EDITORIAL

Stimulants and Narcolepsy

Comment on Auger R; Goodman S; Silber M et al. Risks of High-Dose Stimulants in the Treatment of Disorders of Excessive Somnolence: a Case-Control Study. *SLEEP* 2005:28(6):667-672

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FOR DECADES, STIMULANT MEDICATION HAS BEEN THE MAINSTAY TREATMENT FOR HYPERSOMNIA ASSOCIATED WITH NARCOLEPSY. ALTHOUGH THERE have been concerns regarding dependence, tolerance, abuse, and side-effects such as psychosis and cardiovascular complications, such events have been relatively uncommon, but have not been studied systematically. The article in this issue ("Risks of high-dose stimulants in the treatment of disorders of excessive daytime somnolence: a case control study by Auger et. al.) is the first large-scale retrospective, case-control study of 116 patients with narcolepsy comparing presumed medication complications in two groups separated into "standard" vs. "high" dose stimulant medication. It is concluded that "high" dose stimulant medication is associated with psychosis, alcohol or polysubstance abuse, psychiatric hospitalization, tachyarrhythmias, and anorexia or weight loss. No relationship was found for depression, drug-seeking or suicidal behaviors, hypertension or cardiovascular disease.

Before alarm sets in, reflection would be in order. The determination of "standard" vs. "high" dose stimulant medication was based upon the recommendations formulated by the American Academy of Sleep Medicine Standards of Practice Committee (AASMSPC).[1] These recommendations are consensus-based and thus may not reflect careful science. Amazingly, there has never been a single systematic pharmacokinetic study of the stimulant medications discussed in this study in narcolepsy. In one small study by Mitler, the dose-related serum levels of methamphetamine were substantially lower for narcoleptics than controls.[4] This could suggest differences in absorption of, metabolism of, or sensitivity to the drug in patients with narcolepsy. Interestingly, in that study, the dose of methamphetamine associated with near normalization of the MSLT would have been deemed "high" dose in the Auger study.

Reports of psychosis associated with stimulant use in narcolepsy have been variable, and are rare in patients with narcolepsy.[2] In the current study, although there was an impressive odds ratio of 12 (14 patients in "high dose" vs. 3 patients in "low dose"), in half of the 14 "high dose" psychosis patients, there was no evidence of a temporal or causal relationship between the medication and the psychiatric symptom. The temporal or causal relationship with tachyarrhythmias is likewise unclear, and the numbers are small. Correlation does not establish causality. Likewise, no information is given regarding a relative "high dose" dose-dependent risk. Some of the "high dose" patients were receiving heroic doses of stimulants (i.e., at least one patient received 1400 mg of methylphenidate daily). It would be valuable to know if the complications occurred at the upper end of the "high dose" group. The cutoff point between the "high" and "low" dose was not determined by complication rate, but rather by AASMSPC's arbitrary guideline.

This study does dispel the long-held myths that prescribed stimulant medication is associated with drug-seeking behavior or cardiovascular consequences.

This study will undoubtedly be cited by pharmaceutical companies to promote alternative stimulant medications. It must be kept in mind that newer "wakefulness promoting" drugs have not necessarily withstood the test of time (witness the recent cox2-inhibitor debacle). The conventional stimulants have been used with generally good results and infrequent complications for decades.[3,6] The number of patient/year/doses is huge. Already there are reports of complications of one alternative stimulant are emerging.[5,7]

Regrettably, the pharmaceutical industry prefers to conduct drug studies comparing their new drug to placebo, and is hesitant (or afraid?) to conduct head-to-head studies. Given the extraordinary (if not unconscionable) cost differential between the older and newer stimulants and "wake-promoting" agents, head-to-head clinical and cost-effectiveness studies, not sponsored by industry, are sorely needed before we really know what is best for our patients' symptoms and their pocketbooks.

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REFERENCES

1. American Sleep Disorders Association. Practice parameters for the use of stimulants in the treatment of narcolepsy. Sleep 1994;17:348-51.
2. Boutrel B, Koob GF. What keeps us awake: the neuropharmacology of stimulants and wakefulness-promoting medications. Sleep 2004;27:1181-94.
3. Guillemiault C. Amphetamines and narcolepsy. 1. Amphetamines and narcolepsy: use of the Sanford database. Sleep 1993;16:199-201.
4. Mitler MM, Hajdukovic R, Erman MK. Treatment of narcolepsy with methamphetamine. Sleep 2003;16:306-17.
5. Narendran R, Young CM, Valenti AM, Nickolova MK, Pristach CA. Is psychosis exacerbated by modafinil? Arch Gen Psych 2002;59:292-3.
6. Parkes JD, Dahlitz M. Amphetamines and narcolepsy. 2. Amphetamine prescription. Sleep 1993;16:201-3.
7. Vorspan F, Warot D, Consoli A, Cohen D, Mazet P. Mania in a boy treated with modafinil for narcolepsy. Am J Psychiatry 2005;162:813-4.