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# CNS SPECTRUMS

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CME Review Article

Mechanism of Action of Narcolepsy Medications

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Narcolepsy is a debilitating neurodegenerative disorder that can have deleterious effects on physical and mental health as well as on functioning and work productivity. In the AWAKEN survey, only 34% of physicians reported being “very” or “extremely” knowledgeable about the disorder. Sleep medicine is a largely neglected topic both in medical school and at the postgraduate level.

To help address this professional practice gap and improve outcomes for patients with narcolepsy, quality improvement efforts need to provide education regarding the mechanism of action of medications used to treat narcolepsy.

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After completing this activity, participants should be better able to describe the mechanism of action of medications used to treat narcolepsy.

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# Mechanism of action of narcolepsy medications

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The medications used to treat narcolepsy are targeted toward alleviating symptoms such as excessive sleepiness and cataplexy. The cause of this neurological sleep disorder is still not completely clear, though a destruction of hypocretin/orexin neurons has been implicated. The destruction of these neurons is linked to inactivity of neurotransmitters including histamine, norepinephrine, acetylcholine, and serotonin, causing a disturbance in the sleep/wake cycles of narcoleptic patients. Stimulants and MAOIs have traditionally been used to counteract excessive daytime sleepiness and sleep attacks by inhibiting the breakdown of catecholamines. Newer drugs, called wake-promoting agents, have recently become first-line agents due to their better side-effect profile, efficacy, and lesser potential for abuse. These agents similarly inhibit reuptake of dopamine, but have a novel mechanism of action, as they have been found to increase neuronal activity in the tuberomammillary nucleus and in orexin neurons. Sodium oxybate, a sodium salt of gamma-hydroxybutyrate (GHB), is another class that is used to treat many symptoms of narcolepsy, and is the only U.S. Food and Drug Administration (FDA)-approved medication for cataplexy. It has a different mechanism of action than either stimulants or wake-promoting agents, as it binds to its own unique receptor. Antidepressants, like selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), have also been used, as similar to stimulants, they inhibit reuptake of specific catecholamines. In this article, we seek to review the mechanisms behind these classes of drugs in relation to the proposed pathophysiology of narcolepsy. Appropriate clinical strategies will be discussed, including specific combinations of medications that have been shown to be effective.

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**Key words:** Cataplexy, hypersomnia, hypocretin, narcolepsy, orexin, sleep.

## Introduction

Narcolepsy is a neurologic sleep disorder that affects about 1 in 2,000 individuals, with an equal incidence in both genders and an onset in adolescence. Its main characteristic is excessive daytime sleepiness (EDS), which patients experience as unwanted, sudden, and intrusive attacks of daytime sleep that can last from seconds to minutes. These sleep attacks interfere with daily activities and can even be dangerous, especially if the patient is driving or operating machinery. Patients can also have hypnagogic hallucinations, sleep paralysis, and disordered sleep/wake cycles. These symptoms are due to inappropriate intrusions of rapid eye movement (REM) sleep while a patient is awake. In most patients, narcolepsy is accompanied by cataplexy, an involuntary loss of muscle tone caused by laughter or other strong

emotions. The cause of atonia in cataplexy is unknown, and it is widely debated as to whether it is the same atonic process seen during REM sleep. Patients who experience attacks of cataplexy often retain consciousness, even in their paralytic state. The International Classification of Sleep Disorders, Third Edition (ICSD-3) diagnostic criteria sub-classifies narcolepsy into 2 groups: narcolepsy type 1 and type 2 (those with cataplexy and those without).

According to ICSD-3 criteria, the diagnoses of the 2 types of narcolepsy both require the presence of EDS for at least 3 months. An overnight polysomnogram (PSG) consisting of at least 6 hours of sleep, followed by a multiple sleep latency test (MSLT), must show latency of 8 minutes or less plus 2 or more sleep-onset REM periods (SOR-EMPs). In narcolepsy type 1 (narcolepsy with cataplexy), however, a decreased cerebrospinal fluid (CSF) hypocretin level (<110 pg/mL or <1/3 mean value of normal subjects with the same assay) can alternately be used instead of the PSG and MSLT. In narcolepsy type 2, the hypersomnia must not be better explained by another condition.

The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) diagnostic criteria for

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narcolepsy state that excessive sleepiness must occur at least 3 times per week for the past 3 months, and either cataplexy, CSF hypocretin levels  $\leq 110$  pg/mL, a nocturnal sleep polysomnogram showing REM sleep latency less than or equal to 15 minutes, or MSLT showing a mean sleep latency  $\leq 8$  minutes plus 2 or more sleep-onset REM periods must be present.

### Pathophysiology and Mechanisms of Medications

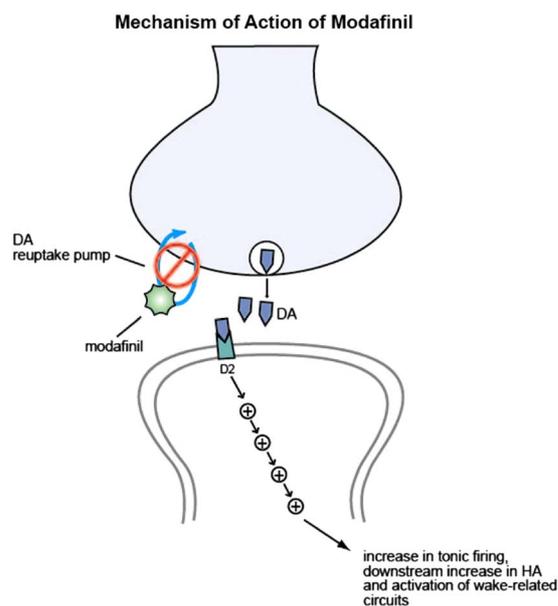
The pathophysiology of narcolepsy has recently become clearer due to animal studies and the subsequent discovery of hypocretin or orexin peptides, which play a role in sleep/wake cycles and REM sleep. Undetectable CSF levels of hypocretin-1, a peptide neurotransmitter produced in the lateral hypothalamus, have been demonstrated in narcolepsy with cataplexy patients.<sup>1</sup> About 90% of these patients have low CSF levels of hypocretin, while only 10–20% of narcoleptic patients without cataplexy lack hypocretin in their CSF.<sup>2</sup> Most individuals with the cataplexy subtype of narcolepsy test positive for HLA-DQB1\*0602, signifying a possible autoimmune basis for the destruction of neurons in the hypocretin/orexin pathway.<sup>3</sup> These neurons project to ascending arousal pathways and bind to receptors found in the ventrolateral preoptic nucleus, the histaminergic tuberomammillary nucleus, and monaminergic and cholinergic systems.<sup>4</sup> Called the sleep/wake switch, these hypothalamic neuronal pathways serve to control when an individual sleeps and stays awake. During sleep, the “off switch” neurons, located mostly in the ventrolateral preoptic nucleus, are active, but during wakefulness, the “on switch” neurons, concentrated mostly in the tuberomammillary nucleus, are dominant.<sup>5</sup> In narcolepsy, the lack of hypocretin/orexin neurons affects the stability of these pathways and the activity of histamine, acetylcholine, norepinephrine, and serotonin, thereby causing a disturbance in sleep/wake cycles.<sup>6</sup>

Historically, the treatment of narcolepsy has been targeted toward preventing sleep attacks and countering EDS with the use of stimulants. This began in 1933 with the use of benzedrine sulfate to treat narcolepsy.<sup>7</sup> Since then, stimulants like amphetamines and methylphenidate have been the main medications used to treat EDS associated with narcolepsy. Amphetamines, which are derived from catecholamines, mainly exert their effect by acting as substrates for the dopamine transporter (DAT) at the presynaptic nerve terminal, competing with dopamine for reuptake into the cell. Once inside the cell, and at higher doses, amphetamines compete with dopamine and norepinephrine for transport into vesicles, displacing these molecules by acting as a substrate for the vesicular monoamine transporter 2 (VMAT2). This leads to an increased concentration of cytoplasmic dopamine and norepinephrine. The increased concentration of cytoplasmic dopamine stimulates a reversal of DAT, so

more dopamine is released into the synaptic cleft. At even higher concentrations, amphetamines can inhibit monoamine oxidase enzymes, preventing degradation of catecholamines. All amphetamines have a similar mechanism, except for methylphenidate, which noncompetitively inhibits DAT and has no effect on DAT reversal or VMAT2.<sup>8</sup> Amphetamines and methylphenidate act mainly to inhibit reuptake of dopamine, and to a lesser extent norepinephrine and serotonin. With methamphetamine, the addition of a methyl group increases the potency of the drug and allows for easier passage into the brain, though it is not used often, as it has a higher potential for abuse. D-Amphetamine is taken in the morning and afternoon orally, with a starting dose of 5–10 mg at 4–6 hour intervals. Doses can be increased incrementally by 10 mg/day for a maximum daily dose of 60 mg. Methylphenidate is dosed similarly. All amphetamines have a high abuse potential and carry side effects such as tachycardia, anorexia, palpitations, and high blood pressure.

Monoamine oxidase inhibitors (MAOIs) are another medication used off-label to treat excessive daytime sleepiness and cataplexy. There are 2 subtypes of monoamine oxidase, type A and type B. Monoamine oxidase type A (MAO-A) degrades primarily serotonin and norepinephrine, while MAO-B degrades mostly trace amines. Both subtypes degrade dopamine and tyramine, and the major subtype found outside the brain is MAO-A. The therapeutic value of MAOIs in treating narcoleptic symptoms lies in their ability to inhibit both subtypes, as selective inhibition of MAO-B would not significantly affect levels of serotonin and norepinephrine. One medication in this class that is used at high doses is selegiline, an irreversible MAO-B inhibitor. The main beneficial effect of selegiline, however, is through its inhibitory effects at high doses on both MAO-A and MAO-B in the brain, which increases the concentration of dopamine, serotonin, and norepinephrine.<sup>5</sup> Selegiline produces a dose-dependent REM suppression during nighttime sleep and naps and an increase of sleep and REM latency. It also significantly improves daytime sleepiness and reduces the number of sleep attacks, naps, and frequency of cataplexy.<sup>9</sup> Selegiline is normally dosed at 10–40 mg to treat narcoleptic symptoms. Since selegiline loses its selectivity at higher doses, a diet low in tyramine must be followed. A way to reduce the risk of hypertensive crisis associated with tyramine would be to use a selegiline patch. Since the drug would be delivered transdermally, it would not undergo first pass metabolism through the gut and liver, avoiding its dangerous interaction with tyramine. Despite its lower risk than the oral form, the U.S. Food and Drug Administration (FDA) still recommends patients to avoid a diet high in tyramine-containing foods while on the patch. Common side effects encountered with MAOIs are hypotension, nausea, headaches, dizziness, and numerous drug interactions.

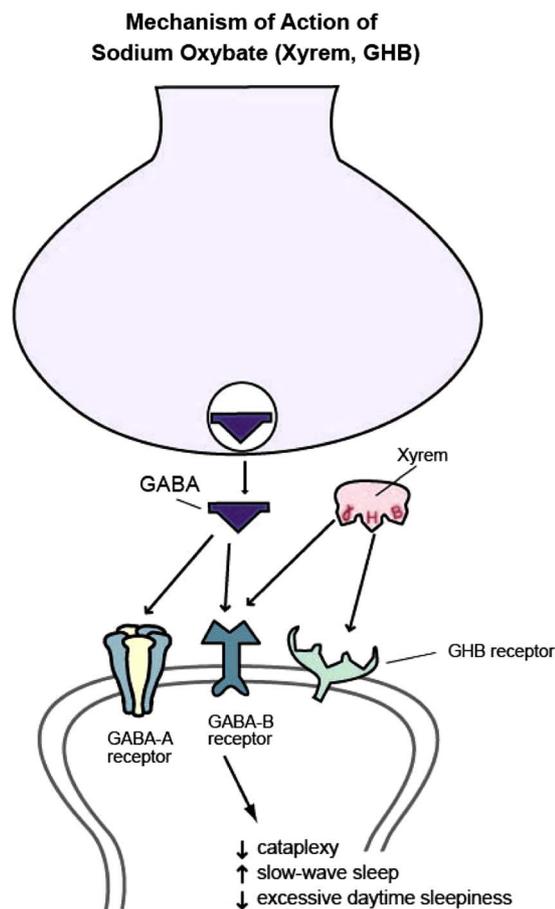
Newer medications called wake-promoting agents are more recently being used and are now the first-line agents to treat excessive daytime sleepiness. A medication called modafinil has been shown in randomized, double-blind, placebo-controlled studies to be effective in treating excessive daytime sleepiness.<sup>10</sup> Although the exact mechanism is unknown, modafinil blocks dopamine transporters and increases extracellular brain levels of dopamine<sup>11</sup> (Figure 1). Despite its actions on dopamine transporters to block reuptake, it is structurally different than amphetamine and methylphenidate, and has a novel mechanism of action. Studies in rats have shown that modafinil increases neuronal activity in the tuberomammillary nucleus and in orexin neurons, indicating that the drug may act through increasing histamine release from the tuberomammillary nucleus and stimulating the lateral hypothalamus to release hypocretin/orexin<sup>12</sup> (Figure 1). The most common side effects reported with its use are nausea, headache, and insomnia. Modafinil (Provigil) is also a preferred agent to treat excessive daytime sleepiness, as it has a lower abuse potential than amphetamine. Modafinil is normally given in 100–200 mg doses once daily, with a maximum daily dose of 400 mg. Armodafinil (Nuvigil), the R enantiomer of modafinil, is a newer, more potent drug within the same class that has a longer half-life and later peak than the racemic modafinil. In-vitro studies have demonstrated a similar effect at norepinephrine, dopamine, and serotonin transporters for both the R- and S-isomers of modafinil, though the S-isomer is



**FIGURE 1.** Mechanism of action of modafinil. Reprinted from *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications* (Essential Psychopharmacology Series). Cambridge, UK: Cambridge University Press, 2013 (used with permission).

eliminated more rapidly. The S-isomer, which represents one-half of a dose of modafinil, results in a biphasic decline in plasma modafinil concentrations from the peak, in contrast to the slow, monophasic elimination of the R-isomer, which is 100% of a dose of armodafinil.<sup>13</sup> Because modafinil is considered a low-potency agent, it can be used concurrently with short-acting stimulants such as methylphenidate in cases where more wakefulness and alertness are needed.<sup>14</sup>

In addition to stimulants and wake-promoting agents to combat excessive daytime sleepiness, sodium oxybate, a sodium salt of gamma-hydroxybutyrate (GHB), has been approved to treat cataplexy and EDS (Figure 2). GHB is a naturally occurring neurotransmitter derived from gamma-aminobutyric acid (GABA) and was first used as an anesthetic and later for the treatment of narcolepsy in the 1970s. It has been shown in many double-blind, randomized studies to effectively reduce stage 1 sleep, decrease wake-after-sleep onset, decrease number of awakenings, and increase slow-wave sleep.<sup>15</sup>



**FIGURE 2.** Mechanism of action of sodium oxybate. Reprinted from *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications* (Essential Psychopharmacology Series). Cambridge, UK: Cambridge University Press, 2013 (used with permission).

The exact mechanism of GHB is unknown, but it is known to act on the GABA-B receptor as well as its own specific GHB receptor. The effects of GHB are thought to be mediated not through its effects on GABA-B however, as a study comparing baclofen, a well-known GABA-B agonist, and GHB to treat excessive daytime sleepiness and cataplexy showed that only GHB had an effect on cataplexy and daytime sleepiness.<sup>16</sup> GHB is sold under the name Xyrem and is tightly regulated. It is a schedule III drug and is a known drug of abuse. As such, it is dispensed from a single central pharmacy and is under a restricted distribution program. Xyrem is a liquid formula taken 2 times during the night, with an initial starting dose of 1.5 g taken at bedtime and again 2–4 hours later. The maximum nightly dose is 9 g. The main side effects of GHB are nausea, weight loss, headache, and respiratory depression. The drug is useful in that it treats almost all symptoms of narcolepsy, including REM sleep disturbances, cataplexy, excessive daytime sleepiness, hypnagogic hallucinations, and sleep paralysis.

Although GHB has been used to treat most symptoms of narcolepsy, it is the only drug that is FDA-approved to treat cataplexy. While stimulants are often not as efficacious for cataplexy symptoms as GHB, antidepressants have also been used off-label to treat cataplexy. Although antidepressants are a commonly used class of psychotropics, a clinically important side effect called status cataplecticus or rebound cataplexy occurs with abrupt discontinuation of them. This manifests as an increase in the number and severity of cataplectic attacks.<sup>8</sup> The first medication that demonstrated a benefit in improving cataplexy symptoms was imipramine, a tricyclic antidepressant (TCA), in the 1960s.<sup>17</sup> Of the TCAs, protriptyline, clomipramine, and imipramine are used off-label to treat cataplexy. TCAs work through presynaptic inhibition of monoamine reuptake, blocking the norepinephrine transporter (NET), serotonin reuptake transporter (SERT), and to a small extent, dopamine reuptake, causing an increased concentration of mostly norepinephrine and serotonin at the synaptic cleft. They also block histamine 1, alpha 1, and cholinergic receptors. While the exact mechanism of how tricyclic antidepressants reduce cataplexy is still unknown, “clomipramine has been shown to have the most REM-suppressing activity, which may be related to its greater ability to block serotonin reuptake than the other tricyclic antidepressants. The use of TCAs may also result in a decrease in other REM-related narcolepsy symptoms, including sleep paralysis and hypnagogic hallucinations; however, they have little beneficial effect on excessive daytime sleepiness”.<sup>18</sup> The doses of TCAs used to treat cataplexy are less than those used to treat depression. With imipramine and clomipramine, the starting dose is usually 10–20 mg daily and given at

bedtime. Protriptyline is primarily a norepinephrine reuptake inhibitor, so starting doses are usually 2.5–10 mg daily.<sup>8</sup> The side effects associated with TCAs are those associated with their anticholinergic, antihistaminic, and alpha-antagonist properties. Patients commonly experience dry mouth, constipation, and dysuria from the cholinergic antagonism; tachycardia and orthostatic hypotension from the alpha antagonism; and sedation from antagonism of all 3 types of receptors.

Selective serotonin reuptake inhibitors (SSRIs) are less effective in treating cataplexy than the tricyclic class of antidepressants, but they similarly inhibit REM sleep. SSRIs are less efficacious than TCAs because of their predilection for only blocking reuptake of serotonin.<sup>19</sup> SSRIs work by initially blocking the serotonin reuptake transporter (SERT) at the somatodendritic area of the serotonin neuron, which increases the concentration of serotonin here more than the axonal area. When serotonin levels rise in this area, they stimulate nearby 5HT1A autoreceptors. The increased serotonin acting at these somatodendritic 5HT1A autoreceptors causes them to eventually downregulate and become desensitized. Once this occurs, 5HT can no longer turn off its own release and is disinhibited, causing an increase in neuronal impulse flow. This increase in neuronal impulse flow stimulates serotonin release at the axon terminal.<sup>5</sup> The most commonly used SSRI to treat cataplexy is fluoxetine, though others such as fluvoxamine and paroxetine are also used. SSRIs have an overall better side effect profile than the tricyclic antidepressants, with the most common side effects being headache, dry mouth, delayed ejaculation, nausea, and weight gain. Serotonin-norepinephrine reuptake inhibitors (SNRIs) have also been used to treat cataplexy and seem to be more effective.<sup>14</sup> At low doses, SNRIs inhibit the serotonin transporter, but as the dose increases, the drug exerts stronger effects on norepinephrine reuptake. SNRIs also increase dopamine release in the prefrontal cortex as a result of inhibiting the norepinephrine transporter, which is not only responsible for norepinephrine reuptake but also dopamine reuptake.<sup>5</sup> The most common SNRI used for cataplexy is venlafaxine. While there have been no double-blind, randomized, placebo-controlled trials for venlafaxine in the treatment of cataplexy, a case study has shown that it was effective in treating cataplexy and hypnagogic hallucinations in children.<sup>20</sup> Venlafaxine is metabolized by CYP2D6 to desvenlafaxine, which also inhibits serotonin and norepinephrine reuptake, but exerts a stronger effect on norepinephrine. Venlafaxine is dosed at initially 37.5 mg daily in the morning, with a maximum daily dose of 300 mg. It is used for cataplexy at doses lower than those used to treat depression. The main side effects of SNRIs are gastrointestinal problems such as constipation, dry mouth, and nausea.

## Conclusion

Since there is no cure for narcolepsy, treatment should be directed at treating the symptoms through medications as well as lifestyle and behavioral modifications. The American Academy of Sleep Medicine has published practice parameters for treating narcolepsy that may help guide the clinician in making decisions about pharmacotherapy. When a patient initially presents with symptoms of daytime somnolence, a thorough exam must be conducted and other etiologies for the excessive sleepiness must be ruled out before making a diagnosis of narcolepsy. Once the diagnosis has been made, appropriate lifestyle modifications must be implemented. Scheduled naps throughout the day are helpful in reducing unplanned sleep episodes, and avoidance or caution with driving and operating heavy machinery must be followed. Medications should be tailored for each patient's symptoms, and combinations of drugs can also be used if single-drug regimens are ineffective. For a patient who presents with excessive daytime sleepiness, modafinil should be the initial drug of choice started at 200–400 mg daily, or alternatively armodafinil, which is dosed at 150–250 mg daily. These long-acting wake-promoting agents are advantageous, as they have a convenient once-daily dosing schedule, and have a lesser abuse potential and better side effect profile than other classes of drugs. In cases where monotherapy with modafinil is not completely effective for symptomatic relief, a short-acting stimulant such as methylphenidate can be added to improve wakefulness and alertness. MAOIs, such as selegiline can also be used off-label, though their use is limited by significant side effects and strict requirements to follow a diet low in tyramine. For these reasons, they should not be used as first-line agents to combat somnolence.

If a patient presents with predominant symptoms of sleep disturbances and cataplexy, sodium oxybate is a first-line agent, as it treats most symptoms of narcolepsy, including sleep paralysis and hypnagogic hallucinations. It has also been shown to have a synergistic effect when taken with modafinil, so treatment with sodium oxybate and modafinil can be used as an effective combination when a patient has a constellation of symptoms such as excessive daytime sleepiness, cataplexy, and nighttime sleep disturbances.<sup>21</sup> Alternatively, cataplexy may be alleviated with SNRIs such as venlafaxine or SSRIs, though these have not been shown to have the same efficacy as sodium oxybate. Tricyclic antidepressants should be considered only if these other treatments are not effective for cataplexy. Their benefits should also be weighed against risks, such as rebound cataplexy and significant anticholinergic side effects.

As more is known about the hypocretin/orexin pathway through studies on rodents and dogs, treatments

are being targeted toward addressing the cause of the disease rather than focusing on symptomatic management. Future treatment modalities that are being explored include hypocretin-centered therapies, immune-based therapies, and novel agents to help promote wakefulness.

## Disclosures

Chandan Gowda has nothing to disclose. Leslie Lundt has the following disclosures: Teva, speaker's bureau, honoraria; Sunovion, speaker's bureau, honoraria.

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CME Credit Expires: November 30, 2017

### CME Posttest Study Guide

**NOTE: The posttest can only be submitted online.** The below posttest questions have been provided solely as a study tool to prepare for your online submission. **Faxed/mailed copies of the posttest cannot be processed and will be returned to the sender.** If you do not have access to a computer, contact NEI customer service at 888-535-5600.

1. The pathophysiology of narcolepsy may be related to the destruction of neurons that produce:
  - A. Acetylcholine
  - B. Dopamine
  - C. Hypocretin/orexin
  - D. Serotonin
2. A 41-year-old nurse is currently taking modafinil as a treatment for narcolepsy. Although modafinil's exact mechanism is unknown, it may promote wakefulness by:
  - A. Increasing dopamine and histamine
  - B. Increasing dopamine and decreasing histamine
  - C. Decreasing dopamine and increasing histamine
  - D. Decreasing dopamine and histamine
3. Which of the following has been shown to increase slow-wave sleep?
  - A. Amphetamine
  - B. Methylphenidate
  - C. Modafinil
  - D. Sodium oxybate

### CME Online Posttest and Certificate

To receive your certificate of CME credit or participation, complete the posttest and activity evaluation, available only online at [www.neiglobal.com/CME](http://www.neiglobal.com/CME) under "CNS Spectrums". If a score of 70% or more is achieved, you will be able to immediately print your certificate. There is no posttest fee nor fee for CME credits for this activity. Questions? call 888-535-5600, or email [customerservice@neiglobal.com](mailto:customerservice@neiglobal.com)

Posttest & Evaluation