Narcolepsy and Its Treatment With Stimulants

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Narcolepsy and Its Treatment With Stimulants

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This review is part of the standards of practice recommendations. It has been commended and reviewed by the Board of the ASDA. It reflects recommendations of the Board for the practice of sleep medicine in North America. The subcommittee is responsible for the presented write-up.

1. INTRODUCTION

Although numerous disorders and diseases lead to excessive somnolence (1,2), multicenter surveys (3,4) based on modern standardized diagnostic techniques and criteria (5,6) indicate that more than 80% of individuals who present this symptom have either: a) sleep apnea (40–50%), characterized by pauses in respiration that disrupt sleep (2), b) narcolepsy (20–25%) characterized by sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations and disturbed nocturnal sleep (2,7) or c) idiopathic hypersomnia (5–10%) characterized by a normal or prolonged major sleep episode and additional daytime [nonrapid eye movement (NREM)] sleep episodes (2). The sleepiness associated with sleep apnea resolves or improves with effective treatment of the apnea (8–12). However, narcolepsy and idiopathic hypersomnia are chronic central nervous system (CNS) disorders, each statistically associated with the presence of specific human leukocyte antigens (HLA): narcolepsy is tightly associated with HLA-DR2 and HLA-DQ1 (13–17) (or, more precisely, under current nomenclature: HLA-DR15 and HLA-DQ6) (18) with the best marker across ethnic groups being DQB1-0602(DQ1) (19,20). Idiopathic hypersomnia may also have a familiogenetic predisposition and is less tightly associated with HLA-C2 (2,13,16,21,22). The sleepiness in these two conditions is chronic, probably associated with neurotransmitter dysfunction and can be treated only symptomatically with behavioral and pharmacologic interventions.

Many patients with these disorders find controlling excessive sleepiness to be critically important in allowing them to function adequately at home, while driving or in the workplace. Furthermore, the sleepiness and fatigue, stemming either from sleep disorders or from sleep deprivation, create major safety problems (23). However, psychomotor stimulants, the primary treatments for sleepiness associated with these disorders, have significant potential for abuse and side effects. Thus, clinicians must weigh the patient's need for adequate treatment and the personal and social risks of inadequate treatment against the potential for side effects and abuse. The clinical problem is heightened by the relative paucity of controlled studies assessing efficacy and side effects of stimulants for the treatment of these disorders (24,25).

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2.0 METHODS

Through its development of clinical guidelines for the treatment of narcolepsy, the Standards of Practice Committee of The American Sleep Disorders Association requested that a task force be formed and charged it with writing a review of the history and current concepts related to narcolepsy and its treatment with stimulant drugs. This paper is the result of the task force's efforts. All of the authors completed American Sleep Disorders Association conflict of interest statements and were found to have no significant conflicts of interest with regard to the topics discussed in the review.

The review was developed in the following way: 1) a *Medline* search (1966–1993) and additional literature review were carried out; 2) specific topics were assigned to each author; 3) key points and concepts pertaining to the review were discussed by conference calls and correspondence; 4) successive drafts of the document were circulated among the authors for revisions; 5) near-final drafts were submitted to the Standards of Practice Committee for advice concerning breadth, organization and degree of detail; 6) outside investigators who were extensively cited in the present review were

contacted and asked to correct any inaccuracies in sections of the text that pertained to their published work; and 7) the final document was agreed upon by all authors.

The organization of topics is designed to foster objective consideration of clinical practice parameters and conforms to The American Sleep Disorders Association's policies and procedures for the development of practice parameters. We first discuss the development of current thinking about narcolepsy. This is followed by a review of clinical studies in the treatment of narcolepsy with stimulant drugs, stimulant pharmacology as it relates to practice parameters, and promising new research directions.

3.0 HISTORY OF NARCOLEPSY AND EARLY TREATMENTS

3.1 A brief overview

The French neuropsychiatrist Gelineau (26) defined narcolepsy as a "rare and little known *neurosis* characterized by an imperative need to sleep at sudden onset in short duration recurring at more or less short intervals" (emphasis added). This early description stimulated a psychiatric/psychological, holistic approach to narcolepsy that continues to influence many clinicians and authors. For example, the early 20th century reviews by Adie (27), Wilson (28) and Daniels (29) do not suggest that caffeine or other medications are effective treatments for sleepiness. Most of the literature prior to the introduction of ephedrine sulfate emphasizes that which we would now consider to be psychological and sleep hygiene factors in narcolepsy. Drake's 1949 article (30) advocated a form of psychotherapy developed by Franklin Ebaugh (31) as an important treatment in narcolepsy. Galena also recommended psychotherapy for narcoleptic patients, and psychoanalytic literature reviewed by Zarcone in 1973 (32) and Zarcone and Fuchs in 1975 (33) describes the use of psychodynamic concepts and Pavlovian conditioning theory to treat narcolepsy. This approach reached its most developed form in the work of Levin (34,35).

Psychostimulants have been used for centuries in tonics and other preparations to allay fatigue and treat a large variety of ailments [for reviews see (36,37)]. However, it is important to note the following concern: The generalizability of data gathered before modern polysomnographic technology was widely employed is compromised in that any early series of excessively sleepy patients may include several types of sleep disorders, such as sleep apnea, and therefore may not be homogeneous for the condition of narcolepsy.

Coffee, along with leaves of sage or rosemary, was prescribed as early as 1672 for disorders associated with sleepiness. In 1931, Doyle and Daniels (38) and Janota (39) described the use of ephedrine. Over the next 2 decades, various forms of amphetamines were introduced for the treatment of narcolepsy. After 1956, methylphenidate hydrochloride came into broad use as suggested by Daly and Yoss (40). Since the mid 1970s, the use of stimulants has been modified by the introduction of rapid eye movement-(REM-) suppressing antidepressants and the reintroduction of psychological and sleep-hygiene advice.

3.2 Amphetamines

The treatment of narcolepsy underwent a dramatic change with the introduction of ephedrine. Despite its clinically noteworthy efficacy, it was soon apparent that side effects, incomplete patient acceptance, rapid development of tolerance and cost would limit its usefulness. In 1935 Prinzmetal and Bloomberg (41) suggested that the use of benzedrine, the racemic mixture of dextro- and levo-amphetamine, would be an appropriate treatment for narcolepsy because of its close relationship to ephedrine and epinephrine, low toxicity and low cost, prolonged action and lack of pronounced sympathomimetic side effects. In the first report from these authors, nine patients noted that they obtained complete relief from sleep attacks and practically complete relief from cataplexy. They also noted that insomnia and restlessness were potential problems and that the medication should not be given late in the day. The authors recommended 10-mg doses initially with a gradual increase until an optimal effect was obtained. Subsequent reports described the benefits of dextroamphetamine sulfate (42) and methamphetamine hydrochloride (43). Brook and Wiesel (44) reported that a 22-year-old male required as much as 80 mg of benzedrine to achieve control of his sleepiness. By 1949, benzedrine had become the treatment of choice for excessive sleepiness, although Drake (30) suggested that dextroamphetamine and ephedrine may be efficacious in some cases. A typical initial treatment was benzedrine, 10 mg tid, with gradual increases in dose until sleepiness was controlled.

Side effects were noted soon after amphetamines were introduced for the treatment of narcolepsy. In 1937, Shapiro (45) noted that two of 15 patients treated with benzedrine experienced side effects. Young and Scoville (46) noted psychotic symptoms in three narcoleptic patients and suggested that benzedrine may have "precipitated the psychotic reaction" in two of them; the patients showed "a great apprehension" amounting to panic, confusion and bewilderment. By 1949, at least four reports noted an association between narcolepsy and paranoid psychosis [further reviewed by Sours (47)]. In 1956, Switzer and Berman (48) attempted to limit adverse reactions by suggesting that a combination of

dextroamphetamine and amobarbital sodium might be useful.

3.3 Methylphenidate

In 1956, Daly and Yoss (40) introduced methylphenidate as a treatment for narcolepsy. They later reported on its effect in 25 and 36 patients treated for 1–6 months (40,49) with daily doses of methylphenide, 20–200 mg. For patients who did not respond well to methylphenidate, Yoss subsequently recommended methamphetamine up to 40 mg daily. In Yoss's opinion, "the total daily dose of methylphenidate may be as little as 30 mg for mild narcolepsy or over 100 mg in severe narcolepsy; rarely amounts as high as 200 mg are required" (50). The use of higher doses of methylphenidate may have been partly motivated by Yoss et al.'s report of methylphenidate 120 mg per day reversing the pupillographic abnormalities in narcoleptic patients. In Daly and Yoss's 1974 summary (51) of their experience with stimulants, they advocated that patients be given initial trials of low to moderate doses of methamphetamine or methylphenidate and that the sleep attacks be titrated with gradual increases in doses to as much as 200 mg of either drug.

3.4 REM sleep and treatment strategies

In the early 1960s Rechtschaffen et al. (52) and Takahashi and Jimbo (53) independently discovered that the nocturnal sleep of narcoleptics is frequently characterized by a transition from wakefulness into REM sleep with little or no intervening NREM sleep, a discovery that became the basis for the hypothesis that narcolepsy was fundamentally a disorder of REM sleep. The concurrent observation that REM-suppressing antidepressant drugs could control the ancillary symptoms of narcolepsy (cataplexy, hypnagogic hallucinations and sleep paralysis) provided added support for this concept (54–56).

Mitchell and Dement, along with other colleagues at Stanford, developed a different strategy for treatment of sleepiness and sleep attacks in narcolepsy based on the view of narcolepsy as a disorder of REM sleep (57). The core of their approach included a combination of REM-suppressing drugs to treat ancillary symptoms, sleep hygiene, naps, counseling, and lower doses of stimulants than those advocated by Yoss and Daly. Experience with this approach was summarized in the report of Guilleminault et al. (58) in 1974 in which low doses of methylphenidate (less than 60 mg per day) were used to treat 50 narcoleptic patients.

3.5 24-hour aspects of narcolepsy

Several studies have documented that narcolepsy cannot properly be considered a condition of true hypersomnia because narcoleptics do not show abnormally high amounts of sleep during round-the-clock recording sessions (59–61). Rather, narcoleptic humans, as well as dogs with an analogous condition, show a pattern of unconsolidated sleep such that sleep bouts can disrupt periods of wakefulness at any time during the 24-hour day (61–65). However, treatments of narcolepsy based exclusively on sleep satiation via ad libitum sleep, daytime naps, pharmacologically mediated consolidation of nocturnal sleep or a combination of these therapies have not yet met with sufficient success to supplant therapy with stimulant drugs (59,60,62,64,66,67). Recent work suggests that narcoleptics have a defect in the circadian timing of alertness (68) or in the homeostatic regulation of sleep (69).

3.6 Nonstimulant medications

A number of medications that are not classified as CNS stimulants have been reported to have some therapeutic effects in narcolepsy. Kales and his colleagues (70) described the elimination of narcoleptic attacks in a patient who was withdrawn from CNS stimulants and treated with the beta-adrenergic-receptor-blocking agent, propranolol, for a coexistent cardiac arrhythmia. Meier-Ewert and colleagues (71) also found mild therapeutic effects of propranolol (8–240 mg/day) in 48 narcoleptic patients but observed that the drug's efficacy was short lived, dropping to doubtful clinical significance after 6 months. Mouret and his associates (72) reported that the amino-acid precursor of norepinephrine and dopamine, L-tyrosine, in average doses of 100 mg/kg, improved the symptoms of eight narcoleptics for as long as 1 year. However, Elwes et al. (73), in a randomized, double-blind, placebo-controlled study of 10 narcoleptics, found no clinically significant differences between placebo and L-tyrosine at doses comparable to those used by Mouret et al.

Fry and her colleagues (74) reported clinically significant effects on the sleepiness of five narcoleptics treated with the opiate alkaloid, codeine sulfate, at doses of 90–120 mg/day. However, in a double-blind placebo-controlled study of eight narcoleptics, she found no statistically significant effects of codeine on nocturnal polysomnography or maintenance of wakefulness testing.

A number of investigators have studied the bedtime and intranightly use of gamma hydroxybutyrate to treat narcolepsy (66,67,75). Data indicate that gamma hydroxybutyrate acts to reduce nocturnal awakenings and reduce daytime cataplexy. Gamma hydroxybutyrate should not be confused with, and is not a precursor of, gamma aminobutyric acid (GABA); its mode of action is unknown (76,77). However, its effects on daytime alertness are not clinically significant (78).

Schmidt and his associates (79) reported that the nonsedating tricyclic antidepressant, protriptyline hydrochloride, is an effective therapeutic agent in the treatment of narcolepsy. However, Mitler and colleagues (7) showed that although protriptyline was an effective anticataplectic agent, its effects on objectively measured daytime alertness in 10 narcoleptic patients at doses up to 60 mg/day were not statistically significant.

Several studies have evaluated the therapeutic effects of viloxazine hydrochloride, a nontricyclic antidepressant with a chemical structure similar to propranolol, in narcolepsy (7,80–82). These studies demonstrated potent anticataplectic effects of viloxazine, but the drug's effects on pathologic somnolence were not sufficiently marked to be clinically useful. Ritanserin, a selective 5-HT_2 receptor blocker that increases the duration of NREM sleep, has measurable effects on the daytime alertness of narcoleptic patients (83), but the alerting effects are probably too small to be clinically useful (78).

3.7 Summary

Although considerable effort has been expended in attempting to identify novel agents outside the classification of CNS stimulants that might be useful in the treatment of narcolepsy, we lack compelling evidence for statistically significant and reproducible therapeutic efficacy of any nonstimulant drugs in the treatment of narcolepsy. We will therefore focus the remainder of this review on the effects and properties of CNS-stimulant drugs.

4.0 CLINICAL STUDIES OF STIMULANT DRUGS

4.1 Definition of stimulant medications

Psychomotor stimulants produce behavioral activation usually accompanied by increases in arousal, motor activity and alertness. Psychomotor stimulants have been divided into three classes for heuristic purposes: 1) direct-acting sympathomimetics such as the alpha-1-adrenergic stimulant, phenylephrine hydrochloride; 2) indirect-acting sympathomimetics such as methylphenidate, amphetamine, mazindol, pemoline, etc.; and 3) stimulants such as caffeine that are not sympathomimetics and have different mechanisms of action. This section and Section 5.0 (Pharmacology of Stimulants) focus on findings associated with the clinical use of sympathomimetics with predominantly indirect action (84–88). It should be recognized, however, that some stimulants have both direct and indirect actions (87,89).

4.2 Criteria of response to stimulant medications

Numerous studies and reports using various clinical and objective criteria of improvement have documented the effectiveness of stimulants for the treatment of sleepiness and sleep attacks in narcolepsy. The initial evaluations of treatment efficacy were based on clinical assessment (38,39,41,42). Yoss and his colleagues were first to apply the pupillographic technique of Lowenstein and Loewenfeld (90) as an objective measure: they measured pupil diameter and stability of pupil diameter (pupillography) to evaluate the response of individual patients to alerting drugs (50,91).

More recently, two polysomnographic techniques, the Multiple Sleep Latency Test (MSLT) (92) and the Maintenance of Wakefulness Test (MWT) (93) have been used to assess sleepiness in a variety of sleep disorders (94) and to evaluate pharmacotherapeutic efficacy (7,66,74,75,81,83,95,96). Because the average MSLT or MWT sleep latency can be regarded as a single numerical measure of sleep tendency, some determinations of relative efficacy of pharmacotherapeutic agents have been calculated (78).

The objectivity and standardization of these polysomnographic techniques (10–12,94,97) and their widespread availability have influenced public transportation policy with respect to sleepy operators. A Federal Highways Administration task force recommended that the MSLT be used in determining fitness for duty of commercial drivers after the diagnosis of sleep apnea has been made (98), and the Federal Aviation Administration now calls for use of the MWT in determining whether noncommercial pilots are licensable after the diagnosis of sleep apnea has been made (99). The following information presents a review of reports on treatment outcome using various clinical and objective criteria.

4.3 Published data

One of the first clinical studies of a series of narcoleptic patients reported that 21 of 25 (84%) patients had a good to excellent response with 40–240 mg/day of methylphenidate; a usual daily dose of 60–80 mg was required by those patients obtaining an excellent result (40). Subsequent clinical reports and clinical trials [see reference (7,40,49,96,100–107)] of a number of medications are summarized in Table 1. Most studies report substantial improvements in 65–85% of subjects. A recent publication reviewed clinical trials that documented statistically significant improvements in sleep tendency assessed by MSLT or MWT for dextroamphetamine, methylphenidate, modafinil [an alerting alpha-adrenergic-receptor agonist not available in the United States (95,108)] and pemoline (78).

Idiopathic hypersomnia has not been studied as ex-

TABLE 1. *Efficacy of stimulants for treatment of sleepiness in narcolepsy*

Reference	Year of report	Type of study	No. of subjects	Medications	Daily dose	Efficacy	Side effects
(40)	1956	Case series	25	Methylphenidate	40–240 mg	Good–excellent in 84%	–
(49)	1959	Case series	60	Methylphenidate	40–80 mg[a]	Good–excellent in 68%	Nervousness and tremulousness, 35%; anorexia, 22%; insomnia, 17%; palpitations, 3%
(100)	1975	Case series	63	Dextroamphetamine	5–150 mg	Moderate–good in 73%	Side effects, 73%; irritability, 49%; headache, 48%; palpitations, 24%; jitteriness, 24%; muscle jerks, 22%; insomnia, 11%; dyskinesias, 5%; hallucinations, 3%; psychosis, 1.6%
(101)	1960	Case series	80	Methamphetamine Methylphenidate Dextroamphetamine	5–15 mg 20–80 mg ?? mg	Disappearance of sleep attacks	–
(96)	1993	Sleep laboratory	8	Methamphetamine	20–60 mg	Improved by MSLT	Disturbed nocturnal sleep
(7)	1990	Sleep laboratory	13	Methylphenidate	10–60 mg	Improved by MWT	–
(7)	1990	Sleep laboratory	5	Dextroamphetamine	30–60 mg	Improved by MWT	–
(7)	1990	Sleep laboratory	14	Pemoline	19–113 mg	Improved by MWT at 113 mg	–
(102)	1987	Placebo-controlled clinical trial	19[b]	Modafinil	200 mg	Decrease of sleep attacks	Side effects in less than 10%
(103)	1988	Clinical trial	42[c]	Modafinil	200–500 mg	Improvement in 71% with narcolepsy and in 83% with idiopathic hypersomnia	Side effects in less than 10%
(104)	1991	Clinical retrospective review	41	Mazindol	1–16 mg	Moderate–good in 78%	39%, mainly gastrointestinal
(105)	1985	Placebo-controlled clinical trial	20	Dextroamphetamine Mazindol Fencamfamin	10–30 mg 4 mg 60 mg	Sleep attacks reduced by 36–52%	Side effects similar to placebo
(106)	1987	Clinical trial	7	Selegiline	20–30 mg	Sleep attacks reduced by 30%	Similar to dextroamphetamine
(107)	1989	Placebo-controlled clinical trial	10[d]	Modafinil Dextroamphetamine	100–200 mg 10–20 mg		Disturbed nocturnal sleep with dextroamphetamine but not with modafinil

[a] 1 took 300 mg.
[b] 12 with narcolepsy; 7 with idiopathic hypersomnia.
[c] 24 with narcolepsy; 18 with idiopathic hypersomnia.
[d] Elderly non-narcoleptic subjects.

tensively as narcolepsy, and there are few controlled studies that objectively evaluate the efficacy of any pharmacologic or nonpharmacologic treatment for idiopathic hypersomnia. Available literature suggests that the sleepiness of idiopathic hypersomnia responds substantially in the same manner to stimulant drugs as does the sleepiness of narcolepsy (109). Many clinicians believe that patients with idiopathic hypersomnia do not benefit from naps or other behavioral approaches (109).

4.4 Relative efficacy of stimulants

Many clinicians have the persistent impression that stimulants vary in the degree to which they control sleepiness. However, the objective measurement of the relative efficacy of stimulants is impossible to ascertain based on available publications. Among the most important problems hampering the objective ranking of stimulants are the facts that a) investigators have used different outcome measures (e.g. clinical assessment, MSLT, MWT, etc.); b) subject samples vary widely in the baseline level of sleepiness; c) some investigators have studied multiple doses, thereby providing a basis for estimating the dose–response curve whereas others have not; and d) little correlation exists between the oral dose and blood level of methylphenidate and probably of other stimulants (110). The lack of full-dose-effect functions limits the determination of efficacy measures. To compare the relative effects of stimulants, we used a normalization technique described by Mitler and Hajdukovic (78). This technique permits some degree of quantitative comparison among previously published treatment–efficacy studies that employ daytime polysomnographic testing of daytime sleepiness. An important feature of this approach is that the greatest effect of each stimulant is normalized

in terms of the degree to which narcoleptics treated with the drug approached normal values on the daytime tests. The following treatment and testing conditions were compared: pemoline, 112.5 mg, using the MWT (7); modafinil, 300 mg, using the MWT (95,108); dextroamphetamine, 60 mg, using the MWT (7); methylphenidate, 60 mg, using the MWT (7); and methamphetamine, 40–60 mg, using the MSLT (96). We extracted the average sleep latencies measured during drug-free baseline and appropriate treatment phases of each study. Sleep latencies were then expressed in terms of the percent of published values for normal subjects (7) for either the MSLT (13.4 minutes) or the MWT (18.9 minutes). Results are summarized in Fig. 1. Although baseline measurements varied, each drug produced a clinically significant change above baseline toward normal levels. Dextroamphetamine, methamphetamine and methylphenidate brought measurements above 60% of normal levels. The largest change from baseline occurred with methamphetamine (96). In the study of methylphenidate (7), although baseline levels were over 50% of normal, measures during treatment were closest to normal levels.

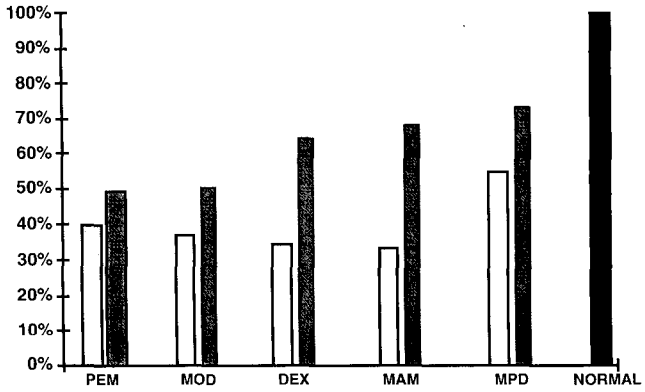

FIG. 1. Relative efficacy of stimulant drugs commonly used to treat narcolepsy. The lighter shading denotes baseline sleep latencies on either MSLT or MWT, expressed in terms of percent of normal levels (13.4 minutes for the MSLT and 18.9 minutes for the MWT), and the darker shading denotes values observed at the highest dose of each drug evaluated. See text for methods. Abbreviations: PEM, pemoline; MOD, modafinil; DEX, dextroamphetamine; MAM, methamphetamine; MPD, methylphenidate.

These treatment studies did not normalize sleepiness, and predicting whether treatment with higher doses of these stimulants would normalize sleepiness is not possible. Additional comparative studies with more and higher dose levels and larger numbers of subjects are needed. However, crude linear projections from the doses used by Mitler et al. (7,96), imply that 636 mg per day of pemoline would have been required for normal alertness. The projected normalization doses for dextroamphetamine, methamphetamine and methylphenidate were 117, 84 and 97 mg per day, respectively. Of course, such linear projections are inaccurate. Indeed, for most stimulant effects, the dose–response curve ultimately shows an inverted U-shape when doses are pushed to levels that approach the limits of physical tolerance (see Sections 5.3–5.5). Furthermore, the projected dose levels do not directly translate into guidelines for clinical practice because they have not been objectively studied and may not even be tolerated by some patients. Clinicians treat individual patients based on their particular therapeutic needs and abilities to tolerate side effects. Nevertheless, some narcoleptic patients report satisfactory control of their sleepiness with certain stimulants in these high-dose ranges.

4.5 Side effects of stimulants

Stimulants commonly produce side effects when used in the treatment of narcolepsy or other conditions. Parkes (111) noted that all stimulants cause sympathomimetic side effects and that high doses of stimulants produce irritability, talkativeness and sweating. The reported frequency of side effects of stimulants in clinical practice and in clinical trials varies from 0 to 73% (Table 1); the extreme variation reflects, at least in part, differences in methods of determining side effects and the definition of a side effect. Common side effects include headaches, irritability, nervousness or tremulousness, anorexia, insomnia, gastrointestinal complaints, dyskinesias and palpitations (49,100,112). One report shows that, in a series of 100 patients, 10% of patients discontinued stimulants due to failure of response, tolerance or side effects (100). However, another 20 narcoleptics participating in a trial of lower doses of dextroamphetamine—10–30 mg/day—reported no increase in side effects compared to baseline (105). Disturbed nocturnal sleep documented with polysomnography occurred in eight narcoleptics given methamphetamine 20–60 mg/day for 4 days (96,113), and Regestein et al. (114) noted their clinical impression that doses of dextroamphetamine or methylphenidate above 50–60 mg/day interfere with sleep. Soldatos et al. (115) reported their impression that the incidence of tolerance and side effects is lower in narcoleptics than in others taking methylphenidate or methamphetamine but did not state the basis for this belief. Little evidence suggests that stimulants cause a clinically significant increase in blood pressure at commonly used doses in normotensive individuals (49,100,116). Side effects may be less frequent with modafinil than with amphetamines (Table 1), whereas side effects with selegiline 20–30 mg/day are comparable to dextroamphetamine in similar doses (106). Pemoline has been reported to cause liver damage (117–120). A recent review of 100 cases concluded that pemoline-induced liver injury was hepatocellular in na-

ture and that the mechanism is idiosyncratic and metabolic rather than immunologic (121).

4.6 Use of stimulants in children

Few studies describe the side effects of stimulants in children with narcolepsy; much of the available data includes the use of stimulants for children with attention deficit/hyperactivity disorder (ADHD). The potential side effect of greatest concern is growth retardation (122). For example, deficits in weight gain and change in stature have been observed after treatment of ADHD with pemoline, dextroamphetamine or methylphenidate (123–126). These deficits may be reversed during summers off medication (127,128). However, most studies have found little or no evidence of long-term effects on growth, and some have found greater than expected increases (129). Satterfield et al. (124) found an adverse effect of methylphenidate on height in the 1st year of treatment with methylphenidate, but the effect was reversed by a greater than expected increase in height in the 2nd year of treatment. One of the few studies that lasted as long as 4 years noted that the growth suppressant effect of methylphenidate accounted for just 2% of the variance in children's final height (125). The effects of methylphenidate on growth in prepubertal children appear not to extend into adolescence (130), and in one study, adult height of treated children was no different from height of control subjects or national norms (131). A recent review concluded that stimulants do not affect adult height in children with ADHD (132). Other side effects of stimulants in the treatment of children with ADHD include anorexia, insomnia and weight loss, effects that are usually transient and diminish with continued treatment (126).

In a study of two groups of children treated for ADHD, one group treated with methylphenidate for 3–5 years (n = 24) and one receiving no treatment (n = 20), there was no difference between the groups on measures of emotional adjustment, delinquency, Wechsler Intelligence Scale for Children, Bender Gestalt visual-motor test or academic performance (133). Tics can occur in children taking stimulants (132), but Eichlseder (134) reviewed records of 1,000 children taking stimulants for up to 10 years and concluded that long-term stimulant treatment is safe in children.

In the absence of evidence to the contrary, it seems reasonable to conclude that the incidence and severity of side effects and the overall safety of stimulants are similar in children with narcolepsy and children with ADHD at comparable dose levels. Some authorities recommend the following initial doses of stimulants for ADHD: methylphenidate, 0.3 mg/kg; dextroamphetamine, 0.15 mg/kg; pemoline, 37.5 mg, with careful titration to achieve optimal effects (132). The safety in narcoleptic children of higher doses than those currently recommended for ADHD is unknown.

4.7 Complications

Psychosis and hallucinations are rare in narcoleptics treated with stimulants (111,114). Four series totaling 243 patients revealed only two cases of amphetamine psychosis, two of hallucinations and three of addiction (58,100,101,135). No published data regarding narcoleptics indicate that the incidence of hallucinations and psychosis differs among various stimulants; however, some authors have suggested that methamphetamine should not be used as initial treatment because of possible development of "hallucinatory paranoid states" (112). Although no systematic published data on the issue exist, some authors suggest that the incidence of side effects is lower with methylphenidate than with dextroamphetamine (136,137).

The likelihood of psychosis or hallucinations induced by stimulants is increased in patients with coexisting psychiatric conditions. Patients with narcolepsy who develop psychosis in association with stimulant use often exhibit evidence of coexisting or preexisting psychiatric illness (46,138–141). The relation of these complications to dose is uncertain, although many clinicians believe that the risk of psychiatric complications is greater at higher doses. Honda (112) noted that hallucinatory paranoid states caused by stimulants decreased markedly with the adoption of a program of regular sleep habits—one afternoon nap and a maximum dose of methylphenidate 80 mg/day or pemoline 100 mg/day.

Cardiac and vascular complications have been reported only rarely in narcoleptics. Three patients in one series had strokes while on amphetamines (100), but this incidence may not have been above baseline. Isolated case reports have been published of narcoleptics who have developed cardiomyopathy after treatment with amphetamine 100 mg/day for 7 years and ischemic colitis after treatment with dextroamphetamine 30 mg/day (142,143). A narcoleptic patient who took more than 200 mg/day of methylphenidate for several years developed diminished peripheral pulses and symptoms suggestive of peripheral vascular occlusive disease; symptoms improved after stimulants were discontinued (Aldrich MS, personal communication). These complications must be assessed in light of the many narcoleptics who have taken stimulants on a regular basis for decades, often into the 7th or 8th decade of life, without developing cardiovascular disturbances. Although some clinicians consider hypertension to be a contraindication for stimulant therapy, no systematic studies indicate that stimulants prescribed to reduce sleepiness exacerbate preexisting hypertension.

Little or no evidence suggests that stimulants given for narcolepsy or for ADHD have any adverse effect on adult height [see (132) for review] or on cognitive function (144). A three- to seven-fold increase in amphetamine content in breast milk compared to plasma in a nursing mother with narcolepsy (145) suggests the potential for complications in such instances, but none have been reported.

Specific studies of narcoleptics who abuse stimulants are not available; therefore, the following information pertains to amphetamine abuse in a general population. A variety of symptoms and complications can occur with amphetamine abuse. In 127 persons diagnosed in emergency centers with amphetamine toxicity, the main symptoms were agitation, hallucinations, suicidal behavior and chest pain (146). Seizures, intracranial hypertension, ischemic strokes, fatal and nonfatal intracranial hemorrhages, and narrowing and dilatation of intracranial arteries have occurred after intravenous, intranasal or oral use of amphetamine or methamphetamine; in one case brain hemorrhage followed a single oral dose of 20 mg of amphetamine (147–155).

The relative risk for stroke is estimated to be 6.5 times greater for young adult drug abusers compared to nonabusers (153); when young adults have strokes and are suspected of abusing drugs, amphetamine is often the drug that is implicated (153,154). Other complications of intravenous use of amphetamines include myocardial infarction and acute left ventricular failure (156,157), mononeuropathy multiplex with angiitis (158), acute renal failure (159–161) and drug-induced elevation of serum thyroxine (162). Although complications are more common after intravenous injection rather than oral intake of large quantities of stimulants, catastrophic cerebrovascular events following oral or inhalational use or after ingestion of relatively modest drug doses have been reported (149). The actual doses ingested are often unknown because of the use of "street" drugs. However, Bruhn and Maage (163) found no evidence of intellectual and neuropsychologic dysfunction in long-term drug abusers of stimulants despite the potential for disastrous complications.

4.8 Tolerance in the clinical setting

Although studies of animals and normal human volunteers clearly show that tolerance develops to many of the effects of amphetamines, the frequency and importance of tolerance to the alerting effects of stimulants in the treatment of sleepiness is controversial. Tolerance to the alerting effects of stimulants in narcoleptics appears to occur with variable frequency. Parkes et al.'s study revealed that 31 of 100 patients required a doubling of their stimulant doses over a 1-year period in order to achieve the same control of their symptoms (100). Passouant and Billiard (135) observed tolerance in 11 of 50 narcoleptics taking stimulants, and tolerance occurred in 14 of 41 patients treated with mazindol up to 16 mg/day (104). Although the specific nature of tolerance was not defined, Parkes (111) concluded that tolerance to central stimulant effects develops in 30–40% of subjects after a few days or weeks of repeated intake and that "all compounds of this class produce tolerance . . .". Not all agree, however. Honda et al. (164) observed no tolerance in 106 narcoleptics treated with methylphenidate for up to several years. No tolerance was noted among 42 patients treated with modafinil 200–500 mg/day for up to 3 years (103) or among 12 narcoleptics treated for 6 months with levo-amphetamine 20–60 mg/day or dextroamphetamine 10–45 mg/day (165).

Several other authorities note that tolerance to stimulants is more likely to occur with high doses (32,136,166,167). Guilleminault et al. (58) described six patients who had increased their intake of dextroamphetamine to more than 100 mg/day because of an increase in sleep attacks and cataplexy but "in all cases the increased amphetamine intake did not help them in any way". With lower doses, none got worse and three improved. In one study, three of four patients who had minimal or no clinical benefit took methylphenidate 160–240 mg/day, whereas 0 of 21 patients with good to excellent responses took more than 140 mg/day (40).

Little evidence exists for or against the views of some authors that the incidence of tolerance and side effects is less in narcoleptics than in other persons taking comparable doses (115), that tolerance reported by some patients is not true tolerance but rather an effect of inadequate nocturnal sleep (50), and that tolerance or other side effects are less likely to occur with the use of methylphenidate than with dextroamphetamine (51,136).

4.9 Use of stimulants in pregnancy

The U.S. Food and Drug Administration (FDA) has established five categories (A, B, C, D and X) to indicate a drug's potential for causing teratogenicity (168,169). In brief, Pregnancy Category A means controlled studies have shown no risk to the human fetus in the first trimester and the possibility of fetal harm appears remote; B means animal studies indicate no fetal risk, and there are no controlled studies in humans; C means animal studies have shown teratogenic or embryocidal effects, and there are no controlled studies in humans; D means there is evidence of risk to human fetuses, but benefits may make risks acceptable; and X means studies in animals or humans have demonstrated fetal abnormalities and the risks outweigh any possible benefit. Below is a list of the

most conservative ratings given by either the manufacturer's package insert, Briggs et al. (169) or both for methylphenidate, dextroamphetamine, methamphetamine, mazindol and pemoline:

methylphenidate: has no adequate animal studies; use if benefits outweigh risks.
dextroamphetamine: Pregnancy Category D rating.
methamphetamine: Pregnancy Category C rating.
mazindol: Pregnancy Category C rating.
pemoline: Pregnancy Category B rating.

We found no well-controlled studies of pregnant women using stimulants. Although the efficacy of stimulants for the treatment of narcolepsy during pregnancy is probably similar to efficacy at other times, commonly used stimulants vary with respect to their Pregnancy Rating Category, and most fall into Category C. Pemoline is the only commonly used stimulant with a Category B rating. As the potential for teratogenicity is unknown, the benefits for any given patient must be weighed carefully against the potential risks to the fetus. For many patients, it may be advisable to reduce or discontinue stimulant use during attempts at conception and for the duration of pregnancy.

4.10 Current practices

Stimulants generally have been accepted, however prescribed, to represent only one element of a comprehensive therapeutic approach to the management of excessive somnolence. Sound sleep hygiene, careful attention to other substances and drugs that may disrupt the sleep–wake cycle, and periodic reassessment of symptom severity and of the need for and adequacy of treatment modalities are other important aspects of management. Current practices in the use of stimulants vary considerably. The only stimulants approved by the FDA for use in narcolepsy are dextroamphetamine and methylphenidate at dosages of 5–60 mg per day. However, a recent survey indicates that substantial numbers of narcoleptic patients take methylphenidate or dextroamphetamine at doses above 60 mg or take other medications. The most common alternative drugs include pemoline and methamphetamine (170). Mazindol, modafinil (not yet available in the United States) and protriptyline are also used. The criteria used to determine stimulant dose, the maximum acceptable dose, the frequency and clinical significance of tolerance and the need for drug holidays are areas of debate.

Many clinicians now recommend methylphenidate as the preferred treatment for daytime sleepiness (49,136,171). Several authorities recommend doses of methylphenidate and dextroamphetamine that are consistent with the manufacturers' package inserts (Table 2), often in conjunction with daytime naps (111,112,171–174) and avoidance of evening doses of stimulants (49,112). A number of clinicians prescribe stimulants in combination, such as a single dose of pemoline in the morning plus small doses of methylphenidate as needed throughout the day (112). Some authorities add the proviso that doses of methylphenidate 60 mg/day or dextroamphetamine 60 mg/day should *usually* not be exceeded (171), whereas others recommend methylphenidate doses of up to 80 mg/day or more (Table 2). Methamphetamine is recommended by some authorities as first line treatment (Table 2), others recommend it as an alternative for patients who do not respond to methylphenidate (50,51), and still others as a "last resort" (112,115).

Another factor that probably influences clinical practice is whether or not a stimulant drug has been placed on Schedule II by the U.S. Federal Drug Enforcement Agency (DEA). In 10 of the most populous states of the United States, the dispensation of Schedule II drugs requires a special triplicate prescription, and throughout the United States the DEA has specified time intervals that must be maintained between the physician prescription date and the pharmacist filled date of a Schedule II drug prescription. Limits are also in place as to the duration of each prescription. Thus, regardless of their perceived efficacy, non-Schedule II drugs such as pemoline and mazindol may be preferentially prescribed. Recommendations for medications are summarized in Table 2.

Although many authorities recommend temporary withdrawal of stimulant medications or reduction of doses for 1–28 days if tolerance occurs, i.e. drug holidays (111,167,172,173), this recommendation appears to be based on clinical experience. No published studies demonstrate the efficacy of drug holidays.

The criteria for determining drug dose are also in question. Many authorities recommend a goal of obtaining maximum alertness at selected times of the day, for example, during work or school hours and while driving, and using scheduled naps to help maintain alertness. Others recommend a goal of maximal or "normal" alertness throughout conventional waking hours. Most data indicate that although daytime sleep episodes can be reduced in the majority of patients, these episodes cannot, unfortunately, be completely abolished in all patients. Success rates of 65–85% have been reported using a variety of regimens, but even with doses of methylphenidate up to 240 mg/day, Daly and Yoss found that 16% of patients had little or no response. Using methamphetamine up to 60 mg/day for 4 days, Mitler et al. reported the MSLT sleep latencies of narcoleptics (96,113) were "normalized" with respect to controls matched for age, sex and work experience. The short duration of treatment in the Mitler et al. study leaves open the question of whether tol-

TABLE 2. *Published recommendations of stimulant dosages for treatment of narcolepsy*

Medication	Daily dose range	References
Methylphenidate (Ritalin®) or	≤60 mg	(32,111,112,114,165–167,171–176)
Dextroamphetamine (Obetrol®, Biphetamine®)	≤60 mg	
Methylphenidate (Ritalin®)	≤80 mg	(40,49,115,176)
	Occasional use of ≤100–300 mg	(103,112,137,174)
	≤40–60 mg in children	(177)
Methamphetamine (Desoxyn®)	5–15 mg	(50,96,103)
	25–100 mg	
Pemoline (Cylert®)	100 mg	(112)
Mazindol (Mazanor®, Sanorex®)	2–8 mg	(111)
Levo-amphetamine (not available in U.S.A.)	20–60 mg	(165)
Fencamfamin (Reactivan®) (not available in U.S.A.)	20–30 mg	(111)

erance develops to alerting effects of methamphetamine at such doses. Moreover, despite the "normalization" with respect to matched controls, Mitler et al.'s methamphetamine-treated narcoleptics did not reach the 13.4-minute normal sleep latency level used in the interstudy comparisons (Fig. 1).

5.0 PHARMACOLOGY OF STIMULANTS

Psychomotor stimulants produce behavioral activation usually accompanied by increases in arousal, motor activity and alertness. The three major classes of psychomotor stimulants include: 1) direct-acting sympathomimetics such as phenylephrine; 2) indirect-acting sympathomimetics such as amphetamine and amphetamine-like compounds; and 3) stimulants that are not sympathomimetics and have different mechanisms of action (see Table 3). Sympathomimetics activate the sympathetic nervous system; indeed, the term "sympathin" was originally used to describe norepinephrine (84–86).

Because of their numerous side effects on the peripheral nervous system, direct sympathomimetics are not used in clinical practice. Most compounds available for clinical use act indirectly on dopaminergic and to a lesser extent on adrenergic systems. This review concentrates on indirectly acting sympathomimetic drugs.

5.1 Neuropharmacology

Most indirect sympathomimetic compounds share a common molecular structure: a benzene ring with an ethylamine side chain. Amphetamine differs from the parent compound, betaphenethylamine, by the addition of a methyl group, whereas methamphetamine has two additional methyl groups. Methylphenidate and cocaine are structurally similar. Figure 2 presents the molecular structures of five stimulants (methylphenidate, dextroamphetamine, methamphetamine, mazindol and pemoline) commonly used for the treatment of narcolepsy along with the molecular structure of cocaine, a naturally occurring alkaloid found in the leaves of *Erythroxylum coca* (178). Amphetamines, originally synthesized for use as inhalants for the treatment of asthma (179), have been used by the military as antifatigue medications and are currently available for medical use as adjuncts for short-term weight control, in ADHD and in narcolepsy.

Indirect sympathomimetics act primarily by increasing the amount of monoamines available within the synaptic cleft of monoamine synapses in the CNS (180–185) and by blocking reuptake and enhancing release of norepinephrine, dopamine and serotonin (180, 181,183–187). Amphetamines are also weak inhibitors of monoamine oxidase (188). The primary action responsible for the psychomotor stimulant effects of in-

TABLE 3. *Psychomotor stimulant drugs*

Direct sympathomimetics	
Isoproterenol	Phenylephrine
Epinephrine	Apomorphine
Norepinephrine	Ephedrine
Indirect sympathomimetics	
Amphetamine	Phenylpropanolamine
Cocaine	Pemoline
Mazindol	Phenmetrazine
Methamphetamine	Pipradol
Methylphenidate	Tyramine
Others	
Caffeine	Scopolamine
Nicotine	Atropine
Theophylline	Strychnine
Aminophylline	Pentylenetetrazol
Modafinil	

direct sympathomimetics appears to be on the dopamine systems in the CNS. The midbrain dopamine systems include two major pathways that project to the forebrain and appear to be responsible for different aspects of psychomotor stimulant actions. The mesocorticolimbic dopamine system projects to the ventral forebrain, including the nucleus accumbens, olfactory tubercle, septum and frontal cortex; the nigrostriatal dopamine system arises primarily in the substantia nigra and projects to the corpus striatum.

Degeneration of the midbrain dopamine system results in the severe motor disturbances of Parkinson's disease, including tremor, dystonic involuntary movements and akinesia (189). In animals, large bilateral lesions of the midbrain dopamine system induced by a selective neurotoxin for dopamine, 6-hydroxy-dopamine, can reproduce many of these deficits (190) and can also cause severe deficits in learning a conditioned avoidance task (191). Selective destruction of the mesocorticolimbic dopamine system blocks amphetamine- and cocaine-stimulated locomotor activity (192–194) and reduces the reinforcing effects of amphetamine and cocaine (195–197). Similar effects have been observed following microinjection of selective dopamine antagonists into the region of the nucleus accumbens (198).

In contrast, disruption of the nigrostriatal dopamine system blocks the stereotyped behavior associated with administration of high doses of dextroamphetamine (194,199,200) but does not block the reinforcing effects of cocaine (201). Subregions of the corpus striatum have been implicated in the stereotyped behavior produced by amphetamine (202). Amphetamine injected into the ventrolateral striatum of rats produced licking, biting and self-gnawing to the exclusion of other psychomotor behaviors. The fact that terminal regions of the nigrostriatal and mesocorticolimbic dopamine systems appear to mediate different aspects of psychomotor stimulant actions may have implications for behavioral effects and psychopathology associated with stimulant abuse.

Five dopamine-receptor subtypes have been cloned (203–207), and selective ligands exist for three of them (D-1, D-2 and D-3). There appear to be different functional actions for the D-1 and D-2 dopamine receptors at the behavioral level. Low doses of the selective D-1 dopamine-receptor antagonist, SCH 23390, potently block amphetamine-induced locomotion (208) and intravenously self-administered cocaine (209), whereas similar effects do not occur with low doses of D-2 antagonists. However, D-2 antagonists but not D-1 antagonists produce impaired responses in a reaction-time task particularly sensitive to disruption of nigrostriatal function (210). The recently discovered D-3 receptor subtype may be restricted in its distribution to the terminal projections of the mesocorticolimbic dopamine system (211). Thus, there may be some differential sensitivity of the dopamine receptors of the mesocorticolimbic and nigrostriatal dopamine system to ligands for the different dopamine receptor subtypes.

5.2 Pharmacokinetics

Oral and intravenous doses of amphetamines increase systolic and diastolic blood pressure and stimulate heart rate, although high doses may induce a reflex slowing of heart rate. Amphetamines produce bronchial dilation and pupillary dilation as well as decreases in glandular secretions, all effects observed after activation of the sympathetic nervous system.

Amphetamine and related drugs are powerful CNS stimulants. This analeptic action is characterized by increased wakefulness, alertness, decreased sense of fatigue, elevations of mood and euphoria, increased motor activity and talkativeness, and increased performance in some tasks and athletic situations. CNS effects are three- to four-fold greater with the dextroisomer than with the levoisomer of amphetamine. The CNS effects of low doses of methamphetamine are more pronounced than are the autonomic effects, presumably due to increased lipophilicity allowing it to readily cross the blood–brain barrier.

The intensity of stimulant effects of amphetamines depends on the route of administration. Intranasal or oral administration of 2.5–15 mg dextroamphetamine produces feelings of alertness, energetic vitality, confident assertiveness and a decrease in appetite and fatigue. Intranasal absorption is faster with more intense effects, and the stimulant effects of amphetamines last up to 4–6 hours. Ten milligrams or more of dextroamphetamine taken intravenously or inhaled produces intense, pleasurable sensations characterized as a "rush" that probably acts as a motivation for the abuse of these drugs.

Amphetamine is deaminated in the liver, oxidized to benzoic acid and then excreted as glucoroxide or glycine conjugates (212). With normal pH urine, approximately 30% of the drug is excreted unchanged. Amphetamine has a half-life of approximately 12 hours, but because it has a pK of 9.9, that half-life can be extended with an alkaline urine to over 16 hours and shortened to 8 hours with acid urine (213). Methamphetamine reaches a peak blood concentration approximately 1 hour after ingestion, which is 1 hour faster than oral dextroamphetamine (214,215). Methamphetamine is the most rapidly absorbed form of amphetamine, presumably due to its lipophilicity, and has a pK and renal excretion similar to the parent compound. Methylphenidate has a metabolic half-life of approximately 2–4 hours and is de-esterized to the

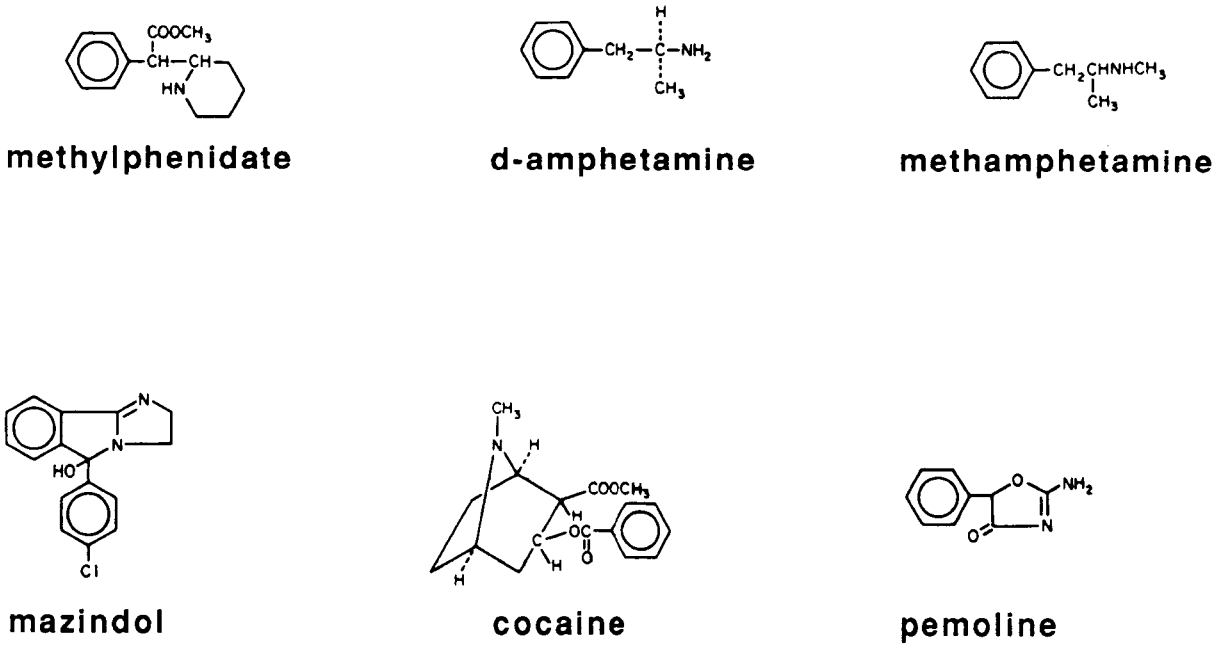

FIG. 2. The molecular structures of methylphenidate, dextroamphetamine, methamphetamine, mazindol and pemoline, which are drugs commonly used for the treatment of narcolepsy. The molecular structure of cocaine, a naturally occurring alkaloid found in the leaves of *Erythroxylum coca* is shown for comparison (bottom center). Molecular structures were redrawn from figures in reference McEvoy (178).

inactive ritalinic acid, which is excreted in the urine. This inactivation accounts for over 80% of the removal of methylphenidate (216).

5.3 Behavioral effects

Amphetamines in doses that produce stimulant effects can also enhance performance in simple motor and cognitive tasks, including reaction time, attention and performance (217,218). Amphetamines can also improve athletic performance by slight amounts (0.5–4%) that may be significant in competitive situations (219). Other reported effects include improved coordination, increased strength and endurance, and increased mental and physical activation, with mood changes of boldness, elation and friendliness (220). The most dramatic effects of amphetamines have been observed in situations of fatigue and boredom (219,221–223). Amphetamines and related compounds decrease appetite, but tolerance to this particular effect develops rapidly (224).

Amphetamines can also impair performance (225), and there is little evidence to suggest that amphetamines can enhance intellectual functioning in complex tasks, including complex attention tasks and tests of intelligence (218,226). Children with ADHD who are treated with methylphenidate have shown impairment in performance of the Wisconsin Card Sorting test that suggested an overfocusing of behavior (227).

Amphetamines and methylphenidate decrease sleepiness, increase sleep latency, increase REM sleep latency and reduce the proportion of REM sleep (228–230). Nocturnal sleep disturbance is common; 15 mg of amphetamine given to normal controls at 8 a.m. decreased the amount of nocturnal stage 3 and 4 and REM sleep, with a rebound increase in REM sleep during drug withdrawal (231). The initial increase in sleep that follows drug withdrawal may be followed, at least in amphetamine abusers, by disturbed sleep lasting from 20 days to as long as 2 months (232,233). Amphetamines improve attention and decrease hyperactivity in children with ADHD (234–236).

5.4 Tolerance in the experimental setting

Tolerance in connection with stimulants refers to a change in drug effect without a change in drug dose. One usually thinks of tolerance having developed when, after repeated administrations, a given dose of a drug produces a decreasing effect or, conversely, when larger doses must be administered to obtain the effects observed with the original dose (237). In studies of normal human volunteers, no tolerance or sensitivity to any response was noted after nine daily oral doses of 10 mg of dextroamphetamine (238), whereas tolerance developed to cardiovascular effects but not to a subjective "high" after 10 mg of methamphetamine daily for 15 days (239). As with many drugs, the effects of amphetamine are not entirely dependent on plasma level; normal volunteers receiving 0.25–0.5 mg/kg of amphetamine had effects on cardiovascular measures, subjective energy level, mood and behavior that peaked

1–3 hours after the drug was given and then declined even though plasma levels were stable or rising (240). These studies suggest that tolerance to alerting effects is limited at low to moderate doses in normal subjects. However, tolerance to psychomotor stimulants is differential with respect to the drug effect under study. In humans, rapid tolerance develops to the anorexic effects and to the morbid cardiovascular effects of amphetamine (37,241). Some tolerance develops to the cardiovascular effects of cocaine even over a 4-hour infusion period (242). Tolerance appears not to develop to the stereotyped behavior and psychosis induced by stimulants. Similarly in animal studies, tolerance develops to the anorexic and lethal effects of amphetamine but not to the stereotyped behaviors, which may become more pronounced after repeated treatment with a given dose of drug (243). The phenomenon of "reverse tolerance" has, in fact, been used to describe behavioral effects that appear to show sensitization (244).

5.5 Behavioral pathology

Use of high doses of amphetamines and related compounds can lead to cognitive and behavioral pathology. In healthy volunteers, repetitive oral administration of 5–10 mg of dextroamphetamine produced paranoid delusions, often with blunted affect, in all subjects after a cumulative dose of 55–75 mg (245). In amphetamine abusers, paranoid psychosis can lead to physical toxicity associated, for example, with the belief that bugs under the skin—"crank bugs"—need to be gouged out. Amphetamine abusers can persist in repetitive thoughts or punding (organized, goal-directed but meaningless activity) (246) such as repetitive cleaning, elaborate sorting of small objects or endless disassembly and reassembly of such items as clocks and radios. These stereotyped behaviors, defined as "integrated behavioral sequences that acquire a stereotyped character being performed at an increasing rate in a repetitive manner" (247), are also observed in animal species (248,249). For example, monkeys pick at their skin, exhibit mouth and tongue movements and stare; rats sniff intensely in one location; pigeons repetitively peck at one location on a stimulus display.

Experimental and theoretical analysis of stereotyped behavior has led to some insight into the nature and behavioral mechanism of action of amphetamine-like drugs (250). Lyon and Robbins (250) hypothesized that as the dose of amphetamines increases, the repetition rate of motor activities increases with the result that the organism will exhibit "increases in response rates within a decreasing number of response categories". This type of analysis makes a number of predictions. Complex behavioral chains or behaviors will be the first to be eliminated as the response categories decrease. Behaviors capable of repetition without long pauses will dominate, and shorter and shorter response sequences will result. As a result, high rates of responding in operant situations would be predicted to decrease and locomotor activity would decrease (251,252). Thus, the inverted U-shaped dose–response function relating amphetamines and locomotor activity may reflect the competitive nature of that activity and the emergence of stereotyped behavior (227). Similar effects on cognition may contribute to paranoid ideation and psychosis.

Amphetamines and related compounds have high abuse potential and produce dependence by most modern definitions (253). Although most users (95%) do not become addicted to the drug, clinical observations indicate that controlled use often shifts to more compulsive use, especially when there is easy access to the drug or when a rapid route of administration is used. The abuse cycle of euphoria, dysphoria, paranoia and psychosis can occur after a single exposure to a high dose or with chronic exposure to low doses. During a binge, the user characteristically administers the drug repeatedly for up to several days. Following a binge, there is the crash: extreme exhaustion, often with depression, anxiety and an intense desire to sleep. The subsequent withdrawal phase is characterized by apathy, anhedonia and strong drug craving. Episodic craving gradually diminishes over weeks and months.

6.0 FUTURE RESEARCH

With respect to clinical practice, there is still a paucity of placebo-controlled, double-blind, randomized studies of stimulant drugs and of the varied treatment strategies that employ such drugs. Many clinicians prescribe combinations of drugs to control the symptoms of narcolepsy: some prescribe stimulants along with anticataplectic agents; others prescribe combinations of stimulants such as pemoline in the morning with methylphenidate given as needed throughout the day. No objective studies delineate the effectiveness and side effects of such treatment strategies. Furthermore, narcoleptics have not been carefully studied for long-term effects of stimulant drugs with respect to tolerance, side-effects or continued efficacy. Moreover, little research exists regarding new pharmacotherapeutic approaches to the treatment of narcolepsy outside the clinical studies with modafinil in Europe that have already been discussed (95,108). However, work with the canine model of narcolepsy has suggested that other agonists selective for alpha adrenoceptors may be clinically useful (254,255). These leads should be pursued with more preclinical and clinical studies.

With respect to basic mechanisms of psychomotor

stimulant action, both from the behavioral and neuropharmacological perspective, still unknown are exactly what differential roles dopamine subtypes may play in psychomotor-stimulant action, particularly the D–3- and D–4-receptor subtypes for which selective ligands have only begun to be developed. With respect to efficacy in the treatment of narcolepsy, current information contains gaps regarding the physiologic mechanisms between the neuropharmacologic and behavioral actions of stimulant drugs. The functional roles of co-neurotransmitters such as neurotensin and cholecystokinin in the mesocorticolimbic dopamine system have yet to be delineated. Finally, a major reevaluation of the neuroanatomic connections within the basal forebrain has given rise to the possibility that a hierarchical circuitry may exist in the afferents and efferents of the basal forebrain that may ultimately define the functional significance of the mesocorticolimbic dopamine system and its role in psychomotor-stimulant action. Recent evidence suggests that the basal forebrain interface between the limbic and extrapyramidal motor systems may comprise at least two major separate neural circuits, the ventral striato-pallidal circuit and the extended amygdala (256). How these circuits are modulated by the dopamine afferents and what implication this has for the actions of psychomotor stimulants is an important area for future research.

7.0 CONCLUSIONS

Narcolepsy is a chronic CNS disorder characterized by sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations and disturbed nocturnal sleep. The most disabling symptom, sleepiness, is treated with psychomotor stimulants. Such drugs produce behavioral activation and increased wakefulness, enhanced alertness, decreased sense of fatigue, elevations of mood and increased performance. Treatment of excessive sleepiness associated with narcolepsy or idiopathic hypersomnia with psychomotor stimulants is indicated when sustained alertness is necessary for the safety of individuals or the public. Stimulant medications improve daytime alertness in 65–85% of narcoleptics; in 15–35%, improvement of alertness is minimal because of lack of efficacy, side effects or other factors. Tolerance to stimulants is variable depending on effect observed, dose and other factors. Side effects (headaches, nervousness, anxiety, palpitations and insomnia) are common, dose related and may require discontinuation of therapy. Stimulant use by young narcoleptics does not cause growth failure or cognitive dysfunction. No evidence suggests that stimulants are safe for use in pregnant women, and their use should be avoided unless no alternatives exist. Narcoleptics are not more prone to complications associated with stimulant use than other individuals. Severe psychiatric complications are rare with amphetamine use in narcolepsy but are more likely to occur with high doses and/or in patients with coexisting psychiatric illness. Although the safety and added efficacy of doses higher than those recommended by the manufacturers of stimulant drugs is not well established with controlled clinical trials, some patients receive higher doses without ill effects and with added benefit. When cataplexy and related symptoms are clinical problems, concomitant treatment is often implemented with a REM–sleep-suppressing antidepressant drug. No data from controlled studies indicate that daytime naps and drug holidays reduce tolerance to or increase efficacy of stimulants. Amphetamines act primarily on dopamine and, to a lesser extent, on norepinephrine systems. The mesocorticolimbic dopamine system appears to be responsible for the low-dose stimulant and the reinforcing effects of amphetamines, whereas the nigrostriatal dopamine system appears to mediate the focused stereotyped behavior produced by high doses of amphetamines. It is not known which of these two systems, the mesocorticolimbic dopamine system or the nigrostriatal system, produces the stimulant-related alerting effects observed in the treatment of narcolepsy.

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