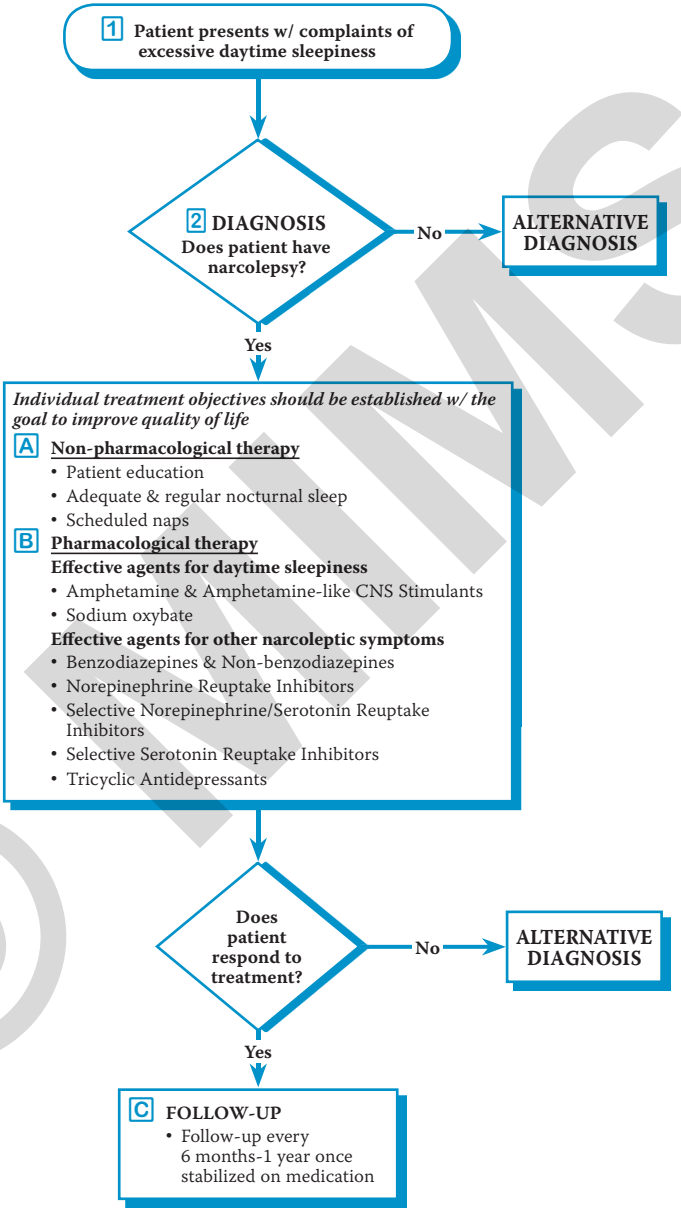
Narcolepsy (1 of 14)



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1 CLINICAL PRESENTATION

Narcolepsy is a chronic neurologic sleep disorder, affecting 1 in 2000 individuals, w/ prevalence of about 0.04% of general population

- Onset at any age, but usually within the first 2 decades of life w/ mean age of onset of 16
  - Rare onset at older adults
- Affects both gender but w/ slight preponderance in males

Etiology

- Exact cause of narcolepsy remains unclear
- Studies suggest a combination of genetic predisposition, abnormal neurotransmitter functioning, & abnormal immune modulation
  - Variation on human leukocyte antigen (HLA) genes, specifically HLA-DR2 & DQB1*0602, on chromosome 6
  - Decreased production of hypocretin secondary to an autoimmune response caused by the HLA abnormalities
    - Hypocretin is a neurotransmitter involved in the regulation of appetite, energy, homeostasis, & sleeping patterns
  - Hypoactive monoaminergic system
- There are current observations of an association of group A streptococcal throat & H1N1 infections

Symptoms of Narcolepsy

Excessive daytime sleepiness

- Present in all narcoleptic patients
- Primary symptom of narcolepsy
- Strong, almost irresistible urge to fall asleep, nod or doze off at inappropriate times whether in sedentary situations or during physically demanding activities
- Patients feel sleep-deprived & have chronic daytime fatigue
- Sleep episodes can occur several times a day & may last from a few seconds to several minutes
- Patients wake up feeling refreshed after the sleep episode
- There is a refractory period of 1 to several hours before the next episode occurs

Cataplexy

- Seen in more than half of narcoleptic patients
- An abrupt & reversible partial or generalized loss of bilateral voluntary muscle tone
- May not appear until weeks or months after onset of excessive daytime sleepiness
- Usually a response to strong emotion (eg laughter, anger, fear)
- Manifestations depend on the muscles affected (eg diplopia, blurred vision, head drooping, sagging jaw, facial sagging, dysarthria, knee buckling, sensation of weakness to partial or complete paralysis)
- Patient remains conscious & aware of surroundings during the cataplexy attack
- Duration of attack is variable lasting for 30 seconds to 2 minutes
- Its presence strongly suggests the diagnosis of narcolepsy
- Pathognomonic sign for narcolepsy

Sleep paralysis

- Occurs in 33% of narcoleptic patients
- Inability to move while falling asleep or during awakening (eg suddenly unable to move the extremities, speak, or even breathe deeply)
- Patient is fully aware of what is happening during the attack & can recall the events clearly
- Brief & benign episodes lasting for a few minutes & resolves spontaneously
- Often associated w/ hypnagogic hallucinations

Sleep-related hallucinations

- Abnormal vivid auditory or visual hallucinations that occur while falling asleep (hypnagogic hallucinations) or during awakening (hypnopompic hallucinations)
- Usually unpleasant experience associated w/ fear, major threat, or feeling of dying
- Combined elements of dream sleep & consciousness & are often bizarre or disturbing to the patients
- Tactile or multisensory hallucinations may also occur

Other symptoms

- Automatic behavior
  - Absent-minded behavior or speech which is nonsensical & often not remembered by the patient because of extreme sleeping
- Fragmented nocturnal sleep (eg frequent awakenings during the night/disturbed nighttime sleep)
- Narcoleptic sleep attack is the irresistable desire to fall asleep in inappropriate circumstances & places
- Insomnia
- Vivid, bizarre & delusional dreams or may have nightmares

2 DIAGNOSIS

- Identify all symptoms that suggest narcolepsy
  - Presence of both excessive daytime sleepiness & cataplexy highly suggest narcolepsy
- Obtain structured sleep history
  - Determine whether main complaint is sleepiness or fatigue
  - Timing, quantity & quality of sleep
  - Snoring or difficulty in breathing
  - Relevant medication or drug use including alcohol intake

Diagnostic Criteria

- According to DSM-5 criteria, narcolepsy is the daily occurrence of uncontrollable need to sleep, daytime lapses or napping for at least 3 times per week for the past 3 months w/ the presence of any of the following:
  - Cataplexy episodes, that occur at least a few times in a month, can be defined as either:
    - Occurrence in patients w/ long-standing disease of sudden bilateral loss of muscle tone w/ intact consciousness for a few seconds to minutes triggered by laughter or joking
    - Presence of unprovoked grimaces or jaw-opening episodes w/ tongue thrusting or global hypotonia without any obvious emotional triggers in children or adult patients within the past 6 months
  - Inadequate hypocretin as measured using cerebrospinal fluid hypocretin-1 immunoreactivity values (≤⅓ of values obtained in healthy individuals tested using the same assay or ≤ 110 pg/mL). Low CSF levels should not be due to acute brain injury, inflammation or infection
  - Nocturnal sleep polysomnography shows ≤15 minutes of rapid eye movement sleep latency or a multiple sleep latency test of ≤8 minutes mean sleep latency & ≥2 sleep-onset rapid eye movement periods
- Based on DSM-5 criteria, narcolepsy can be subclassified as:
  - **Narcolepsy without cataplexy but w/ hypocretin deficiency** if the patient has low CSF hypocretin-1 levels & positive results in polysomnography/multiple sleep latency test but there is no cataplexy
  - **Narcolepsy w/ cataplexy but without hypocretin deficiency** if the patient has normal CSF hypocretin-1 levels but w/ cataplexy & positive results in polysomnography/multiple sleep latency test, this is a rare type of narcolepsy
  - **Autosomal dominant cerebellar ataxia, deafness, & narcolepsy** if the patient has narcolepsy at the age of 30-40 years (late-onset) w/ low or intermediate CSF hypocretin-1 levels, deafness, cerebellar ataxia, & eventually dementia caused by exon 21 DNA (cytosine-5)-methyltransferase-1 mutations
  - **Autosomal dominant narcolepsy, obesity & type 2 diabetes** if the patient has narcolepsy, obesity, & type 2 diabetes & low CSF hypocretin-1 levels associated w/ a mutation in the myelin oligodendrocytes glycoprotein gene
  - **Narcolepsy secondary to another medical condition** if the patient has narcolepsy due to medical conditions that cause infectious (eg, Whipple's disease, sarcoidosis), traumatic or tumoral destruction of hypocretin neurons
- Severity of narcolepsy based on DSM-5 criteria can be classified as:
  - **Mild** if cataplexy occurs <1/week, the need for naps is only once or twice per day, & w/ less disturbing nocturnal sleep
  - **Moderate** if cataplexy occurs once daily or every few days, w/ daily need for multiple naps, & w/ disturbed nocturnal sleep
  - **Severe** if the patient has multiple attacks of drug-resistant cataplexy daily, almost constant sleepiness, & disturbed nocturnal sleep

2 DIAGNOSIS (CONT'D)

Diagnostic Exams
- Confirm the diagnosis, determine severity & exclude other sleep disorders

Polysomnography (PSG)
- Overnight test for concurrent sleep disorders
- Helps to exclude other conditions that produce sleepiness such as obstructive sleep apnea, periodic limb movement disorder & rapid eye movement (REM) sleep behavior disorders
- Accurately documents fragmented sleep patterns w/ a normal amount of REM sleep but a pattern of sleep-onset REM
- A short latency REM sleep can be an evidence for narcolepsy especially if multiple sleep latency test (MSLT) results are vague

Multiple Sleep Latency Test (MSLT)
- Helps to confirm the diagnosis
- Useful in determining the severity of daytime sleepiness
- Performed one day after the nocturnal polysomnography
- ≤8 minutes of multiple sleep latency test & ≥2 sleep-onset REM (SOREM) periods indicate pathological sleepiness in narcolepsy
  - Narcoleptics usually fall asleep & enter REM sleep within 15 minutes of sleep onset

Cerebrospinal Fluid Hypocretin
- Absence of low levels of cerebrospinal fluid hypocretin-1 can confirm the presence of narcolepsy w/ cataplexy
  - ≤110 pg/mL cerebrospinal fluid hypocretin-1 level has a high positive predictive value of 94%
- Most accurate diagnostic technique
- Its use in narcolepsy without cataplexy needs to be determined
  - Normal levels of cerebrospinal fluid hypocretin-1 have been found in narcolepsy without cataplexy & idiopathic hypersomnia

Human Leukocyte Antigen (HLA) Testing
- The clinical use of HLA subtype DQB1*0602 & DQA1*0602 is limited because of genetic variation
- Should not be used for the diagnosis of narcolepsy without cataplexy

Maintenance of Wakefulness Test (MWT)
- Objective test that measures the ability to resist falling asleep
- Narcoleptics usually have short sleep latencies in maintenance of wakefulness test
- This test does not necessarily confirm diagnosis but only indicates that the patient is sleepy

Epworth Sleepiness Scale
- Subjective test in which patients are asked to rate their level of sleepiness in normal daytime situations
- Total score of ≥11 suggests a high probability of sleep disturbance
- Most commonly used index of sleepiness in adults

Stanford Sleepiness Scale
- A 7-point scale that quantifies subjectively the sleepiness of the patient throughout the day

Magnetic Resonance Imaging (MRI)
- Useful in patients w/ atypical symptoms or focal findings on neurological exam to identify structural lesions of the brainstem & diencephalon which can cause narcolepsy

Types of Narcoplepsy

Narcolepsy w/ cataplexy
- ≥ 3 months of excessive daytime sleepiness
- Presence of definitive history of cataplexy
- May be confirmed by:
  - Polysomnography to rule out other causes of disrupted nocturnal sleep & demonstrating at least 6 hours of sleep followed by multiple sleep latency test showing ≤8 minutes of sleep latency & ≥2 SOREM; or
  - ≤110 pg/mL CSF hypocretin-1 level

Narcolepsy without cataplexy
- ≥3 months of excessive daytime sleepiness
- No cataplexy or questionable/atypical cataplexy-like episodes
- Must be confirmed by polysomnography & multiple sleep latency test

Narcolepsy caused by a medical condition
- ≥3 months of excessive daytime sleepiness
- Significant underlying medical or neurologic condition accounts for the daytime sleepiness
- Presence of definitive history of cataplexy; or
- Positive polysomnography & multiple sleep latency test when cataplexy or questionable/atypical cataplexy-like episode is not present
- <110 pg/mL CSF hypocretin-1 level (or 30% of normal control values) if there is absence of cataplexy or negative polysomnography & multiple sleep latency test

A NON-PHARMACOLOGICAL THERAPY

Patient Education

- Educate the patients regarding their condition & its implications at the time of diagnosis
- Regular consultation between the patient & physician is essential to help patients modify their lifestyle & provide optimal management
- Family support can also improve the course of the disease by helping the patients overcome challenges
- Inform family members, friends, & co-workers of the signs of narcoleptic spells to help patients lessen possible injuries
- Advise patients on their activities & jobs
  - Avoid potentially dangerous activities such as operating motor vehicles & machines when feeling sleepy
  - Avoid shift-work, driving, transportation-related jobs, or any work which requires continuous attention for long hours w/ breaks

Adequate & Regular Nocturnal Sleep

- Patient should have adequate & regular nocturnal sleep to avoid exacerbating excessive daytime sleepiness
- Comply w/ a strict sleep schedule of at least 7-8 hours of sleep at night w/ a consistent bedtime & time of morning awakening

Scheduled Naps

- Regular scheduled short daytime naps can decrease sleepiness & improve alertness
  - Fifteen- to twenty-minute naps every 4 hours during daytime are recommended
  - Usually combined w/ other therapies

Other Management Approaches

- Avoid sleep deprivation
- Avoid frequent time zone changes
- Practice good sleep hygiene
- Regular exercise
  - Increases daytime energy & improves sleeping patterns

B PHARMACOLOGICAL THERAPY

There is no cure for narcolepsy

- Its disabling symptoms can be controlled w/ appropriate & targeted therapy
- The goal is to produce the fullest possible return of normal function at home, school, work, & socially w/ minimal side effects

Considerations for Choice of Agent

- Benefit-to-risk ratio (eg efficacy & adverse effects)
- Convenience of administration
- Cost

Effective Agents For Daytime Sleepiness

- If patient has failed adequate doses of stimulant medications, other sleep disorders may be contributing to sleepiness
- Patient may benefit from combination of long- & short-acting stimulants

Amphetamine & Amphetamine-like central nervous system stimulants

- Indirect sympathomimetics that increase monoamine levels within the synaptic cleft by enhancing the release of norepinephrine, dopamine, & serotonin, while blocking their reuptake
- Effective in managing daytime sleepiness
  - Studies show objective improvement in somnolence in 65-85% of patients
  - Low risk of addiction but the risk is greater in patients who are taking high dosages of stimulants, on long-term therapy, & w/ an underlying psychiatric disorder
- Amphetamines are most likely to result in the development of tolerance when used in high doses
- Methylphenidate is usually considered as 1st-line therapy in patients w/ severe narcolepsy & in those who fail in Modafinil
  - Improves sleep tendency
  - Similar efficacy w/ dextroamphetamine but has a better therapeutic index & lower risk of adverse effects
- Modafinil
  - Indirectly increases wakefulness through inhibition of GABA release via serotonergic mechanism or indirectly on dopaminergic stimulation
    - Stimulates norepinephrine inhibition of the ventrolateral preoptic nucleus which is responsible for promoting sleep
  - 1st-line medication in the treatment of excessive daytime sleepiness & irresistible episodes of sleep
  - May be the 1st-line agent in newly diagnosed patients w/ mild-moderate narcolepsy
  - **Effects:**
    - Improves wakefulness in patients w/ excessive sleepiness
    - Does not generally normalize sleep, thus, may be less effective than other stimulants
    - Risk/benefit ratio has been established in a number of studies
    - Has low abuse potential & not associated w/ rebound hypersomnolence
- Armodafinil is the longer half-life enantiomer of Modafinil that has been assessed for treatment of excessive sleepiness in patients w/ narcolepsy
  - A study have shown that it improves sleepiness as measured by the maintenance of wakefulness test mean sleep latency, & in the Clinical Global Impression of Change

Selegiline

- Monoamine oxidase B inhibitor
- May be an effective treatment for daytime sleepiness & cataplexy
  - Improves narcoleptic symptoms, sleep cycles & polysomnographic measurements
  - Decreases occurrence of cataplexy
  - High doses needed; diet-induced hypertension is a risk at effective doses
  - Potential drug & diet-induced interactions limit its use
    - Avoid tyramine or maintain a diet low in tyramine

B PHARMACOLOGICAL THERAPY (CONT'D)

Effective Agents For Daytime Sleepiness (Cont'd)

Sodium oxybate

- **Action:** Inhibits the release of GABA, glutamate, & dopamine
- Effective for the treatment of excessive daytime sleepiness & cataplexy & improvement in the quality of sleep by preventing nocturnal fragmentation
  - Reduces nocturnal awakenings, increases stage non-REM 3 (delta or slow wave) sleep, decreases light sleep & consolidates REM sleep periods
  - Needs high doses of 6-9 g to reach its therapeutic effect
  - Has moderate risk for abuse
  - Better tolerated because it lacks anticholinergic side effects
- Treatment of choice for narcolepsy w/ cataplexy
  - Improvement in cataplexy is much more rapid than effect on daytime sleepiness

Effective Agents For Other Narcoleptic Symptoms

- Stimulant therapy alone, by decreasing drowsiness, often improves cataplexy
- Sleep paralysis & hypnagogic hallucinations seldom need treatment

Benzodiazepines & Non-benzodiazepines

- Triazolam showed improved sleep efficiency & overall sleep quality
- Eszopiclone, & Clonazepam have been used w/ varying success in the treatment of fragmented nocturnal sleep

Norepinephrine Reuptake Inhibitor

- Effective for the treatment of cataplexy & excessive daytime sleepiness
- Recommended drug in patients w/ resistant cataplexy after failure of Venlafaxine, Fluoxetine, & older serotonin reuptake inhibitors
- Less effective than Modafinil & sodium oxybate in teenagers & adults
- Atomoxetine is a highly specific noradrenergic reuptake inhibitor
- Viloxazine significantly reduces cataplexy, helps treat hallucinations & has few adverse effects
- Robexitine exerts anticataplectic effects & improve excessive daytime sleepiness

Selective Norepinephrine/Serotonin Reuptake Inhibitors

- Effective treatment for cataplexy, sleep paralysis, & hypnagogic/hypnopompic hallucinations
- Recommended drugs due to their greater efficacy & improved side-effect profile
- Venlafaxine is the most commonly used drug in this class
  - Potent inhibitor of norepinephrine & serotonin
  - Improves excessive daytime sleepiness & cataplexy
  - Helpful in the treatment of hallucinations
  - Easily obtainable & can be taken during wakefulness
- **Action:** Block the presynaptic reuptake of catecholamines, thereby increasing their activity; however, they are more selective for serotonin
- Effective in decreasing cataplexy & inhibiting nocturnal rapid eye movement sleep
- Selective serotonin reuptake inhibitors (SSRIs) are less effective compared to tricyclic antidepressant
  - However, selective serotonin reuptake inhibitors are safer & better tolerated than other antidepressants
- Not recommended as 1st-line agents for cataplexy because of the availability & better efficacy of newer medications
- Fluoxetine is the most commonly used selective serotonin reuptake inhibitor for the treatment of cataplexy
- Femoxitine, Fluvoxamine, Paroxetine & Zimeldine have also shown efficacy

Tricyclic Antidepressants (TCAs)

- **Action:** Block the presynaptic reuptake of catecholamines, thus enhancing their postsynaptic activity
- Have anticataplectic activity
  - Increase muscle tone & suppress rapid eye movement
  - Effective in treating sleep paralysis & hallucinations
- Clomipramine is the most efficacious & widely used for cataplexy
  - Has the most REM-suppressing activity because of its greater ability to block serotonin reuptake
- Imipramine has shown efficacy in decreasing hallucinations
- Rebound cataplexy phenomenon may occur on abrupt discontinuation of tricyclic antidepressants
  - May lead to status cataplecticus when severe
- Some studies recommend tricyclic antidepressants as last resort due to adverse effects

C FOLLOW-UP

- Regular follow-up every 6 months to 1 year is advised once stabilized on medication
  - Monitor compliance & response to treatment
  - Assess development of side effects (eg sleep disturbances, mood changes, cardiovascular & metabolic problems)
  - Assist patients in adapting to the disorder

Dosage Guidelines

ANTIDEPRESSANTS

Drug	Dosage	Remarks
Monoamine Oxidase B Inhibitor		
Selegiline	**Usual dose:** 20 mg/day PO **Max dose:** 40 mg/day	**Adverse Reactions** • GI effects (nausea, dry mouth, transient elevation in liver enzymes); CNS effects (dizziness, confusion, tremor, anxiety, hallucinations, syncope, insomnia, irritability); CV effects (orthostatic hypotension, palpitations, arrhythmia, chest pain) **Special Instructions** • Do not use w/ other MAO inhibitors, Meperidine, Tramadol, Methadone, Pethidine, Dextromethorphan, Pethidine, TCAs, SSRIs, & Venlafaxine • Use w/ caution in patients w/ peptic ulcerations, uncontrolled hypertension, angina, arrhythmias, psychosis, severe liver or renal dysfunction • Avoid in patients w/ active ulcerations

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Dosage Guidelines

ANTIDEPRESSANTS (CONT'D)		
Drug	**Dosage**	**Remarks**
Nonselective Monoamine Reuptake Inhibitors		
Clomipramine	**Initial dose:** 10 mg/day PO May increase gradually until optimal response is achieved **Usual dose:** 10-75 mg/day	**Adverse Reactions** • Side effects are mostly due to antimuscarinic actions & may be decreased if started at low dose & increased gradually • GI effects (dry mouth, constipation, may lead to paralytic ileus, N/V, gastric irritation); CNS effects (hyperthermia, drowsiness, nervousness, insomnia, headache, peripheral neuropathy, ataxia, tremor, confusion/delirium, extrapyramidal symptoms, tinnitus, dizziness); CV effects (hypotension, tachycardia); Other effects (blurred vision, increased IOP, sexual dysfunction, gynecomastia, galactorrhea) **Special Instructions** • Taper dose over several wks; do not withdraw abruptly • Use w/ caution in patients w/ urinary retention, prostatic hyperplasia, chronic constipation, narrow-angle glaucoma, CV disease, history of epilepsy, diabetes mellitus, impaired hepatic & renal function, hypotension, electroconvulsive therapy, hyperthyroidism or concomitant treatment w/ thyroid preparations • Contraindicated in patients w/ hypersensitivity, mania, porphyria, severe hepatic impairment, concomitant use of MAOIs, recovery phase following MI, heartblock, arrhythmia
Imipramine	75-150 mg/day PO in divided doses	
Protriptyline	5-20 mg/day PO	
Other Antidepressants		
Venlafaxine	75-150 mg PO 12 hrly	**Adverse Reactions** • CNS effects (headache, dizziness, syncope, insomnia, somnolence, tremor, anxiety, visual disturbance, mydriasis); GI effects (dry mouth, N/V, dyspepsia, constipation, increased liver enzymes); CV effect (orthostatic hypotension); GUT effect (sexual dysfunction); Metabolic effects (hyponatremia, hypercholesterolemia); Dermatologic effect (skin rashes) **Special Instructions** • Use w/ caution in patients w/ moderate to severe hepatic or renal dysfunction, history of MI, bleeding disorder, epilepsy, angle-closure glaucoma • Contraindicated in patients w/ uncontrolled hypertension & high risk of ventricular arrhythmia
Viloxazine	100 mg/day PO	**Adverse Reactions** • CNS effects (headache, drowsiness, tremor, ataxia, convulsions); GI effects (dry mouth, N/V, constipation, jaundice); CV effect (mild hypertension); Other effects (musculoskeletal pain, skin rashes) **Special Instructions** • Use w/ caution in patients w/ hepatic or renal dysfunction, CV disease & epilepsy • Avoid in porphyria & recent MI

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Dosage Guidelines

ANTIDEPRESSANTS (CONT'D)		
Drug	**Dosage**	**Remarks**
Selective Serotonin Reuptake Inhibitors		
Fluoxetine	20-60 mg/day PO	**Adverse Reactions** • CNS effects (headache, drowsiness, tremor, anxiety, nervousness, insomnia, mixed manic states); GI effects (dry mouth, N/V, diarrhea, elevation of liver enzymes); Metabolic effect (hyponatremia) **Special Instructions** • Use w/ caution in patients w/ hepatic or renal dysfunction, unstable epilepsy, cardiac diseases, diabetes, bleeding disorders, closed-angle glaucoma • Avoid in patients w/ severe hepatic or renal failure, hypersensitivity, concomitant MAOIs or w/in 2 wks of MAOI withdrawal
Fluvoxamine	25-200 mg/day PO	**Adverse Reactions** • CNS effects (headache, tremor, anxiety, nervousness, insomnia, somnolence, agitation); GI effects (dry mouth, N/V, diarrhea, flatulence, constipation); CV effect (palpitations); Resp effect (dyspnea); GUT effects (urinary frequency, urinary retention, decreased libido, abnormal ejaculation, anorgasmia) **Special Instructions** • Use w/ caution in patients w/ history of mania or seizures, depression, liver dysfunction • Avoid in patients w/ hypersensitivity • Should not be used concomitantly w/ thioridazine, terfenadine, astemizole, cisapride, pimozide, tizanidine
Paroxetine	20 mg/day PO 24 hrly May increase gradually by 10 mg **Max dose:** 50 mg/day	**Adverse Reactions** • CNS effects (headache, tremor, anxiety, nervousness, insomnia, somnolence, agitation, dizziness, weakness, emotional lability); GI effects (dry mouth, N/V, diarrhea, flatulence, constipation, abdominal pain); CV effects (palpitations, chest pain, hypertension, tachycardia); Resp effects (dyspnea, pharyngitis, sinusitis); GUT effects (UTI, urinary frequency, urinary retention, decreased libido, impotence); Musculoskeletal effects (myopathy, back pain, myalgia) **Special Instructions** • Use w/ caution in patients w/ history of mania, cardiac disease, diabetes, bleeding disorder, glaucoma, renal or hepatic dysfunction • Avoid use w/ or w/in 14 days of MAOIs

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Dosage Guidelines

HYPNOTICS & SEDATIVES		
Drug	**Dosage**	**Remarks**
Benzodiazepine Derivatives		
Triazolam	125-250 mcg PO at bedtime **Max dose:** 500 mcg/day	**Adverse Reactions** • CNS effects (drowsiness, sedation, ataxia, vertigo, headache, confusion, depression); Musculoskeletal effect (muscle weakness); GUT effects (urinary retention, changes in libido) **Special Instructions** • Use w/ caution in patients w/ muscle weakness & hepatic or renal dysfunction • Contraindicated in patients w/ pre-existing CNS depression or coma, respiratory depression, acute pulmonary insufficiency, myasthenia gravis, sleep apnea, chronic psychosis, porphyria
Benzodiazepine Related Drugs		
Eszopiclone	**Initial dose:** 2 mg PO at bedtime May increase to 3 mg PO at bedtime	**Adverse Reactions** • CNS effects (headache, dizziness, somnolence, nervousness, depression, confusion, hallucination, anxiety, neuralgia); GI effects (dry mouth, N/V, diarrhea, dyspepsia); Endocrine effects (dysmenorrhea, gynecomastia); GUT effects (urinary retention, decreased libido); Resp effect (dyspnea); CV effects (chest pain, edema) **Special Instructions** • Use w/ caution in patients w/ history of drug or alcohol dependence/abuse & hepatic impairment • Abrupt discontinuation or rapid dose reduction may cause withdrawal symptoms

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Dosage Guidelines

OTHER CNS DRUGS & AGENTS FOR ADHD		
Drug	**Dosage**	**Remarks**
Armodafinil	150-250 mg PO 24 hrly in the morning	**Adverse Reactions** • CNS effects (headache, insomnia, dizziness, anxiety, depression, fatigue); CV effects (palpitations, tachycardia); GI effects (nausea, xerostomia, diarrhea, abdominal pain, dyspepsia) **Special Instructions** • Reduced doses are recommended for the elderly & in patients w/ severe hepatic impairment
Atomoxetine	18-100 mg PO 24 hrly or in 2 divided doses	**Adverse Reactions** • GI effects (anorexia, GI disturbances, weight loss); CNS effects (headache, insomnia, sleep disturbances, dizziness, irritability, emotional lability); Resp effects (cough, sinusitis, rhinorrhea,); GUT effects (urinary hesitancy, urinary retention, reduced libido); Dermatologic effect (skin rashes); Metabolic effects (increased sweating, hot flushes) **Special Instructions** • Use w/ caution in patients w/ history of psychotic illness & urinary obstruction • Contraindicated in angle-closure glaucoma • Should not be used w/ or w/in 14 days of discontinuing MAOIs
Amfetamine (Amphetamine)	**Regular & extended-release:** **Initial dose:** 10 mg/day PO May increase by 10 mg wkly until optimal response is achieved **Max dose:** 60 mg/day	**Adverse Reactions** • CNS effects (restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor/phonic tics, seizures); CV effects (palpitations, tachycardia, hypertension, MI); GI effects (dry mouth, unpleasant taste, diarrhea, constipation) Dermatologic effects (urticaria, rash); GUT effects (impotence, changes in libido) **Special Instructions** • Start w/ a low dose & titrate based on patient response. Continue to increase dose to achieve max response. May need to decrease dose if side effects occur • Give 1st dose upon waking up & additional doses at 4-6 hr intervals • Use w/ caution in patients w/ mild hypertension & Tourette's syndrome • Contraindicated in patients w/ history of drug abuse, advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity, glaucoma • Avoid used during or w/in 14 days of MAOIs administration
Dexamfetamine (Dextroamphetamine)	**Regular & extended-release:** **Initial dose:** 10 mg/day PO May increase by 10 mg wkly until optimal response is achieved **Max dose:** 60 mg/day	
Metamfetamine (Methamphetamine)	**Usual dose:** 5 mg PO 12 hrly **Max dose:** 50 mg/day	

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Dosage Guidelines

OTHER CNS DRUGS & AGENTS FOR ADHD (CONT'D)		
Drug	**Dosage**	**Remarks**
Methylphenidate	**Regular & Slow-release:** **Usual dose:** 20-30 mg/day PO in 2-3 divided doses **Max dose:** 60 mg/day **Extended-release:** **Usual dose:** 20-40 mg PO once daily **Max dose:** 60 mg/day	**Adverse Reactions** • CNS effects (cerebral arteritis, cerebral occlusion, depression, headache, drowsiness, dizziness, insomnia, nervousness, neuroleptic malignant syndrome, blurred vision, dyskinesia); CV effects (angina, arrhythmia, BP changes, MI, necrotizing vasculitis, palpitation, tachycardia); GI effects (anorexia, N/V, diarrhea, abdominal pain, abnormal liver enzymes); Dermatologic effects (erythema multiforme, exfoliative dermatitis, alopecia, urticaria, rash); Resp effects (nasopharyngitis, cough, sinusitis); Hematologic effects (anemia, leukopenia, thrombocytopenia) **Special Instructions** • Start w/ a low dose & titrate based on patient response. Continue to increase dose to achieve max response. May need to decrease dose if side effects occur • Use w/ caution in patients w/ history of alcohol or drug abuse, hypertension, cardiovascular disease, pre-existing psychosis, seizure • Contraindicated in patients w/ glaucoma, Tourette's syndrome, structural cardiac abnormalities, cardiomyopathy, recent MI, heart failure, arrhythmia, hyperthyroidism
Modafinil	**Initial dose:** 200 mg PO 24 hrly in the morning May increase to 400 mg/day PO in 2 divided doses in the morning & noon or 24 hrly in the morning	**Adverse Reactions** • CNS effects (headache, insomnia, nervousness, agitation, confusion, personality disorders, tremors, anxiety, depression, mania); CV effects (tachycardia, hypertension, palpitation); GI effects (abdominal pain, abnormal liver enzymes); Dermatologic effect (angioedema) **Special Instructions** • Use w/ caution in patients w/ history of psychosis, depression, mania, hepatic or renal impairment, Tourette's syndrome • Contraindicated in uncontrolled moderate to severe hypertension, cardiac arrhythmias, left ventricular hypertrophy, ischemic changes, mitral valve prolapse
Reboxetine	2-10 mg PO 24 hrly	**Adverse Reactions** • GI effects (constipation); Other effects (hyperhidrosis, dry mouth, nervousness) **Special Instructions** • Use w/ caution in patients taking other antidepressants, benzodiazepine, statins & beta-blockers • Contraindicated in pregnancy

All dosage recommendations are for non-pregnant & non-breastfeeding women, non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
Not all products are available or approved for above use in all countries.
Products listed above may not be mentioned in the disease management chart but have been placed here based on indications listed in regional manufacturers' product information.

Specific prescribing information may be found in the latest MIMS.

Dosage Guidelines

OTHER NERVOUS SYSTEM DRUGS		
Drug	**Dosage**	**Remarks**
Sodium oxybate	**Initial dose:** 4.5 g/day divided into 2 equal doses: 1st dose given at bedtime while in bed & the 2nd dose given 2.5-4 hrs later Initial dose may be increased in steps of 1.5 g (0.75 g/dose) every 1-2 wks up to a maximum dose of 9 g daily	**Adverse Reactions** • CNS effects (dizziness, headache, abnormal dreams, sleepwalking, confusion, depression, anxiety, insomnia, paresthesia, somnolence, tremor, amnesia); GI effects (N/V); GUT effects (nocturnal enuresis, urinary incontinence) **Special Instructions** • Take on an empty stomach; separate last meal/food & first dose by several hrs • After taking the dose, patient is to lie down & remain in bed • Contraindicated in epilepsy as safety & efficacy in these patients have yet to be established, in patients w/ semialdehyde dehydrogenase insufficiency • Avoid concomitant use w/ alcohol, insomnia agents and other CNS depressant drugs

All dosage recommendations are for non-pregnant & non-breastfeeding women, non-elderly adults w/ normal renal & hepatic function unless otherwise stated.

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Please see the end of this section for the reference list.