

Struggling not to nap: Causes of daytime sleepiness

Depressive symptoms may mask a sleep disorder

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Poor energy, hypersomnia, amotivation, irritability, and frustration can suggest depression or other psychiatric disorders to busy primary care physicians. As a result, psychiatrists often are referred patients with excessive daytime sleepiness (EDS) caused by undiagnosed primary sleep disorders.

Physicians may miss obstructive sleep apnea (OSA), restless legs syndrome, circadian rhythm disorders, or narcolepsy because:

- many have little training in sleep disorders and limited time to diagnose them¹
- patients do not report sleepiness or recognize it as a legitimate medical concern
- definitive diagnostic tests are expensive and usually are not ordered.

Psychiatrists, therefore, need a clear understanding of the EDS differential diagnosis to determine whether a patient's behavioral symptoms are a sleep or psychiatric issue.



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continued



Box 1

Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how each situation would affect you now. Use the scale below to choose the most appropriate number for each situation:

0 no chance of dozing	2 moderate chance of dozing
1 slight chance of dozing	3 high chance of dozing

Chance of dozing

Situation

- Sitting and reading
- Watching TV
- Sitting inactive in a public place (such as in a theater or a meeting)
- As a passenger in a car for an hour without a break
- Lying down to rest in the afternoon when circumstances permit
- Sitting and talking to someone
- Sitting quietly after a lunch without alcohol
- In a car, while stopped for a few minutes in traffic

Scoring key

- 1 to 6 Getting enough sleep
- 7 to 8 Average
- >8 Seek a sleep specialist's advice without delay

ASSESSING THE SLEEPY PATIENT

Sleepiness is an inability to stay awake at appropriate times. Fatigue, by comparison, does not involve sleepiness but very low energy associated with wakefulness. In general, sleepy patients get transient relief from napping, whereas fatigued patients report they cannot fall asleep.

Untreated EDS results in compromised quality of life, reduced productivity, and public safety concerns such as falling asleep while driving.² Sleep complaints fall into three major categories:

- EDS
- insomnia (marked by distress because of poor sleep, but usually with minimal EDS)

- unusual nocturnal behaviors (ranging from arm waving to violent behaviors).

When you evaluate a patient with sleep complaints, valuable sources of data include observation, questionnaires, and screening devices. The most important may be common sense.

Observation. Observe the patient in the waiting room or office before starting the interview. Did he or she nod off while waiting to see you? Pay attention to anyone who appears sleepy—even those who deny having trouble staying awake. Over time, sleepy patients can lose their perspective on alertness. Some have had EDS so long that they no longer recall what it is like to feel fully awake.

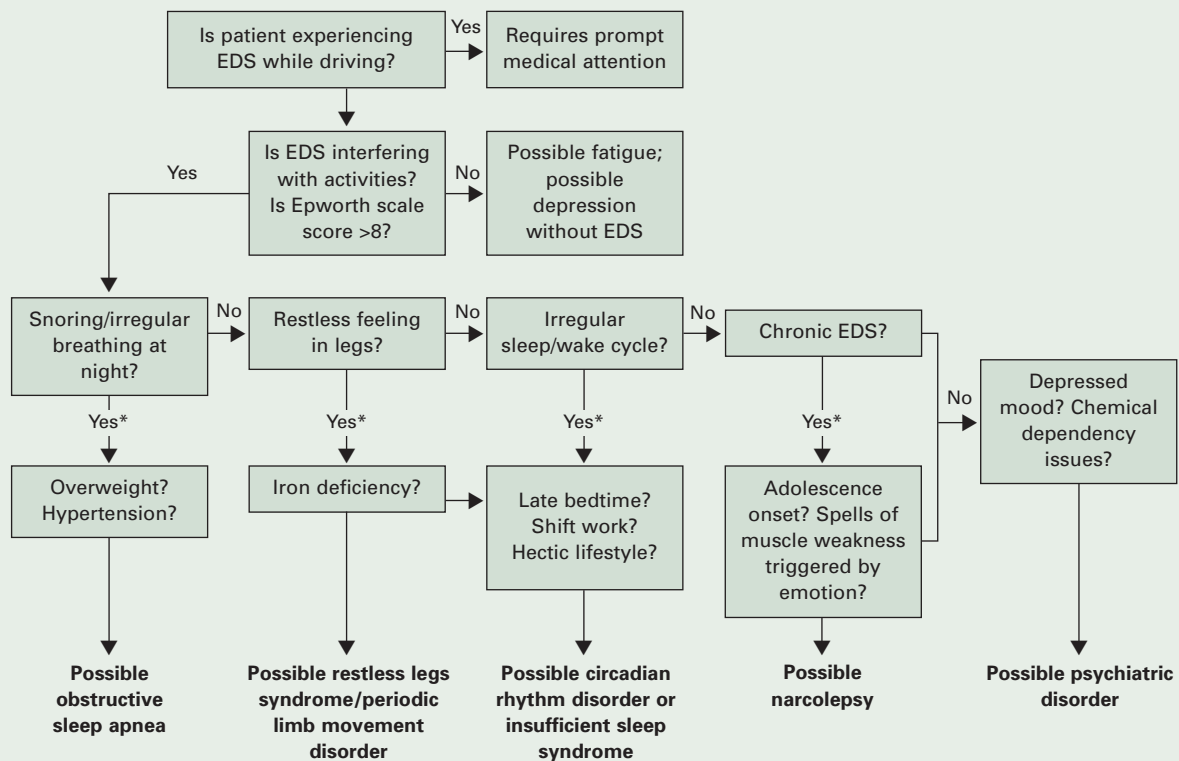
Collateral history often is important because family members probably have observed the sleeping patient. The bed partner can provide information about snoring, irregular breathing, leg kicks, unplanned naps, and strained interpersonal relationships because of EDS. For the patient without a bed partner, consider interviewing a travel companion.

Questionnaires. Few useful screening tests exist for sleepiness; most are neither reliable nor valid. One of the better questionnaires—the Epworth Sleepiness Scale (*Box 1*)—helps confirm the presence of sleepiness with a score >8, differentiating the inability to stay awake from fatigue. This brief questionnaire also provides a useful measure of sleepiness severity.³

The Epworth scale's value is limited because its questions of specific time and context might not represent a patient's experiences. Additional validated surveys include the Pittsburgh Sleep Quality Inventory and several for sleep apnea.⁴

Screening. Electroencephalographic (EEG) monitoring can accurately measure the patient's degree of sleep disruption. This information is key to understanding if a patient's EDS is caused by a physiologic condition that prevents quality nocturnal sleep.

Figure
The sleepy patient: Possible medical and psychiatric explanations



* Supportive factors: Persuasive if present, but if absent do not exclude possible conditions

None of the widely used screening devices that assess leg kicks indicate the presence of possible periodic limb movements.

Overnight pulse oximetry has been used to screen for sleep-disordered breathing⁵ but also has limitations:

- Most pulse oximeters do not provide information about sleep stage or body position.
- Patients with sleep-disordered breathing can lack adequate oxygen desaturations but have frequent EEG arousals related to sleep issues. Because EEG data are not collected during arousals, pulse oximetry would generate a false-negative result in this scenario,

which occurs most often in female and thin patients.

- Oximetry provides only oxygen saturation data and possibly heart rate, whereas other physiologic processes such as body movement or sleep architecture can be disrupted repetitively during sleep.

Common sense. The most productive tools for detecting sleep disorders are intuition and common sense. The *Figure* (above) suggests sequential questions that might uncover specific sleep disorders. Then the decision whether to refer the patient to a sleep disorder center for diagnostic testing depends on the type of sleep disorder you detect.

continued



Box 2

How to help sleep apnea patients adjust to using 'CPAP' machines

Nasal continuous positive airway pressure

(CPAP) should be started in an observed setting so that the clinician can determine the optimal amount of positive pressure needed to keep the upper airway patent.

For some patients, CPAP is started in the second half of a "split-night" sleep study after a diagnosis of obstructive sleep apnea (OSA) is made. Other patients return a second night for a nasal CPAP trial. Those with severe OSA might notice improved sleep quality and reduced EDS after only a few hours of CPAP use. Some wish to start CPAP treatment immediately.

Advances in masks and equipment have improved patient adherence to CPAP. Innovations include auto-titrating machines, in which the pressure level can be varied depending on sleep state or body position. Many machines include a data microchip that

allows the clinician to determine duration of usage, then use that information to counsel the patient about adherence, if necessary.

Patient education also can promote CPAP adherence. When patients are first told they might need to sleep each night wearing a nasal mask, they often voice well-founded concerns about comfort, claustrophobia, or sexual activity.

Obtaining the support of the bed partner by welcoming her or him to all appointments, including educational activities, is optimal. The bed partner's concerns about the patient's excessive snoring or apneas probably were the impetus for the appointment in the first place.

Medication. Some patients benefit from 1 to 2 weeks of a sleeping medication such as zolpidem or trazodone while they acclimate to using nasal CPAP.

OBSTRUCTIVE SLEEP APNEA

Because OSA affects at least 4% of men and 2% of women,⁶ you are virtually assured of seeing undiagnosed patients. OSA is caused by repeated collapse of the soft tissues surrounding the upper airway, decreasing airflow that is restored when the patient briefly awakens. Patients develop EDS because sleep is fragmented by frequent arousals.

Obese patients, because of their body habitus, are at higher risk for OSA than patients at normal weight. Carefully screen patients for OSA if they develop weight problems while taking psychotropics, such as antipsychotics.

Alcohol or sedatives used at bedtime can aggravate OSA. These substances promote muscle relaxation and increase the arousal threshold so that patients do not awaken readily when apneas occur.

Long-term complications of untreated OSA include sleepiness leading to accidents, hyperten-

sion, cerebrovascular disease, and progressive obesity. Data also associate OSA with cardiovascular complications such as arrhythmias, congestive heart failure, and myocardial infarction.⁷

Physical examination focuses on detecting:

- nasal obstruction (have patient sniff separately through each nostril)
- large neck
- crowded oropharynx (low-hanging palate, reddened uvula, enlarged tonsils, large tongue relative to oropharynx diameter)
- jaw structure (particularly a small, retrognathic mandible).

Sleep studies. Referral for nocturnal polysomnography might be the next step. A comprehensive sleep study collects data about respiratory, cardiovascular, and muscle activity at night, as well as the sounds the patient makes—such as snoring or coughing—when asleep. EEG monitoring also is performed.

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OSA may be diagnosed if repeated episodes of reduced airflow and oxygen desaturation (arousals) are observed as brief shifts in EEG frequency.

Treatment. First-line interventions for the patient with OSA include:

- no alcohol 1 to 2 hours before bedtime
- sleeping on the side instead of the back
- weight loss (ideally with exercise)
- nasal sprays for allergies.

If first-line treatments are ineffective, nasal continuous positive airway pressure (CPAP) works well for most patients who adhere to the regimen.⁸ CPAP requires the patient to wear a nasal mask that delivers room air, splinting open the nasopharynx and upper airway (*Box 2, page 130*).

Surgical options. The most common surgeries for OSA are uvulopalatopharyngoplasty and laser-assisted uvulopalatoplasty. Others include tongue reduction and mandibular advancement.

The response rate to surgery averages 50%, depending on patient characteristics and procedure.⁹ Positive outcomes are most likely for thin patients with obvious upper airway obstruction, including deviated nasal septum, large tonsils, low-hanging palate, and large uvula. Postsurgical complications include nasal regurgitation, voice change, pain, bleeding, infection, tongue numbness, and snoring without apnea (silent apnea).

Oral appliances open the oropharynx by moving the mandible and tongue out of way. Patients with mild to moderate OSA accept these devices well. Evidence suggests that oral appliances improve sleep and reduce EDS more effectively than nasal CPAP and are preferred by patients.¹⁰

Oral devices have drawbacks, however. In most settings, their effectiveness cannot be observed during a “split-night” laboratory sleep study because the patient has not yet purchased the device. Also, multiple visits sometimes are

required to custom-fit the appliance; this can pose a hardship for patients who live a distance from the provider.

RESTLESS LEGS SYNDROME

Patients with restless legs syndrome (RLS) typically report a restless, painful feeling in the limbs that occurs in the evening and at night, disrupting sleep.

This condition—which affects 10% of the population—is associated with aging, blood loss, anemia, peripheral neuropathies, and pregnancy.¹¹ Onset can occur in childhood, and in some cases there is a familial tendency.

Most patients with RLS have periodic limb movements (repetitive leg jerks or twitches). The clinical significance of periodic limb movements with no subjective disagreeable feelings in the limbs is controversial, and these cases usually are not treated.

The history usually confirms RLS. Order sleep studies only if you suspect a coexisting sleep problem or the diagnosis is unclear.

A suspected mechanism of restless legs is dopamine deficiency. Low serum ferritin levels have been associated with RLS—presumably because iron is a cofactor necessary for dopamine synthesis¹²—and may be diagnostically helpful.

Delayed sleep phase disorder—common in young adults—is highly comorbid with depression

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continued



Box 3

2 techniques to modify patients' abnormal sleep schedules

The most common technique is to ask the patient to establish a consistent awakening time and a regular bedtime. Initially this could be unconventional by societal standards—such as bedtime at 5 AM and arising at 2 PM. After this pattern is in place, the patient gradually shifts the timing by 1 hour per day. Most patients find it easier to delay rather than advance the bedtime until it conforms to the desired time.

Reinforce this new sleep pattern with a structured daytime schedule that includes predictable mealtimes, regular exercise, social activities, and possibly bright light exposure. Provide reinforcement in the morning for patients with delayed sleep phase disorder and in the evening for advanced sleep phase disorder. These interventions take time and discipline.

Another approach is for the patient to skip sleep one night and, in a sleep-deprived state, establish a new bedtime at the desired time. Use the same modalities listed above to reinforce (“entrain”) this schedule; otherwise the patient will slip back into the previous abnormal sleep-wake rhythm.

Treatment can include iron repletion when indicated. Medications include dopaminergic agents, most notably pramipexole and levodopa/carbidopa. Other options include gabapentin, benzodiazepines, and narcotics.

Antidepressants have been suspected to worsen restless legs syndrome, but definitive studies are lacking.¹³

CIRCADIAN RHYTHM DISORDERS

Instead of compromising the quality or quantity of sleep, circadian rhythm disorders cause sleep to

occur at inappropriate times. These disorders are most common in adolescents and young adults.

Delayed sleep phase disorder—a persistent pattern of staying up late and “sleeping in”—is most common. Careful assessment will reveal that the patient is getting adequate sleep but at a socially unacceptable time, sometimes to the extreme that his or her nights and days are reversed.

Patients' reluctance to acknowledge the severity of this problem can lead to inaccurate sleep diaries and interviews. A portable wrist actigraph can provide data about limb movement and is more objective than self-reports.

Delayed sleep phase disorder is highly comorbid with depressive disorders.¹⁴ The cause of this syndrome is unclear, but light exposure, social patterns, psychological issues, and possibly a genetic substrate are known to contribute.

Advanced sleep phase disorder—a less common circadian rhythm disorder—also can cause EDS. Patients have an inappropriately early time of sleep onset and then are fully awake in the middle of the night. A large family with a severe form of this disorder was found to have an abnormality on chromosome 2.¹⁵

Treatment. Relatively few treatments are effective for circadian rhythm disorders. Some patients elect not to pursue therapy, instead fitting activities around their unconventional sleep schedules.

Individuals with delayed sleep phase who cannot arrange their lives around their sleep schedules are at risk for poor early morning performance because of sleepiness. Their internal circadian clocks can be gradually readjusted with phototherapy or gradual shifting of the major sleep period (*Box 3*). Stimulants usually are not used, but hypnotics can sometimes help these patients fall asleep earlier.

INSUFFICIENT SLEEP SYNDROME

People attempting to “burn the candle at both ends” are at risk for developing insufficient sleep

syndrome.¹⁶ In our 24/7 society, people trying to make do with less than the required 7.5 hours sleep per night may adversely affect their health. The problem is compounded for shift workers because of the difficulty in obtaining sufficient quality sleep during daylight hours.

Many patients do not seek treatment for fatigue or sleepiness because they are aware of their lifestyle choices. Still, they might develop psychological symptoms such as irritability, mood swings, and strained interpersonal relationships. These symptoms can prompt patients to request treatment.

Take a careful history that includes discussing the patient's daily and weekly schedule. Avoid psychostimulants; instead, address the nonnegotiable need to get adequate sleep and challenge the patient to prioritize his or her activities around a full night's sleep.

WHEN TO CONSIDER NARCOLEPSY

Narcolepsy is a CNS disease characterized by abnormal regulation of REM sleep. EDS—the cardinal symptom—is often associated with cataplexy (75%), sleep paralysis (50%), vivid dreams, and insomnia, all of which interfere with REM phenomena. Narcolepsy affects 0.05% of the U.S. population and can lead to severe occupational, educational, and family disruption.

When you obtain a history that suggests narcolepsy, use the history, a sleep diary, or wrist actigraphy to document whether the patient is getting adequate sleep, with a consistent sleep/wake cycle. Next, consider referring the patient for polysomnography, primarily to rule out other causes of EDS such as sleep-disordered breathing. In some cases, REM latency on the overnight sleep study will be <20 minutes after sleep onset, which supports the diagnosis of narcolepsy.

A multiple sleep latency test (MSLT)—a diagnostic session in which the patient takes 4 to 5 daytime naps—is performed the following day.

Box 4

When to refer your patient to a sleep disorder center

The 4 most appropriate indications for an urgent sleep evaluation are:

- difficulty staying alert while driving
- nocturnal cardiac arrhythmias
- frequent observed apneas
- excessive daytime sleepiness (EDS) leading to academic or occupational problems.

Insurance companies usually cover a specialty sleep evaluation, particularly if the referring physician documents a suspicion of sleep-disordered breathing or EDS that jeopardizes safe driving.

Narcolepsy is confirmed if the patient has a mean initial sleep latency of <10 minutes during these naps plus at least two REM episodes within 15 minutes after sleep onset.

Most patients with narcolepsy and cataplexy have undetectable cerebrospinal fluid levels of a neuropeptide called hypocretin or orexin.¹⁷ Hypocretin/orexin replacement therapy is a theoretical possibility, but for now treatment includes a combination of optimal sleep hygiene, psychostimulants, antidepressants, and hypnotics.

OTHER CAUSES OF EDS

EDS can also be caused by unrecognized alcohol dependence, inappropriate or excessive medication use, and depressive disorders. Overnight sleep studies are seldom indicated unless patients endorse the symptoms in the *Figure, page 129*.

Before pursuing polysomnography or an MSLT (*Box 4*), eliminate medications that might confound the results, such as:

- antidepressants, which alter the timing and duration of REM sleep

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adverse events occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. **Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials¹ for the Treatment of Schizophrenia and Bipolar Mania (monotherapy): Body as a Whole:** Headache, Pain, Asthenia, Abdominal, Back Pain, Fever; **Cardiovascular:** Tachycardia, Postural Hypotension; **Digestive:** Dry Mouth, Constipation, Vomiting, Dyspepsia, Gastroenteritis, Gamma Glutamyl Transpeptidase Increased; **Metabolic:** Weight Gain, SGPT increased, SGOT increased; **Nervous:** Agitation, Somnolence, Dizziness, Anxiety; **Respiratory:** Pharyngitis; **Rhinitis;** **Skin and Appendages:** Rash; **Special Senses:** Amblyopia. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%). (Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertension, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.) Table 2, from the full Prescribing Information, enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 3-weeks) of acute mania in 5% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. **Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials¹ for the Treatment of Bipolar Mania (Adjunct Therapy): Body as a Whole:** Headache, Asthenia, Abdominal Pain, Back Pain; **Cardiovascular:** Postural Hypotension; **Digestive:** Dry Mouth, Constipation; **Metabolic and Nutritional:** Weight Gain; **Nervous:** Somnolence, Dizziness, Tremor, Agitation; **Respiratory:** Pharyngitis. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%). (Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea.) Table 3, in the full Prescribing Information, enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 8-weeks) of bipolar depression in 5% or more of patients treated with SEROQUEL (doses of 300 and 600 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. **Treatment-Emergent Adverse Experience Incidence in 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression: Gastrointestinal Disorders:** Dry Mouth, Constipation, Dyspepsia, Vomiting; **General Disorders and Administrative Site Conditions:** Fatigue; **Metabolism and Nutrition Disorders:** Increased Appetite; **Nervous System Disorders:** Sedation, Somnolence, Dizziness, Lethargy; **Respiratory, Thoracic, and Mediastinal Disorders:** Nasal Congestion. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dry mouth (44%), sedation (30%), somnolence (28%), dizziness (18%), constipation (10%), lethargy (5%), and nasal congestion (5%). (Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: nausea, upper respiratory tract infection, and headache.) Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors. **Dose Dependence of Adverse Events in Short-Term, Placebo-Controlled Trials: Dose-Related Adverse Events:** Logistic regression analyses revealed a positive dose response (p<0.05) for the following adverse events: dyspepsia, abdominal pain, and weight gain. **Extrapyramidal Symptoms:** Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertension, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS. In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS. In two placebo-controlled clinical trials for the treatment of bipolar depression using 300 mg and 600 mg of SEROQUEL, the incidence of adverse events potentially related to EPS was 12% in both dose groups and 6% in the placebo group. In these studies, the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group. The 3 treatment groups were similar in mean change in SAS total score and BARS Global Assessment score at the end of treatment. The use of concomitant anticholinergic medications was infrequent and similar across the three treatment groups. **Vital Signs and Laboratory Studies: Vital Sign Changes:** SEROQUEL is associated with orthostatic hypotension (see PRECAUTIONS). **Weight Gain:** In schizophrenia trials the proportions of patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% compared to 2% for placebo. **Laboratory Changes:** An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see PRECAUTIONS). **ECG Changes:** Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/166) for SEROQUEL compared to 0% (0/171) incidence for placebo. In bipolar depression trials, no patients had heart rate increases to > 120 beats per minute. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see PRECAUTIONS). **Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL:** Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those listed in the table of placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Nervous System:** Frequent: hypertension, dysarthria; **Intracranial:** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incontinence, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonia, reaction, hemiplegia; **Rare:** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma. **Body as a Whole:** Frequent: flu syndrome; **Intracranial:** neck pain, pelvic pain*, suicide attempt*, vasodilation, photosensitivity reaction, chills, face edema, moniliasis; **Rare:** abdomen enlarged; **Digestive System:** Frequent: anorexia; **Intracranial:** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; **Rare:** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis; **Cardiovascular System:** Frequent: palpitation; **Intracranial:** vasodilation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, 1 wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; **Rare:** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration; **Respiratory System:** Frequent: pharyngitis, rhinitis, cough increased, dyspnea; **Intracranial:** pneumonia, epistaxis, asthma; **Rare:** hiccups, hyperventilation; **Metabolic and Nutritional System:** Frequent: peripheral edema; **Intracranial:** weight loss, alkaline phosphatase increased, hypokalemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; **Rare:** glycosuria, gout, hand edema, hypokalemia, water intoxication; **Skin and Appendages System:** Frequent: sweating; **Intracranial:** pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; **Rare:** exfoliative dermatitis, psoriasis, skin discoloration; **Urogenital System:** Frequent: vaginitis; **Intracranial:** urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; (*adjusted for gender); **Rare:** gynecostasia*, nocturia, polyuria, acute kidney failure; **Special Senses:** Frequent: conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; **Rare:** abnormality of accommodation, deafness, glaucoma; **Musculoskeletal System:** Frequent: pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain; **Hemic and Lymphatic System:** Frequent: leukopenia; **Intracranial:** leukocytosis, anemia, echymosis, eosinophilia, hypochromic anemia, lymphadenopathy, cyanosis; **Rare:** hemolysis, thrombocytopenia; **Endocrine System:** Frequent: hypothyroidism, diabetes mellitus; **Rare:** hyperthyroidism; **Post Marketing Experience:** Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include: leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia. Other adverse events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, anaphylaxis, hyponatremia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Steven Johnson syndrome (SJS).

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: SEROQUEL is not a controlled substance. **Physical and Psychologic Dependence:** SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE: Human experience: Experience with SEROQUEL in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation. **Management of Overdosage:** In case of acute overdosage, establish and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension. There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine) should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

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- sedating medications, which modify initial sleep latency and sleep efficiency and potentially aggravate sleep disordered breathing.

Initial REM latency provides a potential biologic marker of major depression but is used more often in research than in clinical psychiatry.

Primary insomnia is the distressing inability to sleep at night or nap during the day. It suggests a hyperarousal state—the opposite of EDS.¹⁸ In rare cases, however, patients who cannot sleep at night also have EDS. When evaluated, they typically endorse at least one symptom in the *Figure, page 129*. Sleep studies occasionally reveal OSA or restless legs syndrome.

Treating a patient with chronic insomnia may require several trials of behavioral interventions or sedating medications before you make a referral to a sleep disorder center. Patients can struggle with unrecognized primary sleep disorders for years, and many are given empiric trials of stimulating antidepressants. Antidepressants are unlikely to cause harm, but they might complicate diagnostic testing.

When you confirm coexisting depression and a primary sleep disorder, treatments that separately target each condition provide optimal management of the sleepy patient.

MEDICATIONS TO ENHANCE WAKEFULNESS

Wake-promoting agents are a treatment option when EDS is contributing to compromised functioning. These drugs are no substitute for thoughtful evaluation of hypersomnolence, however. When you diagnose OSA or restless legs syndrome, first try treatments that target these conditions. If residual sleepiness persists, then consider augmenting with stimulating medications.

Modafinil is FDA-approved for residual sleepiness in patients with OSA and for shift work sleep disorder, a condition of circadian misalignment from frequent schedule changes. Evidence does



not support its use for other circadian rhythm disorders, such as delayed sleep phase disorder.

Low-dose modafinil (such as 100 to 200 mg/d) is well tolerated, but its therapeutic effect as augmentation is modest.¹⁹ Increasing the dosage to >200 mg usually does not increase alertness.

Caffeine. Some patients report benefit from caffeine used in moderation and only in the morning. This practice is acceptable as long as patients do not use excessive amounts or experience insomnia, exacerbation of anxiety, or tachycardia.

Psychostimulants such as methylphenidate and amphetamines are less well-studied than modafinil for treating EDS in patients without narcolepsy. Monitor carefully for insomnia, exacerbation of anxiety, tachycardia, or hypertension and to prevent overuse of these habituating agents.

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Depressive symptoms may mask an undiagnosed sleep disorder. Excessive daytime sleepiness (EDS) that occurs while driving requires immediate medical workup. If EDS interferes with daily activities and suggests a sleep disorder, consider referral for a sleep study.

BottomLine

Related resources

- ▶ National Sleep Foundation. www.sleepfoundation.org.
- ▶ American Academy of Sleep Medicine. www.aasmnet.org.
- ▶ American Sleep Apnea Association. www.sleepapnea.org.
- ▶ Restless Legs Syndrome Foundation. www.rls.org.
- ▶ Association for the Study of Light Therapy and Biological Rhythms. www.sltr.org.

DRUG BRAND NAMES

Carbidopa/levodopa • Sinemet	Pramipexole • Mirapex
Gabapentin • Neurontin	Trazodone • Desyrel
Modafinil • Provigil	Zolpidem • Ambien

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