METHYLPHENIDATE (D)

**Brands**
- Focalin
- Focalin XR

*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: dopamine, norepinephrine reuptake inhibitor and releaser (DN-RIRer)
- Stimulant

**Commonly Prescribed for**
(bold for FDA approved)
- Attention deficit hyperactivity disorder (ADHD) in children ages 6–17 (Focalin, Focalin XR) and in adults (Focalin XR)
- Narcolepsy
- Treatment-resistant depression

**How the Drug Works**
- Increases norepinephrine and especially dopamine actions by blocking their reuptake
- Enhancement of dopamine and norepinephrine actions in certain brain regions (e.g., dorsolateral prefrontal cortex) may improve attention, concentration, executive function, and wakefulness
- Enhancement of dopamine actions in other brain regions (e.g., basal ganglia) may improve hyperactivity
- Enhancement of dopamine and norepinephrine in yet other brain regions (e.g., medial prefrontal cortex, hypothalamus) may improve depression, fatigue, and sleepiness

**How Long Until It Works**
- Onset of action can occur 30 minutes post-administration
- Can take several weeks to attain maximum therapeutic benefit

**If It Works (for ADHD)**
- The goal of treatment of ADHD is reduction of symptoms of inattentiveness, motor hyperactivity, and/or impulsiveness that disrupt social, school, and/or occupational functioning
- Continue treatment until all symptoms are under control or improvement is stable and then continue treatment indefinitely as long as improvement persists
- Reevaluate the need for treatment periodically
- Treatment for ADHD begun in childhood may need to be continued into adolescence and adulthood if continued benefit is documented

**If It Doesn’t Work (for ADHD)**
- Consider adjusting dose or switching to a formulation of d,l-methylphenidate or to another agent
- Consider behavioral therapy
- Consider the presence of noncompliance and counsel patient and parents
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., bipolar disorder, substance abuse, medical illness, etc.)
- Some ADHD patients and some depressed patients may experience lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require either augmenting with a mood stabilizer or switching to a mood stabilizer

**Best Augmenting Combos**

**for Partial Response or Treatment Resistance**
- Best to attempt other monotherapies prior to augmenting
- For the expert, can combine immediate-release formulation of d-methylphenidate with a sustained-release formulation of d-methylphenidate for ADHD
- For the expert, can combine with modafinil or atomoxetine for ADHD
- For the expert, can occasionally combine with atypical antipsychotics in highly treatment-resistant cases of bipolar disorder or ADHD
- For the expert, can combine with antidepressants to boost antidepressant efficacy in highly treatment-resistant cases of depression while carefully monitoring patient

**Tests**
- Before treatment, assess for presence of cardiac disease (history, family history, physical exam)
- Blood pressure should be monitored regularly
- In children, monitor weight and height
- Periodic complete blood cell and platelet counts may be considered during prolonged therapy (rare leukopenia and/or anemia)
**SIDE EFFECTS**

**How Drug Causes Side Effects**
- Increases in norepinephrine peripherally can cause autonomic side effects, including tremor, tachycardia, hypertension, and cardiac arrhythmias
- Increases in norepinephrine and dopamine centrally can cause CNS side effects such as insomnia, agitation, psychosis, and substance abuse

**Notable Side Effects**
- Insomnia, headache, exacerbation of tics, nervousness, irritability, overstimulation, tremor, dizziness
- Anorexia, nausea, abdominal pain, weight loss
- Can temporarily slow normal growth in children (controversial)
- Blurred vision

**Life-Threatening or Dangerous Side Effects**
- Psychotic episodes, especially with parenteral abuse
- Rare priapism
- Seizures
- Palpitations, tachycardia, hypertension
- Rare neuroleptic malignant syndrome
- Rare activation of hypomania, mania, or suicidal ideation (controversial)
- Cardiovascular adverse effects, sudden death in patients with preexisting cardiac structural abnormalities

**Weight Gain**
- Reported but not expected
- Some patients may experience weight loss

**Sedation**
- Reported but not expected
- Activation much more common than sedation

**What to Do About Side Effects**
- Wait
- Adjust dose
- Switch to a formulation of d,l-methylphenidate
- Switch to another agent

**For insomnia, avoid dosing in afternoon/evening**

**Best Augmenting Agents for Side Effects**
- Beta blockers for peripheral autonomic side effects
- Dose reduction or switching to another agent may be more effective since most side effects cannot be improved with an augmenting agent

**DOSING AND USE**

**Usual Dosage Range**
- 2.5–10 mg twice per day

**Dosage Forms**
- Immediate-release tablet 2.5 mg, 5 mg, 10 mg
- Extended-release capsule 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg

**How to Dose**
- Immediate-release: for patients who are not taking racemic d,l-methylphenidate, initial 2.5 mg twice per day in 4-hour intervals; may adjust dose in weekly intervals by 2.5–5 mg/day; maximum dose generally 10 mg twice per day
- Immediate-release: for patients currently taking racemic d,l-methylphenidate, initial dose should be half the current dose of racemic d,l-methylphenidate; maximum dose generally 10 mg twice per day
- Extended-release: for children, same titration schedule as immediate-release but dosed once in the morning; maximum dose 30 mg/day
- Extended-release: for adults not taking racemic d,l-methylphenidate, initial 10 mg/day in the morning; may adjust dose in weekly intervals by 10 mg/day; maximum dose generally 40 mg/day

**Dosing Tips**
- Immediate-release d-methylphenidate has the same onset of action and duration of action as immediate-release racemic d,l-methylphenidate (i.e., 2–4 hours) but at half the dose
**How to Stop**
- Taper to avoid withdrawal effects
- Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder and may require follow-up and reinstitution of treatment
- Careful supervision is required during withdrawal from abusive use since severe depression may occur

**Pharmacokinetics**
- d-threo-enantiomer of racemic d,l-methylphenidate
- Mean plasma elimination half-life approximately 2.2 hours (same as d,l-methylphenidate)
- Does not inhibit CYP450 enzymes

**Drug Interactions**
- May affect blood pressure and should be used cautiously with agents used to control blood pressure
- May inhibit metabolism of SSRIs, anticonvulsants (phenobarbital, phenytoin, primidone), TCAs, and coumarin anticoagulants, requiring downward dosage adjustments of these drugs
- Serious adverse effects may occur if combined with clonidine (controversial)
- Use with MAOIs, including within 14 days of MAOI use, is not advised, but this can sometimes be considered by experts who monitor depressed patients closely when other treatment options for depression fail
- CNS and cardiovascular actions of d-methylphenidate could theoretically be enhanced by combination with agents that block norepinephrine reuptake, such as the TCAs desipramine or protriptyline, venlafaxine, duloxetine, atomoxetine, milnacipran, and reboxetine
- Theoretically, antipsychotics should inhibit the stimulatory effects of d-methylphenidate
- Theoretically, d-methylphenidate could inhibit the antipsychotic actions of antipsychotics
- Theoretically, d-methylphenidate could inhibit the mood-stabilizing actions of atypical antipsychotics in some patients
- Combinations of d-methylphenidate with mood stabilizers (lithium, anticonvulsants,
atypical antipsychotics) is generally something for experts only, when monitoring patients closely and when other options fail
• Antacids or acid suppressants could alter the release of extended-release formulation

Other Warnings/Precautions
• Use with caution in patients with any degree of hypertension, hyperthyroidism, or history of drug abuse
• Children who are not growing or gaining weight should stop treatment, at least temporarily
• May worsen motor and phonic tics
• May worsen symptoms of thought disorder and behavioral disturbance in psychotic patients
• Stimulants have a high potential for abuse and must be used with caution in anyone with a current or past history of substance abuse or alcoholism or in emotionally unstable patients
• Administration of stimulants for prolonged periods of time should be avoided whenever possible or done only with close monitoring, as it may lead to marked tolerance and drug dependence, including psychological dependence with varying degrees of abnormal behavior
• Particular attention should be paid to the possibility of subjects obtaining stimulants for nontherapeutic use or distribution to others and the drugs should in general be prescribed sparingly with documentation of appropriate use
• Usual dosing has been associated with sudden death in children with structural cardiac abnormalities
• Not an appropriate first-line treatment for depression or for normal fatigue
• May lower the seizure threshold
• Emergence or worsening of activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of a mood stabilizer and/or discontinuation of d-methylphenidate

Do Not Use
• If patient has extreme anxiety or agitation

• If patient has motor tics or Tourette’s syndrome or if there is a family history of Tourette’s, unless administered by an expert in cases when the potential benefits for ADHD outweigh the risks of worsening tics
• Should generally not be administered with an MAOI, including within 14 days of MAOI use, except in heroic circumstances and by an expert
• If patient has glaucoma
• If patient has structural cardiac abnormalities
• If patient has angioedema or anaphylaxis
• If there is a proven allergy to methylphenidate

SPECIAL POPULATIONS

Renal Impairment
• No dose adjustment necessary

Hepatic Impairment
• No dose adjustment necessary

Cardiac Impairment
• Use with caution, particularly in patients with recent myocardial infarction or other conditions that could be negatively affected by increased blood pressure
• Do not use in patients with structural cardiac abnormalities

Elderly
• Some patients may tolerate lower doses better

Children and Adolescents
• Safety and efficacy not established in children under age 6
• Use in young children should be reserved for the expert
• Methylphenidate has acute effects on growth hormone; long-term effects are unknown but weight and height should be monitored during long-term treatment
• Sudden death in children and adolescents with serious heart problems has been reported
• American Heart Association recommends EKG prior to initiating stimulant treatment in children, although not all experts agree
### Methylenidate (D)

**Impulsiveness**  
**Physical and mental fatigue**  
**Daytime sleepiness**  
**Depression**

**Pearls**

- May be useful for treatment of depressive symptoms in medically ill elderly patients
- May be useful for treatment of post-stroke depression
- A classical augmentation strategy for treatment-refractory depression
- Specifically, may be useful for treatment of cognitive dysfunction and fatigue as residual symptoms of major depressive disorder unresponsive to multiple prior treatments
- May also be useful for the treatment of cognitive impairment, depressive symptoms, and severe fatigue in patients with HIV infection and in cancer patients
- Can be used to potentiate opioid analgesia and reduce sedation, particularly in end-of-life management
- Atypical antipsychotics may be useful in treating stimulant or psychotic consequences of overdose
- Some patients respond to or tolerate methylphenidate better than amphetamine, and vice versa
- Taking with food may delay peak actions of immediate-release d-methylphenidate for 2–3 hours
- Half-life and duration of clinical action tend to be shorter in younger children
- Drug abuse may actually be lower in ADHD adolescents treated with stimulants than in ADHD adolescents who are not treated
- New extended-release formulation is truly a once daily dose
- Extended-release capsule can be sprinkled over applesauce for patients unable to swallow the capsule
- Some patients may benefit from an occasional addition of an immediate-release dose of d-methylphenidate to the daily base dose of extended-release d-methylphenidate

**Pregnancy**

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Infants whose mothers took methylphenidate during pregnancy may experience withdrawal symptoms
- Racemic methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day throughout organogenesis
- Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
- For ADHD patients, methylphenidate should generally be discontinued before anticipated pregnancies

**Breast Feeding**

- Unknown if methylphenidate is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed
- If infant shows signs of irritability, drug may need to be discontinued

**Potential Advantages**

- The active d enantiomer of methylphenidate may be slightly more than twice as efficacious as racemic d,l-methylphenidate

**Potential Disadvantages**

- Patients with current or past substance abuse, bipolar disorder, or psychosis

**Primary Target Symptoms**

- Concentration, attention span
- Motor hyperactivity

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THE ART OF PSYCHOPHARMACOLOGY
Suggested Reading
