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Risks of High-Dose Stimulants in the Treatment of Disorders of Excessive Somnolence: A Case-Control Study

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Study Objectives: To ascertain complications associated with high-dose stimulant therapy in patients with narcolepsy or idiopathic hypersomnia.
Design: Case-control, retrospective chart review.
Setting: Sleep center in an academic hospital.
Patients: 116 patients with narcolepsy or idiopathic hypersomnia were individually matched by sex, diagnosis, age of onset, and duration of follow-up from both onset and diagnosis. Members of the high-dose group (n = 58) had received at least 1 stimulant at a dosage ≥ 120% of the maximum recommended by the American Academy of Sleep Medicine Standards of Practice Committee. The standard-dose control group (n = 58) had received stimulants at a dosage ≤ 100% of the American Academy of Sleep Medicine guidelines.
Interventions: N/A.
Measurements and Results: The prevalence of psychosis (odds ratio = 12.0 [1.6-92.0]), alcohol or polysubstance misuse (odds ratio = 4.3 [1.2-15.2]), and psychiatric hospitalization (odds ratio = 3.2 [1.1-10.0]) was significantly increased in the high-dose group. More high-dose patients also experienced tachyarrhythmias (odds ratio = 3.3 [0.92-12.1] and anorexia or weight loss (odds ratio = 11.0 [1.4-85.2]). The frequency of physician-diagnosed depression, drug-seeking and suicide-related behaviors, hypertension, and cardiovascular disease did not differ significantly between the groups.
Conclusions: This study demonstrated a significantly higher occurrence of psychosis, substance misuse, and psychiatric hospitalizations in patients using high-dose stimulants compared to those using standard doses. Tachyarrhythmias and anorexia or weight loss were also more common in this group as compared with controls. Clinicians should be very cautious in prescribing dosages that exceed maximum guidelines.
Key Words: narcolepsy, stimulants, complications, psychosis
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INTRODUCTION

OCCASIONAL PATIENTS WITH NARCOLEPSY OR IDIOPATHIC HYPERSOMNIA ARE PRESCRIBED STIMULANTS AT DOSAGES EXCEEDING PUBLISHED GUIDELINES,[1] AS standard doses do not provide adequate alertness. While debate exists as to whether such doses are associated with adverse cardiovascular, psychiatric, and other events, little has been published to systematically address these issues, particularly in the realm of psychiatric complications.

A few studies of acute cardiovascular complications of these drugs have been reported. Recreational use of stimulants has been associated with both hemorrhagic and ischemic stroke, but with an unclear relation to drug dose.[2,3] One case report described a healthy 58-year-old narcoleptic who developed an acute myocardial infarction while receiving 40 mg of dextroamphetamine.[4]

Long-term cardiovascular effects of stimulants have also been investigated. As early as 1937, Ulrich reported pretreatment and posttreatment blood pressures of 6 patients receiving 10 to 30 mg of benzedrine, during 2 years of observation.[5] No discernible trend was observed. Mitler et al[6] compared 8 narcoleptic patients with 8 matched controls using a double blind, randomized placebo-controlled crossover design. The stimulant group received both low-dose and high-dose methamphetamine, the latter range defined by the authors as 40 to 60 mg. There was no treatment effect on measurements of blood pressure, pulse, or respiratory rate, either between individual stimulant groups or between the combined groups and controls.

Parkes et al[7] reported on 51 narcoleptic patients receiving 5 to 150 mg of dextroamphetamine daily and showed no significant relationship between dosage or duration and blood pressure, after a treatment period of up to 33 years. Guilleminault investigated blood pressure in 42 subjects receiving high-dose amphetamines (≥ 100 mg daily), both during treatment and after 4 weeks of withdrawal.[8] Four subjects were hypertensive at entry (≥ 165/95) but only 2 at follow-up, and these 2 actually had decreased systolic (SBP) and diastolic (DBP) blood pressures. No subjects developed hypertension during the observation period and, apart from the 2 initially hypertensive subjects, 22 actually had a drop in both SBP and DBP.

Wallin and Mahowald retrospectively studied 54 subjects with narcolepsy or idiopathic hypersomnia who had received uninterrupted stimulant treatment for a minimum of 2 years and a mean of 3.8 years.[9] Methylphenidate, either alone or in combination, was used in 80% of patients, and 30% of subjects were using high-dose stimulants, according to the original American Sleep Disorders Association criteria (see Table 1).[10] No statistically significant change in SBP or DBP was observed during the study period in subjects receiving either the low dose or high dose. More-

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Table 1—American Academy of Sleep Medicine/American Sleep Disorders Association Practice Guidelines for Stimulant Therapy and High-Dose Inclusion Criterion.

Medication	Maximum Recommended Daily Dose, mg	High-Dose Inclusion, mg
Methylphenidate	100	≥ 120
Methamphetamine	80	≥ 100
Dextroamphetamine	100	≥ 120
Pemoline	150	≥ 180
Amphetamine	100	≥ 120

over, preexisting hypertension did not appear to be a significant variable in predicting blood pressure changes.

Various psychiatric complications of stimulants have also been described. Shortly after amphetamines began to be used for the treatment of narcolepsy, Young and Scoville[11] reported the association of benzedrine use with the onset of paranoid psychoses in 2 of 3 patients. Eilenberg[12] later reported 2 additional cases of stimulant-associated psychoses, 1 involving a patient receiving 60 mg methylphenidate and 15 mg methamphetamine for approximately 4 months, and the other receiving an unknown dosage of methamphetamine for a period of 6 years.

Two reports and 1 case series describe the onset of visual hallucinations associated with stimulant use. Symptoms developed in 1 patient receiving methylphenidate at an unknown dosage for a period of 7 years and in another patient receiving 30 mg of dextroamphetamine for 4 years.[13,14] In a series of 100 narcoleptics, visual hallucinations occurred in 2 patients (2%) who were receiving 40 mg and 60 mg of dextroamphetamine.[7]

Inconsistent reporting of drug dose hampers interpretation and comparison of data from other large patient series. In a series of 115 narcoleptic patients followed retrospectively for 29 years, 9% developed psychoses requiring hospitalization.[15] In a series of 31 patients receiving amphetamines followed for a mean of 7.5 years, 1 patient (3.2%) was psychiatrically hospitalized for psychosis, but the dose prescribed is unspecified.[13]

Series that accurately report drug dose often do not report drug duration. Parkes et al[16] described psychosis in only 1 of 300 narcoleptic patients (0.3%) who were receiving 20 mg daily dextroamphetamine, but the duration of treatment was not reported. Three of 487 narcoleptic patients (0.6%) administered amphetamines were hospitalized for stimulant-induced psychoses.[8] Two had been taking more than 60 mg of amphetamine per day, and 1 had been taking 20 mg of dextroamphetamine daily, but duration of treatment was again not reported. Interviews of patients in this series taking 60 mg or more of amphetamines daily, with collateral information from their families, revealed that 80% described disorders in thinking, verbal aggressiveness, agitation, and unpleasant ideations or interactions, particularly after the largest dose of the day.

In a series that addressed psychiatric complications of high-dose stimulants in a more systematic fashion, Pawluk et al[17] reported on 11 narcoleptic patients receiving ≥ 100 mg of methylphenidate daily for at least 5 years. Two (18%) developed psychoses, and 54% showed evidence of depression or dysthymia. Finally, while the presence of stimulant abuse is a frequent psychiatric concern among prescribers, no long-term data have been published demonstrating this complication in narcoleptic populations.

We report a case-control study, comparing a high-dose stimulant group with a matched sample of patients taking standard doses, specifically assessing for many of the complications discussed above, including psychosis, substance misuse, depression, hypertension, cardiovascular disease, tachyarrhythmias, and anorexia or weight loss.

METHODS

We used the Mayo Narcolepsy Research Center database to identify all patients treated between 1950 and 2000 for narcolepsy or idiopathic hypersomnia. Patients in the high-dose group received, during the course of their illness, at least 1 stimulant at a dosage ≥ 120% of the maximum recommended by the American Academy of Sleep Medicine Standards of Practice Committee (see Table 1).[1] If an additional stimulant was prescribed, it did not necessarily exceed maximum recommended dosage. We identified a control subject for each patient, matching for diagnosis, sex, age at onset, and duration of follow-up from both disease onset and diagnosis. Control subjects received stimulants at a dosage ≤ 100% of the maximum recommended by the American Academy of Sleep Medicine.[1] It is important to note that American Academy of Sleep Medicine dosage guidelines are somewhat arbitrary, in that they are based on a review of limited data, and were ultimately defined by expert consensus.[1,10,18]

Mayo Sleep Disorders Center physicians saw all patients, and diagnoses were confirmed according to Mayo Narcolepsy Research Criteria.[19] Patients' records were reviewed, and the data were abstracted and analyzed. The study was approved by the Mayo Foundation Institutional Review Board.

A diagnosis of psychosis was assigned to a patient if there was an explicit reference to the condition, which generally manifested as hallucinations, delusions, or both, of sufficient severity to warrant hospitalization. When symptoms were less clearly described, as in the case of suspiciousness or disordered thinking, diagnoses were assigned after review of the record, according to the judgment of 2 board-certified psychiatrists (LEK and RRA). Diagnoses of depression, hypertension, cardiovascular disease, and tachyarrhythmias were determined by review of a master list of diagnoses for each patient, in addition to a thorough review of the chart for diagnoses inadvertently omitted from the master list. The presence of alcohol or other substance misuse was determined in a similar fashion but was also elicited from the content of the medical notes, as these conditions were not always listed as official diagnoses. Drug-seeking and suicide-related behaviors, psychiatric hospitalization, and anorexia or weight loss were ascertained solely from note content, as they were not entered as specific diagnoses.

Because the study employed matched sets, conditional logistic regression was used to test for associations between the variables of interest and the patients who received high-dose or standard-dose stimulants. The variables of interest included the diagnoses and complications abstracted from the medical records. For binary variables, this analysis is the maximum-likelihood version of McNemar's test. Likelihood ratio test statistics are reported, along with estimates of the odds ratio summarizing the magnitude of the difference, and their corresponding Wald-based confidence intervals. Conditional logistic regression was also used to compare matching variables between the 2 groups to verify that the matching had been successful. Because those treated with a given

drug were usually not concordant within matched sets, 2-sample rank-sum tests were used to compare the duration of medication use between the 2 groups. All statistical analyses were performed using the SAS software system (SAS Institute, Inc., Cary, NC).

RESULTS

Demographic and Treatment Data

Fifty-eight patients and 58 controls were identified. Fifty-four were women (46%) and 62 men. The successful application of the matching strategy insured that there were no significant intergroup differences with regard to sex, diagnoses, age of disease onset, or duration of follow-up from both disease onset (mean high-dose group 34.7 ± 15.8 years versus 36.9 ± 19.1 years in controls, $P = .35$) and diagnosis (mean high-dose group 22.7 ± 12.4 versus 20.3 ± 13.8 years, $P = .18$). See Table 2 for further details.

Methylphenidate was most commonly prescribed in both groups, administered to 100% in the high-dose group (all but 1 of whom were receiving ≥ 120% of recommended maximum dose)[1] and 95% in the standard-dose group. Methamphetamine was the second most commonly prescribed, administered to 55% in the high-dose group (22% receiving ≥ 120% of recommended maximum dose) and 21% in the standard-dose group. There were no significant intergroup differences with respect to duration of treatment with methylphenidate, pemoline, and amphetamine, although the sample sizes did not provide power to detect small differences. Significant intergroup differences were found with respect to mean methamphetamine and dextroamphetamine durations, with those in the standard-dose group receiving the drugs for a longer period of time. See Table 3 for further details.

Thirty-four patients (59%) receiving high-dose methylphenidate received at least 1 additional stimulant. Seven of these (20%) received 1 additional stimulant at a dosage satisfying high-dose inclusion criterion, 1 (3%) received 2 additional stimulants satisfying this criterion, and 1 (3%) received 3 additional stimulants that met this criterion.[1] Sixteen patients (27%) in the control group received 2 stimulants (including methylphenidate) during the course of treatment, and 2 (3%) received 3 stimulants.

Complications Data

The frequency of psychosis (odds ratio = 12.0 [1.6-92.3]), substance misuse (odds ratio = 4.3 [1.2-15.2]), and psychiatric hospitalization (odds ratio = 3.2 [1.1-10.0]) was significantly increased in the high-dose group. Drug-seeking behavior occurred only in the high-dose group, which prevented the calculation of an odds ratio, but the difference did not reach statistical significance (7% vs 0%, $P = .062$). Occurrence of physician-diagnosed depression was not significantly different in the 2 groups (odds ratio = 1.1 [0.5-2.5]). Suicide, attempted suicide, or suicidal ideation (odds ratio = 5.0 [0.6-42.8]) occurred more frequently in the high-dose group, but the difference did not reach statistical significance.

Table 2—Summary of Comparisons Between Patients in the High-Dose Group and Controls.

Group Composition	**High Dose**	**Standard Dose**
Total, no.	58	58
Men/Women, no.	31/27	31/27
Narcolepsy with cataplexy, no. (%)	47 (81)	47 (81)
Narcolepsy without cataplexy, no. (%)	9 (16)	9 (16)
Idiopathic hypersomnia, no. (%)	2 (3)	2 (3)
Characteristics*	**High Dose**	**Standard Dose**
Age at onset, y	18.9 ± 9.6	18.0 ± 9.6
Duration from onset, y	34.7 ± 15.8	36.9 ± 19.1
Duration from diagnosis, y	22.7 ± 12.4	20.3 ± 13.8

*Data are presented as mean ± SD.

Of the 14 patients who developed psychoses in the high-dose group, a definite temporal connection with stimulant use was inferred in 7 (50%), based upon cessation of psychotic symptoms with reduction or discontinuation of the medications. In 6 patients, complications developed in the setting of methylphenidate use, at a median dosage of 170 mg (range 120-500 mg). Symptoms disappeared on reduction of the dose to a median of 80 mg (range 15-260 mg). In 1 patient, symptoms emerged at a dosage of 80 mg of methamphetamine, continued after substitution of 120 mg of methylphenidate, and later disappeared after discontinuation of all stimulants.

In 3 patients with psychosis in the high-dose group, the symptom was not clearly associated with stimulant use, in that a psychotic disorder preceded their administration (2 patients) or persisted after their discontinuation (1 patient). In the remaining 4 patients, the association was indeterminate, due to continuation of stimulant medications despite the emergence of psychotic symptoms or inadequate follow-up information. Of the 3 patients who developed psychoses in the low-dose group, all were receiving methylphenidate, with symptoms developing at a median dosage of 60 mg (range 30-80 mg). In 1 patient, symptoms abated upon discontinuation of the medication, while in the remaining 2, the relationship was indeterminate.

The frequency of hypertension (odds ratio = 1.1[0.5-2.4]) and cardiovascular disease (odds ratio = 1.0 [0.3-3.1]) did not differ substantially between the groups. Significantly more patients in the high-dose group experienced anorexia or weight loss (odds ratio = 11.0 [1.4-85.2]). The odds of developing tachyarrhythmias were 3.3 times higher (95% confidence interval: 0.92-12.1) in patients in the high-dose than in the standard-dose group. While the Wald-based confidence interval for tachyarrhythmias bounds 1.0, the P value from the likelihood-ratio test statistic suggested a statistically significant difference ($P = .046$). See Tables 4 and 5 for details.

In the high-dose group, a direct association between stimulant medications and tachyarrhythmias was indeterminate in 9 of 11 patients (82%), due to a combination of persistent use of the medication at an unaltered or increased dosage, incomplete medical records, or concomitant medical therapy for the arrhythmia. In 1 patient receiving 150 mg of dextroamphetamine, the arrhythmia disappeared after substitution of 45 mg of methamphetamine, recurring 37 years later. One patient was diagnosed with a tachyarrhythmia during an extended abstinence from stimulants. In the low-dose group, an association was also difficult to deduce, for the same reasons mentioned above.

DISCUSSION

To our knowledge, this is the first study investigating complications of high-dose stimulants with a case-control methodology. The high frequency of psychiatric complications in the high-dose

Table 3—Treatment

Medication	Patients, no. (%)		Median Daily Dose, mg (range)		Duration, y, mean ± SD		P Value (Duration)
	High Dose	StandardDose	High Dose*	StandardDose	High Dose	StandardDose	
Methylphenidate	58 (100)	55 (94.8)	195 mg (100-1400)	60 mg (5-100)	14.7 ±11.6	11.7 ±11.4	.140
Methamphetamine	32 (55.2)	12 (20.7)	60 mg (15-225)	27 mg (10-80)	7.2 ±8.1	18.4 ±17.4	.033
Dextroamphetamine	9 (15.5)	9 (15.5)	40 mg (20-375)	30 mg (15-70)	3.2 ±3.9	15.8 ±15.5	.032
Pemoline	8 (13.8)	4 (6.9)	127 mg (56-300)	56 mg (37-90)	3.3 ±5.5	6.2 ±6.2	.570
Amphetamine	1 (1.7)	2 (3.4)	20 mg	25 mg (10-40)	2.0 ±N/A	0.01 ±0.01	.666
Amphetamine/ Dextroamphetamine	3 (5.2)	0	60 mg (50-160)	N/A	2.3 ±3.1	N/A	N/A†

*Patients received at least 1 stimulant ≥ 120% of American Academy of Sleep Medicine/American Sleep Disorders Association practice guidelines, but additional stimulants did not necessarily meet this requirement.
†Insufficient numbers for calculation of *P* value

Table 4—Psychiatric Diagnoses and Consequences

Diagnoses/Consequences	High Dose, no. (%)	Standard Dose, no. (%)	OR (95% CI)	P Value
Psychosis	14 (24)	3 (5)	12.00 (1.56-92.3)	.001
Alcohol/polysubstance misuse	14 (24)	4 (7)	4.33 (1.24-15.2)	.009
Psychiatric hospitalization	13 (22)	4 (7)	3.25 (1.06-9.97)	.025
Depression (physician-diagnosed)	19 (33)	18 (31)	1.09 (0.48-2.47)	.835
Suicide, attempted suicide, or suicidal ideation	5 (9)	1 (2)	5.00 (0.58-42.8)	.088
Drug-seeking behavior (multiple sources or alleged lost prescriptions)	4 (7)	0	N/A*	.062

*Odds ratio (OR) is not estimable because there were no instances of the outcome among the standard-dose group. CI refers to confidence interval.

group is alarming. These patients demonstrated a significantly higher prevalence of psychosis, substance misuse, and psychiatric hospitalizations compared to the standard-dose group. The results suggest that these occurrences are directly related to the use of these drugs. However, it is also possible that patients predisposed to developing certain psychiatric disorders may request or require higher doses of stimulants.

Additional support for the specific association between psychosis and high-dose stimulant use is provided by the fact that a clear temporal association could be established between remission of symptoms and reduction or cessation of the medication in 50% of the affected patients in the high-dose group. In 1 patient in the standard-dose group, an apparent stimulant-induced psychosis occurred at a dosage of 30 mg of methylphenidate, suggesting the possibility that an idiosyncratic reaction may rarely occur at lower doses of stimulants. We were not able to assess for the complication of rebound hypersomnia after discontinuation or reduction of the stimulant dosage in this study.

Major depression was equally prevalent in both groups. Pawluk et al[17] reported a higher prevalence of affective disorders in their high-dose case series, but controls were not available for comparison. Another possible reason for this discrepancy is a lack of rigor in our medical charts with regard to documenting depressive symptoms. Future studies addressing this complication should employ standardized tools to address depressive symptomatology.

Cardiovascular disease was equally prevalent in both groups, but the odds for developing tachyarrhythmias were 3.3 times higher in the high-dose group than in controls. Despite the fact that the confidence interval affiliated with this odds ratio bounds

Table 5—Nonpsychiatric Symptoms and Disorders

Symptom/Disorder	High Dose, no. (%)	Standard Dose, no. (%)	OR (95% CI)	P Value
Hypertension	25 (43)	24 (41)	1.08 (0.49-2.37)	.842
Cardiovascular disease	10 (17)	10 (17)	1.00 (0.32-3.10)	1.000
Tachyarrhythmias	11 (19)	4 (7)	3.33 (0.92-12.1)	.046
Anorexia or weight loss	11 (19)	1 (2)	11.00 (1.42-85.2)	.002

*OR refers to odds ratio; CI, confidence interval.

1.0, the likelihood ratio statistical test nevertheless suggested a significantly higher prevalence in the high-dose group, implying that high-dose stimulants may increase the risk of this complication. To our knowledge, neither of these conditions has been studied in those receiving high-dose stimulants for an extended period of time.

Expanding on previous data,[5-9] high-dose stimulants do not appear to confer additional risk to the development of hypertension. However, low blood pressure has been reported in narcoleptic patients,[8,20] and this phenomenon may have masked a relative rise in blood pressure with treatment. We did not have data to assess whether blood pressure fell on reduction of dose or withdrawal of drugs, as has been previously described.[8] It is possible that a change in blood pressure from treatment onset, rather than a threshold value for hypertension, may be more indicative of stimulant effect.

Anorexia or weight loss occurred more frequently in the high-dose group, but because body mass index information was not available, the precise magnitude of this finding is not known. Weight loss has previously been reported in 25% to 43% of patients treated with low-dose stimulants, but this finding was in a study without controls for proper comparison.[5,6]

Other limitations of our study need to be addressed. The retrospective nature of the data collection was susceptible to any inaccuracies reported in the medical chart. However, detailed records were available, allowing data to be easily abstracted. As mentioned previously, our study design does not make it possible to conclusively determine if the observed differences are caused by high-dose stimulants or if those prone to the described complications are more likely to be resistant to standard doses. Moreover, we did not compare the prevalence of preexisting complications between the groups, nor did we compare the administration of nonstimulant medications. With regard to the first point, however, follow-up data were available for all subjects beginning at a young age, so that the presence of preexisting complications should have been minimal, or at least comparable, between the 2 groups.

Some of the psychiatric symptoms may have been variably documented by physicians in the medical records. In most instances, this would have resulted in underreporting of symptoms, however, because we only tabulated physician-entered diagnoses and not isolated complaints. In addition, the description of psychosis was at times subject to interpretation, but a consensus was reached among the board-certified psychiatrists in our group as to proper categorization in ambiguous cases. Clearly, a long-term prospective case-control study would be more definitive in ascertaining increased psychiatric risks associated with high-dose stimulants.

Our study design does not allow us to delineate differential effect with regard to stimulant type, although the vast majority of patients in both groups were receiving methylphenidate. However, 60% of the high-dose group received at least 1 additional stimulant, and 26% of these individuals received at least 1 additional stimulant that met criterion for high-dose inclusion. In comparison, 33% of the standard-dose group received more than 1 stimulant during the course of treatment. While it is our overwhelming observation that these instances represented sequential rather than combination therapy, our database did not permit us to analyze this formally. Consequently, it is unclear whether these results can be generalized to all stimulants at high dosages, to stimulants used in combination, or to specific types of stimulants. A larger prospective study with specific analysis of individual or combination treatment regimens would resolve many of these issues.

Other possible confounding variables are drug duration and dose. Mean methamphetamine and dextroamphetamine durations were significantly increased in the standard-dose group compared with the high-dose group. This would presumably have served to increase the rate of stimulant-induced complications in this group, however, and therefore does not detract from our overall findings. Moreover, no statistical difference in mean drug duration was found between groups for methylphenidate (the most commonly prescribed stimulant), which should have mitigated any confounding influences of the remaining medications. While there was a wide range of doses in the high-dose group (some exceedingly high), the median values suggest that most doses were within the range of those used in refractory cases.

Finally, because there was no placebo arm, we cannot compare the risks of low-dose stimulants to those abstaining entirely from these drugs. Given the high prevalence of many of the complications in the standard-dose group, it would be useful to explore whether these patients are also at risk of complications.

Despite these limitations, our current study suggests that high-dose stimulants should only be used with great care. A history of a preexisting psychotic disorder should be obtained, and patients

should be carefully monitored for the development of psychosis, substance misuse, tachyarrhythmias, and anorexia or weight loss. Furthermore, although a threshold dose cannot be clearly determined from our data, our results lend support to the dosage guidelines created by the American Academy of Sleep Medicine, particularly with regard to the complication of psychosis.[1,10,18] Future studies should be prospective and include larger sample sizes to further elucidate stimulant risks and determine whether these effects are medication and dose specific.

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