Meeting Managed Care's Challenge to Identify and Manage **Narcolepsy**

THE NARCOLEPSY MANAGED CARE TOOL KIT

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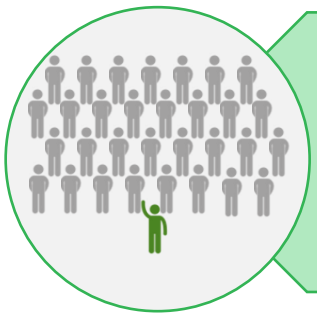
Burden of Disease Overview

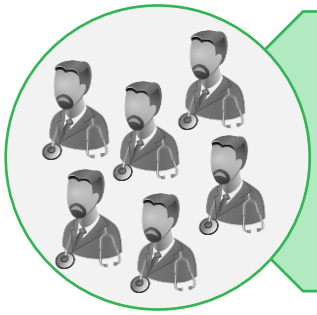
Effective Treatment in Managed Care Is Hindered by Under-Recognition and Misdiagnosis[1,2,3]



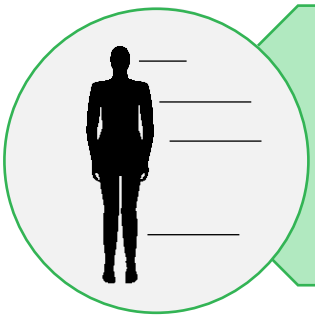
1 in 2,000 Americans are estimated to have narcolepsy

>50%

More than half of Americans with narcolepsy are undiagnosed



It can take >10 years after symptom onset and an average of 6 specifically directed physician visits to identify and diagnose narcolepsy



Common comorbidities such as cardiovascular disease, digestive diseases, and depression/anxiety further complicate diagnosis

Diagnosis, Coding, and Assessment

DSM-5* NARCOLEPSY DIAGNOSTIC CRITERIA[4]

A. Recurrent periods of an irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day. These must have been occurring at least 3 times per week over the past 3 months.

B. The presence of at least one of the following:

1. Episodes of cataplexy, defined as either (a) or (b), occurring at least a few times per month:
    a. In individuals with long-standing disease, brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking.
    b. In children or in individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers.
2. Hypocretin deficiency, as measured using CSF (cerebrospinal fluid) hypocretin-1 immunoreactivity values (≤⅓ of values obtained in healthy subjects tested using the same assay, or ≤110 pg/mL).
    a. Low CSF levels of hypocretin-1 must not be observed in the context of acute brain injury, inflammation, or infection.
3. Nocturnal sleep polysomnography showing REM (rapid eye movement) sleep latency ≤15 minutes, or an MSLT (multiple sleep latency test) showing a mean sleep latency ≤8 minutes and ≥2 SOREMPs (sleep onset rapid eye movement periods).

*Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

DSM-5 NARCOLEPSY SEVERITY CRITERIA[4]

MILD

Infrequent cataplexy (less than once per week), need for naps only once or twice per day, and less disturbed nocturnal sleep.

MODERATE

Cataplexy once daily or every few days, disturbed nocturnal sleep, and need for multiple naps daily.

SEVERE

Drug-resistant cataplexy with multiple attacks daily, nearly constant sleepiness, and disturbed nocturnal sleep (ie, movements, insomnia, and vivid dreaming).

DSM-5 NARCOLEPSY SUBTYPES – DIAGNOSTIC CRITERIA AND CODING[4]

Including ICD-9 code (ICD-10 code in parentheses)
ICD: International Classification of Diseases

347.00 (G47.419)

Narcolepsy without cataplexy but with hypocretin deficiency: Criterion B requirements of low CSF hypocretin-1 levels and positive PSG (polysomnography)/MSLT are met, but no cataplexy is present (Criterion B1 not met).

347.01 (G47.411)

Narcolepsy with cataplexy but without hypocretin deficiency: In this rare subtype (less than 5% of narcolepsy cases), Criterion B requirements of cataplexy and positive PSG/MSLT are met, but CSF hypocretin-1 levels are normal (Criterion B2 not met).

347.00 (G47.419)

Autosomal dominant cerebellar ataxia, deafness, and narcolepsy: This subtype is caused by exon 21 DNA (cytosine-5)-methyltransferase-1 mutations and is characterized by late-onset (age 30-40 years) narcolepsy (with low or intermediate CSF hypocretin-1 levels), deafness, cerebellar ataxia, and eventually dementia.

347.00 (G47.419)

Autosomal dominant narcolepsy, obesity, and type 2 diabetes: Narcolepsy, obesity, and type 2 diabetes and low CSF hypocretin-1 levels have been described in rare cases and are associated with a mutation in the myelin oligodendrocyte glycoprotein gene.

347.10 (G47.429)

Narcolepsy secondary to another medical condition: This subtype is for narcolepsy that develops secondary to medical conditions that cause infectious (eg, Whipple's disease, sarcoidosis), traumatic, or tumoral destruction of hypocretin neurons.

ICSD-3 HYPERSOMNIA DISORDERS – DIAGNOSTIC CRITERIA AND CODING[1]

ICSD: International Classification of Sleep Disorders
Including ICD-9 code (ICD-10 code in parentheses)

- **347.01 (G47.411)** Narcolepsy Type 1 (Narcolepsy with Cataplexy)
- **347.00 (G47.419)** Narcolepsy Type 2 (Narcolepsy without Cataplexy)
- Idiopathic Hypersomnia
- Kleine-Levin Syndrome
- Hypersomnia due to a medical condition, psychiatric disorder, or medications
- Behaviorally Induced Insufficient Sleep Syndrome

ICSD-3 NARCOLEPSY DIAGNOSTIC CRITERIA[1]

347.01 (G47.411) Narcolepsy Type 1 (Narcolepsy with Cataplexy): Excessive sleepiness for 3 months
At least 1 of the following:

1. Cataplexy, and on MSLT, MSL <8 mins, ≥2 SOREMPs (one SOREMP may be on the preceding night's PSG)

OR

2. CSF hypocretin-1 levels <110 pg/mL or <⅓ the baseline normal levels, and on MSLT MSL <8 mins, ≥2 SOREMPs (one SOREMP may be on the preceding night's PSG)

In children, actigraphy is required before the MSLT

347.00 (G47.419) Narcolepsy Type 2 (Narcolepsy without Cataplexy): Positive polysomnography/multiple sleep latency test are met, but no cataplexy is present

ICSD-3 Narcolepsy Diagnostic Criteria: Narcolepsy Type 1[1]

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for ≥3 months

Note: In young children, narcolepsy may sometimes present as excessively long night sleep or by resumption of previously discontinued daytime napping

Sleep log and/or actigraphy is recommended before laboratory sleep testing, and in children, actigraphy is required before the MSLT

B. The presence of ≥2 of the following:

1. Cataplexy

2. Mean sleep latency of <8 minutes and ≥2 SOREMPs on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT

   Note: If narcolepsy Type 1 is strongly suspected clinically but criteria B2 are not met, a possible strategy is to repeat the MSLT

3. CSF hypocretin-1 concentrations measured by immunoreactivity either <110 pg/mL or <⅓ of mean values obtained in normal subjects with the same assay

ICSD-3 Narcolepsy Diagnostic Criteria: Narcolepsy Type 2[1]

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months

Note: In young children, narcolepsy may sometimes present as excessively long night sleep or by resumption of previously discontinued daytime napping

B. Mean sleep latency of <8 minutes and ≥2 SOREMPs on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT

In children, actigraphy is required before the MSLT

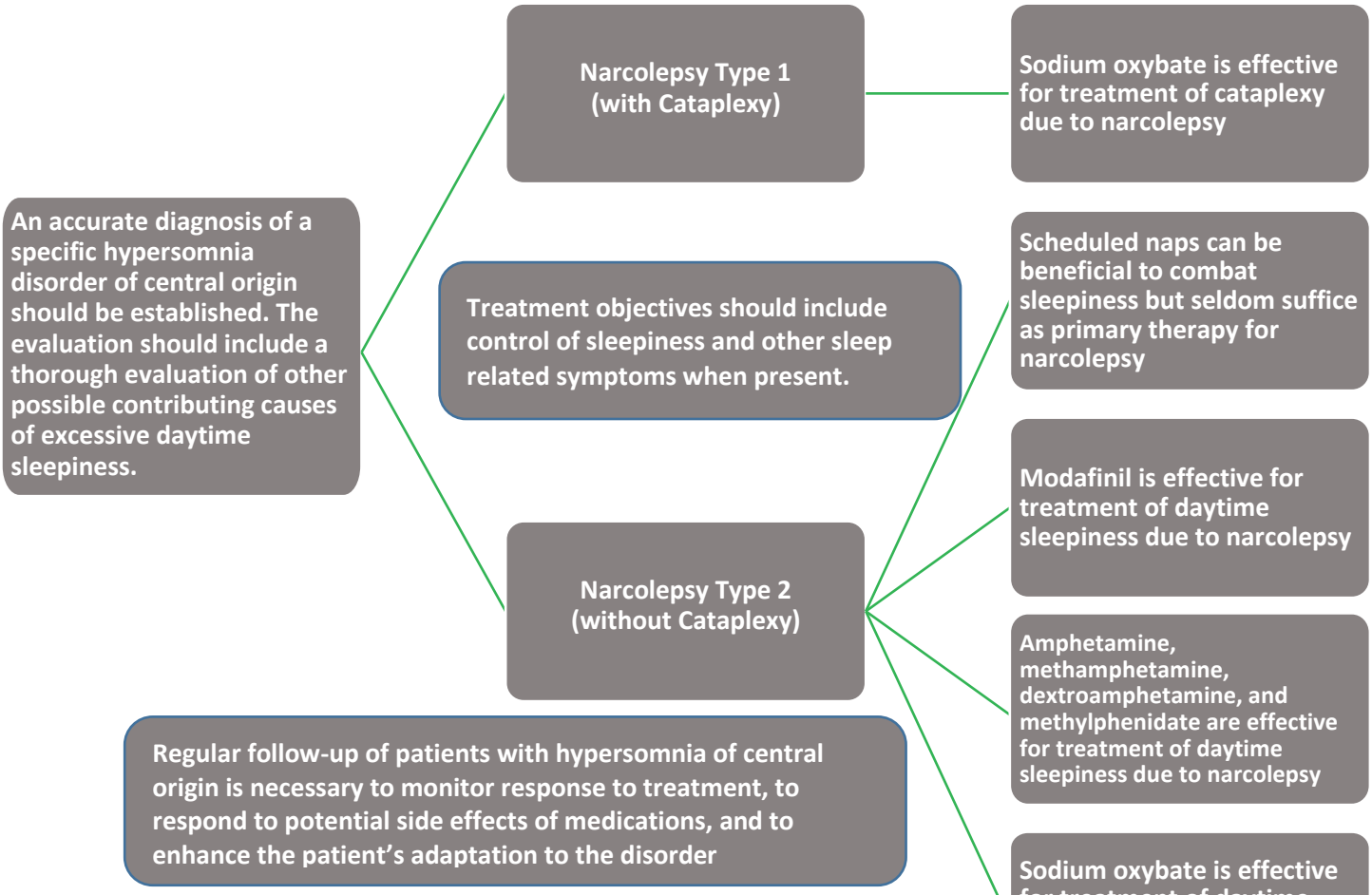
C. Hypersomnia not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder

SUGGESTED CLINICAL INTERVIEW TOPICS FOR DECISION SUPPORT IN THE DIAGNOSIS AND ASSESSMENT OF NARCOLEPSY[5]

Topic	Issues for discussion with patient
General	Age at onset of EDS (excessive daytime sleepiness) and cataplexy, and initial presenting symptoms; are there any possible triggers around onset (eg, infection, vaccination, trauma, or concurrent neurologic illness)?
Sleepiness	How does sleepiness interfere with daily function, with regard to the magnitude of the effects and the quality of the outcomes? What is the pattern of excessive sleepiness: continuous somnolence or sleep attacks? What is the frequency and duration of both involuntary and planned sleep episodes? Are sleep episodes freshening? Can sleep be resisted? Are there dreams or similar phenomena during short naps? What circumstances worsen or improve sleepiness? Since onset, has there been any freedom from sleepiness? Variability of daytime sleepiness during the week versus weekends.
Cataplexy	What is the description of a typical attack, including pattern of weakness? Are attacks mostly partial or complete, unilateral versus bilateral? What is the frequency and duration of episodes? Ensure there is no loss of consciousness. Inquire about spectrum of triggers. Have there been any physical injuries?
Nocturnal sleep	Habitual sleep duration and sleep–wake schedule during the week versus the weekend; subjective sleep latency, and number and duration of awakenings; symptoms of other possible sleep disorders (such as SDB [sleep-disordered breathing] or RLS [restless leg syndrome]). Assess sleep hygiene.
Hallucinations	Hypnagogic or hypnopompic? Duration, frequency, and content; associated symptoms of fear and anxiety. Place and time of occurrence of hallucinations.
Sleep paralysis	Duration and frequency. Co-occurrence with hypnagogic/hypnopompic hallucinations?
Automatic behaviors	Establish any examples of automatic behaviors and their circumstances and frequency.
Dreams	Frequent, vivid, bizarre dreams, out-of-body experiences, dreams, and naps.
Weight change	Current weight and height to calculate BMI [body mass index]. Was there any change around the onset of narcolepsy symptoms? Current stability of weight; is there any influence of medication on weight?
Eating habits	Abnormal appetite (eg, binge eating or eating at night); influence of meals and their type (eg, high carbohydrate load) on (postprandial) sleepiness.
Mood/anxiety	Are there mood disturbances? Is there a history of depression, anxiety, panic attacks, phobias, or suicide ideation?
Other symptoms	Are there any memory or concentration complaints? If appropriate, ask about sexual problems. Specifically assess fatigue (separate from actual sleepiness).
Psychosocial aspects	Have narcolepsy symptoms of sleepiness or cataplexy influenced social interactions at school or work? Ask about driving.
Family history	Are there any relatives with narcolepsy, daytime sleepiness, or other sleep disorders?
Comorbidities and comedications	History of cardiovascular diseases, sleep apnea, diabetes, RLS, RBD (REM sleep behavior disorder), sleepwalking/enuresis, and circadian rhythm sleep-wake disorders. Review of medications or substances acting on central nervous system.

Clinical Management

SAMPLE HEALTH PLAN DIAGNOSIS AND TREATMENT ALGORITHM FOR DECISION SUPPORT IN NARCOLEPSY[6]

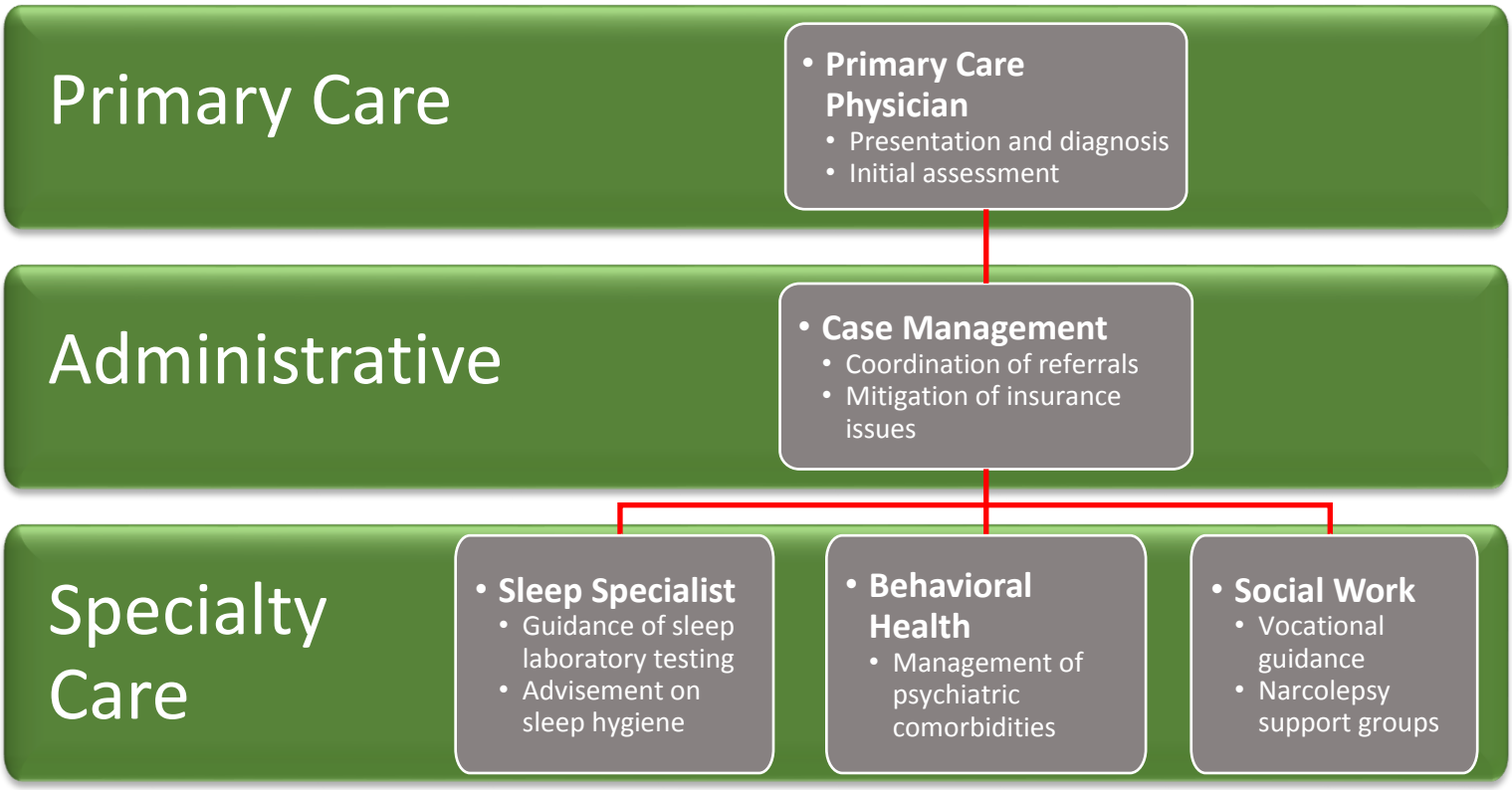


Based on the below criteria from the AASM Practice Parameters for the treatment of Narcolepsy

Standard: This is a generally accepted patient-care strategy that reflects a high degree of clinical certainty. The term standard generally implies the use of level 1 evidence, which directly addresses the clinical issue, or overwhelming level 2 evidence.

Guideline: This is a patient-care strategy that reflects a moderate degree of clinical certainty. The term guideline implies the use of level 2 evidence or a consensus of level 3 evidence.

SAMPLE HEALTH PLAN CARE COORDINATION AND MEDICAL MANAGEMENT HIERARCHY



BEHAVIORAL APPROACHES FOR THE MANAGEMENT OF NARCOLEPSY[7]

Technique	Description
Structuring nocturnal sleep habits	Maintain a structured sleep schedule and set time according to need, despite the quality or continuity of nocturnal sleep
Avoid sleep deprivation and changes in sleep time; maintain a regular schedule of nocturnal sleep (eg, from 10:30 PM to 7PM)	If patients awaken during the night and have difficulty returning to sleep, then they can take a short break and perform a sedentary activity such as reading for a short period of time. However, they should return to bed and attempt to sleep
Relaxation techniques before nocturnal sleep prevent intense stimulation before sleep	The estimated time to sleep at night should be 8 hours or more, depending on individual differences
Planning naps	Naps during the day are a fundamental aspect of the treatment of the daytime sleepiness associated with narcolepsy. Naps can range from 15 to 20 minutes to over 1 hour. For many patients, 2 short naps during the day (<30 minutes) are helpful
Fifteen-minute naps between 12:30PM and 5:00PM are highly effective	Overall, people with narcolepsy show no significant effects related to sleep inertia after taking a nap; however, if the duration of the nap is longer (>15 minutes), then it does not provide additional benefits
Take 15-minute naps	A single nap (or even two) benefits virtually all patients with narcolepsy
Plan nap strategies before using drugs	Moreover, adding a brief morning nap can reduce deterioration in the morning (ie, continual performance decreases since waking)
Exercise	Regular exercise is encouraged
Initiate and maintain a regular exercise schedule	Exercise develops strength and endurance and improves metabolism. This helps to reduce daytime sleepiness and promotes better quality sleep
Diet	Little is known regarding the effects of diet with regard to alertness and sleep among patients with narcolepsy; overall, however, healthy eating habits are useful to ensure sleep hygiene
Over-the-counter stimulants (eg, tea, coffee, yerba mate, and so on) should only be used on a planned schedule and according to doctor's recommendations	
The caffeine content of six cups of strong coffee has the same stimulating effect as 5 mg of dexamphetamine	Certain over-the-counter stimulants (eg, tea and coffee) are not accepted drug treatments; thus, these drinks should be consumed responsibly to allow for more accurate schedule tracking, and they should be alternated with accepted drug treatments
Sweets and carbohydrates should be avoided from the time of awakening in the morning until 12:00PM.	
Abstinence or minimal use of alcohol	
Avoidance of drugs that increase daytime sleepiness	
Counseling or other assistance	A recent study revealed that over 500 patients with narcolepsy suffered from declining quality of life, which is similar to the experience of patients with Parkinson's disease. Special considerations at work or school are required for most patients with narcolepsy
Counseling for lifestyle reorganization	It is extremely difficult for patients with narcolepsy who work late shifts or have changes in their working hours to maintain work productivity. Work during the day is highly recommended
Counseling to review the type of work or individual or group psychotherapy	
Help with programming the mental alertness required by everyday activities	Advice concerning the psychosocial effects of this syndrome should be provided so that patients can optimize their adaptation to the disease and are realistic in their expectations when making decisions regarding daily activities
Professional advocacy for office workers	

Pharmacy Coverage and Benefit Design

PHARMACOTHERAPIES AVAILABLE FOR THE MANAGEMENT OF NARCOLEPSY[5]

Medication	FDA approval for narcolepsy	EMA approval for narcolepsy	Guideline indication
Antidepressants including SSRIs, SNRIs, and TCAs	No	No	Cataplexy; option for hypnagogic hallucinations and sleep paralysis
Amphetamine salts	Yes (narcolepsy general indication)	No	Daytime sleepiness
Methamphetamine	No	No	Daytime sleepiness
Dextroamphetamine sulfate	Yes (narcolepsy general indication)	No	Daytime sleepiness
Lisdexamfetamine	No	No	Daytime sleepiness
Methylphenidate HCl	Yes (narcolepsy general indication)	Yes, but immediate release only (narcolepsy with or without cataplexy in adults when modafinil is ineffective and in children over 6 years)	Daytime sleepiness
Dexmethylphenidate (Focalin)	No	No	Daytime sleepiness
Modafinil	Yes (excessive sleepiness)	Yes (promote wakefulness in narcolepsy)	Daytime sleepiness
Armodafinil	Yes (excessive sleepiness)	No	Developed subsequent to the guidelines
Selegiline	No	No	Cataplexy and daytime sleepiness
Sodium oxybate	Yes (excessive sleepiness and cataplexy)	Yes (narcolepsy with cataplexy)	Cataplexy, daytime sleepiness, and disrupted sleep; option for hypnagogic hallucinations and sleep paralysis
Mazindol	No	No	Daytime sleepiness and cataplexy

SAMPLE MONOGRAPH TEMPLATE FOR P&T REVIEW AND BENEFIT DESIGN CONSIDERATION[8]

NARCOLEPSY: Formulary Monograph Template

Individual Drug Review

Generic Name:	[Name]
Brand Name:	[Name]
Manufacturer:	[Text]
Date of Review:	Month Year
Reason for Review:	[Text]

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Abbreviations used in this monograph:

MEDICATION THERAPY MANAGEMENT: MEDICAL CONTRAINDICATIONS AND POTENTIAL DRUG INTERACTIONS ASSOCIATED WITH PHARMACOTHERAPIES AVAILABLE FOR THE MANAGEMENT OF NARCOLEPSY[5]

Drug	Disease contraindication	Drug interactions
SSRIs	None specified, but depending on individual drug, cautious use in patients with renal or hepatic impairment and in patients with seizure disorders	Potential interactions with drugs that inhibit, induce, or are metabolized by specific cytochrome P450 pathways; alcohol; drugs affecting hemostasis; MAOIs; SNRIs; TCAs
SNRIs	Glaucoma	Potential interactions with drugs that inhibit, induce, or are metabolized by specific cytochrome P450 pathways; alcohol; drugs affecting hemostasis; MAOIs; SSRIs; TCAs
TCAs	Glaucoma; seizure	Alcohol; MAOIs; potential interactions with drugs that inhibit, induce, or are metabolized by specific cytochrome P450 pathways; SSRIs; SNRIs
Amphetamines	Structural cardiac abnormalities or other serious heart problems; glaucoma	Insulin; antihistamines; antihypertensives; MAOIs; TCAs
Methylphenidate	Structural cardiac abnormalities or other serious heart problems; glaucoma; Tourette's syndrome	Coumarin-type anticoagulants; MAOIs; TCAs
Modafinil/armodafinil	None specified	Oral contraceptives; potential interactions with drugs that inhibit, induce, or are metabolized by cytochrome P450 pathways
Selegiline	None specified	Dextromethorphan; meperidine; SSRIs; SNRIs; tramadol; TCAs
Sodium oxybate	Succinic semialdehyde dehydrogenase deficiency; cautious use in patients with heart failure, hypertension, or impaired renal function	Sedative hypnotics; divalproex sodium; alcohol
Mazindol	May cause valvular cardiac disease	Antihistamines; antihypertensives; MAOIs; TCAs
Pitolisant	None specified	Antihistamines
Antipsychotics	Severe depression; bone marrow depression; blood dyscrasias; Parkinson's disease; liver impairment; coronary artery disease; severe hypotension or hypertension; use cautiously in patients with respiratory disorders, glaucoma, prostatic hypertrophy, epilepsy, decreased renal function, and peptic ulcer disease	Alcohol, loop diuretics; potential interactions with other drugs that prolong the QTc interval, other drugs with anticholinergic effects, drugs metabolized by cytochrome P450 pathways, and other drugs that stimulate the 5-HT_{2A} receptor, such as antidepressants, opioids, CNS stimulants, 5-HT_1 agonists (triptans), dextromethorphan, and certain herbal products available OTC (eg, St. John's wort)
Benzodiazepines and sedative hypnotics	Acute low-angle glaucoma, myasthenia gravis, sleep apnea, bronchitis, and COPD; positive evidence of risk in pregnancy for some benzodiazepines	Potential interactions with phenothiazines, opiates, barbiturates, MAOIs, antidepressants, alcohol, illicit drugs, CYP3A4 or CYP2C19 inhibitors, kava, St. John's wort, and grapefruit/grapefruit juice

Abbreviations and References

Abbreviations

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ICSD-3 = International Classification of Sleep Disorders, 3rd Edition
ICD-9 = International Classification of Diseases, 9th Edition
ICD-10 = International Classification of Diseases, 10th Edition
CSF = Cerebrospinal fluid
REM = Rapid eye movement
SOREMP = Sleep onset rapid eye movement period
MSLT = Multiple sleep latency test
PSG = Polysomnography
EDS = Excessive daytime sleepiness
SDB = Sleep-disordered breathing
RLS = Restless leg syndrome
BMI = Body mass index
RBD = REM sleep behavior disorder

References

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[8] Academy of Managed Care Pharmacy. *The AMCP Format for Formulary Submissions, Version 4.0*. http://www.amcp.org/FormatV4/ Accessed November 2, 2016.