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Letter to the Editor

Modafinil and Pramipexole-Associated Somnolence

We read with interest the paper by Hauser et al.[1] on one case of modafinil use in a parkinsonian patient suffering from pramipexole-associated somnolence. The authors conclude that "modafinil may be a useful treatment for dopamine agonist and levodopa-induced somnolence and sudden episodes of sleepiness." As with any single case report, this interesting observation deserves, from a pharmacological point of view, some comments. First, prospective randomized double-blind studies remain to be conducted to verify the efficacy suggested by this preliminary observation. Second, the safety of modafinil in parkinsonian patients should be investigated. It is known that the safety profile of a drug can differ according to the underlying disease. What about the risk of pharmacodependence (drug addiction) which was largely discussed with modafinil?[2,3] In fact, because of such a concern, modafinil is only marketed in France for narcolepsy or idiopathic hypersomnia under strict electrophysiological survey and can only be prescribed by neurologists and/or sleep specialists. The long-term effects of such a drug on extrapyramidal symptoms remain also unknown, although some antiparkinsonian and possibly neuroprotective effects were described in the MPTP-treated common marmoset.[4] Moreover, some cases of bucco-facial dyskinesias have been reported with modafinil.[5] Third, in the absence of comparative drugs or dechallenge/rechallenge design, a spontaneous improvement, although unlikely, cannot be excluded to allow definite imputability (causality) analysis. Fourth, and maybe more important, addition of a drug (with its own potential adverse reactions) to suppress (or decrease) adverse reactions related to another drug is not in accordance with pharmacological logic and best therapeutic practice and guidelines. It might be preferable, safer, and less expensive to try first to replace the offending drug by an alternative antiparkinsonian therapy, although little is known about the respective risk of somnolence among various antiparkinsonian medications.

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Reply

In clinical practice we attempt to offer therapeutic interventions that provide the best ratio of likely benefit to risk/cost/inconvenience. Our patient experienced intolerable head dyskinesia on levodopa/carbidopa, and amantadine alone provided insufficient benefit.[1] The addition of pramipexole to amantadine provided good clinical benefit for signs and symptoms of Parkinson's disease (PD) but was associated with episodes of unintended daytime sleep, particularly while she was driving. We therefore elected to add modafinil (Provigil) in an effort to overcome this potentially dangerous side effect.

An alternative approach might have been to attempt to switch from pramipexole to another dopamine agonist. However, switching agonists is not without side effects[2] and little is known about the likelihood of success in undertaking such a strategy in this situation. It has been suggested that somnolence and sleep episodes may be a class effect of dopamine medications.[3] Information regarding the relative propensity of various antiparkinsonian medications to cause sleep episodes and the likelihood of improvement when switching agonists in patients with somnolence is greatly needed. An important consideration for our young patient was that she had been experiencing either side effects or inadequate control of parkinsonian symptoms for almost a year while trying to maintain employment. In part, we wanted to initiate the therapy that we felt had the greatest likelihood of success in a relatively short time.

The correspondents state that the addition of a drug to suppress adverse reactions related to another drug is not in accordance with pharmacological logic and best therapeutic practice guidelines. However, there are several widely employed examples of this strategy in the treatment of PD alone. Domperidone is commonly used to treat dopaminergic medication-induced nausea and atypical neuroleptics are commonly used to suppress medication-induced psychosis. In addition, several new drugs are in clinical testing to evaluate their ability to suppress dyskinesia. Although it is wise to carefully consider using one medication to treat the side effects of another, this strategy clearly has its place in clinical care.

Modafinil appears to be associated with substantially less potential for abuse and dependence than other wake-promoting agents.[4–6] The amphetamine-like stimulants, including amphet-

amine, methamphetamine, and methylphenidate have good wake-promoting effects but are Schedule II drugs. They are considered to have a high potential for abuse and may lead to severe psychological or physical dependence. Modafinil has a mechanism of action that, while not completely elucidated, differs markedly from that of amphetamine-like stimulants. It binds weakly to dopamine reuptake sites, but unlike amphetamine, its wake-promoting effects are not antagonized by haloperidol. Narcolepxy is associated with a deficiency of orexin (hypocretin)[7] and modafinil may activate orexin-containing neurons in the lateral thalamus.[8] However, the role of orexin in modafinil-induced wakefulness is unclear, as modafinil promotes wakefulness in narcoleptic canines with an orexin receptor mutation. Preclinical and clinical data suggest that modafinil has a much lower potential for dependency and abuse than amphetamine-like stimulants. Withdrawal of modafinil in patients with narcolepsy does not result in amphetamine-like withdrawal symptoms such as hypersomnia, vivid dreams, fatigue, dysphoria, increased appetite, and psychomotor retardation, or agitation. In addition, modafanil has low water solubility and is unstable at high temperatures, physical properties that reduce potential for abuse via intravenous injection and smoking, respectively. However, modafinil can produce psychoactive and euphoric effects, and alterations in mood, perception, thinking, and feelings typical of other central nervous system (CNS) stimulants. In cocaine-treated monkeys, high doses of modafinil have reinforcing effects. Modafinil is therefore classified as a Schedule IV drug. In clinical practice, patients should be observed for signs of misuse or abuse, incrementation of doses or drug-seeking behavior.

Our major concern regarding the use of modafinil at the current time is the possibility that it may mask symptoms of undiagnosed sleep apnea. Our patient was a thin 33-year-old woman who did not snore, had no family history of sleep disorders, and had never experienced daytime sleepiness until she was treated with pramipexole. Her clinical picture was very similar to other patients we have described with pramipexole-induced somnolence.[9] Two of these patients experiencing sleep episodes under went sleep tests while on pramipexole and were found to have no evidence of sleep apnea or narcolepsy, but exhibited decreased time to sleep on Multiple Sleep Latency Testing (MSLT). We therefore felt it was highly likely that our patient had pramipexole-induced somnolence and not sleep apnea. However, experience with other PD patients with different clinical pictures has suggested that we must have a high index of suspicion for sleep apnea in individuals complaining of sleepiness or fatigue. We speculate that modafinil may improve sleepiness in patients with sleep apnea but ongoing hypoxia may lead to neurologic and systemic damage unless measures are taken to restore airflow. Polysomnography may also reveal other treatable conditions such as REM sleep behavior disorder (RBD) or Periodic Limb Movement Disorder (PLMD). We therefore believe that polysomnography should be obtained in patients for whom the cause of sleepiness is unclear prior to initiating modafinil therapy. Further studies are required to determine how often sleep apnea is the cause of sleepiness in PD patients and how often sleep apnea is present in patients who appear clinically to have dopaminergic medication-induced somnolence and sleep episodes.

We wholeheartedly agree that prospective double-blind studies to assess the tolerability, safety, and efficacy of modafinil in PD are required. Already identified as possible indications for study are medication-induced somnolence and sleep episodes, sleepiness without identifiable cause, fatigue, depression, and PD symptoms and progression.[10] We recently conducted an informal survey and identified approximately 80 PD patients at three centers (excluding ours) currently on modafinil for sleepiness. We continue to believe that modafinil *may* be a useful treatment for dopamine agonist and levodopa-induced somnolence and unintended episodes of sleep. Its use is expanding and we anticipate that it will become an important therapeutic tool in the management of PD.

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