Practice Parameters for the Treatment of Narcolepsy: An Update for 2000

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Abstract: Successful treatment of narcolepsy requires an accurate diagnosis to exclude patients with other sleep disorders, which have different treatments, and to avoid unnecessary complications of drug treatment. Treatment objectives should be tailored to individual circumstances. Modafinil, amphetamine, methamphetamine, dextroamphetamine, methylphenidate, selegiline, pemoline, tricyclic antidepressants, and fluoxetine are effective treatments for narcolepsy, but the quality of published clinical evidence supporting them varies. Scheduled naps can be beneficial to combat sleepiness, but naps seldom suffice as primary therapy. Regular follow up of patients with narcolepsy is necessary to educate patients and their families, monitor for complications of therapy and emergent of other sleep disorders, and help the patient adapt to the disease.

INTRODUCTION

NARCOLEPSY IS CHARACTERIZED BY UNCONTROLLABLE SLEEPINESS (ALSO CALLED EXCESSIVE DAYTIME SLEEPINESS) AND INTERMITTENT MANIFESTATIONS OF REM SLEEP AT TIMES WHEN A PERSON WOULD NORMALLY BE AWAKE. Beside sleepiness, the REM manifestations may include cataplexy, sleep paralysis, and hypnagogic hallucinations. Narcolepsy is not a common disease. The largest population study estimates the prevalence of narcolepsy at 26 per 100,000 people in Finland, which is similar to the prevalence of myasthenia gravis, Marfan's syndrome, systemic lupus erythematosis, and Crohn's disease. The actual prevalence may be higher in the United States,[1] where approximately 5% of patients seen at AASM accredited sleep disorder centers have narcolepsy.[2]

Narcolepsy has clinical importance which exceeds its prevalence. A lifelong, often disabling, condition such as narcolepsy demands that many health care providers besides sleep specialists must be familiar with optimum treatments. Sleep attacks associated with narcolepsy can lead to serious accidents or loss of employment, so treatment to reduce excessive sleepiness has clinical and societal value. Nevertheless, many health care providers are overly cautious in approaching treatment of narcolepsy, because stimulant medications, which are the mainstay of narcolepsy treatment, are regulated by government agencies to prevent abuse.

Because of the importance of narcolepsy treatment, the American Academy of Sleep Medicine (AASM) sponsored a review paper on the use of stimulants for treatment of narcolepsy in 1994.[3] Based on that review, the Standards of Practice Committee (SPC) of the AASM published practice parameters on narcolepsy therapy with stimulants[4]

Since publication of the initial review and practice parameters several developments have occurred. Researchers have identified a potential biochemical basis of narcolepsy in dogs and humans.[5,6] The genetic defect in canine narcolepsy associated with cataplexy results in a nonfunctional receptor (OX2R) for hypocretin (orexin), a neurotransmitter previously associated with feeding behavior and energy metabolism. In humans, hypocretin is reduced or undetectable in many but not all patients with narcolepsy associated with cataplexy. Also, the United States Food and Drug Administration (FDA) approved modafinil for treatment of narcolepsy. There is optimism that these research and clinical developments will result in better treatment and quality of life for patients with narcolepsy.

In 1999, the Agency for Healthcare Research and Quality in partnership with the American Medical Association (AMA) and the American Association of Healthplans, established the National Guideline Clearinghouse™ (NGC), a comprehensive database of evidence-based clinical practice guidelines and related documents. The clearinghouse provides a central repository of practice parameters from all medical specialties. To be listed, practice parameters must have been developed, reviewed, or revised every five years and must be based on a systematic review of scientific evidence published in peer-reviewed journals.[7]

In view of the new treatments, basic research advances, and the NGC protocol, the AASM decided to update the practice parameters for treatment of narcolepsy. This update concerns advances in therapy for narcolepsy since the publication of the expert review;[3] grades the evidence available; and modifies and replaces the1994 practice parameters.

METHODS

The SPC examined the published practice parameters and the review upon which they were based.[3,4] The references cited in

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Table 1 of the 1994 review paper were included in this reassessment, unless they were conference abstracts or letters to the editor.[3] Medline was searched from 1993 through and including articles published up to August 2000 with subject headings narcolepsy or cataplexy. In addition, human clinical trials, Americans with Disabilities Act, quality of life, driving, and compliance each were used as limiting terms. Finally, pemoline and methylphenidate were used as subject headings to discover information about toxic side effects. For information about teratogenicity, a textbook[8] about prescription medication use in pregnancy was employed and the medication graded according to the FDA system as described in the *Physicians' Desk Reference*, 2000 edition. Case reports, abstracts, editorials, letters, and reviews were excluded except for reports of adverse effects of treatments. All clinical trials of therapy were considered for the evidence tables. Case series and database articles about diagnosis of narcolepsy were incorporated in the evidence tables only if they included greater than 20 subjects. Examination of the reference lists from the articles found in the Medline search provided a few relevant studies from literature published prior to 1993. Evidence from the 1994 review and the updated Medline search was rated for the studies according to the classification outlined in Table 1.

For an economic indicator about drug costs, the wholesale price, as listed in the *Drug Topics Red Book Update* was used.[10] This is the current benchmark for drug price information.

The Board of Directors of the American Academy of Sleep Medicine reviewed the SPC for material conflicts of interest relevant to the recommendations and approved the final version of the parameters prior to publication.

On the basis of this review, the SPC of the American Academy of Sleep Medicine rated the recommendations of this paper as standards, guidelines, and options (Table 2), based on evidence from studies published in peer-reviewed journals that were evaluated as noted in the evidence tables (Tables 3 and 4). However, when scientific data are absent, insufficient, or inconclusive, the recommendations were based on consensus opinion. Each recommendation is based on the level and grade of the evidence available, or on consensus when evidence is lacking.

These practice parameters define principles of practice that should meet the needs of most patients in most situations. These guidelines should not, however, be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed toward obtaining the same results. The ultimate judgment regarding the propriety of any specific care must be made by health care providers in light of the individual circumstances presented by the patient and the available diagnostic and treatment options as resources.

The American Academy of Sleep Medicine expects these guidelines to have a positive impact on professional behavior, patient outcomes, and, possibly, health care costs. These practice parameters reflect the state of knowledge at the time of development and will be reviewed, updated, and revised, as new information becomes available.

RESULTS

The Medline search for narcolepsy and clinical trials yielded 29 articles, of which 14 were relevant to this paper. The Medline search of narcolepsy and human returned 450 articles. In the narcolepsy and human search, several clinical trials were found which did not show up in the more limited search. The Medline search for narcolepsy and compliance yielded one relevant article. The search for narcolepsy and driving yielded 26 references, of which six proved relevant. Narcolepsy and quality of life yielded 15 references of which three proved to contain original

Table 1—AASM classification of evidence

Recommendation Grades	Evidence Levels	Study Design
A	I	Randomized well-designed trials with low-alpha & low-beta errors*
B	II	Randomized trials with high-beta errors*
C	III	Nonrandomized controlled or concurrent cohort studies
C	IV	Nonrandomized historical cohort studies
C	V	Case series

Adapted from Sackett[9]

*Alpha error refers to the probability (generally set at 95% or greater) that a significant result (e.g., $p<0.05$) is the correct conclusion of the study or studies. Beta error refers to the probability (generally set at 80% or 90% or greater) that a nonsignificant result (e.g., $p>0.05$) is the correct conclusion of the study or studies. The estimation of beta error is generally the result of a power analysis. The power analysis includes a sample size analysis which projects the size of the study population necessary to ensure that significant differences will be observed if actually present.

Table 2—AASM recommendations

Term	Definition
Standard	This is a generally accepted patient care strategy which reflects a high degree of clinical certainty. The term *standard* generally implies the use of Level I Evidence, which directly addresses the clinical issue, or overwhelming Level II Evidence.
Guideline	This is a patient care strategy which reflects a moderate degree of clinical certainty. The term *guideline* implies the use of Level II Evidence or a consensus of Level III Evidence.
Option	This is a patient care strategy which reflects uncertain clinical use. The term *option* implies either inconclusive or conflicting evidence, or conflicting expert opinion.

Adapted from Eddy[11]

data. Other articles about quality of life in narcolepsy were found in the reference sections of these articles. Although the search under Americans with Disabilities Act yielded 469 references, none were directly related to narcolepsy. The search under cataplexy yielded 169 articles, of which 36 were human clinical studies, but many turned out to be case reports or small case series. Tables 3 and 4 list most of the citations on which the updated practice parameters are based.

Recommendations

Recommendations that are similar to, or an expansion of, previous ones and new recommendations are noted as such in the text.

1. **An accurate diagnosis of narcolepsy should be established which shall include a thorough evaluation of other possible contributing causes, apart from narcolepsy, to the excessive daytime sleepiness {Standard}.**

   For patients suspected of having narcolepsy, an all-night polysomnogram is done primarily to ascertain the presence of concurrent sleep disorders and is followed immediately by a multiple sleep latency test[50,51] (MSLT) to help confirm the diagnosis. The MSLT also helps determine the severity of daytime sleepiness. The reader is referred for diagnostic criteria[33-35,50] (Table 4). Other methods to evaluate sleepiness include objective tests such as the maintenance of wakefulness test[51] (MWT), and subjective approaches such as the Epworth Sleepiness Scale.[52] This part of the recommendation is based on committee consensus and is similar to a recommendation made previously.[4]

   Chronic daytime sleepiness is a nonspecific symptom and conditions that produce such sleepiness may coexist with narcolepsy. For example, the obstructive sleep apnea syndrome (OSAS) and periodic limb movement disorder (PLMD) may be present as determined by the results of the all-night polysomnogram. Insufficient sleep, idiopathic hypersomnia, inadequate sleep hygiene, and circadian rhythm disorders, among others should be considered as possible contributors to sleepiness independent of narcolepsy.[50] Management of other disorders possibly contributing to sleepiness in a patient with narcolepsy may require approaches apart from stimulants to treat sleepiness either directly or as therapy of the underlying condition. This part of the recommendation is new and is based on committee consensus.

2. **Individual treatment objectives should be established for each patient with narcolepsy to improve quality of life {Standard}.**

   One level II, grade B, four level III, grade C, and one level V, grade C, studies, and committee consensus, provide evidence that symptoms of narcolepsy may adversely impact quality of life[18,36-41] (Tables 3 and 4). In keeping with the previous practice parameters,[4] a major objective of treatment should be to alleviate daytime sleepiness with stimulants. The goal should be to produce the fullest possible return of normal function for patients at work, at school, at home, and socially. A new recommendation is to control cataplexy, hypnagogic hallucinations, and sleep paralysis, when present and troublesome. The health care provider should consider the benefit-to-risk ratio of medication for an individual patient, the cost of medication, convenience of administration, and the cost of ongoing care including possible laboratory tests when selecting a medication for treatment of narcolepsy.

3. **The following medications are effective treatments for narcolepsy. Comparative safety and efficacy of the stimulant medications are not defined. The rating of the recommendation is based on the grade of evidence for each. See Table 5 for dosages.**

   a. **Modafinil is effective for treatment of daytime sleepiness due to narcolepsy {Standard}.** [Table 3] This conclusion is based on the favorable benefit-to-risk ratio for modafinil established in three level I, grade A studies with confirmation from additional studies.[20-27] This is a new recommendation.

   b. **Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy {Guideline}.** [Table 3] These medications are mainstays of narcolepsy treatment. Based on 3 level II, grade B and 4 level V, grade C studies and long clinical practice, they have a long record of efficacy. However, the benefit-to-risk ratio is not well documented, because the published clinical trials include only small numbers of patients.[12-18,53] This recommendation is similar to that made previously.

   c. **Selegiline is an effective treatment for all narcoleptic symptoms {Guideline}.** [Table 3] Based on two level II, grade B and one level IV, grade C studies, selegiline is effective, but the cost of the medication is very high, experience with the high doses needed for narcolepsy is limited, and diet-induced hypertension is a danger at effective doses.[28-30] This is a new recommendation.

   d. **Pemoline is effective for treatment of daytime sleepiness in narcolepsy {Option).** [Table 3] Pemoline can produce rare and potentially lethal liver toxicity that may be unpredictable. See the Appendix product alert from Abbott Laboratories for more details and recommendations for ongoing monitoring for liver toxicity. Because of this toxicity, the use of pemoline in patients with narcolepsy is rarely indicated. Based on one level II, grade B study, pemoline may be less potent than amphetamines,[13] but adherence to pemoline therapy may be better than adherence to amphetamines or methylphenidate.[49] This is a modification of a recommendation made previously. In particular, the warning on liver toxic-

ity is emphasized to a greater degree than previously.

e. **Tricyclic antidepressants and fluoxetine may be effective treatment for cataplexy, sleep paralysis, and hypnagogic hallucinations {Guideline}.** [Table 4] The recommendation for tricyclic agents is based on one level V, Grade C study, long clinical experience and committee consensus. This is a new recommendation. The recommendation for fluoxetine is based on one level II, grade B and one level V, grade C study. This is a new recommendation.

f. **Combinations of long- and short-acting forms of stimulants may be effective for some patients {Option}.**
Some stimulants have a short (3 to 4 hour) effective period (e.g., methylphenidate). Others have longer duration of activity and longer onset of action (e.g., modafinil, sustained release amphetamine). By combining stimulants with different activity characteristics, it may be possible to achieve alertness quickly and for longer periods of time and also not produce insomnia as an unwanted side effect. In addition, combinations of stimulants and antidepressants may be of benefit for treatment of sleepiness and REM-related symptoms such as cataplexy. For example, modafinil appears compatible with antidepressant medications, but published evidence is limited.[54] This recommendation is similar to that made previously and is based on committee consensus.

4. **Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy {Guideline}.** [Table 2] This recommendation is based on two level II, grade B, one level IV, grade C and one level V, grade C studies and long clinical experience.[42-45] This recommendation is similar to that made previously.

5. **Regular follow-up of patients with narcolepsy is necessary to monitor response to treatment, to respond to potential side effects of medications, and to enhance the patient's adaptation to the disorder {Standard}.**

   a. **A patient stabilized on stimulant medication should be seen regularly by a health care provider at least once per year, and preferably once every 6 months, to assess the development of medication side effects, including sleep disturbances, mood changes, and cardiovascular or metabolic abnormalities.** This is the same recommendation as made previously and is based on committee consensus.

   b. **Follow-up is necessary to determine adherence and response to treatment; to monitor for the safety of medications in individual patients; and to assist the patient with occupational and social problems.**
   Adherence to stimulant drug treatment in narcolepsy is impeded by inconvenient dosage, but not by age, educational level, gender, or response to therapy.[49] Of note, many patients with narcolepsy can not be restored to normal levels of daytime alertness, even when adhering to optimum doses of stimulant medications (Table 5). Most often, response to therapy can be determined by interview of the patient and associates as well as by self-report questionnaires, such as the Epworth Sleepiness Scale. Objective measures, such as the MWT or the MSLT, may play a role when occupational or public safety concerns are at issue. This is an expansion of a similar recommendation made previously and is based on committee consensus.

   c. **Patients with severe sleepiness should be advised to avoid potentially dangerous activities at home and at work, and should not operate a motor vehicle until sleepiness is appropriately controlled by stimulant medications.**
   This recommendation is the same as that previously and is based on one level II, grade B and one level III, grade B study[36,40] (Table 4) and committee consensus.

   d. **Of the stimulants used to treat narcolepsy, amphetamines, especially at high doses, are the most likely to result in the development of tolerance.**
   This is the same recommendation as previously. Reiteration of the discussion and literature cited in the previous review paper[3] are beyond the scope of the current review and the reader is referred for further information.

   e. **Patients who fail to respond to adequate doses of stimulant medication should be carefully assessed for other sleep disorders such as insufficient sleep, inadequate sleep hygiene, circadian rhythm disorders, obstructive sleep apnea syndrome, or periodic limb movement disorder, that may contribute to excessive sleepiness.**
   This is essentially the same recommendation as previously and is based on committee consensus.

   f. **For side effects, dosage ranges, use in pregnancy and by nursing mothers, class of medication and use in narcolepsy, see Table 5.**
   The information of Table 5 on stimulants is similar and, in some cases, an expansion of information provided previously. The information on the other classes of medications is new. Note that any of the stimulant medications can be abused.

   g. **Treatment of narcolepsy with methylphenidate in children between the ages of 6 and 15 appears relatively safe, but**

caution must be used if other medications are employed. See Table 5 for dosages.
This recommendation is similar to that previously and is based on the considerable experience with use of methylphenidate for treatment of attention deficit disorder.[55]

h. **Health care providers should assist the patient with occupational and social accommodation for disabilities due to narcolepsy.**
The Americans with Disabilities Act provides legal guidance.[56] Patients deserve appropriate help from health care providers to insure that the intent of the law is realized. Because sustained alertness often is difficult to achieve even with optimum treatment, some patients should be advised to avoid potentially dangerous activities, such as driving, climbing, or working in the vicinity of dangerous machinery, which could result in injury to the patient or others.[36,40,57] This recommendation is similar to that previously and is based on committee consensus.

i. **Polysomnographic reevaluation of patients should be considered if symptoms of sleepiness increase significantly or if specific symptoms develop that suggest new or increased sleep abnormalities as might occur in disorders such as sleep apnea or periodic limb movement disorder.**
This is the same recommendation as that previously and is based on committee consensus.

Further Research

The preparation of these practice parameters revealed significant weaknesses in the published literature about treatment of narcolepsy. Better studies of diagnostic criteria are needed. Studies which explicitly consider patient preferences about therapeutic objectives, should be undertaken. Further research on selective serotonin reuptake inhibitors (SSRIs), including ones besides fluoxetine available in the United States, should be undertaken. A large comparative clinical trial of amphetamine, methylphenidate, modafinil, and selegiline for treatment of narcolepsy would be of benefit for patient management. Such a study could establish the relative efficacy, side effects, and patient preferences for treatments. A registry should be established to track the outcome of pregnancy in patients who take modafinil and other stimulants that do not have adequate human data. Treatment of cataplexy needs better assessment, and a clinical trial comparing fluoxetine, tricyclic agents, and placebo would be helpful to clinicians. Research about social interventions to improve function of narcoleptic patients at work and home should be a priority. Gamma hydroxybutyrate is being evaluated experimentally and may have a role to play in treating nocturnal awakenings and cataplexy.[58] However, it is not approved by the FDA. Finally, investigation about whether case management of narcolepsy patients might lead to better patient outcomes is needed.

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Table 3. EVIDENCE ABOUT STIMULANT DRUG TREATMENTS FOR NARCOLEPSY

Amphetamines and Methylphenidate

Reference / Evidence Level	Study design	Diagnostic criteria	Sample size (Completed Study)/Mean age (range)	Medication used: Agent; Duration; Administration protocol	Outcome measures	Comments	Conclusions
Mitler (12) Level II-B	RCT CO	ICSD	16(16) / 42 (21-67)	Placebo vs methamphetamine Dose range: 0, 5, 10, 20, 40, and 60 mg QAM	MSLT	Excluded any other sleep disorders. Only 3 day washout between Rx. Excluded patients with severe cataplexy and insufficient duration of Rx.	Methamphetamine is efficacious in reducing sleepiness and errors with driving simulator. The performance of treated narcolepsy patients was similar to control group.
Mitler (13) Level II-B	RCT	1)Hx of EDS 2)one REM -related symptom 3) ≥ 2 SOREMPS on MSLT	107 - 56, 13, 14, 10, 5, & 9 in separate trials /(39-50 in 5 separate trials)	Viloxazine:100mg Methylphenidate: 10, 30, and 60 mg Pemoline: 18.75, 56.25, and 112.5 mg Dextroamphetamine.: 10, 30, and 60 mg Protriptyline: 10, 30, and 60 mg	MWT	Each of these were separate trials, w/o randomization between trials. Excluded OSA, medical illness and psychiatric disorder.	Higher doses of methylphenidate and dextroamphetamine reduce sleepiness. Pemoline at 112.5 mg QD is effective in reducing sleepiness, but probably not comparable to methylphenidate and dexedrine at 60 mg. Viloxazine and protriptyline do not appear to be stimulants.
Shindler (14) Level II-B	RCT	A history of sleepiness	20 (15)/49 (28-65)	Dexedrine: 5 BID Dexedrine spansules: 10AM Mazindol: 2 BID Dexedrine:10 TID Fencafamin: 20 TID	Self-ratings for sleepiness, appetite, and mood.	Modern diagnostic criteria were not used. Not necessarily a drug free interval between treatments. Only used self-assessment of sleepiness with unclear comparisons.	All the active treatments were effective in reducing daytime sleepiness without impacting on cataplexy.
Daly (15) Level V-C	Clinical series	Clinical (12 patients had cataplexy)	29 (25) / 32.4 (12-67)	Methylphenidate: 20 to 240 mg per day	Patient opinion	No exclusion criteria noted.	Methylphenidate relieves sleepiness but does not work as well for narcolepsy.
Yoss (16) Level V-C	Unblinded clinical series	Yoss RE, Daly D. Criteria for the diagnosis of the narcoleptic syndrome. Proceedings of the Staff Meetings of the Mayo Clinic. 1957;32:320-328.	68 (60) / (12-67)	Methylphenidate: titrated range: 15 mg to 300 mg daily Mean = 60mg	Self report	No systematic measurement of outcome or modern Dx criteria.	Excellent or good relief of EDS in 75% and cataplexy in 56%.

Reference / Evidence Level	Study design	Diagnostic criteria	Sample size (Completed Study)/Mean age (range)	Medication used: Agent; Duration; Administration protocol	Outcome measures	Comments	Conclusions
Chen (17) Level V-C	Clinical Series with 2 Control: patient estimate of sleepiness w/no Tx and 188 normal subjects	ICSD	60 (205 contacted, drop outs due to not meeting Dx criteria, didn't return questionnaire, incomplete responses to questionnaire, or taking medication in addition to dextroamphetamine.)	Dextroamphetamine: 5-60 mg/day	Epworth Sleepiness Scale, Cataplexy Atonia Reading Scale, Self-report of insomnia, sleep latency, total night sleep time, and arousals.	Narcolepsy not confirmed with MSLT. PSG not done to exclude OSA or PLM. Didn't assess compliance.	Long term, dextroamphetamine treatment of sleepiness in narcolepsy is not as effective as short-term treatment.
Parkes (18) Level V-C	Clinical series	ICSD	100 / 46 (22-66)	Various stimulants with various doses	Interview	No R/O of OSA, no systematic outcome measurements, possible multiple stimulant exposure of patients over period of years, and lacking modern Dx criteria.	Stimulants are efficacious for narcolepsy-related EDS, and are safe when combined w/ TCAS.
Modafinil							
Beusterien (19) Level I-A	RCT, Unblinded for follow-up	ICSD	558 (48) / 42 (18-68)	Placebo Modafinil: 200 mg and 400 mg QAM	SF36	Not off Rx 14 days. Adverse reaction to CNS stimulants. No anti-cataplectic Rx.	Improved Quality of Life.
U.S. Modafinil in Narcolepsy (20) Level I-A	RCT	ICSD	271 / 42 (17-67)	Modafinil: 200 mg and 400 mg daily	MSLT, MWT, and Epworth Sleepiness Scale	Confounding factors-drop outs not explained by adverse effects	Effective for treatment of daytime sleepiness in narcolepsy for nine weeks.
U.S. Modafinil in Narcolepsy (21) Level I-A	RCT and unblinded parallel design, then open label for follow-up	ICSD	447 - 164 not Ran because of inclusion criteria or consent /Not reported	Modafinil: 200 mg and 400 mg, placebo QAM.	MSLT, Epworth Sleepiness Scale, Stanford Sleepiness Scale, Global Symptoms Index, and self-reports.	Not off Rx 14 days. Adverse reaction to CNS stimulants. No anti-cataplectic Rx.	Modafinil 200 mg and 400 mg more effective for control of Excessive Daytime Sleepiness (EDS).

Reference / Evidence Level	Study design	Diagnostic criteria	Sample size (Completed Study)/Mean age (range)	Medication used: Agent; Duration; Administration protocol	Outcome measures	Comments	Conclusions
Broughton (22) Level II-B	RCT CO	ICSD	75 (71) / 43 3 adverse drop-outs	Modafinil and placebo: 100 and 200 mg	MWT and Epworth Sleepiness Scale	Exclusion criteria were the following: amphetamines within 2 months, OSA, PLMD, alcoholism, shift work, circadian, head trauma, anxiety, psychosis, medical disease affecting sleep.	Modafinil effective in keeping narcolepsy patients awake.
Billiard (23) Level II-B	RCT CO	ICSD	50 (46) / 41	Modafinil: 300 mg (2 divided doses); 100 mg in AM and 200 mg at noon or vice versa	MWT and Global Symptoms Index		Modafinil improves daytime alertness.
Boivin (24) Level II-B	RCT CO	ICSD	10 (10) / 46 (31-61)	Modafinil: 200 mg in AM, 100 mg at noon	PSG, before and after, and Four Choice Reaction Time Test	Able to stop Rx for 2 weeks.	Improved subjective alertness while on Modafinil. No harmful effects on nocturnal sleep by PSG.
Bastuji (25) Level V-C	Clinical Series	Clinical Dx and 24 hour PSG	24 (22) / 40	Modafinil: 200 to 500 mg daily	Self report		Modafinil is effective for narcolepsy sleep attacks and drowsiness attacks.
Laffont (26) Level V-C	Clinical Series	≥ 2 SOREMPs on MSLT (26 had cataplexy)	94 (48) / 45 (15-71) 46 lost during follow up.	Modafinil: 100-400 mg QAM or BID	Interview	Sleep disordered breathing excluded.	Modafinil was subjectively helpful in reducing EDS in 90% of narcolepsy patients. It had low utility in cataplexy or nocturnal sleep disturbance.
Besset (27) Level V-C	Clinical series	ICSD	140 / 42 (8-79) Drop out due to loss of efficacy.	Modafinil: 200-400mg/day, QAM, and noon.	Interview	No standard measurement of efficacy. No measurement of compliance.	Modafinil 200-400 mg per day reduced EDS in 64% of all patients. Fifty percent of patients stopped modafinil after about 2 years because of perceived lack of efficacy.
Selegiline							
Hublin (28) Level II-B	RCT CO	ICSD	20 (17) / Not reported	Selegiline: 0-40 mg	MSLT and Cataplexy count		40 mg Selegiline effective for both EDS and cataplexy.

Reference / Evidence Level	Study design	Diagnostic criteria	Sample size (Completed Study)/Mean age (range)	Medication used: Agent; Duration; Administration protocol	Outcome measures	Comments	Conclusions
Anonymous (47) Level V-C	Expert review	Not Reported	Not Reported	Modafinil	Not applicable		Modafinil has not been studied well enough to determine effects in the future.
Whitaker-Azmitia (48) Evidence N/A-Animal study	Unblinded Ran	Animal study	64 rat pups exposed to each drug prenatally	Clorgyline and deprenyl	Exposure of rat fetuses in utero to clorgyline or deprenyl was associated with reduction of brain serotonin innervation at birth, and associated with subsequent behavioral abnormalities.		The authors suggest that MAOIs should be avoided in pregnant women.
Rogers (49) IV-C	Cross-sectional study	ICSD	51 (43) / 42 (18-64)	Varied doses of dextroamp., methylphenidate, and pemoline	Health and sleep questionnaire, sleep diary, and medical records.	Bias present in patient-selection and confounding factors.	Health care providers can't assume that patients with narcolepsy are taking medication as prescribed. Adherence didn't correlate with age, education level, or objective response to medication. Compliance was better with once/day pemoline than with methylphenidate or dextroamphetamine.

Notes: RCT – ramdomized controlled trial; ICSD – international classification of sleep disorders [50]; MSLT – multiple sleep latency test; Hx – history; Dx – diagnosis; PSG – polysomnogram; MWT – maintenance of wakefulness test; Rx – treatment; CO – crossed over; OSA – obstructive sleep apnea; w/o – without; PLMD – periodic limb disorder; CNS – central nervous system; SOREMPs – sleep onset rapid eye movement periods; EDS – excessive daytime sleepiness (an uncontrollable urge to fall asleep at inappropriate times).

Table 4. OTHER EVIDENCE ABOUT NARCOLEPSY

Cataplexy

Reference / Evidence Level	Study design	Diagnostic criteria	Sample size (Completed Study)/Mean age (range)	Medication used: Agent; Duration; Administration protocol	Outcome measures	Comments	Conclusions
Schrader (31) Level II-B	RCT	ICSD	10 / 50 (36-67)	Femoxetine (not available in U.S.) 300 mg BID vs placebo	MSLT ambulatory EEG, self-report of sleep attack frequency and cataplexy.	MSLT was done at home. Unclear whether narcoleptics had such mild EDS that they went untreated with standard stimulants.	Femoxetine reduces cataplexy, but not EDS.
Frey (32) Level V-C	Clinical series	ICSD	6 (5) / 54 (44-69) Headaches due to fluoxetine	Fluoxetine: 20 mg daily	Self report of cataplexy	Exclusion criteria were high frequency cataplexy and Failure of tricyclics.	Fluoxetine may be effective for control of cataplexy.
Chen (17) Level V-C	Clinical Series with 2 Control: patient estimate of sleepiness w/no Tx and 188 normal subjects	ICSD	16 (205 contacted, drop outs due to not meeting Dx criteria, didn't return questionnaire, incomplete responses to questionnaire, or taking medication in addition to dextroamphetamine.)	Clomipramine: 25-125 mg/day	Epworth Sleepiness Scale, Cataplexy Atonia Reading Scale Self report of insomnia, sleep latency, total night sleep time, and arousals.	Narcolepsy not confirmed with MSLT. PSG not done to exclude OSA or PLM. Didn't assess compliance.	Long term, clomipramine treatment of cataplexy in narcolepsy is not as effective as short-term treatment.

Diagnosis

Hayduk (33) Level III-C	Cohort study	ICSD	32 probands and 57 relatives of patients / Probands-42 (13-70) Relatives-39 (10-83)	Not applicable	Clinical follow-up with MSLT and HLA phenotyping.	Well defined Cohort	ICSD criteria for narcolepsy are adequate for this group. HLA phenotyping: 10/32 false negative, so sensitivity 69%. HLA phenotyping is not useful.

Reference / Evidence Level	Study design	Diagnostic criteria	Sample size (Completed Study)/Mean age (range)	Medication used: Agent; Duration; Administration protocol	Outcome measures	Comments	Conclusions
Aldrich (34) Level V-C	Database review	ICSD	157 / 40	Not applicable	MSLT	Exclusion criteria were the following: No stimulant or sedating Rx, and single Dx. No confusional, remedial or psych disorder.	Narcolepsy diagnosis more challenging if no cataplexy.
Aldrich (35) Level V-C	Database review	ICSD	2083-170 narcolepsy, 1251 sleep apnea, 662 other sleep / 39 (6-79)	Not applicable	MSLT	Study was free of psychoactive and REM sleep suppressing Rx.	MSLT by itself is neither sensitive nor specific enough to identify narcolepsy unless used with other clinical criteria (ICSD).
Driving and Quality of Life							
George (36) Level II-B	Unblinded case-control study	Not specified	16 narcolepsy, 21 OSA, 21 controls / Not reported	Untreated	Driving Simulator and Mean sleep onset latency	Exclusion criteria were the following: No driver's license, physical disability, sedative, and stimulants.	Untreated narcolepsy patients have significant impairment of skills needed to drive safely.
Broughton (37) Level III-C	Case-control study	EDS or sleep attacks, and cataplexy, sleep paralysis, or hypnagogic hallucinations	180 cases and 180 controls	Standard Treatment	Questionnaire	Exclusion criteria not specified.	Narcolepsy patients have poorer quality of life compared to controls.
Broughton (38) Level III-C	Case-control study	EDS or sleep attacks, and cataplexy, sleep paralysis, or hypnagogic hallucinations	180 cases and 180 controls	Standard Treatment	Questionnaire	Exclusion criteria not specified.	Effects are same in Canada, Japan and Czechoslovakia—so narcolepsy patient's problems are independent of culture.
Broughton (39) Level III-C	Cross-sectional study	Clinical	180 (180) / 32 for epilepsy and control - 42 for Narcolepsy	Standard Treatment	Questionnaire	Self report	Narcolepsy patients are more socially impaired than epilepsy patients or controls.

Reference / Evidence Level	Study design	Diagnostic criteria	Sample size (Completed Study)/Mean age (range)	Medication used: Agent; Duration; Administration protocol	Outcome measures	Comments	Conclusions
Findley (40) Level III-C	Case-control study	5 nap MSLT w/ Mean sleep latency of < 10 plus 1 SOREMPS	10 / 37	Untreated	Self-reported auto accidents and "Steer Clear" hits.	"Steer Clear" may not be a good measure of highway skills.	"Steer clear" results were worse in untreated narcolepsy patients.
Kales (41) Level V-C	Single blinded case control	Not specified	50 (47) / 42 (18-72)	Standard Treatment	MMPI, projective tests, and psychiatric interviews	Control group and narcolepsy cases not well defined.	Narcolepsy seriously interfered with work, marital, and social relationships.
Naps							
Godbout (42) Level II-B	Unblinded case control	ICSD	10 / 44 (37-51)	100 min. Nap vs. 5 Naps at 20 min.		Small study size	Naps improve performance in narcolepsy patients but not to normal level.
Mullington (43) Level II-B	RCT	ICSD	8 (8) / (19-55)	No naps vs multiple brief naps vs a single long nap	24 Hr Ambulatory EEG and Four Choice Reaction Time Test		Unscheduled naps were not significantly less frequent after a long daytime nap than after no nap. With a long nap, reaction performance is much improved, but no naps improved logical reasoning. However, logical reasoning performance was best in the no-nap condition.
Helmus (44) Level III-C	Control Unblinded Non-Ran CO	Mean MSLT <5min and 2 SOREMPS	11 narcolepsy and 22 controls/ 39 (21-60)	Naps: 15 min vs. 120 min	MSLT	Cross over bias	120-min. naps are more effective than 15-min. naps for improving MSLT scores.
Rogers (45) Level IV-C	Unblinded Cohort	Clinical complaint of EDS and one symptom of narcolepsy	60 / 46 (21-65)	Prescribed 15 min naps TID	MWT and Mean sleep latency.	Compliance with nap therapy verified only by daily diary. Patients took various amounts of stimulants. No stringent Dx criteria.	Twice-daily naps reduce objective sleepiness.
Toxicity							
Shevell (46) Level V-C	Case review	Patients had Attention Deficit Disorder not narcolepsy.	Not Reported / (10-18)	Pemoline	Not applicable	These were not narcoleptic patients.	Pemoline has potential hepatotoxicity, but the frequency of pemoline-related fulminant hepatic failure is unknown.

Reference / Evidence Level	Study design	Diagnostic criteria	Sample size (Completed Study)/Mean age (range)	Medication used: Agent; Duration; Administration protocol	Outcome measures	Comments	Conclusions
Anonymous (47) Level V-C	Expert review	Not Reported	Not Reported	Modafinil	Not applicable		Modafinil has not been studied well enough to determine effects in the future.
Whitaker-Azmitia (48) Evidence N/A-Animal study	Unblinded Ran	Animal study	64 rat pups exposed to each drug prenatally	Clorgyline and deprenyl	Exposure of rat fetuses in utero to clorgyline or deprenyl was associated with reduction of brain serotonin innervation at birth, and associated with subsequent behavioral abnormalities.		The authors suggest that MAOIs should be avoided in pregnant women.
Rogers (49) IV-C	Cross-sectional study	ICSD	51 (43) / 42 (18-64)	Varied doses of dextroamp., methylphenidate, and pemoline	Health and sleep questionnaire, sleep diary, and medical records.	Bias present in patient-selection and confounding factors.	Health care providers can't assume that patients with narcolepsy are taking medication as prescribed. Adherence didn't correlate with age, education level, or objective response to medication. Compliance was better with once/day pemoline than with methylphenidate or dextroamphetamine.

Notes: RCT – ramdomized controlled trial; ICSD – international classification of sleep disorders [50]; MSLT – multiple sleep latency test; Hx – history; Dx – diagnosis; PSG – polysomnogram; MWT – maintenance of wakefulness test; Rx – treatment; CO – crossed over; OSA – obstructive sleep apnea; w/o – without; PLMD – periodic limb disorder; CNS – central nervous system; SOREMPs – sleep onset rapid eye movement periods; EDS – excessive daytime sleepiness (an uncontrollable urge to fall asleep at inappropriate times).

TABLE 5. MEDICATION CHARACTERISTICS AND WHOLESALE COSTS OF MEDICATIONS FOR NARCOLEPSY (Medication characteristics and doses based primarily on PDR, 2000 edition with some recommendations based on references 3 and 4*) (Costs based on the *Drug Topic Red Book Update*, 2000)[10]

MEDICATION	Usual daily dose (maximum doses)	Pediatric use and dosage	Use in nursing mothers	Pregnancy category*	Class of medication	Major Side effects (not in order of occurrence)	Cost per month (usual dose)
Amphetamine	30 mg (100 mg)	Not recommended under age 3 Dose to start at 5 mg, possible suppression of growth in children	Three to seven fold increase in milk	C**	Stimulant, Amphetamine	Insomnia, restlessness, tachycardia, psychotic episodes (rare), dizziness, diarrhea, constipation, hypertension, impotence,	$46.80
Amphetamine (sustained release)	30 mg (100 mg)	Same as amphetamine	Three to seven fold increase in milk	C**	Stimulant, Amphetamine	same	$59.43
Methamphetamine	40 mg (80 mg)	Same as amphetamine	Three to seven fold increase in milk	C**	Stimulant, Amphetamine	same	$186.22
Methylphenidate	30 mg (100 mg)	Maximum dose of 60 mg, use in age 6 and older	Not established	Not established	Stimulant, otherwise not defined	Nervousness, insomnia, anorexia, nausea, dizziness, hypertension, hypotension, hypersensitivity reactions, tachycardia, headache, very rare reports of neuroleptic malignant syndrome	$64.29
Modafinil	200 mg (400 mg)	Not established below 16 years of age	Not established	Not established	Stimulant, otherwise not defined	Headache, nausea, eosinophilia, diarrhea, dry mouth, anorexia,	$291.00

Pemoline	75 mg (150 mg)	Maximum dose of 112.5 mg.	Not established	B	Oxazolidine	Seizures, liver failure, isolated cases of aplastic anemia, insomnia, hallucinations, anorexia and weight loss	$81.96
Selegiline	20 mg (40 mg)	Not established	Not established	C	Stimulant and anti-cataplectic and anti- other REM-related symptoms, MAO inhibitor	Nausea, dizziness, confusion, tremor, orthostatic hypotension, diet-induced hypertension	$489.68
Fluoxetine	20 mg (80 mg)	Not established	Excreted in milk	C	Anti-cataplectic and anti- other REM-related symptoms, SSRI	Asthenia, nausea, diarrhea, anorexia, insomnia, tremor, anxiety, somnolence	$79.50
Protriptyline (non-sedating TCA; other TCAs are usually sedating; characteristics except dose are otherwise similar among TCAs such as imipramine.)	10 mg (60 mg)	Not established	Not established	Not established	Anti-cataplectic and anti- other REM-related symptoms, TCA	Orthostatic hypotension, hypertension, seizures, headache, anticholinergic symptoms, impotence, impaired liver function, myocardial infarction, stroke	$17.34

SSRI – selective serotonin reuptake inhibitor; TCA – tricyclic antidepressant; MAO – monoamine oxidase

*- The FDA classifies drugs as A, B, C, D, or X, indicating increasing levels of toxicity, according to embryotoxic and teratogenic effects. Class A means controlled human studies show no risk to the human fetus in the first trimester and the possibility of fetal harm is remote, B means animal studies indicate no fetal risk, and there are no controlled human studies, C means animal studies have shown teratogenic or embryocidal effects, and there are no controlled human studies, D means there is evidence of risk to human fetuses but benefits may make risks acceptable, X means studies in animals or humans have demonstrated fetal abnormalities and the risks outweigh any possible benefit.

** - infants born to mothers on amphetamines may be premature, have low birth weight and experience withdrawal symptoms.

ABBOTT

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Dear Health Care Professional:

This communication is to advise you of an update to the WARNINGS section in the labeling for CYLERT® (pemoline, Abbott), a central nervous system stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD). Although there has been no change in the reported rate of acute hepatic failure associated with CYLERT use, based on discussions with the Food and Drug Administration (FDA), the labeling has been revised to provide updated recommendations for liver function monitoring and a "Patient Information/Consent Form".

Before prescribing CYLERT, the physician should be thoroughly familiar with the details of the CYLERT prescribing information. CYLERT should not be prescribed until there has been a complete discussion of the risks with the patient. The Patient Information/Consent Form should be reviewed with any patient currently taking CYLERT or any new patient for whom CYLERT is to be prescribed. In addition, written informed consent should be obtained.

The revised black box warning reads as follows:

Because of its association with life threatening hepatic failure, CYLERT should not ordinarily be considered as first line drug therapy for ADHD (see INDICATIONS AND USAGE). Because CYLERT provides an observable symptomatic benefit, patients who fail to show substantial clinical benefit within 3 weeks of completing dose titration, should be withdrawn from CYLERT therapy.

Since CYLERT's marketing in 1975, 15 cases of acute hepatic failure have been reported to the FDA. While the absolute number of reported cases is not large, the rate of reporting ranges from 4 to 17 times the rate expected in the general population. This estimate may be conservative because of under reporting and because the long latency between initiation of CYLERT treatment and the occurrence of hepatic failure may limit recognition of the association. If only a portion of actual cases were recognized and reported, the risk could be substantially higher.

Of the 15 cases reported as of December 1998, 12 resulted in death or liver transplantation, usually within four weeks of the onset of signs and symptoms of liver failure. The earliest onset of hepatic abnormalities occurred six months after initiation of CYLERT. Although some reports described dark urine and nonspecific prodromal symptoms (e.g., anorexia, malaise, and gastrointestinal symptoms), in other reports it was not clear if any prodromal symptoms preceded the onset of jaundice.

Treatment with CYLERT should be initiated only in individuals without liver disease and with normal baseline liver function tests. It is not clear if baseline and periodic liver function testing are predictive of these instances of acute liver failure; however, it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Accordingly, the following liver monitoring program is recommended: Serum ALT (SGPT) levels should be determined at baseline, and every two weeks thereafter. If CYLERT therapy is discontinued and then restarted, liver function test monitoring should be done at baseline and reinitiated at the frequency above.

CYLERT should be discontinued if serum ALT (SGPT) is increased to a clinically significant level, or any increase ≥2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure (see PRECAUTIONS).

The physician who elects to use CYLERT should obtain written informed consent from the patient prior to initiation of CYLERT therapy (see PATIENT INFORMATION/CONSENT FORM).

Changes consistent with the revised black box warning have been made to the PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the labeling. An enlarged copy of the Patient Information/Consent Form and a full copy of the revised package insert are enclosed. A supply of Patient Information/Consent Forms may be obtained, free of charge, by calling (847) 937-7302. Permission to use the enclosed Patient Information/Consent Form by photocopy reproduction is also hereby granted by Abbott Laboratories.

As with all medical products, health care professionals are strongly encouraged to report any serious adverse events that occur with the use of CYLERT (pemoline) either to Abbott Laboratories (1-800-633-9110), or to the FDA's MedWatch program by phone (1-800-FDA-1088), fax (1-800-FDA-0178), via the MedWatch website at www.FDA.gov/medwatch, or mail (using postage-paid form) to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787.

If you have any questions, please contact our Medical Services Department at 1-800-633-9110.

Sincerely,

David Pizzuti, M.D.
Divisional Vice President
Medical Affairs

Enclosure: CYLERT® (pemoline) Product Information, Abbott Laboratories
CYLERT® (pemoline) Patient Information/Consent Form, Abbott Laboratories

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