Methylphenidate

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Continuing Education Activity

Methylphenidate is FDA-approved for the treatment of ADHD in adults and children 6 years and older. Additionally, methylphenidate serves as a second-line therapy for narcolepsy in adults. Off-label uses include cancer-related fatigue, refractory depression in older adults, apathy in patients with Alzheimer disease, and cognitive enhancement (eg, memory improvement); the efficacy of methylphenidate for these conditions is moderate at best.

This activity reviews the mechanism of action, adverse event profile, toxicity, pharmacology, and monitoring parameters associated with methylphenidate therapy. Special attention is given to drug interactions and the importance of proper oversight to prevent misuse. Additional emphasis is placed on the role of the interprofessional healthcare team in optimizing therapy outcomes when treating patients prescribed methylphenidate.

Objectives:

- Identify the mechanism of action of methylphenidate.
- Identify the FDA-approved and off-label uses of methylphenidate.
- Assess the contraindications and adverse events associated with methylphenidate administration.
- Develop interprofessional team strategies for improving care coordination and communication so that methylphenidate can be appropriately administered to improve patient outcomes.

Access free multiple choice questions on this topic.

Indications

FDA-Approved Indications

Methylphenidate is approved by the United States Food and Drug Administration (FDA) for treating attention deficit hyperactivity disorder (ADHD) in children and adults and as a second-line treatment for narcolepsy in adults. Children receiving this medication should be 6 years or older. Methylphenidate therapy for patients with ADHD and narcolepsy leads to significantly better outcomes when supplemented with nonpharmacologic therapies (ie, social skills training for ADHD or sleep hygiene measures for narcolepsy).

Off-Label Uses

Off-label uses of methylphenidate include treating fatigue in patients with cancer, refractory depression in older adults, apathy in Alzheimer disease, and enhancing cognitive performance (eg, memory). Since methylphenidate's cognitive enhancement properties present a potential risk for abuse and addiction, the Drug Enforcement Administration (DEA) has classified this medication as a Schedule II substance under the Controlled Substance Act (CSA). The efficacy of methylphenidate for its off-label uses ranges from limited to moderate. Most of these relatively newer uses are currently being studied and implemented in clinical practice.

Mechanism of Action

Methylphenidate is chemically derived from phenethylamine and benzylpiperazine. This medication blocks the reuptake of the neurotransmitters norepinephrine (NE) and dopamine in presynaptic neurons while inhibiting the transport of these neurotransmitters, increasing the concentration of dopamine and NE in the synaptic cleft. This creates the classic stimulant effect within the central nervous system (CNS), primarily in the prefrontal cortex. Methylphenidate undergoes metabolism to ritalinic acid in the liver through de-esterification via carboxylesterase 1 (CES1A1). Compared to other phenethylamine derivatives (eg, amphetamines), methylphenidate appears to increase the firing rate of neurons. Methylphenidate is also a weak agonist at the serotonin 1A receptor (5HT1A), an additional mechanism contributing to the increased dopamine levels.

Given its effect on dopamine levels in the synapse, methylphenidate can provide neuroprotection in conditions like Parkinson disease, which involves the loss of dopaminergic neurons, and methamphetamine abuse. This effect results from direct inhibition of the dopamine transporter and indirect regulation of the vesicular monoamine transporter 2 (VMAT2). The combined interactions reduce the amount of dopamine that accumulates within the cytoplasm, preventing the formation of toxic reactive oxygen species in the brain.

Dependence

The therapeutic dosages for ADHD or narcolepsy that clinicians prescribe are not harmful enough to activate the reward system within the CNS, which centers around the nucleus accumbens. However, excessively higher dosages lead to an overexpression of ΔFosB (a transcriptional activator) in specific neurons within the striatum. The accumulation of ΔFosB in the nucleus accumbens activates a series of signaling cascades that further contribute to the addiction mechanism.

Pharmacokinetics

Absorption: Slow but extensive; the relative bioavailability for extended-release tablets is 105% in children and 101% in adults (versus immediate-release tablets); the absolute oral bioavailability for extended-release capsules in children is 22% and 5% for d-methylphenidate and l-

methylphenidate, respectively. The time of peak plasma concentration is 1.9 hours for immediate-release tablets and 4.7 hours for extended-release tablets. When taken with food, the total exposure and peak plasma concentration of methylphenidate are increased; the time for peak plasma concentration of extended-release tablets is reduced. The effect of alcohol was determined during an in vitro study: 98% of the drug contained in a 40 mg extended-release capsule was released in an alcohol concentration of 40%.

Distribution: The volume of distribution was 2.65 and 1.80 L/kg for d-methylphenidate and l-methylphenidate, respectively. Methylphenidate's plasma protein binding ranges from 10% to 33%.

Metabolism: Methylphenidate is primarily metabolized by de-esterification to ritalinic acid, which is pharmacologically inactive.

Elimination: Most of the drug (78% to 97%) is excreted in the urine, while small amounts are excreted in feces.

Administration

Available Dosage Forms and Strengths

For medical purposes, methylphenidate is typically given orally and less commonly as a transdermal patch. Multiple oral formulations are available that are categorized according to how quickly the drug is released: immediate (IR), extended (XR or ER), and sustained. Various methylphenidate formulations are distributed using the ER sphenoidal oral drug absorption system with bimodal release and the osmotic (ie, controlled) release delivery system. Chewable tablets (IR or ER) for children and an IR solution are also available.

If using the transdermal patch, the patient must be aware of placing the patch on the opposite hip each time to achieve its full effect. Those who misuse methylphenidate for recreational purposes prefer to use the intravenous (IV) or intranasal route. Clinicians should assess the risk of abuse before prescribing methylphenidate in any form.

Methylphenidate is available as a solution, dermal patch, and tablet or capsule (immediate-release, extended-release, or chewable) in the following dosage strengths:

- Chewable tablets: 2.5 mg, 5 mg, and 10 mg
- Orally disintegrating tablets: 8.6 mg, 13.7 mg, and 25.9 mg
- Immediate-release tablets: 5 mg, 10 mg, and 20 mg
- Extended-release tablets: 10 mg, 20 mg, 18 mg, 27 mg, 36mg, 54 mg, and 72 mg
- Extended-release capsules: 10 mg, 20 mg, 30 mg, and 40 mg

- Extended-release capsules CD: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg
- Solution: 5 mg/5 mL and 10 mg/5 mL (in 500 mL bottle)
- Patch: 10 mg, 15 mg, 20 mg, and 30 mg (nominal dose over 9 hours)

Adult and Pediatric Dosage

Attention deficit disorder (ADD) in adults and pediatric patients (6 years and older) and for narcolepsy
- Chewable tablets: 2.5 mg, 5 mg, and 10 mg
- Immediate-release tablets: 5 mg, 10 mg, and 20 mg

ADHD in adults and pediatric patients (6 and older) and for narcolepsy
- Immediate-release tablets: 5 mg, 10 mg, and 20 mg
- Extended-release tablets: 10 mg, 20 mg, 18 mg, 27 mg, 36 mg, 54 mg, and 72 mg
- Extended-release tablets (24 hours): 18 mg, 27 mg, 36 mg, and 54 mg
- Extended-release capsules: 10 mg, 20 mg, 30 mg, and 40 mg
- Extended-release capsules CD: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg
- Solution: 5 mg/5 mL and 10 mg/5 mL in 500 mL bottle
- ADHD in adults and pediatric patients (6 years and older) as well as for narcolepsy

ADHD in pediatric patients (aged 6 to 17 years)
- Orally disintegrating tablets: 8.6 mg, 13.7 mg, and 25.9 mg
- Patch: 10 mg, 15 mg, 20 mg, and 30 mg (nominal dose over 9 hours)

Attention-Deficit Hyperactivity Disorder (ADHD)

Due to pharmacokinetic differences, many products are not bioequivalent and cannot be exchanged on a mg-for-mg basis.

Immediate-release (short-acting): These products include chewable tablets, Ritalin tablets, and Methylin oral solution. Therapy should be initiated at 10 to 20 mg daily, divided into 2 doses before breakfast and lunch. Based on patient response, doses may be increased by 5 to 10 mg weekly or longer intervals, up to a maximum of 60 mg per day, divided into 2 to 3 doses.

Extended-release (intermediate-acting): These products include methylphenidate ER tablets (AB-rated generics to Metadate ER or Methylin ER). Therapy should be initiated with a dose of 10 mg twice daily. Based on patient response, doses may be increased in increments of 10 mg

weekly or longer intervals, up to a maximum of 60 mg daily, divided into 2 doses.

Extended-release and transdermal (long-acting):

- Adhansia XR capsules: Initiate with 25 mg orally once daily in the morning. Doses may be increased in increments of 10 to 15 mg at 5 days or longer intervals, up to a maximum of 100 mg per day. Doses exceeding 85 mg are associated with a higher rate of adverse effects.
- Aptensio XR capsules: Initiate with 10 mg orally once daily in the morning. Doses may be increased in increments of 10 mg weekly or longer intervals, up to a maximum of 60 mg daily.
- Concerta and Relexxii tablets: Initiate therapy with 18 to 36 mg once daily in the morning. Doses may be increased in increments of 18 mg weekly or longer intervals, up to a maximum of 72 mg daily.
- Jornay PM capsules**:** Initiate with 20 mg once daily in the evening within 3 hours of bedtime. Based on response, doses may be increased in increments of 20 mg at weekly or longer intervals, up to a maximum of 100 mg per day.
- Metadate CD capsules, QuilliChew ER chewable tablets, and Quillivant XR oral suspension: Initiate therapy with 20 mg once daily in the morning. Based on response, doses may be increased in increments of 10 to 20 mg at weekly or longer intervals, up to 60 mg daily.

Transdermal (long-acting): These products include the Daytrana transdermal patch. A 10 mg patch is applied to the hip once daily and removed 9 hours later. Absorption may take up to 2 hours before the patient experiences the desired effect. Based on response, 1 patch may be added at weekly or longer intervals, up to a daily maximum of 30 mg (3 patches). Some patients may require up to 60 mg daily for optimal efficacy, but a physician should be consulted before exceeding the recommended maximum dose of 30 mg. The patch can be removed before 9 hours if a shorter duration of action is desired or if late-day side effects occur. Alternatively, the patch can be worn for up to 16 hours if a longer duration of effect is required. Plasma concentrations typically decline once the patch is removed, but drug absorption may continue for several hours afterward.

Specific Patient Populations

Hepatic impairment: The manufacturer label does not provide dose adjustment guidance for patients with hepatic impairment.

Renal impairment: The manufacturer label does not provide dose adjustment guidance for patients with renal impairment. However, most of the drug and its metabolites are excreted in the urine.

Pregnancy considerations: Methylphenidate is a pregnancy category C medicine. Various studies have examined methylphenidate during pregnancy to treat ADHD and narcolepsy. The results of these studies have been inconclusive, so the medication should be administered to pregnant women with caution.

Breastfeeding considerations: Clinicians should monitor and maintain the relative infant dose below 10% while administering methylphenidate to nursing mothers, as the drug is present in breast milk.

Pediatric patients: Multiple dosage forms and strengths are available for children aged 6 to 17. The AAP considers methylphenidate IR the drug of choice for pediatric patients (3 to 5 years old) when pharmacological treatment is necessary.

- Immediate release (short-acting) (chewable tablets, Ritalin tablets, and Methylin oral solution): The recommended starting dose is 5 mg orally twice daily before breakfast and lunch, ideally 30 to 45 minutes before meals. Gradually increase the dosage in increments of 5 to 10 mg each week. A daily dose above 60 mg is not advised.

- Extended-release (intermediate-acting) (AB-rated generics to Metadate ER or Methylin ER): The recommended starting dose is 10 mg twice daily. Based on tolerability and response, doses may be increased in increments of 10 mg weekly or longer intervals, up to a maximum of 60 mg daily, divided into 2 doses.

- Extended-release (long-acting):
    - Adhansia XR capsules: Start with 25 mg orally once daily in the morning. Based on tolerability and response, doses may be increased in increments of 10 to 15 mg at 5 days or longer intervals, up to a maximum of 100 mg per day. Doses of more than 85 mg are related to a higher rate of adverse effects.
    - Aptensio XR capsules: Start with 10 mg orally once daily in the morning. Based on tolerability and response, doses may be increased in increments of 10 mg weekly or longer intervals, up to a maximum of 60 mg daily.
    - Concerta and Relexxii tablets: Start with 18 to 36 mg once daily in the morning. Based on tolerability and response, doses may be increased in increments of 18 mg weekly or longer intervals, up to a maximum of 72 mg per day.
    - Jornay PM capsules: Start 20 mg once daily in the evening between 6:30 PM and 9:30 PM. Based on tolerability and response, doses may be increased in increments of 20 mg at weekly or longer intervals, up to a maximum of 100 mg per day.
    - Metadate CD capsules, QuilliChew ER chewable tablets, and Quillivant XR oral suspension: Start with 20 mg once daily in the morning. Based on tolerability and response, doses may be increased in increments of 10 to 20 mg at weekly or longer intervals, up to 60 mg daily.
- Transdermal (long-acting): These products include the Daytrana transdermal patch. One 10 mg patch is applied to the hip once daily, 2 hours before the desired effect, and removed 9 hours after placement. Based on tolerability and response, 1 patch may be added at weekly or longer intervals, up to a maximum of 30 mg per day. Some patients may need up to 60 mg per day for optimal efficacy. The patch can be removed before 9 hours if a shorter duration of action is desired or if late-day side effects occur. Alternatively, it can be worn for up to 16 hours if a longer duration of effect is required. Plasma concentrations typically decline once the patch is removed, but drug absorption may continue for several hours afterward.

Older patients: No specific dose adjustment guidance is available regarding older adults.

Adverse Effects

Insomnia and nervousness are the most commonly reported adverse effects in patients using methylphenidate. Growth retardation (reduced height, weight, and bone marrow density) is observed when prescribed to children long-term. Other frequent side effects primarily involve the CNS (dizziness, headache, tics, restlessness/akathisia), gastrointestinal (nausea/vomiting, dry mouth, decreased appetite, weight loss, abdominal pain), and cardiovascular systems (tachycardia, palpitations). Dermatologically, patients can complain of excessive sweating and ulceration of their digits. Some patients may even develop blurry vision or decreased libido. While

it rarely occurs, priapism is a medical emergency that requires immediate attention. Patients are more prone to become easily agitated, irritable, or depressed and go through mood swings or lability. While many common side effects can be relieved by adjusting the dosage or avoiding an afternoon or evening dose, some require treatment emergently to prevent complications.

Sudden death in both children and adults with a pre-existing structural cardiac abnormality has been reported. Stroke and myocardial infarction also have been observed in adults. Due to the risk of such fatal side effects, it is advisable to avoid methylphenidate in patients with a structural cardiac abnormality, cardiomyopathy, or arrhythmias.

Drug-Drug Interactions

- Methylphenidate can inhibit the metabolism of warfarin, phenytoin, tricyclic antidepressants, or selective serotonin reuptake inhibitors and increase plasma concentration.
- Methylphenidate may lower the effectiveness of medicines used to treat hypertension; blood pressure should be monitored, and the dosage of the antihypertensive drug should be adjusted as needed.
- The concurrent administration of halogenated anesthetics and methylphenidate may enhance the risk of sudden heart rate and blood pressure increases during surgery; methylphenidate should not be administered to patients receiving anesthetics on the day of the surgical procedure.
- Combined use of risperidone with methylphenidate may increase the risk of extrapyramidal symptoms (EPS), particularly when there is a change (increase or decrease) in the dosage of either medication.
- Patients receiving monoamine oxidase inhibitors (MAOIs) should not be administered methylphenidate. A minimum of 14 days after discontinuing MAOIs must elapse before methylphenidate can be considered a safe treatment option to begin due to the risk of hypertensive crisis.

Contraindications

Medical conditions that are not compatible with methylphenidate include glaucoma, severe hypertension, motor tics, Tourette syndrome, or a family history of Tourette syndrome. Any patient who is noticeably anxious, tense, or agitated should receive alternative treatment. However, it can be given cautiously in patients with a history of bipolar disorder or psychosis as long as clinicians are wary of mania or psychotic episodes induced by the medication.

Any patient who develops a hypersensitive reaction to methylphenidate or an individual component of a formulation should have the medication immediately discontinued and switch to another pharmacologic agent. Children younger than 6 should not be prescribed this medication

as there are limited studies to prove its safety or benefit, and it could cause learning impairments.

Monitoring

Since it has the potential risk of abuse, patients receiving methylphenidate should be monitored for signs of dependence and or abuse while on therapy. A complete blood count with differential should be obtained periodically for those on methylphenidate. The primary vital signs to record at each visit are blood pressure and heart rate, especially in patients with underlying hypertension, heart failure, a recent MI, or ventricular arrhythmia, as slight elevations can occur with methylphenidate use. Additionally, if a patient complains of cardiac symptoms, such as chest pain, that worsens with exertion or has a near-syncope episode, then a full cardiac workup should be performed.

Children receiving methylphenidate should have their growth curves closely monitored for a stable progression in height and weight, as this medication is known to suppress growth when used daily and long-term. The medication should either be readjusted or discontinued if children are not in a healthy percentile on their growth curve. Clinicians should screen for symptoms of depression, agitation, aggressiveness, new-onset or pre-existing psychosis or mania, and suicidality, as these can be exacerbated during treatment initiation. Clinicians should also monitor for signs of intravenous abuse as frank psychotic episodes can develop. Clinicians should look for peripheral vasculitis (digital ulceration) during physical exams.

Controversial evidence exists regarding the potential for methylphenidate to affect seizure threshold. If seizures develop while being treated with methylphenidate, treatment should immediately stop. Adults should limit their alcohol use while taking methylphenidate as its stimulant action can mask the actual sedative effect caused by alcohol intoxication, possibly inducing severe respiratory depression. Additionally, a patient who is concurrently on warfarin, phenytoin, tricyclic antidepressants, or selective serotonin reuptake inhibitors should have their drug levels monitored and adjust doses as needed.

Toxicity

The first step in a medication overdose is to immediately contact a poison control center for the appropriate management steps. Doses that exceed 60 mg of the immediate-release formulation or 120 mg of the extended-release formulation can be considered toxic. If the overdosed quantity is unknown, the patient should be assessed for signs and symptoms such as tremors, hyperreflexia, convulsions, euphoria, confusion, hallucinations, delirium, flushing, and fever, in addition to the common adverse effects mentioned above. Supportive care with supplemental oxygen, intravenous fluids, and external cooling methods is the mainstay of treatment. Multiple studies have shown that benzodiazepines are an option, especially if dystonia, agitation, or convulsions are present.

Enhancing Healthcare Team Outcomes

Gathering a thorough history from the patient (or the patient's legal guardian) regarding their past medical history, current medications, and social history (obtain a developmental history if the patient is a child) is essential. An interprofessional healthcare team consisting of the patient's primary care provider, psychiatrist, nurse practitioners, clinician assistants, social workers, therapists, school teachers, and pharmacists should oversee the patient's case. Communication between each healthcare team member is crucial as medication combined with non-pharmacologic treatment measures provide the most long-term success. Evaluation of adverse effects requires close monitoring at each visit. Educating the patient's legal guardian on the medication and its side effects is crucial if the patient is a child. This interprofessional approach will optimize therapeutic results while limiting adverse events.

Outcomes

Studies have shown that medication alone is not as effective as when methylphenidate is combined with non-pharmacologic treatment measures. Patients with ADHD managed on both medication and non-pharmacologic treatments have been shown to have higher self-esteem and social functioning skills versus those untreated. Long-term beneficial effects have been shown in adults with ADHD who continue to take methylphenidate. Further long-term studies are still in progress.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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