

## Euphorigenic and Abusive Properties of Modafinil

TO THE EDITOR: In the August issue of the *Journal*, Charles P. O'Brien, M.D., Ph.D. (1) stated the following about modafinil, a drug that he reported may decrease cocaine use in some cocaine users: "The medication has not been reported to produce euphoria, and there has been no indication of excessive use or abuse in clinical trials" (p. 1428). As the scientific basis for his comment, the author referenced his own group's work (2).

The author's statement does not appear to be supported by his referenced work, nor is it supported by information widely available in the 2004 edition of the *Physicians' Desk Reference (PDR)*. The referenced article, for example, may demonstrate that modafinil can, in some cases, blunt cocaine euphoria. However, it does not say anything about modafinil's intrinsic ability to produce euphoria (or not). Separately, the 2004 *PDR* raises specific concerns about modafinil, saying that it can produce "psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS stimulants." The *PDR* also states that "modafinil is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine."

The author's comment about the lack of euphorigenic effects of modafinil is also contradicted by the U.S. Food and Drug Administration (FDA) in its warning letter of Jan. 14, 2002, sent to Paul M. Kirsch, the senior director of regulatory affairs of Cephalon, Inc., the makers of modafinil. It is available online (3). That letter specifically reiterates the package insert for modafinil, addressing its abuse potential and euphorigenic effects.

That the euphorigenic side effects or abuse potential may be minimized has current treatment implications because modafinil is increasingly promoted for fatigue and excessive sleepiness unrelated to narcolepsy as well as for cocaine abuse. However, the implications loom even larger because the makers of modafinil have submitted the "reformulated" drug to the FDA under a new name—Attenace—for the treatment of attention deficit hyperactivity disorder (4).

### References

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## Osteoporosis and Schizophrenia

TO THE EDITOR: Martina Hummer, M.D., et al. (1) reported the occurrence of low bone mineral density in a group of young male subjects with schizophrenia. Levine et al. (2) and Applebaum et al. (3) reported elevated plasma homocysteine levels in young male schizophrenic patients.

Elevated homocysteine plasma levels were recently reported to be associated with osteoporotic bone fractures in the elderly in two large follow-up studies (4, 5). McLean et al. (4) analyzed blood samples obtained and stored from 1,999 men and women as part of the long-term Framingham Study. These researchers found that men and women in the upper quartile of homocysteine concentrations were nearly four and two times, respectively, as likely to later have a hip fracture in comparison to the lower quartile of homocysteine concentrations. Van Meurs et al. (5) analyzed blood samples and health data from 2,406 people. Men and women in the upper quartile of homocysteine concentrations were about twice as likely to have a hip or other bone fracture as were those in the lower quartile of homocysteine concentrations.

The mechanism underlying homocysteine's effect on bone metabolism is not yet clear. However, several mechanisms were suggested, including that elevated homocysteine disturbs the cross-linking of collagen in bone and disturbs osteoblast formation (6).

Thus, it is suggested that elevated homocysteine levels may be a mechanism of the low bone mineral density reported by Dr. Hummer et al. (1) among young male subjects suffering from schizophrenia.

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