

Treating chronic insomnia: An alternating medication strategy

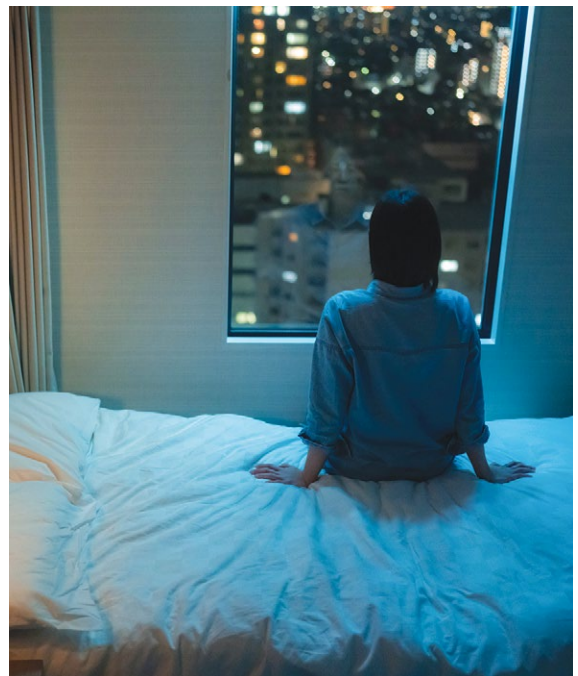
Alternating between 2 agents from different classes can help avoid tolerance/tachyphylaxis

Patients with chronic insomnia that does not improve with nonpharmacologic techniques often develop tolerance to sedative medications (benzodiazepines) prescribed for nightly use. When nonbenzodiazepine medications are used, tachyphylaxis can develop and these medications no longer initiate or maintain sleep. Strategies that alternate between these 2 types of agents are simple to follow and may allow patients to maintain sensitivity to both types of medications. In this article, I review the types, causes, evaluation, and treatment of insomnia; describe an alternating medication strategy to help patients avoid developing tolerance/tachyphylaxis; and present 3 fictional case vignettes to illustrate this approach.

A common, troubling condition

Insomnia is a common problem among psychiatric patients. Approximately 30% to 50% of adults experience occasional, short-term (<3 months) insomnia, and 5% to 10% experience chronic (≥3 months) insomnia,¹ with associated negative impacts on health and quality of life. Insomnia is sometimes primary and may have a hereditary component, but more often is associated with medical, neurologic, or psychiatric disorders.

Patterns of insomnia include difficulty falling asleep (initial or sleep-onset insomnia), remaining asleep (middle or sleep-maintenance insomnia), or falling back asleep after



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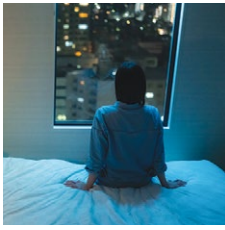
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Insomnia predisposes some patients to develop mood and anxiety symptoms



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early awakening (late or sleep-offset insomnia). Sleep-onset insomnia correlates with high levels of anxiety and worrying, but once asleep, patients usually stay asleep. Sleep-maintenance problems involve multiple awakenings after falling asleep and taking hours to fall back to sleep. These patients experience inadequate sleep when they must wake up early for school or work. Early-awakening patients report feeling wide awake by 4 to 5 AM and being unable to get back to sleep.

Caffeine is an important consideration for patients with sleep difficulties. Its use is widespread in much of the world, whether ingested as coffee, tea, in soft drinks, or in “energy” drinks that may contain as much as 200 mg of caffeine (twice the amount in a typical cup of brewed coffee). Caffeine may also be ingested as an ingredient of medications for headache or migraine. While some individuals maintain that they can fall asleep easily after drinking caffeinated coffee, many may not recognize the amount of caffeine they consume and its negative impact on sleep.² Author Michael Pollan stopped use of all caffeine and reported on the surprising positive effect on his sleep.³

Patients with mood, anxiety, or psychotic disorders are likely to experience insomnia intermittently or chronically, and insomnia predisposes some individuals to develop mood and anxiety symptoms.⁴ Patients with insomnia often experience anxiety focused on a fear of not getting adequate sleep, which creates a vicious cycle in which hyperarousal associated with fear of not sleeping complicates other causes of insomnia. A patient’s chronotype (preference for the time of day in which they carry out activities vs sleeping) also may play a role in sleep difficulties (*Box, 5 page 27*).

Certain medications may contribute to insomnia, particularly stimulants. It is important to understand and explain to patients the time frame during which immediate-release or extended-release (ER) stimulants are active, which varies in individuals depending on liver enzyme activity. Other commonly used psychotropic medications—including bupropion, modafinil, armodafinil,

atomoxetine, amphetamine salts, and methylphenidate—may interfere with sleep if used later in the day.⁶

Patients typically do not mention their use of alcohol and/or marijuana unless asked. Those who are binge drinkers or alcohol-dependent may expect alcohol to help them fall asleep, but usually find their sleep is disrupted and difficult to maintain. Patients may use marijuana to help them sleep, particularly marijuana high in tetrahydrocannabinol (THC). While it may help with sleep initiation, THC can disrupt sleep maintenance. Cannabidiol does not have intrinsic sedating effects and may even interfere with sleep.^{7,8}

Women may be more likely than men to experience insomnia.⁹ The onset of menopause can bring hot flashes that interfere with sleep. Women with a history of mood disorders are more likely to have a history of premenstrual dysphoric disorder, postpartum depression, and unusual responses to oral contraceptives.¹⁰ These women are more likely to report problems with mood, energy, and sleep at perimenopause. Treatment with estrogen replacement may be an option for women without risk factors, such as clotting disorders, smoking history, or a personal or family history of breast or uterine cancer. For many who are not candidates for or who refuse estrogen replacement, use of a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor at low doses may help with vasomotor symptoms but not with insomnia.

Insomnia symptoms typically increase with age.¹¹ When sleep is adequate early in life but becomes a problem in midlife, an individual’s eating habits, obesity, and lack of exercise may be contributing factors. The typical American diet includes highly refined carbohydrates with excess salt; such foods are often readily available to the exclusion of healthy options. Overweight and obese patients may insist they eat a healthy diet with 3 meals per day, but a careful history often uncovers nighttime binge eating. Nighttime binge eating is rarely reported. This not only maintains obesity, but also interferes with sleep, since patients stay up late to avoid discovery by

family members.¹² This lack of sleep can lead to an endless loop because insufficient sleep is a risk factor for obesity.¹³

Evaluating sleep difficulties

New patient evaluations should include a careful history beginning with childhood, including personal early childhood history and family psychiatric history. Patients often report the onset of sleep difficulty and anxiety during childhood, which should raise further questions about aspects of mood regulation from early life such as concentration, energy, motivation, appetite, and academic performance. While many children and adolescents are diagnosed with attention-deficit/hyperactivity disorder due to concentration problems that cause difficulties at school, be aware this might be part of a syndrome related to mood regulation.¹⁴ Unexpected responses to an SSRI—such as agitation, euphoria, or an immediate response with the first dose—should also raise suspicion of a mood disorder. Once the underlying mood disorder is stabilized, many patients report improved sleep.¹⁵

If a patient reports having difficulty falling and remaining asleep but is not sure if there is a pattern, keeping a sleep diary can help. Further questioning may uncover the cause. Does the patient have spontaneous jerks of lower extremities (restless leg syndrome) that interfere with falling asleep or wake them up? Have they noticed problems with dreams/nightmares that wake them, which could be associated with posttraumatic stress, anxiety, or depression? Have they been told by a partner that they act out dreams or are seemingly awake but not responsive, which could point to REM sleep behavior disorder or early Parkinson's disease? Referral to a sleep laboratory and a neurologist can help establish the correct diagnosis and point to appropriate treatment.¹⁶⁻¹⁸

Treatment options

Several cognitive-behavioral techniques, including cognitive-behavioral therapy for insomnia (CBT-I), yogic breathing,

Box

Early birds vs night owls

Chronotypes—the expression of circadian rhythmicity in an individual—have been studied extensively.⁵ Psychiatrists may encounter patients who sleep most of the day and stay awake at night, those who sleep up to 20 hours per day, and those who sleep <4 hours in 24 hours. Patients typically know which category they fall into. The early bird typically is awake by 6 or 7 AM, remains alert through most of the day, and feels sleepy by 10 PM. The usual diurnal variation in cortisol, with peaks at 7 AM and 7 PM and nadirs at 1 PM and 1 AM, correspond with the early bird's habits.

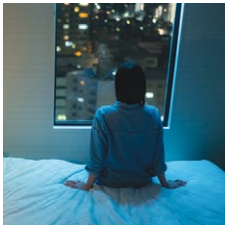
Night owls typically report feeling exhausted and irritable in the early morning; prefer to sleep past noon; feel energized around dark, when they can do their best studying, concentrating, etc; and do not feel sleepy until early morning. While this night owl pattern is a natural variation and not necessarily associated with psychiatric illness, patients with mood disorders frequently have chaotic sleep patterns that may not conform to a pattern. Night owls maintain the same diurnal pattern of cortisol secretion as early birds.

progressive relaxation, mindfulness meditation, and sleep hygiene techniques may help considerably,^{19,20} but insomnia often remains difficult to treat. Pharmacotherapy is not necessarily more effective than nonpharmacologic approaches. Both options require the patient to take initiative to either find nonpharmacologic approaches or discuss the problem with a physician and agree to take medication.²¹ A trial comparing CBT-I to sedatives or the combination of CBT-I plus sedatives found higher rates of sleep with CBT-I for 3 months, after which improvement fluctuated; the combination showed sustained improvement for the entire 6-month trial.²² CBT-I has also been shown to be as effective with patients who do not have psychiatric illness as for those who are depressed, anxious, or stressed.²³ However, behavioral techniques that require regular practice may be difficult for individuals to maintain, particularly when they are depressed or anxious.

Clinicians should understand the distinctions among the various types of

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Behavioral techniques that require regular practice may be difficult to maintain for a patient who is depressed or anxious



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Patients helped by a specific medication may need to take a break from that medication to maintain its sedative effects

pharmacotherapy for insomnia. Sedative-hypnotics include medications with varying half-lives and metabolic pathways. Short-acting benzodiazepines such as triazolam or alprazolam and the “z-drugs” zolpidem or zaleplon may help initiate sleep in patients with sleep-onset insomnia. Longer-acting benzodiazepines such as diazepam, clonazepam, or temazepam and the z-drug eszopiclone may also help with sleep maintenance.²³ Based on my clinical experience, individual patients may respond better to 1 type of medication over another, or even to different agents within the same class of sedative-hypnotics.

Some clinicians prescribe nonbenzodiazepine medications for sleep, such as doxepin (which is FDA-approved for treating insomnia) or off-label trazodone, mirtazapine, or quetiapine. Their antihistaminic properties confer sedating effects. Virtually all over-the-counter (OTC) medications for insomnia are antihistaminic. These OTC medications are not designed to treat insomnia, and the optimal dosage to maintain sleep without daytime sedation must be determined by trial and error. Sedating nonbenzodiazepine medications may be slowly absorbed if taken at bedtime (depending on whether they are taken with or without food) and cause daytime sedation and cognitive slowness in patients with sleep-onset and maintenance insomnia who must wake up early. Starting trazodone at 50 to 75 mg may cause slow metabolizers to wake up with considerable sedation, while fast metabolizers might never feel soundly asleep.²⁴

Patients with mood and anxiety disorders that complicate insomnia are often prescribed second-generation antipsychotics such as quetiapine, lurasidone, or olanzapine, which are sedating as well as mood-stabilizing. These approaches require careful attention to titrating doses and timing their use.

Problems with pharmacotherapy

When either benzodiazepines or nonbenzodiazepine medications are used on a long-standing, nightly basis, they often stop working well. It is not unusual that after days to weeks of taking a benzodiazepine,

patients find they no longer stay asleep but can't fall asleep if they don't take them. Once tolerance develops, the individual experiences pharmacologic withdrawal with an inability to fall asleep or stay asleep. The medication becomes necessary but ineffective, and many patients increase their use to higher doses to fall asleep, and sometimes in early morning to maintain sleep. This leads to negative effects on cognition, coordination/balance, and mood during the day, especially in older patients.

Nonbenzodiazepine sedating medications do not lead to pharmacologic tolerance but do lead to tachyphylaxis as the CNS attempts to downregulate sedation to keep the organism safe. For some patients, this happens quickly, within a matter of days.²⁵ Others increase doses to stay asleep. For example, a patient with a starting dose of trazodone 75 mg/d might increase the dosage to 300 mg/d. While trazodone is approved in doses of 300 to 600 mg as an antidepressant, it is preferable to keep doses lower when used only for sedation.

An alternating medication strategy

Alternating between medications from different classes can help patients avoid developing tolerance with benzodiazepines or tachyphylaxis as occurs with antihistaminic medications. It can be effective for patients with primary insomnia as well as for those whose sleep problems are associated with mood or anxiety disorders. Patients typically maintain sensitivity to any form of pharmacologic sedation for several nights without loss of effect but need to take a break to maintain the sedation effect. For example, in 1 case study, a 30-year-old female who rapidly developed tachyphylaxis to the sedative action of mirtazapine experienced a return of the medication's sedative effects after taking a 3-day break.²⁵

To initiate an alternating strategy, the clinician must first help the patient establish a sedating dose of 2 medications from different classes, such as trazodone and zolpidem, and then instruct the patient to use each for 2 to 3 consecutive nights on an alternating basis. Patients can use calendars or pillboxes to avoid confusion

about which medication to take on a given night. In many cases, this approach can work indefinitely.

The following 3 case vignettes illustrate how this alternating medication strategy can work.

CASE 1

Mr. B, age 58, is a married salesman whose territory includes 3 states. He drives from client to client from Monday through Thursday each week, staying overnight in hotels. He is comfortable talking to clients, has a close and supportive relationship with his wife, and enjoys socializing with friends. Mr. B has a high level of trait anxiety and perfectionism and is proud of his sales record throughout his career, but this leads to insomnia during his nights on the road, and often on Sunday night as he starts anticipating the week ahead. Mr. B denies having a depressed mood or cognitive problems. When on vacation with his wife he has no trouble sleeping. He has no psychiatric family history or any substantial medical problems. He simply wishes that he could sleep on work nights.

We set up an alternating medication approach. Mr. B takes trazodone 100 mg on the first night and 150 mg on the second and third nights. He then takes triazolam 0.25 mg for 2 nights; previously, he had found that zolpidem did not work as well for maintaining sleep. He can sleep adequately for the 2 weekend nights, then restarts the alternating pattern. Mr. B has done well with this regimen for >10 years.

CASE 2

Ms. C, age 60, is widowed and has a successful career as a corporate attorney. She has been anxious since early childhood and has had trouble falling asleep for much of her life. Once she falls asleep on her sofa—often between 1 and 2 AM—Ms. C can sleep soundly for 7 to 8 hours, but early morning work meetings require her to set an alarm for 6 AM daily. Ms. C feels irritable and anxious on awakening but arrives at her office by 7:30 AM, where she maintains a full schedule, with frequent 12-hour workdays. Ms. C did not experience significant

insomnia or hot flashes with menopause at age 52 and does not use hormone replacement therapy.

Ms. C denies having depression, but experienced appropriate grief related to her husband's illness and death from metastatic cancer 3 years ago. At the time, her internist prescribed escitalopram and zolpidem; escitalopram caused greater agitation and distress, so she stopped it after 10 days. Zolpidem 10 mg/d allowed her to sleep but she worried about taking it because her mother had long-standing sedative dependence. Ms. C lives alone, but her adult children live nearby, and she has a strong support system that includes colleagues at her firm, friends at her book club, and a support group for partners of cancer patients.

Ms. C tries trazodone, starting with 50 mg, but reports feeling agitated rather than sleepy and has cognitive fogginess in the morning. She is switched to quetiapine 50 mg, which she tolerates well and allows her to sleep soundly. To avoid developing tachyphylaxis with quetiapine, she takes eszopiclone 3 mg for 2 nights, alternating with quetiapine for 3 nights. This strategy allows her to reliably fall asleep by 11 PM, wake up at 6 AM, and feel rested throughout the day.

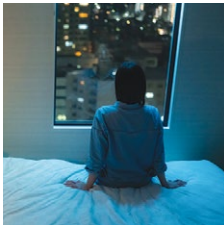
CASE 3

Ms. D, age 55, is married with a long-standing diagnosis of generalized anxiety disorder (GAD), panic disorder, and depression so severe she is unable to work as a preschool teacher. She notes that past clinicians have prescribed a wide array of antidepressants and benzodiazepines but she remains anxious, agitated, and unable to sleep. She worries constantly about running out of benzodiazepines, which are “the only medication that helps me.” At the time of evaluation, her medications are venlafaxine ER 150 mg/d, lorazepam 1 mg 3 times daily and 2 mg at bedtime, and buspirone 15 mg 3 times daily, which she admits to not taking. She is overweight and does not exercise. She spends her days snacking and watching television. She can't settle down enough to read and feels overwhelmed most of the time. Her adult children won't allow her to babysit their young children because she dozes during the day.

Clinical Point

Establish a sedating dose of 2 agents from different classes, and instruct the patient to alternate their use every 2 or 3 nights

continued



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Patients can use a calendar or pillbox to avoid confusion about which medication to take on a given night

Related Resources

- Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2017;13(2):307-349. doi:10.5664/jcsm.6470
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Drug Brand Names

Alprazolam • Xanax	Methylphenidate • Concerta
Armodafinil • Nuvigil	Mirtazapine • Remeron
Atomoxetine • Strattera	Modafinil • Provigil
Bupropion • Wellbutrin	Olanzapine • Zyprexa
Clonazepam • Klonopin	Quetiapine • Seroquel
Diazepam • Valium	Temazepam • Restoril
Divalproex • Depakote	Trazodone • Desyrel
Doxepin • Sinequan	Triazolam • Halcion
Escitalopram • Lexapro	Venlafaxine • Effexor
Eszopiclone • Lunesta	Zaleplon • Sonata
Lorazepam • Ativan	Zolpidem • Ambien
Lurasidone • Latuda	

Ms. D has a strong family history of psychiatric illness, including a father with bipolar I disorder and alcohol use disorder and a sister with schizoaffective disorder. Ms. D has never felt overtly manic, but has spent most of her life feeling depressed, anxious, and hopeless, and at times she has wished she was dead. She has had poor responses to many antidepressants, with transient euphoria followed by more anxiety.

Rather than major depressive disorder or GAD, Ms. D's symptoms better meet the criteria for bipolar II disorder. She agrees to a slow taper of venlafaxine and a slow increase of divalproex, starting with 125 mg each evening. While taking venlafaxine 75 mg/d and divalproex 375 mg/d, she experiences distinct improvement in anxiety and agitation, which further improve after venlafaxine is stopped and divalproex is increased to 750 mg in the evening. She finds that she forgets daytime doses of lorazepam but depends on it to fall asleep. While taking quetiapine 50 mg and lorazepam 1 mg at bedtime, Ms. D reports

sleeping soundly and feeling alert in the morning. Over several weeks, she tapers lorazepam slowly by 0.5 mg every 2 weeks. She finds she needs a higher dose of quetiapine to stay asleep, eventually requiring 400 mg each night. Ms. D says overall she feels better but is distressed because she has gained 25 lbs since starting divalproex and quetiapine.

To avoid further increases in quetiapine and maintain its sedating effect, Ms. D is switched to an alternating schedule of clonazepam 1.5 mg for 2 nights and quetiapine 300 mg for 3 nights. She agrees to begin exercising by walking in her neighborhood daily, and gradually increases this to 1 hour per day. After starting to exercise regularly, she finds she is oversedated by quetiapine at night, so she is gradually decreased to a dose of 150 mg, while still alternating with clonazepam 1.5 mg. Ms. D loses most of the weight she had gained and begins volunteering as a reading coach in the elementary school in her neighborhood.

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Bottom Line

Patients with chronic insomnia can often maintain adequate sedation without developing tolerance to benzodiazepines or tachyphylaxis with nonsedating agents by using 2 sleep medications that have different mechanisms of action on an alternating schedule.

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**For some patients,
an alternating
medication strategy
might work
indefinitely**