior vice president for pharmaceutical development, said "You remember absolutely that this product is promoted only for the sleepiness associated with narcolepsy. But because of the terrific array of clinical data becoming available . . . physicians are able to learn about the much broader utility of the product than that which the current label would indicate."

And in fact, in January 2002, the FDA rebuked Cephalon for running advertisements that provided the "overwhelming misleading impression that Provigil can be used to improve wakefulness in all patients presenting with symptoms of daytime sleepiness . . ." and ordered the company to tie claims about banishing sleepiness explicitly to narcolepsy.

Nevertheless, according to sales figures from Cephalon, more and more sleep experts, psychiatrists, and general physicians are prescribing modafinil for sleepiness not caused by narcolepsy. Depression tops the list, with nearly 40% of the market, followed by multiple sclerosis, at 12%, according to company figures. Medicaid records show physicians submitting claims for attention deficit disorder and "miscellaneous fatigue."

It's the drug's safety record that is winning over clinicians. Cephalon's trials revealed few adverse effects, with a handful of patients stopping the drug after headaches and nausea. "In my own experience, there are very few problems with modafinil," said Ronald Chervin, MD, director of the sleep disorders clinic at the University of Michigan, Ann Arbor. "I've had a few patients feel jittery," he added, but a much smaller proportion than complain when taking methylphenidate (Ritalin).

While amphetamines work by revving up the entire body, increasing blood pressure and heart rate, modafinil somehow—no one knows how—

targets the hypothalamus and other sleep-regulating areas of the brain. Patients feel alert without the "hyperarousal" caused by amphetamines, said Vaught. And although the Drug Enforcement Agency classifies modafinil as a schedule IV drug, one with some potential for abuse, Cephalon executives and sleep experts chafe when modafinil is called a stimulant, preferring to characterize it as an alertness-promoting agent.

In laboratory trials, tired shift workers taking modafinil nodded off fewer times when performing a boring task compared with the placebo group. At the same time, the drug cleared from their blood quickly enough that they could sleep when they were ready.

Outside the laboratory, sleep specialists say that they have repeatedly seen modafinil rejuvenate miserable patients. "I have patients on disability because they're so sleepy," said Chervin, who advocates broader insurance coverage of the drug. "A lot of them pay out of pocket" even though the drug runs several hundred dollars per month.

SYMPTOM RELIEF ONLY

All of the sleep specialists interviewed for this article expressed concern that patients and physicians will confuse modafinil's symptom relief with a treatment for the underlying condition.

"It may only provide a superficial benefit," said Carl Hunt, MD, director of the National Center for Sleep Disorder Research at the National Heart, Lung, and Blood Institute. "The danger is, a lot of people will try to use it to stay awake instead of getting a good night's sleep."

Chronic short sleepers, those getting fewer than 6 hours per night, put themselves at risk of cardiovascular problems, namely hypertension, heart failure, and stroke, said Hunt. Short sleepers also have a higher overall mortality rate than good sleepers. Physicians, then, need to seek the underlying cause of sleepiness when bleary-eyed patients appear.

Many simply fail to head to bed. "You have to work with the patient on sleep

hygiene and habits," said Chervin. For patients with sleep apnea, he said, it would be "borderline malpractice" to prescribe modafinil without trying a continuous positive airway pressure machine first.

As far as the unknown potential for long-term dangers of modafinil—it has been on the U.S. market for 5 years, with fewer than 300 study patients taking it for more than 2 years—Chervin is matter-of-fact. "The choice is this: do you want your patient to walk out of your office and cause an accident, or do you want to give them a medication with a small risk that something bad will happen at year 6?"

Cephalon is now ramping up for a marketing blitz to coincide with the debut of the expanded indications (at press time, the company and the FDA were negotiating final labeling language). The company beefed up its sales force to 500 individuals, who are expected to "detail" 75 000 physicians in 2004. Direct-to-consumer advertising, while targeting shift workers and individuals with sleep apnea, will undoubtedly attract many of the other estimated 70 million individuals in the United States with sleeping problems.

OBVIATING SLEEP?

The stellar rise of modafinil recalls the success of Prozac in the 1980s. Both work in new and not completely understood ways. Both provide relief for a set of patients who have run out of options. Both blur lines between illness and enhancement. And the warnings that modafinil will radically alter society are reminiscent of the anti-Prozac backlash.

Critics of modafinil and Prozac charge that each provides a shortcut through a biological, or at least a psychological, resolution—a good night's sleep or the fruits of psychotherapy—but that messing with Mother Nature will ultimately backfire. Such warnings were anticipated by a 1960s pulp science fiction story, "Chronopolis," that imagined a world accelerated to an absurd degree: harried citizens regularly popped pills that carved out six or seven hours of



nighttime wakefulness, with nightmares the accepted price of getting by on an hour of sleep. For some individuals, the short-term benefits of modafinil appear to eclipse any unknown risks, but just as the drug's long-term effects are unknown, so is whether widespread use will

make the societal balance sheet run with red ink or black.

The FDA's Robert Temple, among others, is pragmatic. "If you read the newspapers, a lot of people are existing on less sleep than they need already . . . It's not completely obvious that off-label use that

helps them deal with their bad behavior is worse or better than not doing anything," he said at the modafinil advisory committee meeting.

"Those aren't easy questions. If they're driving next to me, I think I'd prefer they be on it." □

Markers in Prenatal Ultrasound Debated

Tracy Hampton, PhD

CHICAGO—A pregnant woman in her second trimester comes to the clinic for a prenatal visit, hoping to hear her physician say that everything looks fine. Anything less than confident enthusiasm from her obstetrician will keep her awake nights for the remainder of her pregnancy. But as was made clear during the annual meeting of the Radiological Society of North America last month, the precision of today's ultrasound imaging techniques often makes it difficult for physicians to provide such unqualified reassurance.

Modern ultrasound allows physicians to see clear and detailed morphological features of the fetus. Scans can show many potential "abnormalities" or markers, such as a slightly short femur or a bright spot on the heart. Studies in high-risk women (age >35 years) have revealed that some of these features may be linked to chromosomal defects. The most common clinically significant genetic abnormality in newborns—Down syndrome—is often detected through ultrasound.

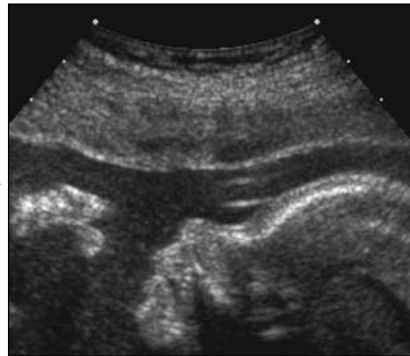
But many markers linked to Down syndrome are also found in some normal fetuses. Physicians now struggle with what to tell their patients—whether to alert them to all potential anomalies or withhold some information to prevent them often needless worry.

TO SEE, OR NOT TO SEE

Clinicians are divided on whether to use ultrasound to look for most of these markers, and the issue was vigorously

debated during a point-counterpoint session at the meeting.

"What I'm proposing to do by ultrasound is . . . the same thing that pediatricians do when the babies are born: look for the features of Down syndrome," said Beryl Benacerraf, MD, of Harvard Medical School, Boston, Mass, and a staunch proponent of using the technique to detect fetal markers of Down syndrome in high-risk women.



The use of certain features revealed by a prenatal ultrasound scan as potential markers of Down syndrome and other disorders is controversial because the markers also can be found in unaffected fetuses.

One of the most prominent markers, a thickened nuchal fold is found in 40% to 50% of fetuses with Down syndrome, with a false-positive rate of less than 1%, said Benacerraf. Other markers include a slightly shorter femur or humerus, an echogenic intracardiac focus, hyperechoic bowel, and renal pyelectasis. But many of these are more prevalent than thickened nuchal folds in normal fetuses.

Rebecca Smith-Bindman, MD, of the University of California, San Francisco, opposes the use of ultrasound to detect these markers. "In low-risk women, if you see a nuchal fold, the [fetus] is likely to have an increased risk of Down syndrome, although it's still small. But there is no evidence that you should act on the presence of other markers, nor is there evidence that you should look for or observe these markers," she said. Smith-Bindman and several colleagues came to that conclusion after performing a meta-analysis on 56 articles describing ultrasound in 1930 fetuses with Down syndrome and 130 365 unaffected fetuses (*JAMA*. 2001;285:1044-1055).

But physicians cannot help but see these markers during an ultrasound. So what should they tell their patients?

"By all means, provide information," said Smith-Bindman. "It's not clear to me, though, what information you're going to provide." She stressed that every pregnant woman is at risk of having a baby with Down syndrome, but said that it's too difficult to define that risk by taking minor markers into account.

Benacerraf argued that the presence of one minor marker may not mean much, but two or more are significant.

"I am not in favor of alarming a patient for a single minor marker because her risk really does not change substantially. But a cluster of minor markers increases the risk," she said. In a study of 164 fetuses with Down syndrome and 656 unaffected fetuses, Benacerraf and others showed that the presence of two minor markers increased the baseline risk six fold; the presence of three minor