

The individual reports in the supplement were derived from the planning teleconference of the same title as noted above. Dr. Biederman's article provided an introduction and overview to other articles that followed his. Dr. Biederman fully disclosed that he has received research support from Cephalon and that he also serves on the company's speaker's bureau and advisory board.³

In his article, Dr. Biederman stated:

The pharmacologic profile and structure of modafinil are notably different from those of stimulants and other agents used to treat ADHD, and modafinil may reduce the core symptoms of ADHD via the same mechanism by which it improves wakefulness—selective activation of the cortex without generalized effects on the central nervous system. This mechanism results in reduced abuse potential and less likelihood of jitteriness, anxiety, or excess locomotor activity than traditional stimulants.^{1(p4)}

That statement, however, is contradicted by 2 federal drug enforcement agencies. The U.S. Food and Drug Administration (FDA)—approved product label for modafinil (Provigil), in the section “Abuse Potential and Dependence,” states:

In addition to its wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS [central nervous system] stimulants.^{4(p1005)}

Furthermore, the product label continues:

The abuse potential of modafinil (200, 400, and 800 mg) was assessed relative to methylphenidate (45 and 90 mg) in an inpatient study in individuals experienced with drugs of abuse. Results from this clinical study demonstrated that modafinil produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate).^{4(pp1005–1006)}

Additionally, the Drug and Chemical Evaluation Section of the Drug Enforcement Administration (DEA), Office of Diversion Control, evaluation previously stated:

Modafinil is a central nervous system stimulant that is being considered for approval by the FDA, under the trade name Provigil®. Modafinil is being considered for marketing as a prescription drug product for the treatment of excessive daytime sleepiness associated with narcolepsy. Modafinil produces many of the same pharmacological effects and adverse reactions as classic psychomotor stimulants. . . .⁵

Our concern with Dr. Biederman's commentary is that it appears to seriously misrepresent modafinil's neuropharmacologic characteristics, contradicting the science-based evaluation of the data by the U.S. FDA and DEA. Dr. Biederman may have misrepresented modafinil's pharmacologic (stimulant) properties and minimized modafinil's abuse potential—as described in the authoritative FDA-approved product label. Dr. Biederman's misrepresentation of the serious risks posed by this drug, whose target population is children with ADHD, requires reexamination and correction.

Of note, if Cephalon, Inc., were to directly mischaracterize modafinil's pharmacocharacteristics—as Dr. Biederman has—they could be prosecuted under federal law.

Dr. Klotz is on the speaker's bureau of Pfizer Inc and has been a speaker for and consultant to Bristol-Myers Squibb/Otsuka. As of 2007, Dr. Kruszewski does not have any current business or financial arrangements with any pharmaceutical company. Dr. Kruszewski previously participated on the speakers bureaus of the following companies: Pfizer Inc, GlaxoSmithKline, Janssen (Johnson & Johnson),

AstraZeneca, Wallace Labs, Eli Lilly, and GE-Amersham Biosciences; and he previously served on an Eli Lilly Northeast Advisory Panel (1998). Dr. Kruszewski served as general and case-specific expert for national OxyContin MP litigation. Dr. Kruszewski owns less than a \$25,000 holding of Millennium pharmaceuticals.

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Dr. Biederman Replies

Sir: The background research to support the claims of Drs. Kruszewski and Klotz begins and ends with the manufacturer's package insert. However, the manufacturer's package insert is neither a standard of care nor the most comprehensive and up-to-date review of the preclinical or clinical science about a molecule. Were that so, new knowledge or findings would never be able to be conveyed to the field until the company or the U.S. Food and Drug Administration (FDA) determined to alter the manufacturer's package insert. Further, the labeling reflects information provided to the FDA at the time of submission of the compound and not necessarily the universe of scientific information available.

A search of the scientific literature indicates that there have been numerous studies conducted with modafinil which report that modafinil blunts cocaine-induced euphoria,^{1–4} does not produce amphetamine-like effects,^{5,6} and is indistinguishable from the subjective stimulant effects of caffeine.⁷ Additionally, all of the evidence from the literature on the abuse liability of modafinil suggests a much lower potential for abuse and dependency than for amphetamine-like stimulants.⁸ As an independent clinician-researcher and not the agent of the manufacturer, I am compelled to base my teaching on all the information and knowledge available to me.

The authors' primary concern appears to be what they believe are the “serious” consequences of abuse and addiction associated with modafinil (hence, “mischaracterization”). However, both the FDA and the Drug Enforcement Administration (DEA) documents are in complete agreement with my very clear position that modafinil has reduced abuse potential and less likelihood for jitteriness, anxiety, and locomotor activity than traditional stimulants. In fact, the key supporting evidence could be taken directly from those documents:

- First and perhaps most importantly, the definitions of Schedule II and Schedule IV clearly make my statements consistent with DEA documentation and their own determination about the relative potential abuse liability for modafinil compared to traditional stimulants. Traditional stimulants are classified in Schedule II (“the drug or other substance has a high potential for abuse”), while modafinil is in the less-restricted Schedule IV (“the drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule [I, II, and] III”).⁹
- The authors mischaracterize the evaluation of the Drug and Chemical Evaluation Section of the DEA, Office of Diversion Control,¹⁰ by including a partial quotation in their letter. The full quotation reads as follows:

Modafinil is a central nervous system stimulant that is being considered for approval by the FDA, under the trade name Provigil®. Modafinil is being considered for marketing as a prescription drug product for the treatment of excessive daytime sleepiness associated with narcolepsy. Modafinil produces many of the same pharmacological effects and adverse reactions as classic psychomotor stimulants, *but appears to have chemical properties that may limit its abuse (i.e., not water soluble, decomposes in heat). DEA is unaware of any reports of modafinil abuse.*¹⁰ [Italics added to highlight omitted text.]

- The FDA labels for methylphenidate and amphetamines include a black box warning for a high potential for abuse and dependence, and modafinil’s label does not.
- Methylphenidate and amphetamines have contraindications for agitated states and patients with a history of drug abuse in their product information^{11–14}; modafinil has no such contraindication.
- Methylphenidate is contraindicated in patients with marked anxiety, tension, and agitation^{12–14}; modafinil has no such contraindications.
- Finally, as stated in my remarks, the pharmacologic profile and structure of modafinil are notably different from those of stimulants and other agents used to treat attention-deficit/hyperactivity disorder (ADHD). As stated, modafinil is a chemically unique molecule unrelated to stimulants or other treatments for ADHD.

The letter by Drs. Kruszewski and Klotz seriously misrepresents the facts, shows ignorance about the neuropharmacologic characteristics of modafinil, and demonstrates a failure to understand the clinical significance of alternative treatments for ADHD. The accusation that my statement may have misrepresented modafinil’s pharmacologic (stimulant) properties and minimized modafinil’s abuse potential is baseless.

Dr. Biederman receives or has received research support from, is or has been a speaker for, or is or has been on the advisory board for Shire, Eli Lilly, Pfizer, McNeil, Abbott, Bristol-Myers Squibb, New River, Cephalon, Janssen, Novartis, UCB Pharma, AstraZeneca, Forest, GlaxoSmithKline, and Neurosearch and has received research support from Stanley Medical Institute, Lilly Foundation, Prechter Foundation, the National Institute of Mental Health, the National Institute of Child Health and Human Development, and the National Institute on Drug Abuse.

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