METHYLPHENIDATE (D,L)

Therapeutics

Brands
• Concerta
• Metadate CD
• Ritalin
• Ritalin LA
• Methylin
• QuilliChew ER
• Quillivant XR
• Aptensio XR
• Daytrana

see index for additional brand names

Generic? Yes

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

Commonly Prescribed for
(bold for FDA approved)
• Attention deficit hyperactivity disorder (ADHD) in children and adults (approved ages vary based on formulation)
• Narcolepsy (Metadate ER, Methylin ER, Ritalin, Ritalin SR)
• 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
• Some immediate effects can be seen with first dosing
• 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 another 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 with a sustained-release formulation of d,l-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
METHYLPHENIDATE (D,L) (continued)

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
- Transdermal: application site reactions, including contact sensitization (erythema, edema, papules, vesicles) and chemical leukoderma

Life-Threatening or Dangerous Side Effects
- Rare priapism
- Psychotic episodes, especially with parenteral abuse
- 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 another 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
- ADHD (oral): up to 2 mg/kg per day in children 6 years and older, with a maximum daily dose of 60 mg/day; in adults usually 20–30 mg/day, but may use up to 40–60 mg/day
- ADHD (transdermal): 10–30 mg/9 hours
- Narcolepsy: 20–60 mg/day in 2–3 divided doses

Dosage Forms
- Immediate-release tablets 5 mg, 10 mg, 20 mg (Ritalin, generic methylphenidate)
- Oral solution 5 mg/mL, 10 mg/5 mL (Methylin)
- Older sustained-release tablets 10 mg, 20 mg (Methylin ER); 20 mg (Ritalin SR, Metadate ER)
- Newer sustained-release capsules 10 mg, 20 mg, 30 mg, 40 mg, 60 mg (Ritalin LA);
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (Methadate CD)

> Newer sustained-release tablets 18 mg, 27 mg, 36 mg, 54 mg (Concerta)

- Sustained-release chewable tablets 20 mg scored, 30 mg, 40 mg (QuilliChew ER)
- Extended-release capsule, multi-layer release (Aptensio XR) 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg
- Extended-release oral suspension 5 mg/mL (Quillivant XR)
- Transdermal formulation for ADHD
  - Initial 10 mg/9 hours; can increase by 5 mg/9 hours every week; maximum dose generally 30 mg/9 hours
  - Patch should be applied 2 hours before effect is needed and should be worn for 9 hours
  - Patients should follow the same titration schedule when they are naive to methylphenidate or are switching from another formulation

**How to Dose**

- Immediate-release Ritalin, generic methylphenidate (2–4 hour duration of action)
  - ADHD: initial 5 mg in morning, 5 mg at lunch; can increase by 5–10 mg each week; maximum dose generally 60 mg/day
  - Narcolepsy: give each dose 30–45 minutes before meals; maximum dose generally 60 mg/day
- Older extended-release Ritalin SR, Methylin SR, and Metadate ER
  - These formulations have a duration of action of approximately 4–6 hours; therefore, these formulations may be used in place of immediate-release formulations when the 4–6 hour dosage of these sustained-release formulations corresponds to the titrated 4–6 hour dosage of the immediate-release formulation
  - Average dose is 20–30 mg/day, usually in 2 divided doses
- Newer sustained-release formulations for ADHD
  - Concerta (up to 12 hours duration of action): initial 18 mg/day in morning; can increase by 18 mg each week; maximum dose generally 72 mg/day
  - Ritalin LA, Metadate CD, QuilliChew ER (up to 8 hours duration of action): initial 20 mg once daily; dosage may be adjusted in weekly increments of 10 mg or 20 mg (QuilliChew ER only) to a maximum of 60 mg/day taken in the morning

- Quillivant XR (up to 12-hour duration): initial 20 mg once daily; dosage may be adjusted in weekly increments of 10–20 mg to a maximum of 60 mg/day taken in the morning
- Aptensio XR (up to 12-hour duration): initial 10 mg once daily; dosage may be adjusted in weekly increments of 10 mg to a maximum of 60 mg/day taken in the morning

**Dosing Tips**

- Clinical duration of action often differs from pharmacokinetic half-life
- Taking oral formulations with food may delay peak actions for 2–3 hours
- Immediate-release formulations (Ritalin, Methylin, generic methylphenidate) have 2–4 hour durations of clinical action
- Older sustained-release formulations such as Methylin ER, Ritalin SR, Metadate ER, and generic methylphenidate sustained-release all have approximately 4–6 hour durations of clinical action, which for most patients is generally not long enough for once daily dosing in the morning and thus generally requires lunchtime dosing at school
- The newer sustained-release Metadate CD has an early peak and an 8-hour duration of action
- The newer sustained-release Ritalin LA also has an early peak and an 8-hour duration of action, with 2 pulses (immediate and after 4 hours)
- The newer sustained-release Concerta tri-layer tablet has longest duration of action (12 hours)
- Most sustained-release formulations (especially Concerta, Metadate CD, and Ritalin LA) should not be chewed but rather should only be swallowed whole
Overdose
- Vomiting, tremor, coma, convulsion, hyperreflexia, euphoria, confusion, hallucination, tachycardia, flushing, palpitations, sweating, hyperpyrexia, hypertension, arrhythmia, mydriasis

Long-Term Use
- Often used long-term for ADHD when ongoing monitoring documents continued efficacy
- Dependence and/or abuse may develop
- Tolerance to therapeutic effects may develop in some patients
- Long-term stimulant use may be associated with growth suppression in children (controversial)
- Periodic monitoring of weight, blood pressure, CBC, platelet counts, and liver function may be prudent

Habit Forming
- High abuse potential, Schedule II drug
- Patients may develop tolerance, psychological dependence

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
- Average half-life in adults is 3.5 hours (1.3–7.7 hours)
- Average half-life in children is 2.5 hours (1.5–5 hours)
- First-pass metabolism is not extensive with transdermal dosing, thus resulting in notably higher exposure to methylphenidate and lower exposure to metabolites as compared to oral dosing

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
METHYLPHENIDATE (D,L)

-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,l-methylphenidate

-Permanent skin color loss, known as chemical leukoderma, may occur with use of the transdermal Daytrana patch; patients should be advised to watch for signs of skin color changes and if they occur alternative treatment options should be considered

-Some transdermal patches containing even small traces of aluminum or other metals in the adhesive backing can cause skin burns if worn during MRI, so warn patients taking the transdermal formulation about this possibility and advise them to disclose this information if they need an MRI

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

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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 there is a proven allergy to methylphenidate

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(continued)
METHYLPHENIDATE (D,L) (continued)

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

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

Renal Impairment
• 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

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
• Established long-term efficacy as a first-line treatment for ADHD
• Multiple options for drug delivery, peak actions, and duration of action

Potential Disadvantages
• Patients with current or past substance abuse
• Patients with current or past bipolar disorder or psychosis

Primary Target Symptoms
• Concentration, attention span
• Motor hyperactivity
• 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

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 (PLLRR 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
METHYLPHENIDATE (D,L)

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 oral formulations 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

• Older sustained-release technologies for methylphenidate were not significant advances over immediate-release methylphenidate because they did not eliminate the need for lunchtime dosing or allow once daily administration

★ Newer sustained-release technologies are truly once a day dosing systems

★ Metadate CD and Ritalin LA are somewhat similar to each other, both with an early peak and duration of action of about 8 hours

★ Concerta has less of an early peak but a longer duration of action (up to 12 hours)

★ Concerta trilayer tablet consists of 3 compartments (2 containing drug, 1 a “push” compartment) and an orifice at the head of the first drug compartment; water fills the push compartment and gradually pushes drug up and out of the tablet through the orifice

★ Concerta may be preferable for those ADHD patients who work in the evening or do homework up to 12 hours after morning dosing

★ Metadate CD and Ritalin LA may be preferable for those ADHD patients who lose their appetite for dinner or have insomnia with Concerta

• Some patients may benefit from an occasional addition of 5–10 mg of immediate-release methylphenidate to their daily base of sustained-release methylphenidate

• Transdermal formulation may confer lower abuse potential than oral formulations

• Transdermal formulation may enhance adherence to treatment compared to some oral formulations because it allows once daily application with all day efficacy, has a smoother absorption curve, and allows for daily customization of treatment (i.e., it can be removed early if desired)

• On the other hand, transdermal formulation has slower onset than oral formulations, requires a specific removal time, can cause skin sensitization, can be large depending on dose, and may lead to reduced efficacy if removed prematurely

Suggested Reading

