

DRUGDEX-EV 0875

MICROMEDEX

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METHYLPHENIDATE

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0.0] Overview

1] Class

a)] This drug is a member of the following class(es):

Central Nervous System Agent
CNS Stimulant

2] Dosing Information

a)] [Methylphenidate](#)

1] Pediatric

a)] [Attention deficit hyperactivity disorder](#)

1)] apply TOPICALLY 2 hours before needed effect and remove 9 hours after application; week 1: 10 mg (12.5 cm(2)); week 2: 15 mg (18.75 cm(2)); week 3: 20 mg (25 cm(2)); week 4: 30 mg (37.5 cm(2)); titrate dose to effect [1]

b)] [Methylphenidate Hydrochloride](#)

1] Adult

a)] individualize dose according to need and response of patient [14][10][11][13][12][15]

1] Attention deficit hyperactivity disorder

a)] (immediate-release tablets, solution, and chewable tablets) 10 to 60 mg/day ORALLY divided 2 to 3 times daily, preferably 30 to 45 minutes before meals [10][11][12]

b)] (extended-release (Concerta(R)) (age up to 65 years) no prior methylphenidate therapy, initial, 18 or 36 mg ORALLY once daily in the

morning; may adjust dosage at weekly intervals in 18 mg increments; MAX 72 mg/day [13]

c) (extended-release (Concerta(R)) (age up to 65 years) conversion from prior methylphenidate therapy, taken 2 or 3 times a day (prior therapy of 10 to 15 mg/day), 18 mg ORALLY in morning; (prior therapy of 20 to 30 mg/day); 36 mg in morning; (prior therapy of 30 to 45 mg/day), 54 mg in morning; (prior therapy of 40 to 60 mg/day), 72 mg in morning [13]

d) (extended-release (Metadate(R) CD) 20 mg ORALLY once daily in the morning; may adjust dosage at weekly intervals in 20 mg increments; MAX 60 mg/day

e) (extended-release (Ritalin LA(R)) no prior methylphenidate therapy, 20 mg ORALLY once daily in the morning; may adjust dosage at weekly intervals in 10 mg increments; MAX 60 mg/day

f) (extended-release (Ritalin LA(R)) prior methylphenidate therapy, once daily (taken in the morning) ORAL dose of Ritalin LA(R) equivalent to the total daily oral dose of prior methylphenidate therapy; may adjust dosage at weekly intervals in 10 mg increments; MAX 60 mg/day

g) (extended-release oral suspension) 20 mg ORALLY once daily in the morning; titrate at weekly intervals in 10 to 20 mg increments; MAX 60 mg/day [14]

h) (sustained-release (Ritalin SR(R)) 20 to 60 mg/day ORALLY divided every 8 hours [15]

2j) Narcolepsy

a) (immediate-release tablets, solution, and chewable tablets) 10 to 60 mg/day ORALLY divided 2 to 3 times daily, preferably 30 to 45 minutes before meals [10][11][12]

b) (sustained-release (Ritalin SR(R)) 20 to 60 mg/day ORALLY divided every 8 hours [15]

2j) Pediatric

a) Attention deficit hyperactivity disorder

1) (immediate-release tablets, solution, and chewable tablets) (age 6 years and older) initial, 5 mg ORALLY twice daily (before breakfast and lunch); dose adjustments of 5 to 10 mg at weekly intervals; doses above 60 mg/day not recommended [10][11][12]

2) (extended-release (Concerta(R)) (age 6 to 12 years) no prior methylphenidate therapy, initial, 18 mg ORALLY once daily in the morning; may adjust dosage at weekly intervals in 18 mg increments; MAX 54 mg/day [13]

3j) (extended-release (Concerta(R)) (age 13 to 17 years) no prior methylphenidate therapy, initial, 18 mg ORALLY once daily in the morning; may adjust dosage at weekly intervals in 18 mg increments; MAX 72 mg/day or 2 mg/kg/day [13]

4j)(extended-release (Concerta(R)) (age 6 to 17 years) conversion from prior methylphenidate therapy taken 2 or 3 times a day, (prior therapy of 10 to 15 mg/day), 18 mg ORALLY in morning; (prior therapy of 20 to 30 mg/day), 36 mg in morning; (prior therapy of 30 to 45 mg/day), 54 mg in morning [13]

5j) (extended-release (Concerta(R)) (age 13 to 17 years) conversion from prior methylphenidate therapy taken 2 or 3 times a day (prior therapy of 40 to 60 mg/day), 72 mg ORALLY in the morning [13]

6j) (extended-release (Metadate(R) CD), (age 6 years or older) 20 mg ORALLY once daily in the morning; may adjust dosage at weekly intervals in 20 mg increments; MAX 60 mg/day

7j) (extended-release (Ritalin LA(R)), (no prior methylphenidate therapy), 20 mg ORALLY once daily in the morning; may adjust dosage at weekly intervals in 10 mg increments; MAX 60 mg/day

8j) (extended-release (Ritalin LA(R)), (prior methylphenidate therapy), once daily (taken in the morning) ORAL dose of Ritalin LA(R) equivalent to the total daily oral dose of prior methylphenidate therapy; may adjust dosage at weekly intervals in 10 mg increments; MAX 60 mg/day

9j) (extended-release oral suspension) 20 mg ORALLY once daily in the morning; titrate at weekly intervals in 10 to 20 mg increments; MAX 60 mg/day [14]

10j) (sustained-release, Ritalin-SR(R) (age 6 years or older) 20 to 60 mg/day ORALLY divided every 8 hours; doses above 60 mg/day not recommended [15]

bj) Narcolepsy

1j) (immediate-release tablets, solution, and chewable tablets) (6 years or older) 5 mg ORALLY twice daily (before breakfast and lunch); dose adjustments of 5 to 10 mg at weekly intervals; doses above 60 mg/day not recommended [10][11][12]

2j) (sustained-release (Ritalin-SR(R)) (6 years or older) 20 to 60 mg/day ORALLY divided every 8 hours; doses above 60 mg/day not recommended [15]

3j) Contraindications

aj) Methylphenidate

1j) concomitant use of MAOIs, or use within 14 days of MAOI administration [29]

2j) glaucoma [29]

3j) hypersensitivity to methylphenidate or other components of the product [29]

- 4)) marked agitation, anxiety, and tension; may aggravate symptoms [29]
- 5)) motor tics [29]
- 6)) [Tourette syndrome](#) with a family history or diagnosis [29]

b)) [Methylphenidate](#) Hydrochloride

- 1)) angina pectoris [36]
- 2)) [cardiac arrhythmias](#) [36]
- 3)) concomitant use of MAOIs, or use within 14 days of MAOI administration [35][36][14][37]
- 4)) concomitant use with halogenated anesthetics; do not take on day of surgery [36]
- 5)) family history or diagnosis of [Tourette syndrome](#) [35][36][37]
- 6)) fructose intolerance, [glucose-galactose malabsorption](#), or sucrase-isomaltase insufficiency; contains sucrose [36]
- 7)) [glaucoma](#) [35][36][37]
- 8)) [heart failure](#) [36]
- 9)) hypersensitivity to [methylphenidate](#) or other components of the product [35][36][14][37]
- 10)) [hyperthyroidism](#) or [thyrotoxicosis](#) [36]
- 11)) marked agitation, anxiety, and tension; may aggravate symptoms [35][36][37]
- 12)) motor tics [35][36][37]
- 13)) recent [myocardial infarction](#) [36]
- 14)) severe [hypertension](#) [36]

4)) Serious Adverse Effects

a)) [Methylphenidate](#)

- 1)) [Contact dermatitis](#)
- 2)) Decreased body growth
- 3)) Drug dependence
- 4)) Lowered convulsive threshold
- 5)) Mania
- 6)) [Peripheral vascular disease](#)
- 7)) [Priapism](#)

- 8)) Psychotic disorder
- 9)) Raynaud's disease
- 10)) Skin hypopigmented
- 11)) Tic

b)) Methylphenidate Hydrochloride

- 1)) Abnormal liver function
- 2)) Aggressive behavior
- 3)) Blurred vision
- 4)) Cerebral artery occlusion
- 5)) Cerebral hemorrhage
- 6)) Cerebrovascular accident
- 7)) Decreased body growth
- 8)) Gastrointestinal obstruction, With preexisting severe gastrointestinal narrowing and use of controlled-release formulations
- 9)) Mania
- 10)) Myocardial infarction
- 11)) Priapism
- 12)) Psychotic disorder
- 13)) Raynaud's phenomenon
- 14)) Seizure
- 15)) Sudden cardiac death

5)) Clinical Applications

a)) Methylphenidate

- 1)) FDA Approved Indications
 - a)) Attention deficit hyperactivity disorder

b)) Methylphenidate Hydrochloride

- 1)) FDA Approved Indications

a) [Attention deficit hyperactivity disorder](#)

b) [Narcolepsy](#)

1.0] Dosing Information

[Drug Properties](#)

[Storage and Stability](#)

[Adult Dosage](#)

[Pediatric Dosage](#)

1.1] Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

[Methylphenidate](#)

[Methylphenidate HCl](#)

[Methylphenidate Hydrochloride](#)

Methylphenidylacetate

C) Physicochemical Properties

1) Molecular Weight

a) [Methylphenidate](#): 233.31 [1]; [Methylphenidate](#) hydrochloride: 269.77 [276]

2) Solubility

a) [Methylphenidate](#) is soluble in alcohol, ethyl acetate, and ether and practically insoluble in water and petrol ether [1]. [Methylphenidate](#) hydrochloride is freely soluble in water and methanol, soluble in alcohol, and slightly soluble in chloroform and acetone [276].

1.2] Storage and Stability

A) [Methylphenidate](#)

1) Preparation

a) Topical application route

1) Application

a) Apply the patch to a clean, dry area of the hip area 2 hours before effect is needed. Avoid the waistline, since clothing may cause the patch to rub off. The next morning, apply the patch on the opposite hip at a new site if possible [1].

b) Apply the patch immediately after opening the pouch and removing the protective liner. Do not use if the pouch seal is broken. Apply the patch, then press firmly in place with palm of the hand for approximately 30 seconds. Ensure

good contact with the skin, especially around the edges. Once the patch has been properly placed, bathing, swimming, or showering will not affect patch adherence. If a patch should fall off, a new patch may be applied at a different site, but the total recommended wear time for that day should remain 9 hours. Do not expose the patch application site to a direct external heat source. Temperature-dependent increases in methylphenidate exposure of greater than 2 times from the patch may occur [1].

2) Disposal Of Patch

a) After removal, fold so the patch adheres to itself. The folded patch may be flushed down the toilet or disposed of in a lidded container. If the patient discontinues the prescription, each unused patch should be removed from its pouch, separated from the protective liner, folded onto itself, and flushed down the toilet or disposed of in a lidded container [1].

B) Methylphenidate Hydrochloride

1) Preparation

a) Oral route

1) For extended-release tablets, the dose should be given once daily in the morning, with or without food. The tablets should be swallowed whole with liquids and must not be chewed, divided, or crushed [13].

2) For extended-release capsules, the dose should be given once daily in the morning. Capsules may be swallowed (whole) or the contents sprinkled over a spoonful of applesauce; the applesauce should not be warm, and the drug/applesauce mixture should be consumed immediately in its entirety [25]. Capsule contents of Ritalin(R) LA should not be crushed, chewed, or divided [25].

3) For immediate-release tablets, solution, and chewable tablets, take 30 to 45 minutes before meals. If patient is unable to sleep when medication is taken late in the day, the last dose should be taken before 6 PM [10][11][12]

4) For the extended-release oral suspension, shake the reconstituted suspension vigorously for 10 seconds before each dose is measured. May be taken with or without food. Extended-release suspension is stable for up to 4 months after reconstitution [14].

5) For sustained-release tablets, swallow whole; do not chew or crush [15].

C) Methylphenidate

1) Transdermal route

a) Patch, Extended Release

1j) Store at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted between 15 and 30 degrees Celsius (59 and 86 degrees Fahrenheit). Do not store patches unpouched. Use within 2 months after opening tray [82].

Dj) Methylphenidate Hydrochloride

1j) Oral route

aj) Capsule, Extended Release/Powder for Suspension, Extended Release/Tablet/Tablet, Extended Release

1j) Store at controlled room temperature, 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [14][168]. Protect tablets (immediate-release) from light [38] and protect sustained- and extended-release tablets from moisture [169][13].

2j) Reconstituted extended-released suspension is stable for up to 4 months at 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [14].

bj) Solution/Tablet, Chewable

1j) Store at controlled room temperature, between 20 and 25 degrees C (68 and 77 degrees F) [166]. Protect chewable tablets from moisture [167].

1.3j Adult Dosage

1.3.1j Normal Dosage

1.3.1.Aj Methylphenidate Hydrochloride

1.3.1.A.1j Oral route

1.3.1.A.1.aj Attention deficit hyperactivity disorder

1j) Immediate Release

aj) Usual dose: 10 to 60 mg/day orally in 2 or 3 divided doses; the average dose is usually 20 to 30 mg/day [10][11][12]

2j) Extended Release Capsule (Metadate(R) CD)

aj) Initial dose: 20 mg orally once daily in the morning before breakfast

bj) Dose titration: 20-mg increments at weekly intervals

cj) Maximum dose: 60 mg/day [23]

3j) Extended Release Suspension (Quillivant(TM))

aj) Initial dose: 20 mg orally once daily in the morning

bj) Dose titration: 10- to 20-mg increments at weekly intervals

c) Maximum dose: 60 mg/day

d) If extended treatment durations are needed, consider periodic evaluation of long-term usefulness and attempt medication holidays to assess patient functioning without pharmacotherapy [14].

4) Extended Release Tablet ([Concerta\(R\)](#))

a) Initial dose for new patients: 18 or 36 mg orally once daily in the morning

b) Titration: 18-mg increments at weekly intervals

c) Maximum dose: 72 mg/day

d) Patients converting from 2- to 3-times-daily [methylphenidate](#) regimens may follow the dosage conversion recommendation below:

Previous Methylphenidate Daily Dose	Recommended Concerta(R) Starting Dose
5 mg twice or 3 times daily	18 mg in the morning
10 mg twice or 3 times daily	36 mg in the morning
15 mg twice or 3 times daily	54 mg in the morning
20 mg twice or 3 times daily	72 mg in the morning

e) Periodically evaluate the long-term usefulness with trials off medication. Improvement may be maintained when the drug is either temporarily or permanently discontinued. The dosage should be reduced or discontinued if paradoxical aggravation of symptoms or other adverse events occur. If improvement is not observed after appropriate dosage adjustments over a 1-month period, discontinue the drug [13].

5) Sustained Release

a) Usual dose: 20 to 60 mg/day orally, divided every 8 hours [15]

1.3.1.A.1.b) [Narcolepsy](#)

1) Immediate Release

a) Usual dose: 10 to 60 mg orally daily in 2 or 3 divided doses; average dose is 20 to 30 mg/day, 30 to 45 minutes before meals [10][11][12]

2) Sustained Release

a) Usual dose: 20 to 60 mg/day orally, divided every 8 hours [15]

1.3.1.A.2) Individualize dose according to the needs and response of the patient [14][10][11][13][12][15].

1.4) Pediatric Dosage

1.4.1) Normal Dosage

1.4.1.A) [Methylphenidate](#)

1.4.1.A.1) Transdermal route

1.4.1.A.1.a) [Attention deficit hyperactivity disorder](#)

1)) Recommended dose titration schedule for methylphenidate-naïve and methylphenidate-experienced patients aged 6 to 17 years for the treatment of ADHD [1]:

	Titration, if Response is Not Maximized		
	Week 1	Week 2	Week 3
Patch size	12.5 cm(2)	18.75 cm(2)	25 cm(2)
Nominal Delivered Dose *	10 mg/9 hr	15 mg/9 hr	20 mg/9 hr
Delivery rate *	1.1 mg/hr	1.6 mg/hr	2.2 mg/hr

Key: * = Nominal in vivo delivery rate in children and adolescents when applied to the hip, based on a 9-hour wear period

Individualize titration, final dosage, and wear time according to the needs and response of the patient. Apply the patch 2 hours before desired effect and remove 9 hours after application. The patch may be removed earlier than 9 hours, if a shorter duration of effect is preferred or late day side effects occur [1].

1.4.1.B] Methylphenidate Hydrochloride

1.4.1.B.1] Oral route

1.4.1.B.1.a] Attention deficit hyperactivity disorder

1)) Immediate Release

- a)) Initial dose: 5 mg orally twice daily before breakfast and lunch
- b)) Dose titration: 5- to 10-mg increments at weekly intervals based on clinical response
- c)) Maximum dose: 60 mg/day
- d)) Discontinue if there is no improvement after 1 month [10][11][12].
- e)) Dose: 0.3 mg/kg twice daily at 8 am and 12 noon for 14 days improved the attention and concentration behaviors of 14 children with acquired attention disorder secondary to brain injury in a study [24].

2)) Extended Release Capsules (Ritalin LA(R))

- a)) Initial dose: 20 mg orally once daily
- b)) Dose titration: 10-mg increments gradually based on efficacy and tolerability
- c)) Maximum dose: 60 mg/day
- d)) When a lower initial dose is desired, low doses of immediate-release methylphenidate may given; patients can be switched to Ritalin LA(R) following titration to 10 mg twice daily of the immediate-release formulation. The following Ritalin(R) LA dose guidelines are for these latter patients, and those currently receiving immediate-release or sustained-release (SR) methylphenidate who are to be switched to Ritalin(R) LA:

1)) Patients currently receiving methylphenidate 10 mg twice daily or 20-mg methylphenidate-SR should be given Ritalin(R) LA 20 mg once daily

2)) Patients currently receiving methylphenidate 15 mg twice daily should be given Ritalin(R) LA 30 mg once daily

3)) Patients currently receiving methylphenidate 20 mg twice daily or 40-mg methylphenidate-SR should be given Ritalin(R) LA 40 mg once daily

4)) Patients currently receiving methylphenidate 30 mg twice daily or 60-mg methylphenidate-SR should be given Ritalin(R) LA 60 mg once daily [25]

3)) Extended Release Capsule (Metadate(R) CD)

a)) Initial dose: 20 mg orally once daily in the morning before breakfast

b)) Dose titration: 20-mg increments at weekly intervals

c)) Maximum dose: 60 mg/day [23]

4)) Extended Release Suspension (Quillivant(TM))

a)) Initial dose: 20 mg orally once daily in the morning

b)) Dose titration: 10- to 20-mg increments at weekly intervals

c)) Maximum dose: 60 mg/day

d)) If extended treatment durations are needed, consider periodic evaluation of long-term usefulness and attempt medication holidays to assess patient functioning without pharmacotherapy. If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued [14].

5)) Extended Release Tablet (Concerta(R))

a)) Initial dose for patients 6 to 17 years: 18 mg orally once daily in the morning

b)) Titration: 18-mg increments at weekly intervals

c)) Maximum dose: 54 mg/day in children 6 to 12 years and 72 mg/day (not to exceed 2 mg/kg/day) in adolescents 13 to 17 years

d)) Patients converting from 2- to 3-times-daily methylphenidate regimens may follow the dosage conversion recommendation below:

Previous Methylphenidate Daily Dose
5 mg twice or 3 times daily
10 mg twice or 3 times daily
15 mg twice or 3 times daily
20 mg twice or 3 times daily

Recommended Concerta(R) Starting Dose
18 mg in the morning
36 mg in the morning
54 mg in the morning
72 mg in the morning (age 13 to 17 years)

e)) Following conversion, doses may be adjusted weekly if needed, up to the maximum recommended doses.

f)) Periodically evaluate the long-term usefulness with trials off medication. Improvement may be maintained when the drug is either temporarily or permanently discontinued. The dosage should be reduced or discontinued if paradoxical aggravation of symptoms or other adverse events occur. If improvement is not observed after appropriate dosage adjustments over a 1-month period, discontinue the drug [13].

6)) Sustained Release

a) Usual dose: 20 to 60 mg/day orally, divided every 8 hours

b) Maximum dose: 60 mg/day [15]

1.4.1.B.2] Narcolepsy

a) Immediate Release

1) Usual dose: 5 mg orally twice daily, preferably 30 to 45 minutes before breakfast and lunch

2) Dose titration: 5- to 10-mg increments at weekly intervals, based on clinical effect

3) Maximum dose: 60 mg/day [10][11][12]

4) Discontinue if there is no improvement after 1 month [10][11][12].

b) Sustained Release

1) Usual dose: 20 to 60 mg/day orally, divided every 8 hours

2) Maximum dose: 60 mg/day [15]

2.0] Pharmacokinetics

Drug Concentration Levels

ADME

2.2] Drug Concentration Levels

A) Methylphenidate

1) Peak Concentration

a) Transdermal

1) Transdermal: 39 nanograms/mL [44].

a) The mean peak d-methylphenidate plasma concentration was 39 nanograms (ng)/mL (0 to 114 ng/mL) in pediatric children after at least 6 weeks of therapy with 9 hour wear times of transdermal methylphenidate. These mean peak concentrations varied inversely by age ranging from 25 ng/mL (2 to 80 ng/mL) in 12 year olds, to 53 ng/mL (18 to 83 ng/mL) in 6 year olds [44].

b) The mean peak d-methylphenidate concentrations were 1.9 times higher for transdermal methylphenidate compared with once-daily oral methylphenidate over a period of 7.5 to 10.5 hours, when T_{max} usually occurs. These higher concentrations were consistent across all ages. Compared with single dosing and 4 days of multiple dosing, the C_{max} was higher with chronic dosing of transdermal methylphenidate. Single doses of transdermal methylphenidate produced a similar C_{max} as single doses of the once daily oral methylphenidate [44].

2) Time to Peak Concentration

a) Transdermal**1) Transdermal: 7.5 to 10.5 hr [44]**

a) Tmax typically occurs 7.5 to 10.5 hours after patch application. The average lag time (time to any d-methylphenidate is detectable in the circulation) is 3.1 hours (range 1 to 6 hours) [44].

3) Area Under the Curve**a) Transdermal**

1) The AUC of methylphenidate is 2.5 times higher when heat is applied after patch application. The AUC is 3 times higher when the patch is applied to inflamed skin [44].

B) Methylphenidate Hydrochloride**1) Peak Concentration****a) Immediate-release**

1) Oral, multiple-dose, ADHD children: 15.3 nanograms (ng)/mL (10 mg); Adults: 5.3 ng/mL (10 mg) [45], 4.2 ng/mL (5 mg) [151][152]

a) The Cmax following oral administration of 2 immediate-release methylphenidate 10 mg tablets given 4 hours apart was 15.3 +/- 7 nanograms (ng)/mL in ADHD children and 5.3 +/- 1.4 ng/mL in healthy adult males (n=15) [45].

b) The mean Cmax following oral administration of 3 immediate-release methylphenidate 5 mg tablets given every 4 hours was 4.2 +/- 1 ng/mL in healthy adults (n=35) [151][152].

2) Oral, single-dose: ADHD children: 10.2 nanograms (ng)/mL (10 mg)[45]; Adults: 9 to 10 ng/mL (20 mg) [154]; 4.3 ng/mL (10 mg) [45]

a) The Cmax following single-dose oral administration of immediate-release methylphenidate 10 mg tablet was 10.2 +/- 4.2 nanograms (ng)/mL in ADHD children and 4.3 +/- 2.3 ng/mL in healthy adult males (n=15) [45].

b) The mean Cmax following single-dose administration of methylphenidate 20 mg oral solution was 9 nanograms/mL [154].

c) The mean Cmax following single-dose oral administration of a methylphenidate 20 mg chewable tablet was 10 nanograms/mL [155].

b) Extended-release Capsules (Metadate-CD(R); Ritalin-LA(R))

1j) Oral, multiple-dose, ADHD children: 10.9 nanograms/mL (20 mg); 16.8 ng/mL (40 mg) [153]

a) Two distinct peaks are produced following oral administration of Metadate-CD(R) extended-release capsules. The mean first and second C_{max} in ADHD children 7 to 10 years of age following 1 week of once-daily oral administration of Metadate-CD(R) were 8.6 +/- 2.2 and 10.9 +/- 3.9 nanograms (ng)/mL for the 20 mg dose and 16.8 +/- 5.1 and 15.1 +/- 5.8 ng/mL for the 40 mg dose. Approximately one-quarter to one-third of patients experienced only one peak [153].

2j) Oral, single-dose, 20 mg: ADHD children: 10.3 nanograms (ng)/mL; Adults: 6.2 ng/mL [45][152]

a) Two distinct peaks are produced following oral administration of Ritalin-LA(R) extended-release capsules. The mean first and second C_{max} in ADHD children following single-dose oral administration of Ritalin-LA(R) 20 mg were 10.3 +/- 5.1 and 10.2 +/- 5.9 nanograms (ng)/mL and 5.3 +/- 0.9 and 6.2 +/- 1.6 ng/mL in healthy male adults [45].

b) Following single-dose oral administration of Metadate-CD(R) 20 mg extended-release capsules, the mean C_{max} and AUC were slightly lower than the values seen following administration of 2 immediate-release methylphenidate formulations 4 hr apart (at 0 and 4 hr) [153].

c) Extended-release Tablets ([Concerta\(R\)](#))

1j) Oral, single-dose, 18 mg: 3.7 nanograms/mL [151]

a) Following oral administration of Concerta(R) extended-release tablets, methylphenidate levels rise sharply to an initial maximum in about 1 hr, and then gradually increase over the next 5 to 9 hours before gradually decreasing. The mean C_{max} following single-dose oral administration of Concerta(R) 18 mg extended-release tablets was 3.7 +/- 1 nanograms/mL occurring at a mean of 6.8 hr postdose in healthy adults (n=36) [151].

d) Extended-Release Oral Suspension (Quillivant XR (TM))

1j) Oral, single-dose, healthy adults, 60 mg: 13.6 to 17 nanograms/mL [14]

a) In a crossover pharmacokinetic study under fasting conditions, the mean d-methylphenidate plasma C_{max} was 13.6 +/- 5.8 nanograms(ng)/mL in 28 adult healthy volunteers following a single 60 mg oral dose of extended-release methylphenidate oral suspension. When administered 30 minutes after breakfast (n=27), the mean d-methylphenidate plasma C_{max} was 17 +/- 7.7 ng/mL [14].

2j) Oral, single dose, children with ADHD, 60 mg: 34.4 nanograms/mL [14]

a) In a pharmacokinetic study of children 9 to 12 years of age with ADHD (n=3), the mean total methylphenidate plasma C_{max} was 34.4 +/- 14 nanograms/mL following a single 60 mg dose of extended-release methylphenidate oral suspension given 30 minutes after breakfast. The proportion of l-methylphenidate was less than 2% of the d-methylphenidate in circulation [14].

3) Oral, single-dose, adolescents with ADHD, 60 mg: 21.1 nanograms/mL [14]

a) In a pharmacokinetic study of adolescents 13 to 15 years of age with ADHD (n=4), the mean total methylphenidate plasma C_{max} was 21.2 +/- 5.9 nanograms/mL following a single 60 mg dose of extended-release methylphenidate oral suspension given 30 minutes after breakfast. The proportion of l-methylphenidate was less than 2% of the d-methylphenidate in circulation [14].

2) Time to Peak Concentration

a) Immediate Release

1) Oral: 1 to 2 hours [154][12][154]

a) Following oral administration of methylphenidate oral solution, T_{max} is achieved in 1 to 2 hr [154].

b) Following oral administration of immediate-release methylphenidate tablets in children, T_{max} was achieved in 1.9 hr (range 0.3 to 4.4 hr) [12].

c) Following oral administration of methylphenidate chewable tablet, T_{max} is achieved in 1 to 2 hr [155].

b) Extended-release Capsules (Metadate-CD(R); [Ritalin LA\(R\)](#))

1) Oral, 2 distinct peaks: early peak: 1.5 to 3 hr; second peak: 4.5 to 6.6 hr [45][153]

a) Metadate-CD(R) extended-release capsules produce 2 distinct peaks. In ADHD children 7 to 10 years of age, the mean initial peak occurred 1.5 hr post dose and a second T_{max} occurred at a approximately 4.5 hr post dose. Approximately one-quarter to one-third of patients experienced only one peak [153].

b) Ritalin-LA(R) extended-release capsules produce 2 distinct peaks. In ADHD children, the initial T_{max} occurred at 2 +/- 0.8 hr and a second peak at 6.6 +/- 1.5 hr post dose. In healthy male adults, the first and second T_{max} occurred at 2 +/- 0.9 and 5.5 +/- 0.8 hr, respectively [45].

c) Extended-release Tablets ([Concerta\(R\)](#))

1) Oral: 6.8 hr [151]

a) Following oral administration of Concerta(R) extended-release tablets, methylphenidate levels rise sharply to an initial maximum in about 1 hr, and then gradually increase over the next 5 to 9 hours before gradually decreasing. The mean C_{max} following single-dose oral administration of Concerta(R) 18 mg extended-release tablets was 3.7+/- 1 nanogram/mL occurring at a mean of 6.8 hr postdose in healthy adults (n=36) [151].

d) Sustained-release Tablets (Ritalin-SR(R))

1) Oral: 4.7 hr [156]

a) T_{max} occurs at 4.7 hr (range 1.3 to 8.2 hr) in children following oral administration of Ritalin-SR(R) sustained-release tablets [156].

e) Extended-Release Oral Suspension (Quillivant XR (TM))

1) Oral, healthy adults: 4 to 5 hours [14]

a) In a crossover pharmacokinetic study under fasting conditions (n=287), a mean C_{max} of d-methylphenidate of 17 +/- 7.7 nanograms/mL was achieved at a median T_{max} of 5 hours following a single 60 mg oral dose of extended-release methylphenidate oral suspension. When administered 30 minutes after breakfast (n=27), the C_{max} of d-methylphenidate was achieved at a median T_{max} of 4 hours (range, 1.3 to 7.3 hours) [14].

2) Oral, ADHD children: 4.05 hours [14]

a) In a pharmacokinetic study of children 9 to 12 years of age with ADHD (n=3), the mean total methylphenidate C_{max} was achieved at a median T_{max} of 4.05 hours (range, 3.98 to 6 hours) following a single 60 mg dose of extended-release methylphenidate oral suspension given 30 minutes after breakfast [14].

3) Oral, ADHD adolescents: 2 hours [14]

a) In a pharmacokinetic study of adolescents 13 to 15 years of age with ADHD (n=4), the mean total methylphenidate C_{max} was achieved at a median T_{max} of 2 hours (range, 1.98 to 4 hours) following a single 60 mg dose of extended-release methylphenidate oral suspension given 30 minutes after breakfast [14].

3) Area Under the Curve

a) Immediate-release

1) Oral, multiple-dose, ADHD children: 102.4 nanograms (ng) x hr/mL (10 mg); Adults: 37.8 ng x hr/mL (10 mg) [45], 38 ng x hr/mL (5 mg) [151][152]

a) The mean AUC following oral administration of 2 immediate-release methylphenidate 10 mg tablets given 4 hours apart was 102.4 +/- 54.6 nanograms (ng) x hr/mL in ADHD children and 37.8 +/- 21.9 ng x hr/mL in healthy adult males (n=15) [45].

b) The mean AUC following oral administration of 3 immediate-release methylphenidate 5 mg tablets given every 4 hours in healthy adults was 38 +/- 11 nanograms x hr/mL (n=35) [151][152].

b)) Extended-release Capsules (Metadate-CD(R); Ritalin-LA(R))

1) Oral, multiple-dose, ADHD children: 63 nanograms x hr/mL (20 mg); 120 ng x hr/mL (40 mg) [153]

a) The AUC(0 to 9 hr) following oral administration of Metadate-CD(R) 20 mg and 40 mg both once-daily for one week in ADHD children 7 to 12 years of age was 63 +/- 16.8 nanograms (ng) x hr/mL and 120 +/- 39.6 ng x hr/mL, respectively [153].

2) Oral, single-dose, 20 mg: ADHD children: 86.6 nanograms (ng) x hr/mL; Adults: 45.8 ng x hr/mL [45]

a) The mean AUC following single-dose oral administration of Ritalin-LA(R) 20 mg extended-release capsules in ADHD children was 86.6 +/- 64 nanograms (ng) x hr/mL and 45.8 +/- 10 ng x hr/mL in healthy adult males (n=15) [45].

b) Following single-dose oral administration of Metadate-CD(R) 20 mg extended-release capsules, the mean C_{max} and AUC were slightly lower than the values seen following administration of 2 immediate-release methylphenidate formulations 4 hr apart (at 0 and 4 hr) [153].

c)) Extended-release Tablets (Concerta(R))

1) Oral, single-dose, 18 mg: 41.8 nanograms x hr/mL [151]

a) The mean AUC following single-dose oral administration of Concerta(R) 18 mg extended-release tablets in healthy adults was 41.8 +/- 13.9 nanograms x hr/mL (n=36) [151].

d)) Extended-Release Oral Suspension (Quillivant XR (TM))

1) Oral, single-dose, healthy adults, 60 mg: 163.2 nanograms x hr/mL [14]

a) In a pharmacokinetic study of healthy adults (n=27), the mean AUC of d-methylphenidate was 163.2 +/- 80.3 nanograms x hr/mL following a single 60 mg dose of extended-release methylphenidate oral suspension given 30 minutes after breakfast [14].

2j) Oral, single-dose, children with ADHD, 60 mg: 378 nanograms x hr/mL [14]

a) In a pharmacokinetic study of children 9 to 12 years of age with ADHD (n=3), the mean total methylphenidate AUC was 378 +/- 175 nanograms x hr/mL following a single 60 mg dose of extended-release methylphenidate oral suspension given 30 minutes after breakfast. The proportion of l-methylphenidate was less than 2% of the d-methylphenidate in circulation [14].

3j) Oral, single-dose, adolescents with ADHD, 60 mg: 178 nanograms x hr/mL [14]

a) In a pharmacokinetic study of adolescents 13 to 15 years of age with ADHD (n=4), the mean total methylphenidate AUC was 178 +/- 54.2 nanograms x hr/mL following a single 60 mg dose of extended-release methylphenidate oral suspension given 30 minutes after breakfast. The proportion of l-methylphenidate was less than 2% of the d-methylphenidate in circulation [14].

2.3] ADME**2.3.1] Absorption****A) Methylphenidate****1j) Bioavailability****a) Transdermal**

1j) The methylphenidate transdermal patch consists of three layers, the outside backing, the adhesive layer from which methylphenidate is dispersed and the protective liner which is removed prior to application. Transdermal application of methylphenidate results in less of a first pass effect than oral administration and consequently, the mg/kg dose of transdermal methylphenidate is lower compared to oral dosages [44].

2j) Effects of Food

a) Food is not expected to alter the pharmacokinetics of transdermal methylphenidate [44].

B) Methylphenidate Hydrochloride**1j) Bioavailability**

a) Oral: 22% (d-methylphenidate); 5% (l-methylphenidate) [45]

1j) In children, the absolute oral bioavailability of d-methylphenidate is 22% +/- 8% and l-methylphenidate is 5% +/- 3%. This suggests a significant first pass effect [45].

2j) DOSAGE FORM ABSORPTION

a) Extended-release Capsules (Metadate-CD(R); Ritalin-LA(R))

1j) Metadate-CD(R) extended-release capsules consist of 30% immediate-release beads and 70% extended-release beads [153].

2j) Ritalin-LA(R) extended-release capsules have a bimodal release profile, utilizing the SODAS(R) (Spheroidal Oral Drug Absorption System) proprietary technology. Each capsule contains 50% of the dose as immediate-release beads, with the remainder as enteric-coated, delayed-release beads. The relative bioavailability of Ritalin-LA(R) dosed once daily is comparable to the same total dose of immediate-release methylphenidate given twice-daily 4 hours apart in both children and adults [45].

b) Extended-release Tablets

1j) Concerta(R) extended-release tablet uses osmotic pressure to deliver methylphenidate at a constant rate providing a 12-hr duration of effect. The tablet comprises an osmotically active tri-layer core surrounded by a semipermeable membrane with an immediate-release overcoat, which dissolves within 1 hour in an aqueous environment (such as the gastrointestinal tract) providing the initial dose. As water permeates through a laser-drilled orifice on the tablet, methylphenidate is released through the orifice by the osmotic pressure created by the polymer excipients in the core. The membrane controls the delivery of drug by controlling the rate at which water enters the tablet core. The relative bioavailability of Concerta(R) dosed once daily is comparable to immediate-release methylphenidate given 3 times daily in adults [151].

c) Sustained-release Tablets

1j) Ritalin-SR(R) sustained-release tablets are formulated with a wax matrix core in which the medication is placed into channels within the wax matrix [157]. The relative bioavailability of the Ritalin-SR(R) sustained-release tablet (measured by urinary excretion of ritalinic acid) is 105% (range 49% to 168%) in children and 101% (range 85% to 152%) in adult [156].

d) Extended-Release Oral Suspension (Quillivant XR (TM))

1j) Quillivant (TM) extended-release methylphenidate suspension contains approximately 80% extended-release methylphenidate and 20% immediate release methylphenidate. The relative bioavailability of the extended-release oral suspensions is 95%, compared with the immediate-release oral solution administered as two 30 mg doses every 6 hours [14].

2j) Effects of Food**a) Variable based on food composition [14][155][154][45][153]****1j) Extended Release Suspension**

2j) A study in adult volunteers given a single 60 mg dose of extended-release methylphenidate oral suspension demonstrated that the presence of a high-fat meal reduced the T_{max} by approximately 1 hour and increased C_{max} and AUC by approximately 28% and 19%, respectively. However, these effects were not considered clinically significant and there was no observed effect on the overall bioavailability [14].

3j) Extended Release Capsules

4j) Administration of Ritalin-LA(R) extended-release capsules in the fasting state or with applesauce was comparable. Administration of Ritalin-LA(R) extended-release capsules with a high fat breakfast delayed absorption but did not effect extent of absorption in adults. Variable delays occurred in both initial and second T_{max}, and the second C_{max} was approximately 25% lower compared with the fasting state. The manufacturer suggests administration times relative to meals and meal composition may need to be individualized [45].

5j) A study in 26 healthy adults, demonstrated that opening a Metadate-CD(R) 20 mg extended-release capsule and placing its contents onto 1 tablespoon of applesauce was bioequivalent to administration of the intact capsule. Administration of Metadate-CD(R) extended-release 40 mg capsules with a high-fat meal delayed the early peak by approximately 1 hour (range, 2 to 5 hour) and increased C_{max} and AUC by about 30% and 17% respectively, in adult volunteers [153].

6j) Extended Release Tablets

7j) Administration of Concerta(R) extended-release tablets with a high-fat breakfast did not affect the pharmacokinetics or the pharmacodynamics of methylphenidate [151].

8j) Oral Solution

9j) Administration of methylphenidate 20 mg oral solution with high-fat food resulted in a delay of T_{max} by almost 1 hour (1.7 hour fasted; 2.7 hour fed), an increase in AUC and C_{max} by almost about 25% and 13%, respectively, in adult volunteers. A cross-study comparison found the magnitude of this food effect was comparable to immediate-release methylphenidate tablets [154].

10j) Chewable Tablets

11j) Administration of immediate-release methylphenidate 20 mg chewable tablets with high-fat food resulted in a delay of T_{max} by almost 1 hour (1.5 hour fasted; 2.4 hour fed) and increased the AUC by about 20% in adult volunteers. A cross-study comparison found the magnitude of this food effect was comparable to immediate-release methylphenidate tablets [155].

2.3.2] Distribution

A) Distribution Sites

1) Methylphenidate Hydrochloride

a) Protein Binding

1) 10% to 33% [45][158].

a) Binding to plasma proteins is low ranging between 10% and 30% [45].

B) Distribution Kinetics

1) Methylphenidate Hydrochloride

a) Volume of Distribution

1) 2.65 L/kg (d-methylphenidate); 1.8 L/kg (l-methylphenidate) [45].

a) The volume of distribution is 2.65 +/- 1.11 L/kg for d-methylphenidate and 1.8 +/- 0.91 L/kg for l-methylphenidate [45][158].

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

1) Methylphenidate Hydrochloride

a) Tissues, extensive [45][159].

1) Methylphenidate is rapidly and extensively metabolized by nonmicrosomal hydrolytic esterases in liver and other tissues (wide tissue distribution) [45].

B) Metabolites

1) Methylphenidate

a) Ritalinic acid (major; essentially inactive) [44].

1) The major metabolite of methylphenidate is ritalinic acid (alpha-phenyl-piperidine acetic acid) which possess minimal-to-no pharmacologic activity. [44].

2) Compared to oral administration on a mg/kg basis, transdermal methylphenidate results in higher exposures to d-methylphenidate due to less first pass effect. Minimal to no l-methylphenidate is systemically available after oral administration. In contrast, exposure to l-methylphenidate is almost as high as d-methylphenidate after transdermal methylphenidate administration [44].

2) Methylphenidate Hydrochloride

a) Ritalinic acid (alpha-phenyl-piperidine acetic acid): major; inactive [14][45].

1) The major metabolite of methylphenidate is ritalinic acid (alpha-phenyl-piperidine acetic acid) which possess minimal-to-no pharmacologic activity [14][45].

2) In vitro studies demonstrate that methylphenidate is not metabolized by CYP isoenzymes and does not inhibit CYP isoenzymes at clinically observed plasma drug concentrations [153].

b) Hydroxymethylphenidate and hydroxyritalinic acid (minor, inactive) [45].

1) Small amounts of the hydroxylated metabolites, hydroxymethylphenidate and hydroxyritalinic acid, are detectable in plasma. [45].

2.3.4] Excretion**A) Kidney****1) Methylphenidate Hydrochloride**

a) Renal Excretion (%)

1) 78% to 97% [14][45][160][159][161], less than 1% unchanged [45][160][159][161].

a) Following oral administration of immediate-release methylphenidate, 78% to 97% of the dose is excreted in the urine in the form of metabolites within 48 to 96 hours. Ritalinic acid accounted for the majority of metabolite excretion (60% to 86%) with the remainder appearing as minor metabolites. Less than 1% appeared as unchanged drug [45].

b) Following oral administration of radiolabeled-methylphenidate, about 90% of the radioactivity was recovered in the urine. Ritalinic acid (alpha-phenyl-piperidine acetic acid) accounted for approximately 80% of the dose [14][154][151][153][155].

B) Feces**1) Methylphenidate Hydrochloride**

a) 1% to 3% [45]

1) Following oral administration of an immediate-release formulation of methylphenidate, 1% to 3% of the dose is excreted in the feces within 48 to 96 hr [45]

C) Total Body Clearance**1) Methylphenidate Hydrochloride**

a) 0.4 L/hr/kg (d-methylphenidate); 0.73 L/hr/kg (l-methylphenidate) [45]

1) Systemic clearance is 0.4 +/- 0.12 L/hr/kg for d-methylphenidate and 0.73 +/- 0.28 L/hr/kg for l-methylphenidate [45].

2) Extended-Release Oral Suspension (Quillivant XR (TM))

a) Adults, 5.66 L/hr/kg (d-methylphenidate) [14]

1) In a pharmacokinetic study of healthy adults (n=27) the mean systemic clearance of d-methylphenidate was 5.66 +/- 2.15 L/hr/kg following a single 60 mg dose of extended-release methylphenidate oral suspension given 30 minutes after breakfast [14].

b) Children, 4.27 L/hr/kg [14]

1) In a pharmacokinetic study of children 9 to 12 years of age with ADHD (n=3), the mean systemic clearance of total methylphenidate was 4.27 +/- 0.7 L/hr/kg following a single 60 mg dose of extended-release methylphenidate oral suspension given 30 minutes after breakfast [14].

c) Adolescents, 5.06 L/hr/kg [14]

1) In a pharmacokinetic study of adolescents 13 to 15 years of age with ADHD (n=4), the mean systemic clearance of total methylphenidate was 5.06 +/- 1.42 L/hr/kg following a single 60 mg dose of extended-release methylphenidate oral suspension given 30 minutes after breakfast [14].

2.3.5] Elimination Half-life

A) Parent Compound

1) Methylphenidate

a) Children: 3 to 4 hr [44]

1) In children aged 6 to 12 years, the mean elimination half-life for transdermal methylphenidate applied to the hip for 9 hours was 3 to 4 hours after removal of the patch; and 1.4 to 2.9 hours for d-methylphenidate and l-methylphenidate, respectively [44].

2) Methylphenidate Hydrochloride

a) Immediate-Release

1j) Adults: 2.7 to 3.5 hours [45][154]; Children: 2.5 hours [45]

a) In studies in adults, the average elimination half-life of methylphenidate from immediate-release (Ritalin(R)) tablets and extended-release (Ritalin-LA(R)) capsules was 3.5 hours (range, 1.3 to 7.7 hours). In children, the half-life is about 2.5 hours (range, 1.5 to 5 hours) [45].

b) In adults, the half-life of methylphenidate following administration of methylphenidate 20 mg chewable tablets was 3 hours [155].

c) In adults, the half-life of methylphenidate following administration of methylphenidate 20 mg oral solution was 2.7 hours [154].

d) In adults, the half-life of methylphenidate following administration of immediate-release methylphenidate tablets was 2.8 hours [155].

b) Extended-Release Capsules (Metadate-CD(R); [Ritalin LA\(R\)](#))**1j) Adults: 2.5 to 6.8 hours [45][153]; Children: 2.5 hours [45]**

a) In studies in adults, the average elimination half-life of methylphenidate from immediate-release (Ritalin(R)) tablets and extended-release (Ritalin-LA(R)) capsules was 3.5 hours (range 1.3 to 7.7 hours). In children, the half-life is about 2.5 hours (range, 1.5 to 5 hours) [45].

b) In adults, the half-life of methylphenidate following administration of Metadate-CD(R) extended-release capsules was 6.8 hours. This suggests that the elimination process for Metadate-CD(R) extended-release capsule is controlled by the release rate of methylphenidate, and that drug absorption is the rate-limiting process [153].

c) Extended-Release Oral Suspension (Quillivant XR (TM))**1j) 5 to 5.6 hours [14]**

a) In a pharmacokinetic study under fasting conditions, a mean plasma terminal elimination half-life of d-methylphenidate of 5.6 +/- 0.8 hours was observed in 28 adult healthy volunteers following a single 60 mg oral dose of extended-release methylphenidate oral suspension. When administered 30 minutes after breakfast (n=27), the mean terminal half life was 5.2 +/- 1 hours [14].

b) In a pharmacokinetic study of children 9 to 12 years of age with ADHD (n=3), a mean elimination half-life of total methylphenidate of 5.2 +/- 0.1 hours was observed following a single 60 mg dose of extended-release methylphenidate oral suspension given 30 minutes after breakfast [14].

c) In a pharmacokinetic study of adolescents 13 to 15 years of age with ADHD (n=4), a mean elimination half-life of total methylphenidate of 5 +/-

0.2 hours was observed following a single 60 mg dose of extended-release methylphenidate oral suspension given 30 minutes after breakfast [14].

d) Extended-Release Tablets (Concerta(R))

1) 3.5 hours [151]

a) In 36 healthy adults, the plasma half-life of methylphenidate following a single dose of Concerta(R) 18 mg extended-release tablet , or 3 doses of immediate-release methylphenidate 5 mg every 4 hours was 3.5 +/- 0.4 hours and 3 +/- 0.5 hours after, respectively [151][152].

2.3.6] Extracorporeal Elimination

A) Hemodialysis

1) Methylphenidate Hydrochloride

a) Dialyzable: unknown[155][154][45][153][151]

1) The efficacy of hemodialysis for the removal of methylphenidate has not been established [155][154][45][153][151]

B) Peritoneal

1) Methylphenidate Hydrochloride

a) Dialyzable: unknown[155][154][45][153][151]

1) The efficacy of peritoneal dialysis for the removal of methylphenidate has not been established [155][154][45][153][151].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

[Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

[Drug Interactions](#)

3.0.A] Black Box WARNING

Methylphenidate

Transdermal (Patch, Extended Release)

Give cautiously to patients with a history of drug dependence or alcoholism. Chronic, abusive use can lead to marked tolerance and psychological dependence with varying degrees of

abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal from abusive use since severe depression may occur [29].

Methylphenidate Hydrochloride

Oral (Tablet; Tablet, Extended Release; Tablet, Chewable; Solution)

Use cautiously in emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because of abuse potential. Chronic abuse can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior, including psychotic episodes. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked [32][33][34].

Oral (Powder for Suspension, Extended Release)

CNS stimulants, including methylphenidate hydrochloride, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [14].

Oral (Capsule, Extended Release)

Use caution when prescribing to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with abnormal behavior. Psychotic episodes can occur, especially with parenteral abuse. Carefully supervise withdrawal from abusive use to avoid the onset of severe depression. Follow-up may be required following withdrawal from chronic therapeutic use, as symptoms of the underlying disorder may emerge [35][36].

3.1] Contraindications

A) Methylphenidate

- 1) concomitant use of MAOIs, or use within 14 days of MAOI administration [29]
- 2) [glaucoma](#) [29]
- 3) hypersensitivity to [methylphenidate](#) or other components of the product [29]
- 4) marked agitation, anxiety, and tension; may aggravate symptoms [29]
- 5) motor tics [29]
- 6) [Tourette syndrome](#) with a family history or diagnosis [29]

B) Methylphenidate Hydrochloride

- 1) angina pectoris [36]
- 2) [cardiac arrhythmias](#) [36]

- 3)) concomitant use of MAOIs, or use within 14 days of MAOI administration [35][36][14][37]
- 4)) concomitant use with halogenated anesthetics; do not take on day of surgery [36]
- 5)) family history or diagnosis of [Tourette syndrome](#) [35][36][37]
- 6)) fructose intolerance, [glucose-galactose malabsorption](#), or sucrase-isomaltase insufficiency; contains sucrose [36]
- 7)) [glaucoma](#) [35][36][37]
- 8)) [heart failure](#) [36]
- 9)) hypersensitivity to [methylphenidate](#) or other components of the product [35][36][14][37]
- 10)) [hyperthyroidism](#) or [thyrotoxicosis](#) [36]
- 11)) marked agitation, anxiety, and tension; may aggravate symptoms [35][36][37]
- 12)) motor tics [35][36][37]
- 13)) recent [myocardial infarction](#) [36]
- 14)) severe [hypertension](#) [36]

3.2) Precautions

A)) [Methylphenidate](#)

- 1)) Black Box Warning:
- 2)) -- give cautiously to patients with a history of drug dependence or alcoholism because of high potential for abuse and dependence; monitoring recommended [29]
- 3)) Cardiovascular:
- 4)) -- sudden death has been reported at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems; avoid use [29]
- 5)) -- sudden deaths, [strokes](#), and [myocardial infarctions](#) have been reported at usual doses in adults [29]
- 6)) -- blood pressure and heart rate increases have been reported and may impact underlying medical conditions; monitoring recommended [29]
- 7)) -- peripheral vasculopathy, including [Raynaud phenomenon](#), has been reported; monitoring recommended and dosage adjustment or discontinuation may be necessary [29]
- 8)) Dermatologic:
- 9)) -- contact sensitization may occur; discontinue if suspected [29]
- 10)) -- permanent chemical [leukoderma](#) has been reported; monitoring recommended and discontinue if occurs [30]
- 11)) Endocrine:

12)) -- chronic use may cause long-term growth suppression in pediatric patients; monitoring recommended and dose interruption may be required [29]

13)) Neurologic:

14)) -- may lower seizure threshold; discontinuation may be necessary [29]

15)) Ophthalmic:

16)) -- vision disturbances such as accommodation difficulties and blurred vision have been reported [29]

17)) Psychiatric:

18)) -- preexisting [bipolar disorder](#) due to risk of inducing mixed/[manic episodes](#) [29]

19)) -- new psychotic or manic symptoms can occur at recommended doses; discontinuation may be necessary [29]

20)) -- aggressive behavior and hostility have been reported; monitoring recommended [29]

21)) Reproductive:

22)) -- [priapism](#), sometimes requiring surgical intervention, has been reported in both pediatric and adult patients [31]

23)) Other:

24)) -- external heat source exposure; not recommended [29]

B)) [Methylphenidate](#) Hydrochloride

1)) Black Box Warning:

2)) -- give cautiously to patients with history of drug dependence or alcoholism because of high potential for abuse and dependence; monitoring recommended [14][35][36][37]

3)) Cardiovascular:

4)) -- sudden death has been reported at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems [35][36][14][38]

5)) -- sudden deaths, [strokes](#), and [myocardial infarctions](#) have been reported at usual doses in adults [35][36][14][38]

6)) -- blood pressure and heart rate increases have been reported and may impact underlying medical conditions; monitoring recommended [35][36][14][37]

7)) -- sudden increase in blood pressure may occur during surgery; avoid use on day of surgery [39]

8)) -- peripheral vasculopathy (including [Raynaud phenomenon](#)) has been reported; monitoring recommended and dosage adjustment or discontinuation may be necessary [39]

9)) Endocrine:

10)) -- chronic use may cause long-term growth suppression in pediatric patients; monitoring recommended and dose interruption may be necessary [35][36][14][38]

11)) Neurologic:

12)) -- may lower seizure threshold; discontinuation may be necessary [35][36][38]

13)) Ophthalmic:

14)) -- visual disturbances, including accommodation difficulties and blurred vision, have been reported [35][36]

15)) Psychiatric:

16)) -- preexisting [psychotic disorder](#) may be exacerbated [35][36][14][38]

17)) -- preexisting [bipolar disorder](#) because of risk of inducing mixed/[manic episodes](#) [35][36][14][38]

18)) -- new psychotic or manic symptoms can occur at recommended doses; discontinuation may be necessary [35][36][14][38]

19)) -- aggressive behavior and hostility have been reported; monitoring recommended [35][36][38]

20)) Reproductive:

21)) -- [priapism](#), sometimes requiring surgical intervention, has been reported in both pediatric and adult patients [40][41][42][43]

22)) Concomitant use:

23)) -- avoid alcohol during therapy [35][36]

3.3] Adverse Reactions**3.3.1] Cardiovascular Effects****3.3.1.A] [Methylphenidate](#)****3.3.1.A.1] [Increased blood pressure](#)**

a)) Modest increases in systolic and diastolic blood pressure have been reported in studies. Use [methylphenidate](#) cautiously in patients whose underlying medical conditions (such as preexisting [hypertension](#), [heart failure](#), or recent [myocardial infarction](#)) may be compromised with increases in blood pressure [44].

3.3.1.A.2] [Increased heart rate](#)

a)) Modest increases in heart rate have been reported in studies. Use [methylphenidate](#) cautiously in patients whose underlying medical conditions (such as preexisting [hypertension](#), [heart failure](#), or recent [myocardial infarction](#)) may be compromised with increases in heart rate [44].

3.3.1.A.3] [Peripheral vascular disease](#)

a)) Effects of peripheral vasculopathy, including [Raynaud's phenomenon](#), were reported with postmarketing use of [methylphenidate](#) at therapeutic doses. Reducing the dose or discontinuing therapy may improve signs and symptoms. Monitor patients carefully for digital changes during

treatment, and if clinically appropriate, refer patients to a rheumatologist for further clinical evaluation [29].

3.3.1.A.4] Raynaud's disease

a) Effects of peripheral vasculopathy, including [Raynaud's phenomenon](#), were reported with postmarketing use of [methylphenidate](#) at therapeutic doses. Reducing the dose or discontinuing therapy may improve signs and symptoms. Monitor patients carefully for digital changes during treatment, and if clinically appropriate, refer patients to a rheumatologist for further clinical evaluation [29].

3.3.1.A.5] Summary

a) Sudden death, [stroke](#), and [myocardial infarction](#) have been reported in patients (both adults and children) taking usual doses of stimulant drugs [45][13]. Large cohort studies have shown there is no significant difference in the incidence of serious cardiovascular events (sudden death, [stroke](#), and acute [myocardial infarction](#)) in both children [46] and adults [47] currently receiving stimulant medications compared with nonusers, however a slight to modest increase in risk cannot be ruled out. Patients with serious heart problems or those in whom an increase in blood pressure or heart rate would be problematic, should not be prescribed stimulant medications. Perform a thorough history to determine if there is a family history of sudden death or [ventricular arrhythmia](#) and a physical exam to assess the existence of cardiac disease prior to prescribing these drugs to patients. Periodic monitoring for changes in heart rate or blood pressure is recommended in all patients taking stimulant medications [48].

3.3.1.B] Methylphenidate Hydrochloride

3.3.1.B.1] Angina

- a) Angina has occurred in patients receiving [methylphenidate](#) hydrochloride [45].
b) Angina pectoris has been reported during postmarketing experience with [methylphenidate](#) hydrochloride extended-release tablets [101].

3.3.1.B.2] Cardiac arrest

- a) [Cardiac arrest](#) has been reported with [methylphenidate](#) hydrochloride use in postmarketing surveillance [39].

3.3.1.B.3] Cardiac dysrhythmia

- a) [Arrhythmias](#) have occurred in patients receiving [methylphenidate](#) hydrochloride [45].

3.3.1.B.4] Cerebral vasculitis

- a) Cerebrovascular [vasculitis](#) has occurred in patients receiving [methylphenidate](#) hydrochloride [45].
b) A case of [cerebral vasculitis](#) was reported in an 8-year-old boy who was taking [methylphenidate](#) 20 mg/day for hyperactivity and behavioral problems. A year and a half after he started the [methylphenidate](#) treatment, he suddenly had 3 episodes of paresthesias with increasing intensity over a 4-month period. At the third episode, the paresthesias resulted in ataxia, dysmetria in the left hemibody, and dystonic movements of the left upper limb. [Cerebral angiogram](#) revealed bilateral complete occlusion of the posterior cerebral arteries distal to the origin of choroidal arteries, indicating localized [vasculitis](#). After discontinuing the [methylphenidate](#) treatment, he was free of symptoms [103].

3.3.1.B.5] Hypertension

a) Modest increases in average blood pressure (about 2 to 4 mmHg) have been caused by the use of stimulant medications, although there may be larger increases experienced by individual patients. Monitor patients for larger changes in blood pressure during treatment [39][14][101]. Medical conditions that place patients at risk when blood pressure increases include those with preexisting [hypertension](#), [heart failure](#), recent [myocardial infarction](#), or [ventricular arrhythmia](#) [39][45][101].

b) In placebo-controlled trials, [increased blood pressure](#) was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving [methylphenidate](#) products [14].

c) [Increased blood pressure](#) has been reported in patients receiving [methylphenidate](#) hydrochloride [45].

d) [Hypertension](#) was reported in clinical trials of [methylphenidate](#) hydrochloride extended-release tablets [101].

e) Adults

1) During a double-blind, randomized, 5-week, fixed-dose study (n=401), adults taking [methylphenidate](#) hydrochloride extended-release (18, 36, or 72 mg/day) had mean changes from baseline in standing blood pressure that ranged from 0.1 to 2.2 mmHg systolic and -0.7 to 2.2 mmHg diastolic, compared with 1.1 mmHg and -1.8 mmHg systolic and diastolic, respectively, for placebo-treated patients. At the end of double-blind treatment in a 7-week dose-titration study (n=226), adults taking [methylphenidate](#) hydrochloride extended-release (36 to 108 mg/day) experienced mean changes from baseline blood pressure of -1.2 mmHg systolic and 1.1 mmHg diastolic, compared with -0.5 mmHg and 0.4 mmHg, systolic and diastolic, respectively, for placebo-treated patients [101].

f) Pediatrics

1) Compared to placebo, systolic and diastolic [blood pressure increased](#) approximately 1 to 4 mmHg during the day in children 6 to 12 years old who received [methylphenidate](#) once daily (18, 36, or 54 mg) or 3 times a day over 12 hours (15, 30, or 45 mg total daily dose). In a randomized, placebo-controlled trial of 177 adolescent subjects 13 to 18 years old, mean increases of 0.7 mmHg systolic and 2.6 mmHg diastolic above baseline blood pressures for subjects taking [methylphenidate](#) hydrochloride (up to 72 mg/day [1.4 mg/kg/day]) were experienced compared to 0.7 mmHg systolic and 1.4 mmHg diastolic for patients receiving the placebo [101].

2) An analysis of heart rate and blood pressure from the Multimodal Treatment Study of Children with ADHD (MAT: a randomized 14-month controlled trial in 7 to 9 year olds) showed no treatment effect at 14-months on either systolic or diastolic blood pressure. Continued follow-up at 2, 3, 6, 8, and 10 years as these children received naturalistic community treatment revealed that children receiving stimulant medication were not at increased risk for prehypertension or [hypertension](#) [104].

3.3.1.B.6] Myocardial infarction

a) Adults

1) [Myocardial infarction](#), sudden deaths, and [stroke](#) have occurred in adults taking usual doses of stimulant drugs [39][14][101]. The role of stimulants in adult cases is unknown, however, adults have a greater likelihood than children of having serious structural cardiac

abnormalities, [cardiomyopathy](#), serious heart rhythm abnormalities, [coronary artery disease](#), or other serious cardiac problems. Adults with cardiac abnormalities should not be treated with stimulant drugs [39][101]. Perform a thorough history to determine if there is a family history of sudden death or [ventricular arrhythmia](#) and a physical exam to assess the existence of cardiac disease prior to prescribing these drugs to patients [39][14][101]. Patients who develop symptoms of cardiac disease (eg, chest pain, unexplained syncope) during stimulant therapy should receive a prompt cardiac evaluation [39][101].

2j) In a retrospective cohort study of 443,198 adults aged 25 to 64 years (mean age, 42 years), a slightly reduced risk in the combined primary endpoint of serious cardiovascular events (sudden cardiac death (SCD), acute [myocardial infarction](#) (MI), and [stroke](#)) was observed in those persons currently receiving an ADHD medication compared with nonusers of ADHD medications (adjusted relative risk, 0.83; 95% CI, 0.72 to 0.96). Electronic health records at 4 sites supplied the data for the study populations. Users of ADHD medications (n=150,359; [methylphenidate](#), 45%; [amphetamines](#), 44%; [atomoxetine](#), 8%; or [pemoline](#), 4%) were matched in a 2:1 ratio with persons who had no record of ADHD medication use in the 365 days prior to cohort entry (n=292,839). Each user was matched with 2 nonusers by study site, birth year, sex, and calendar year. A total of 1357 cases of MI, 296 cases of SCD, and 575 cases of [stroke](#) occurred during the 806,182 person-years of follow-up (median 1.3 years per person) [47].

b) Pediatrics

1j) In a retrospective cohort study involving 1,200,438 children and young adults aged 2 to 24 years (mean age, 11.1 years) and 2,579,104 person-years of follow up (373,667 person-years of current use of ADHD drugs), there was no significant difference in the combined primary endpoint of serious cardiovascular events (sudden cardiac death, acute [myocardial infarction](#), and [stroke](#)) in those who received an ADHD drugs ([methylphenidate](#), [dexmethylphenidate](#), [dextroamphetamine](#), [amphetamine](#) salts, [atomoxetine](#), or [pemoline](#)) compared with those who did not (adjusted hazard ratio, 0.75; 95% CI, 0.31 to 1.85) [46]. Although this study found no association between the use of ADHD drugs and serious cardiovascular events, the possibility of a small to modest increase in risk cannot be excluded because of the small number of serious cardiovascular events in the children and young adults studied. Patients with serious heart problems or for whom an increase in blood pressure or heart rate would be problematic should not be prescribed stimulant medications. Monitoring for changes in heart rate or blood pressure is recommended in all patients [48].

2j) A retrospective, case-controlled study examines the association between stimulant medication, including [methylphenidate](#) and unexplained sudden death in healthy children and adolescents. In a collection of data from state vital statistics and surveys across the United States, 564 cases of sudden death in children and adolescents between the ages of 7 to 19 years were matched and compared with 564 youngsters who died as passengers in motor vehicle accidents. The study determined that 1.8% (n=10) of youths who experienced sudden unexplained deaths were taking stimulant medication compared with 0.4% (n=2) of youths in the motor vehicle accident group (odds ratio, 7.4; 95% CI, 1.4 to 74.9; p=0.02). Limitations to this study included the time lag between the youths stimulant medication use and when the data was collected, family recall of information regarding clinical diagnoses, inconsistent postmortem inquiry, and the exclusion of deaths in youth with heart conditions [105].

3.3.1.B.7] Palpitations

a) Incidence: Adult, 3.1% [101]

b) In placebo-controlled trials, palpitations were among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

c) Adults

1) Palpitations occurred in 3.1% of adult patients with ADHD who received methylphenidate hydrochloride extended-release tablets (n=415) compared with 0.9% of patients who received placebo (n=212), in 2 double-blind, placebo-controlled clinical trials [101].

3.3.1.B.8] Raynaud's phenomenon

a) Peripheral vasculopathy, including Raynaud's phenomenon, has been reported with stimulant therapy in all age groups and with different therapeutic doses in postmarketing surveillance. Mild and intermittent signs and symptoms may very rarely progress to digital ulceration, soft tissue breakdown, or both. Dose reduction or discontinuation generally improves symptoms; monitor for digital changes during stimulant therapy and consider further clinical evaluation (eg, rheumatology referral) if indicated [39].

b) Raynaud's phenomenon has been reported during postmarketing experience with methylphenidate hydrochloride extended-release tablets [101].

3.3.1.B.9] Sudden cardiac death

a) Adults

1) Myocardial infarction, sudden deaths, and stroke have occurred in adults taking usual doses of stimulant drugs [39][14][101]. The role of stimulants in adult cases is unknown, however, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with cardiac abnormalities should not be treated with stimulant drugs [39][101]. Perform a thorough history to determine if there is a family history of sudden death or ventricular arrhythmia and a physical exam to assess the existence of cardiac disease prior to prescribing these drugs to patients [39][14][101]. Patients who develop symptoms of cardiac disease (eg, chest pain, unexplained syncope) during stimulant therapy should receive a prompt cardiac evaluation [39][101].

2) In a retrospective cohort study of 443,198 adults aged 25 to 64 years (mean age 42 years), a slightly reduced risk in the combined primary endpoint of serious cardiovascular events (sudden cardiac death (SCD), acute myocardial infarction (MI), and stroke) was observed in those persons currently receiving an ADHD medication compared with nonusers of ADHD medications (adjusted relative risk, 0.83; 95% CI, 0.72 to 0.96). Electronic health records at 4 sites supplied the data for the study populations. Users of ADHD medications (n=150,359; methylphenidate, 45%; amphetamines, 44%; atomoxetine, 8%; or pemoline, 4%) were matched in a 2:1 ratio with persons who had no record of ADHD medication use in the 365 days prior to cohort entry (n=292,839). Each user was matched with 2 nonusers by study site, birth year, sex, and calendar year. A total of 1357 cases of MI, 296 cases of SCD, and 575 cases of stroke occurred during the 806,182 person-years of follow-up (median 1.3 years per person) [47].

b) Pediatrics

1) Sudden death has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions while receiving recommended doses of CNS

stimulants. Avoid using [methylphenidate](#) in patients with known cardiac abnormalities [14], [cardiomyopathy](#), serious heart rhythm abnormalities, or other serious cardiac problems [39] [101].

2j) In a retrospective cohort study involving 1,200,438 children and young adults aged 2 to 24 years (mean age, 11.1 years) and 2,579,104 person-years of follow up (373,667 person-years of current use of ADHD drugs), there was no significant difference in the combined primary endpoint of serious cardiovascular events (sudden cardiac death, acute [myocardial infarction](#), and [stroke](#)) in those who received an ADHD drugs ([methylphenidate](#), [dexmethylphenidate](#), [dextroamphetamine](#), [amphetamine](#) salts, [atomoxetine](#), or [pemoline](#)) compared with those who did not (adjusted hazard ratio, 0.75; 95% CI, 0.31 to 1.85) [46]. Although this study found no association between the use of ADHD drugs and serious cardiovascular events, the possibility of a small to modest increase in risk cannot be excluded because of the small number of serious cardiovascular events in the patients studied. Patients with serious heart problems or for whom an increase in blood pressure or heart rate would be problematic should not be prescribed stimulant medications. Monitoring for changes in heart rate or blood pressure is recommended in all patients [48].

3j) A retrospective, case-controlled study examines the association between stimulant medication, including [methylphenidate](#) and unexplained sudden death in healthy children and adolescents. In a collection of data from state vital statistics and surveys across the United States, 564 cases of sudden death in children and adolescents between the ages of 7 to 19 years were matched and compared with 564 youngsters who died as passengers in motor vehicle accidents. The study determined that 1.8% (n=10) of youths who experienced sudden unexplained deaths were taking stimulant medication compared with 0.4% (n=2) of youths in the motor vehicle accident group (odds ratio, 7.4; 95% CI, 1.4 to 74.9; p=0.02). Limitations to this study included the time lag between the youths stimulant medication use and when the data was collected, family recall of information regarding clinical diagnoses, inconsistent postmortem inquiry, and the exclusion of deaths in youth with heart conditions [105].

3.3.1.B.10] Summary

a) Sudden death, [stroke](#), and [myocardial infarction](#) have been reported in patients (both adults and children) taking usual doses of stimulant drugs [39][14][45][101]. Large cohort studies have shown there is no significant difference in the incidence of serious cardiovascular events (sudden death, [stroke](#), and acute [myocardial infarction](#)) in both children [46] and adults [47] currently receiving stimulant medications compared with nonusers, however a slight to modest increase in risk cannot be ruled out. Patients with serious heart problems or those in whom an increase in blood pressure or heart rate would be problematic, should not be prescribed stimulant medications. Perform a thorough history to determine if there is a family history of sudden death or [ventricular arrhythmia](#) and a physical exam to assess the existence of cardiac disease prior to prescribing these drugs to patients. Periodic monitoring for changes in heart rate or blood pressure is recommended in all patients taking stimulant medications [48].

3.3.1.B.11] Tachycardia

a) Incidence: Adult, 4.8% [101]

b) In placebo-controlled trials, increased heart rate was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving [methylphenidate](#) products. All patients receiving treatment with [methylphenidate](#) should be monitored for signs and symptoms of [tachycardia](#) [14].

c) Adults

1) **Tachycardia** occurred in 4.8% of adult patients with ADHD who received **methylphenidate** hydrochloride extended-release (n=415) compared with 0% of patients who received placebo (n=212), in 2 double-blind, placebo-controlled clinical trials [101].

2) During a double-blind, randomized, 5-week, fixed-dose study (n=401), adults taking **methylphenidate** hydrochloride extended-release (18, 36, or 72 mg/day) experienced dose-dependent mean increases of 3.9 to 9.8 bpm from baseline in standing pulse rate compared with 2.7 bpm in the placebo group. At the end of double-blind treatment in a 7-week dose-titration study (n=226), adults taking **methylphenidate** hydrochloride extended-release (36 to 108 mg/day) experienced mean increase from baseline in resting pulse of 3.6 bpm compared with a decrease of 1.6 bpm in the placebo group. Monitor patients for larger changes in heart rate. Medical conditions that place patients at risk when heart rate increases include those with preexisting **hypertension**, **heart failure**, recent **myocardial infarction**, or **ventricular arrhythmia** [101].

d) Pediatrics

1) Compared with placebo, resting pulses increased approximately 2 to 6 beats per minute (bpm) during the day in children who received **methylphenidate** once daily (18, 36, or 54 mg) or 3 times a day over 12 hours (15, 30, or 45 mg total daily dose). In a randomized, placebo-controlled trial of 177 adolescent subjects 13 to 18 years old, mean increases of 5 bpm from baseline in resting pulse rate for subjects taking **methylphenidate** hydrochloride extended-release (up to 72 mg/day [1.4 mg/kg/day]) were experienced compared to 3 bpm for patients receiving the placebo [101].

2) An analysis of heart rate and blood pressure from the Multimodal Treatment Study of Children with ADHD (MAT: a randomized 14-month controlled trial in 7 to 9 year olds) showed a significant difference (p=0.02) at 14-months in treatment-by-time effect on heart rate among children receiving stimulant medication (medication only, mean heart rate, 84.2 +/- 12.4 beats per minute [bpm]; **behavioral therapy** plus medication, mean heart rate, 84.6 +/- 12 bpm; no medication (**behavioral therapy** only), 79.1 +/- 12 bpm; usual community treatment, 78.9 +/- 12 bpm); however, the incidence of **tachycardia** did not differ by treatment group (medication only, 0.8% (1/128); **behavioral therapy** plus medication 2.2% (3/135); **behavioral therapy** only, 0.8% (1/125); community treatment, 2.5% (3/119)). Continued follow-up at 2, 3, 6, 8, and 10 years as these children received naturalistic community treatment revealed that children receiving stimulant medication had a significantly increased heart rate at year 8, but not at year 10 [104].

3.3.2] Dermatologic Effects

3.3.2.A] **Methylphenidate**3.3.2.A.1] **Contact dermatitis**

a) Contact sensitization with transdermal **methylphenidate** may occur. However, **contact dermatitis** was not specifically assessed in clinical effectiveness studies. Contact sensitization is characterized by erythema with intense local reaction (edema, papules, vesicles) that does not significantly improve within 2 days or spreads beyond the patch site. Diagnosis should be confirmed by appropriate diagnostic testing. Solely erythema is not indicative of contact sensitization. Once a patient is sensitized to transdermal **methylphenidate**, administration by the oral route may lead to systemic

sensitization or other systemic reactions. Systemic reactions include flare-up of previous [dermatitis](#) or of prior positive patch-test sites; generalized skin eruptions in previously unaffected skin; headache; fever; malaise; arthralgia; diarrhea; or vomiting. Patients who develop a contact sensitization to transdermal [methylphenidate](#) might not be able to take [methylphenidate](#) in any form [44].

b) A study designed to provoke skin sensitization demonstrated transdermal [methylphenidate](#) to be an irritant and also a contact sensitizer. Patients were exposed continuously for 3 weeks, followed by a 2-week rest period, and then the challenge/rechallenge. Transdermal [methylphenidate](#) was more irritating than both the placebo control and the saline control. At least 18 (13.5%) subjects (n=133 in the challenge phase) were sensitized to [methylphenidate](#) based on the results of the challenge and/or rechallenge phases of the study [44].

c) A case report described [allergic contact dermatitis](#) following use of transdermal [methylphenidate](#) in a 9-year-old girl with ADHD. Previous therapy with oral [dextroamphetamine](#) and [amphetamine](#) had been tolerated without complications. However, 8 months after starting the [methylphenidate](#) patch, the patient presented with [pruritic dermatitis](#) characterized by itchy, burning, red lesions that first appeared at the hip (site of application), then progressed to the arms, legs, abdomen, and back, and persisted for 2 months after patch removal. Histopathology was consistent with contact and [nummular dermatitis](#), and infection was ruled out. Patch testing revealed a 1+ reaction to 0.5%, 1%, and 5% [methylphenidate](#), and a 2+ and 3+ reaction to 10% and 20% [methylphenidate](#), respectively. The patient experienced recurrent [pruritic dermatitis](#) on her entire back 9 days after patch testing. Treatment with twice daily [desonide](#) 0.05% led to symptom resolution within 5 days [84].

d) [Allergic contact dermatitis](#) was reported in 1 patient (0.3%) in an open-label study of children with ADHD treated with [methylphenidate](#) transdermal patches for a 9-hour wear time. Erythema and edema developed at application sites with concurrent urticarial lesions on the abdomen and legs. Subsequently, transdermal [methylphenidate](#) patches were discontinued and the patient was not transitioned to oral [methylphenidate](#) [44].

3.3.2.A.2] Erythema

a) Erythema of no or minimal discomfort is a common adverse effect with the use of transdermal [methylphenidate](#). During pivotal, phase III, clinical efficacy studies, the majority of subjects experienced minimal to definite erythema. In general, the erythema was not associated with interruption of therapy or discontinuation from treatment. If erythema is accompanied by intense local reaction (edema, papules, vesicles) that does not significantly improve within 2 days or spreads beyond the patch site, then contact sensitization should be suspected. Evaluate further if erythema, edema, and/or papules do not resolve or significantly reduce within 24 hours after patch removal [44].

3.3.2.A.3] Skin hypopigmented

a) General Information

- 1)** All of the 51 reported cases were permanent [30].
- 2)** Time to onset ranged from 2 months to 4 years, and occurred after treatment discontinuation in some patients [30].
- 3)** Although most cases occurred only around where the patch was applied, some cases also occurred in areas the patch was never applied [30].
- 4)** Of the 13 patients prescribed medicine to reverse the loss of skin color, 3 of those patients reported a slight improvement [30].

b) Prevention and Management

- 1j) If loss of pigmentation occurs, discontinue and consider alternative therapies [30].
- c) Postmarketing

- 1j) Skin depigmentation or [hypopigmentation](#) consistent with chemical [leukoderma](#) has been reported during postmarketing surveillance with transdermal [methylphenidate](#) [30].

3.3.2.Bj [Methylphenidate](#) Hydrochloride

3.3.2.B.1j [Alopecia](#)

- a) Scalp hair loss has occurred in patients receiving [methylphenidate](#) hydrochloride [45].
- b) [Alopecia](#) has been reported in postmarketing experience with [methylphenidate](#) hydrochloride extended-release tablets [101].

3.3.2.B.2j [Diaphoresis](#)

- a) Incidence: Adult, 5.1% [101]
- b) In placebo-controlled trials, hyperhidrosis was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving [methylphenidate](#) products [14].
- c) Adults

- 1j) Hyperhidrosis was reported in 5.1% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=415) compared with 0.9% of patients who received placebo (n=212), in 2 double-blind, placebo-controlled clinical trials [101].

3.3.2.B.3j [Erythroderma](#)

- a) A 73-year-old white woman treated with [methylphenidate](#) 10 mg twice daily for fatigue developed [exfoliative dermatitis](#). Two days after initiating therapy, the patient developed an itching rash with blisters which was accompanied by a fever. Discontinuation of the drug and treatment with antihistamines and [prednisone](#) resulted in resolution of the patient's [dermatitis](#) and fever. Upon reinstitution of [methylphenidate](#), the [dermatitis](#) reappeared and was again abolished upon discontinuing the drug (Weil, 1968).

3.3.2.B.4j [Excoriation of skin](#)

- a) Incidence: Pediatric, 4% [14]
- b) Pediatrics

- 1j) In a placebo-controlled cross-over trial (n=45), [excoriation](#) was among the most commonly reported events occurring 4% of children (6 to 12 years) receiving [methylphenidate](#) extended release oral suspension compared with 0% with placebo .[14].

3.3.2.B.5j [Rash](#)

- a) Incidence: Pediatric, 2% [14]
- b) Rash and macular rash have been reported in clinical trials of patients with who received [methylphenidate](#) hydrochloride extended-release tablets [101].
- c) Pediatrics

- 1j) In a placebo-controlled cross-over trial (n=45), rash was among the most commonly reported events occurring 2% of children (6 to 12 years) receiving methylphenidate extended release oral suspension compared with 0% with placebo [14].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] Methylphenidate

3.3.3.A.1] Decreased body growth

a) Summary

- 1j) It is unknown if chronic use of stimulants, including methylphenidate, in children may cause suppression of growth [44]. However, multiple studies identified growth suppression with oral methylphenidate [61][62][63][64][65][66][67][68][69][70][71][72][73][64].
- b) Long-term treatment with oral methylphenidate, especially with doses greater than 20 mg/day, may result in some minor suppression of growth in some hyperactive children; however, the growth retarding effects appear transient, and overall stature would not be expected to be reduced with prolonged therapy in most children. The duration of growth suppression and the doses at which this occurs is unclear. Height and weight deficits after the first year of treatment may be offset by growth spurts in the second year of treatment. Interpretation of data in studies pertaining to the effects of stimulants on growth is complicated since methods of measuring growth vary greatly. However, long-term studies which have had a follow-up period ranging from 1 to 16 years have generally failed to demonstrate a significant effect on growth among children treated with CNS stimulants [61][62][63][64][65][66][67][68][69][70][71][72][73]. Investigators supporting the observation that methylphenidate can induce some growth suppression have suggested that this effect may result from some disorder in growth hormone secretion. However, data evaluating this hypothesis have been conflicting [74][75][76][77][78]. It has also been suggested that, in children with ADHD treated with stimulants, the temporary deficit in height gain that occurs is related to ADHD-associated delayed maturation and not to the use of stimulants. ADHD is associated with dysregulation of several neurotransmitter systems that may alter neuroendocrine function and result in growth delays [79].
- c) In 1 study, use of methylphenidate was shown to slightly diminish the response to growth hormone (GH) therapy in children with idiopathic GH deficiency (IGHD), but not those with idiopathic short stature (ISS). Methylphenidate therapy had a negative effect on the change in height, but the magnitude of the effect was small and the magnitude of the difference in the change in height between children with IGHD treated with methylphenidate and children with IGHD not treated with methylphenidate decreased with time [80].
- d) One study compared the growth of 63 hyperactive children of which 29 received dextroamphetamine (median, 12.5 mg/day), 20 received methylphenidate (median, 20 mg/day) and 14 received no medication. Height measurements were retrieved annually over a period of 2 or more years from student health records. Long-term administration of dextroamphetamine and methylphenidate demonstrated a statistically significant inhibition of growth when compared with the control group; however, when the mean percentile loss was extrapolated to annual lag in height in centimeters (cm), growth suppression was only minimal, 1.5 and 1 cm/year, respectively. Growth inhibition was only noticeable with methylphenidate doses greater than 20 mg/day [81]. A follow-up study demonstrated that rebound growth occurred upon discontinuing the CNS stimulant during the summer months [70].
- e) One study involving 72 hyperactive children found a statistically significant decrease in height after 1 year of methylphenidate therapy (loss of 1.03 centimeters (cm)), but the initial first year height deficits were made up the second year by a greater than expected growth rate. The authors suggested the development of tolerance to growth suppression with prolonged treatment [64]. A

similar compensatory rebound in growth with continued treatment was eluded to by another study. In this study of 60 children treated with [methylphenidate](#) (mean dose, 34 mg/day), no significant decrease in height was noticed during the first year and by the end of the follow-up period (mean duration, 5.1 years), the height was statistically greater than the predicted norms [67].

3.3.3.A.2] Weight decreased

a) Incidence: 9% [44]

b) A decreased weight occurred in 9% of patients treated with transdermal [methylphenidate](#) compared with 0% of patients treated with placebo during a 7-week study (n=183) [44].

3.3.3.B] [Methylphenidate](#) Hydrochloride

3.3.3.B.1] Decreased body growth

a) Pediatrics

1) Studies of children ages 7 to 10 years who were randomized to either [methylphenidate](#) or non-medication treatment groups over a 14-month time-frame, and children to the ages 10 to 13 years in naturalistic subgroups of newly treated and non-medication treatment over a 36-month time-frame suggest that children who are treated 7 days per week throughout the year experience slowed growth rates (on average a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years) without growth rebound during this developmental period. Monitor growth during treatment with stimulants [39][14][45][101].

2) Long-term treatment with [methylphenidate](#), especially with doses greater than 20 mg/day, may result in some minor suppression of growth in some hyperactive children; however, the growth retarding effects appear transient, and overall stature would not be expected to be reduced with prolonged therapy in most children. The duration of growth suppression and the doses at which this occurs is unclear. Height and weight deficits after the first year of treatment may be offset by growth spurts in the second year of treatment. Interpretation of data in studies pertaining to the effects of stimulants on growth is complicated since methods of measuring growth vary greatly. However, long-term studies which have had a follow-up period ranging from 1 to 16 years have generally failed to demonstrate a significant effect on growth among children treated with CNS stimulants [61][62][63][64][65][66][67][68][67][69][70][71][72][73]. Investigators supporting the observation that [methylphenidate](#) can induce some growth suppression have suggested that this effect may result from some disorder in growth hormone secretion. However, data evaluating this hypothesis have been conflicting [74][75][76][77][78]. It has also been suggested that, in children with ADHD treated with stimulants, the temporary deficit in height gain that occurs is related to ADHD-associated delayed maturation and not to the use of stimulants. ADHD is associated with dysregulation of several neurotransmitter systems that may alter neuroendocrine function and result in growth delays [79].

3) In 1 study, use of [methylphenidate](#) was shown to slightly diminish the response to growth hormone (GH) therapy in children with idiopathic GH deficiency (IGHD), but not those with idiopathic short stature (ISS). [Methylphenidate](#) therapy had a negative effect on the change in height, but the magnitude of the effect was small and the magnitude of the difference in the change in height between children with IGHD treated with [methylphenidate](#) and children with IGHD not treated with [methylphenidate](#) decreased with time [80].

4) One study compared the growth of 63 hyperactive children, 29 received [dextroamphetamine](#) (median, 12.5 mg/day), 20 received [methylphenidate](#) (median, 20 mg/day) and 14 received no medication. Height measurements were retrieved annually over a period of 2 or more years from student health records. Long-term administration of [dextroamphetamine](#) and [methylphenidate](#) demonstrated a statistically significant inhibition of growth when compared with the control group; however, when the mean percentile loss was extrapolated to annual lag in height in cm, growth suppression was only minimal, 1.5 and 1 cm/year, respectively. Growth inhibition was only noticeable with doses greater than 20 mg/day of [methylphenidate](#) [81]. A follow-up study demonstrated that rebound growth occurred upon discontinuing the CNS stimulant during the summer months [70].

5) One study involving 72 hyperactive children found a statistically significant decrease in height after 1 year of [methylphenidate](#) therapy (loss of 1.03 cm), but the initial first year height deficits were made up the second year by a greater than expected growth rate. The authors suggested the development of tolerance to growth suppression with prolonged treatment [64]. A similar compensatory rebound in growth with continued treatment was eluded to by another study. In this study of 60 children treated with [methylphenidate](#) (mean dose, 34 mg)/day, no significant decrease in height was noticed during the first year and by the end of the follow-up period (mean duration 5.1 years), the height was statistically greater than the predicted norms [67].

3.3.3.B.2] Weight decreased

a) Incidence: Adult, 6.5% [101]

b) In placebo-controlled trials, decreased weight was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving [methylphenidate](#) products [14].

c) Adults

1) Decreased weight occurred in 6.5% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=415) compared with 3.3% of patients who received placebo (n=212), in 2 double-blind, placebo-controlled clinical trials [101].

d) Pediatrics

1) Weight loss may occur frequently in children who receive prolonged [methylphenidate](#) hydrochloride therapy [45].

3.3.4] Gastrointestinal Effects

3.3.4.A] [Methylphenidate](#)

3.3.4.A.1] Decrease in appetite

a) Incidence: 26% [44]

b) Decreased appetite occurred in 26% of patients treated with transdermal [methylphenidate](#) compared with 5% of patients treated with placebo during a 7-week study (n=183) [44].

3.3.4.A.2] Loss of appetite

a) Incidence: 5% [44]

b) Anorexia occurred in 5% of patients treated with transdermal methylphenidate compared with 1% of patients treated with placebo during a 7-week study (n=183) [82]. During an open-label study (n=191) of 40-month duration with transdermal methylphenidate worn for 12 hours daily, anorexia occurred in 46% of subjects leading to a 4% discontinuation rate [44].

3.3.4.A.3] Nausea

a) Incidence: 12% [44]

b) Nausea occurred in 12% of patients treated with transdermal methylphenidate compared with 2% of patients treated with placebo during a 7-week study (n=183) [44].

3.3.4.A.4] Vomiting

a) Incidence: 10% [44]

b) Vomiting occurred in 10% of patients treated with transdermal methylphenidate compared with 5% of patients treated with placebo during a 7-week study (n=183) [44].

3.3.4.B] Methylphenidate Hydrochloride

3.3.4.B.1] Abdominal pain

a) Incidence: 2% or greater [14][39]

b) In placebo-controlled trials, abdominal pain was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

c) Pediatrics

1) Abdominal pain (stomach ache) occurred in 7% of pediatric patients treated with methylphenidate hydrochloride extended-release (dose range, 20 mg to 60 mg/day) for ADHD (n=188) compared with 4% of patients who received placebo (n=190) in pooled analysis of 3 clinical trials of up to 4 weeks' duration [39].

2) Abdominal pain may occur frequently in children who receive methylphenidate hydrochloride therapy [45].

3) Upper abdominal pain was reported in 6.2% of children and adolescent patients with ADHD who received methylphenidate hydrochloride extended-release tablets (n=321) compared with 3.8% of patients who received placebo (n=318), in 4 double-blind, placebo-controlled clinical trials [101].

4) In a 4-week titration period leading up to a placebo-controlled, double-blind, parallel-group study, upper abdominal pain occurred in greater than 5% of children aged 6 to 12 years who received methylphenidate hydrochloride extended-release capsules (dose range, 10 to 40 mg) [45].

3.3.4.B.2] Decrease in appetite

a) Incidence: Adult, 25.3% [13]; pediatric, 2% to 9% or greater [39][14][45]

b) In placebo-controlled trials, decreased appetite was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

c) Adults

1j) Decreased appetite was reported in 25.3% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=415) compared with 6.6% of patients who received placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

dj) Pediatrics

1j) Loss of appetite occurred in 9% of pediatric patients treated with [methylphenidate](#) hydrochloride (dose range, 20 mg to 60 mg/day) for ADHD (n=188) compared with 2% of placebo-treated patients (n=190) in clinical trials of up to 4 weeks' duration [39].

2j) In a placebo-controlled cross-over trial (n=45), decreased appetite was among the most commonly reported events occurring 2% of children (6 to 12 years) receiving [methylphenidate](#) extended release oral suspension compared with 0% with placebo [14].

3j) In a 4-week titration period leading up to a placebo-controlled, double-blind, parallel-group study, decreased appetite occurred in greater than 5% of children aged 6 to 12 years who received [methylphenidate](#) extended-release capsules (dose range, 10 to 40 mg) [45].

4j) In a direct, double-blind, crossover comparison of adverse effect profiles, both [dextroamphetamine](#) 0.15 mg/kg twice daily and [methylphenidate](#) 0.3 mg/kg twice daily were well-tolerated in 125 children with [attention deficit disorder](#) (mean age 8.7 years). The only adverse effects reported more frequently during drug therapy than at baseline were appetite suppression (both drugs) and insomnia ([dextroamphetamine](#) only). The mean severity of adverse effects was significantly higher in the [dextroamphetamine](#) group. However, only 1.6% of children in each group had to discontinue therapy because of adverse effects [109].

3.3.4.B.3] Gastrointestinal obstruction, With preexisting severe gastrointestinal narrowing and use of controlled-release formulations

a) Rare cases of obstructive symptoms have been reported in patients with known gastrointestinal narrowing disorders and strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Preexisting severe gastrointestinal narrowing conditions include [esophageal motility disorders](#), small [bowel inflammatory disease](#), "[short gut](#)" [syndrome](#) due to adhesions or decreased transit time, past history of [peritonitis](#), [cystic fibrosis](#), chronic [intestinal pseudoobstruction](#), and [Meckel's diverticulum](#). This drug should only be used in patients who are able to swallow the tablet whole [101].

3.3.4.B.4] Indigestion

a) Incidence: Adult, 2.2% [101]

b) In placebo-controlled trials, [dyspepsia](#) was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving [methylphenidate](#) products [14].

c) Adults

1j) Indigestion was reported in 2.2% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=415) compared with 0.9% of patients who received placebo (n=212), in 2 double-blind, placebo-controlled clinical trials [101].

3.3.4.B.5] Loss of appetite

a) Incidence: Adult, 1.7% [101]; pediatric, 3.1% to 9% or greater [39][45]

b) Adults

1) Anorexia was reported in 1.7% of adult patients with ADHD who received methylphenidate hydrochloride extended-release tablets (n=415) compared with 0% of patients who received placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

c) Pediatrics

1) Anorexia occurred in 9% of pediatric patients treated with methylphenidate hydrochloride extended-release (dose range, 20 mg to 60 mg/day) for ADHD (n=188) compared with 2% of patients receiving placebo (n=190) in pooled analysis of 3 clinical trials of up to 4 weeks' duration [39].

2) In a 4-week titration period leading up to a placebo-controlled, double-blind, parallel-group study, anorexia occurred in greater than 5% of children aged 6 to 12 years who received methylphenidate extended-release capsules (dose range, 10 to 40 mg). During the study, anorexia was reported in 3.1% of children receiving methylphenidate therapy (n=65), compared with 0% of children receiving placebo (n=71) [45].

3.3.4.B.6] Nausea

a) Incidence: Adult, 12.8% [101]

b) In placebo-controlled trials, nausea was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

c) Adults

1) Nausea was reported in 12.8% of adult patients with ADHD who received methylphenidate hydrochloride extended-release tablets (n=415) compared with 3.3% of patients who received placebo (n=212), in 2 double-blind, placebo-controlled clinical trials [101].

3.3.4.B.7] Vomiting

a) Incidence: 2% or greater [14][101]

b) In placebo-controlled trials, vomiting was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

c) Adults

1) Vomiting was reported in 1.7% of adult patients with ADHD who received methylphenidate hydrochloride extended-release (n=415) compared with 0.5% of patients who received placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

d) Pediatrics

1) In a placebo-controlled cross-over trial (n=45), vomiting was among the most commonly reported events occurring 2% of children (6 to 12 years) receiving methylphenidate extended release oral suspension compared with 0% with placebo [14].[14].

2) Vomiting was reported in 2.8% of children and adolescent patients with ADHD who received methylphenidate hydrochloride extended-release tablets (n=321) compared with

1.6% of patients who received placebo (n=318) in 4 double-blind, placebo-controlled clinical trials [101].

3.3.4.B.8] Xerostomia

a) Incidence: Adult, 14% [101]

b) In placebo-controlled trials, dry mouth was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

c) Adults

1) Dry mouth was reported in 14% of adult patients with ADHD who received methylphenidate hydrochloride extended-release (n=415) compared with 3.8% of patients who received placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

3.3.5] Hematologic Effects

3.3.5.A] Methylphenidate Hydrochloride

3.3.5.A.1] Anemia

a) Anemia has occurred in patients receiving methylphenidate hydrochloride [45].

3.3.5.A.2] Leukopenia

a) Leukopenia has been reported in clinical trials [101].

3.3.5.A.3] Pancytopenia

a) Pancytopenia has been reported during postmarketing experience with methylphenidate products [14], including methylphenidate hydrochloride extended-release tablets [101].

3.3.5.A.4] Summary

a) Periodically monitor CBC, differential, and platelet counts during prolonged therapy with methylphenidate hydrochloride [101][45].

3.3.5.A.5] Thrombocytopenia

a) Thrombocytopenia has been reported during postmarketing experience with methylphenidate products [14], including methylphenidate hydrochloride extended-release tablets [101].

b) Thrombocytopenia was reported in a 10-year-old boy who received methylphenidate for ADHD. The patient had been treated with methylphenidate for 10 months when a routine blood count revealed thrombocytopenia. Blood counts returned to normal within 2 weeks of drug discontinuation [102].

3.3.5.A.6] Thrombocytopenic purpura

a) Hypersensitivity reactions including thrombocytopenic purpura have occurred in patients receiving methylphenidate hydrochloride[45].

b) Thrombocytopenic purpura has been reported during postmarketing experience with methylphenidate products [14], including methylphenidate hydrochloride extended-release tablets [101].

3.3.6] Hepatic Effects

3.3.6.A] Methylphenidate Hydrochloride

3.3.6.A.1] Abnormal liver function

a) **Abnormal liver function** (ranging from transaminase elevations to **hepatic coma**) has been reported in patients receiving **methylphenidate** hydrochloride [45].

3.3.6.A.2] Autoimmune hepatitis

a) **Autoimmune hepatitis** occurred in a 57-year-old, asymptomatic Caucasian man 1 month following initiation of **methylphenidate**. The patient, who had a history of **orthotopic liver transplantation** secondary to **chronic hepatitis C** infection 4 years prior, was found to have sudden-onset liver elevation of liver chemistries during a routine scheduled follow-up. Baseline liver chemistries had been stable in the months prior to presentation. His current values for AST, **ALT**, and **total bilirubin** were 572 units/L, 338 units/L, and 2.7 mg/dL, respectively. Medications taken over the previous year were **cyclosporine**, **venlafaxine**, **omeprazole**, **hydrochlorothiazide**, **fosinopril**, and a multivitamin. Long-acting **methylphenidate** had been initiated 1 month prior to current presentation for impaired concentration and depressive symptoms. The patient denied alcohol abuse and use of herbal or complementary medicines, and did not have any fever, chills, abdominal pain, or urine discoloration. Physical examination revealed a flat, nondistended abdomen, with no ascites or hepatosplenomegaly evident. No change in mental status or asterixis was found on neurological examination. Laboratory exam showed positive **titers for anti-smooth muscle antibody** (1:40) and antinuclear antibody (1:80), with a nucleolar pattern, and an elevated IgG of 1950 mg/dL, all of which had been normal at baseline. A liver biopsy showed severe lobular and periportal necroinflammatory infiltrate with predominant **lymphocytes**, plasma cells, and eosinophils, but lacking endothelialitis and bile duct damage. Subsequently, **methylphenidate** therapy was discontinued and liver chemistries began to normalize. Besides **methylphenidate**, other prior medications were continued and **prednisone** 10 mg/day was added approximately 1 month later. Liver chemistries returned to patient's approximate baseline values over the next few months, and a liver biopsy 1 year following this episode showed marked improvement. Later, the patient was started on combination **amphetamine/dextroamphetamine** with no further elevation of liver enzymes [110].

3.3.7] Immunologic Effects

3.3.7.A] Methylphenidate Hydrochloride

3.3.7.A.1] Anaphylaxis

a) **Hypersensitivity reactions** have been reported in patients receiving **methylphenidate** hydrochloride[45]. **Angioedema** and **anaphylactic reactions** have been reported [14].

b) **Hypersensitivity reactions**, including **anaphylactic reactions**, have been reported in postmarketing experience with **methylphenidate** hydrochloride extended-release tablets [101].

3.3.7.A.2] Hypersensitivity reaction

a) **Hypersensitivity reactions** have been reported in patients receiving **methylphenidate** hydrochloride[45]. **Angioedema** and **anaphylactic reactions** have been reported [14]. **Hypersensitivity reactions**, including **anaphylactic reactions**, have been reported in postmarketing experience with **methylphenidate** hydrochloride extended-release tablets [101].

b) **Hypersensitivity reactions** to **methylphenidate** are rare in occurrence. However, 2 cases have been reported. In 1 case, edema of the eyes was noted, and in the other case, **erythema multiforme** was described [113](Weil, 1968).

3.3.8] Musculoskeletal Effects

3.3.8.A] **Methylphenidate**

3.3.8.A.1] **Bone finding**

a) Oral **methylphenidate** did not significantly affect **bone mineral density** and bone turnover in children. In a study of 9 boys (age ranging from 3 to 10 years), who were treated with a mean dose of **methylphenidate** 10 milligrams for an average of 13 months for ADHD, **bone mineral density** (as measured by using **dual photon absorptiometry**), serum bone-specific **alkaline phosphatase** (a marker for bone mineralization), urinary deoxypyridinoline excretion (an indicator of bone resorption), and serum **calcium** and **phosphate** were not significantly different compared with boys in the control group (n=9). All the children in the treatment group were within their height percentile during the treatment period [85].

b) In a retrospective, cohort study of 42 male and female children (between 7 and 16 years old), dental maturation was not compromised after an average dose of 30 milligrams (mg) of oral **methylphenidate** for a mean duration of 54 months. Inclusion criteria were administration of at least 20 mg/day of **methylphenidate** for a minimum of 2 years at the time of panoramic **radiograph**. The gender- and age-matched control cohort consisted of those who were healthy and had not ingested any long-term medication. An oral, written, and radiographic review of gender- and age-matched subjects were compared. The main outcome of the study was the dental age difference score, which was defined as dental age score for **methylphenidate** subjects minus dental age score for control subjects. The mean dental age score for **methylphenidate** subjects was approximately 6 months behind matched control subjects. However, when the median differences were compared, **methylphenidate** and control subjects were similar (p=0.27). Multiple regression demonstrated that there was no difference in scores when gender, age, or length of drug use were considered [86].

3.3.8.B] **Methylphenidate Hydrochloride**

3.3.8.B.1] **Rhabdomyolysis**

a) Adult and Pediatric Clinical Trials

1) ADHD or **narcolepsy** (oral route): Has been reported; incidence unknown [111][112]

3.3.9] Neurologic Effects

3.3.9.A] **Methylphenidate**

3.3.9.A.1] **Headache**

a) During an open-label study (n=191) of 40-month duration with transdermal **methylphenidate** worn for 12 hours daily, headache occurred in 28% of subjects[44]

3.3.9.A.2] **Insomnia**

a) Incidence: 13% [44]

b) Insomnia occurred in 13% of patients treated with transdermal **methylphenidate** compared with 5% of patients treated with placebo during a 7-week study (n=183) [44]. During an open-label study

(n=191) of 40-month duration with transdermal methylphenidate worn for 12 hours daily, insomnia occurred in 30% of subjects leading to a 4% discontinuation rate [44].

3.3.9.A.3] Lowered convulsive threshold

a) There is some clinical evidence that methylphenidate may lower convulsive threshold in patients with a prior history of seizures, in patients with prior EEG abnormalities in the absence of a history of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. Discontinue methylphenidate if seizures develop [44].

b) Children with ADHD who have normal EEGs have minimal risk for seizures should they receive stimulant therapy for ADHD (methylphenidate, dextroamphetamine, or combination amphetamine and dextroamphetamine (Adderall(R))). However, children with epileptiform EEGs may have considerable risk for eventual seizure, although the occurrence of seizure may or may not be attributable to use of the stimulant. These conclusions were based on a study of 234 children without known epilepsy who were diagnosed with ADHD. All had EEGs prior to parental choosing of stimulant treatment or foregoing stimulant treatment for their children's ADHD. Overall, 36 children (15.4%) demonstrated epileptiform abnormalities compared with 198 with normal EEGs. Of the 36 with abnormalities, 30 received stimulant treatment for ADHD. Three of the 30 who received stimulant therapy experienced seizures (p less than 0.03), including a 9-year-old female, a 7-year-old male, and a 6-year-old male. The girl was treated uneventfully with methylphenidate for 12 months, then 2 months after withdrawal of methylphenidate experienced a 4-minute generalized tonic-clonic seizure. Her EEG had revealed a non-focal epileptiform abnormality. Of the 2 boys, the first experienced a 2-minute generalized tonic clonic seizure with focal onset 3 years after starting methylphenidate. The second boy had an episode at 10 months after initiation of methylphenidate; he fell and was unresponsive with upward eye deviation for 2 minutes. EEGs of both boys had shown rolandic spikes, a focal epileptiform abnormality. One child who had a normal EEG had a seizure 6 weeks after beginning methylphenidate [49].

3.3.9.A.4] Tic

a) Summary

1) Tics and Tourette's syndrome have developed or been exacerbated in patients treated with methylphenidate [44]. In patients diagnosed as having an attention deficit disorder, clinical evaluation for tics and Tourette's syndrome in the children and their families should precede the use of stimulant medication. In children with no symptoms of Tourette's syndrome but with a familial history, stimulants should be used very cautiously. The use of stimulants is contraindicated in children with Tourette's syndrome. If tics occur during stimulant treatment, stimulant therapy should be discontinued [50]. In one study, there was a significant correlation occurred between younger age and development of tics [51]. In another trial, long-term methylphenidate treatment appeared to be safe and effective in children with ADHD and chronic multiple tic disorder or Tourette's syndrome [52].

b) Incidence: 7% [44]

c) Tics occurred in 7% of patients treated with transdermal methylphenidate compared with 0% of patients treated with placebo during a 7-week study (n=183). Transdermal methylphenidate is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome [44].

d) Tics developed in 7.8% of children treated with stimulant medication (methylphenidate, dextroamphetamine, or pemoline) for ADHD, based on a retrospective chart review (n=555). These stimulant medications were initiated only in children if they were free of tics and without a history of tics, according to the practice of the settings in which the study was performed. Tics developed

in 8.3% of subjects treated with methylphenidate, 6.3% treated with dextroamphetamine, and 7.7% treated with pemoline. Onset of tics was unrelated to dose or duration of stimulant therapy. Mean age of subjects was 11 years. A significant correlation occurred between younger age and development of tics. As the authors noted, these children may have developed tics, regardless of treatment with the medications in question [51].

e) Although stimulant therapy was suspected to exacerbate tics, long-term methylphenidate treatment in this study appeared to be safe and effective in children with ADHD and chronic multiple tic disorder or Tourette's syndrome. In this 2-year, non-blinded, prospective, follow-up study, 32 children (age ranging from 6.1 and 11.9 years) received minimal effective doses of methylphenidate from a previous trial (mean, 16.5 mg; range, 5 to 40 mg). The children were evaluated in a simulated classroom every 6 months for 2 years for their on-task, fidgeting, worksheet behaviors, and vocal and motor tic frequency. In almost every measure, tics were significantly worse at baseline than placebo (p ranging from less than 0.001 to 0.03). There was no difference in tic condition between placebo and methylphenidate. ADHD behaviors were not significantly different between baseline and placebo, whereas children spent significantly more time on task during the medication conditions than placebo (p less than 0.001). There was no significant difference between children's height and weight when compared with growth table values. Systolic blood pressure and heart rate were significantly increased (p=0.02 and 0.01, respectively), but were considered clinically insignificant. Although this study showed methylphenidate did not worsen tics in patients with ADHD and Tourette's syndrome, the possibility of individual exacerbation of tic cannot be ruled out [52]. In another study of 19 children with ADHD and Tourette's syndrome, abrupt withdrawal of methylphenidate and dextroamphetamine in long-term therapy did not cause worsening of tic severity and frequency [53].

f) Tourette's syndrome may be exacerbated or precipitated by the use of stimulant medications for the treatment of attention deficit disorders in children. Early signs of Tourette's syndrome or tics are difficult to distinguish from hyperactive and attention deficit disorder symptoms. Children may, therefore, mistakenly be treated with stimulant medications (dextroamphetamine, methylphenidate, pemoline). Stimulants may, therefore, exacerbate the severe motor and phonic tics requiring discontinuation of the stimulants and possible institution of haloperidol therapy. In patients diagnosed as having an attention deficit disorder, clinical evaluation for tics and Tourette's syndrome in the children and their families should precede the use of stimulant medication. In children with no symptoms of Tourette's syndrome but with a familial history, stimulants should be used very cautiously. The use of stimulants is contraindicated in children with Tourette's syndrome. If tics occur during stimulant treatment, stimulant therapy should be discontinued [50].

g) Numerous case reports have demonstrated tics either starting or worsening after methylphenidate, pemoline or dextroamphetamine use. There is no correlation between stimulant dosages (high or low) or duration of treatment, and tic development. Tics have developed or worsened over days, months, or even years. Many of the patients who developed tics years later were within the age range where tics frequently begin spontaneously, so it is unknown if disease onset was independent of stimulant use. The highest risk for tic exacerbation appears to be in susceptible patients who are treated with stimulant medication early in life and/or for a long duration. Investigators have noted that in those patients without a prior history of tics, discontinuing the stimulant decreased tic severity but did not necessarily completely resolve the condition [54][55][50]; (Balhman, 1981)[56][57][58][59][60]; (Myerhoff & Synder, 1973).

h) One group of investigators evaluated 1500 children who received methylphenidate in the treatment of minimal brain dysfunction to study the incidence of tics following methylphenidate administration. The authors found that the incidence of tics developing or worsening was 1.3% (20 patients). The types of tics described included eyelid, facial muscle, head, jaw, neck, limb and trunk tics. The author noted that the development of tics had no relation to dose or duration of therapy and that in most

patients discontinuing the drug resulted in resolution of the tics [59]. In contrast, another study found that stimulant medications aggravated existing tics in 13% to 33% of patients [55].

3.3.9.B| Methylphenidate Hydrochloride

3.3.9.B.1| Akathisia

a) Symptoms of [akathisia](#) occurred in a 46-year-old Caucasian woman following initiation of [methylphenidate](#). The woman, who had a history of recurrent type [major depressive disorder](#), alcohol dependence in full sustained remission, nicotine dependence, COPD, [multiple sclerosis](#), and multiple [pulmonary eosinophilic granulomas](#), was prescribed oral [methylphenidate](#) 10 mg twice daily for the treatment of apathy. The patient was additionally receiving a complex regimen of medications, which included [quetiapine](#). Although she experienced restlessness following the third dose of [methylphenidate](#), she continued treatment. By the fifth day, she was restless, pacing, and felt like she wanted to crawl out of her skin. Taking [clonazepam](#) and [diazepam](#) (part of her regular regimen of medications) did not resolve the symptoms, and by day 6 her left leg stiffened and she began experiencing tremors in her left arm. She presented to the emergency room where she was administered IM [benztropine](#), which led to a prompt relief of symptoms. She was advised to discontinue [methylphenidate](#) and following discharge with a week's supply of oral [benztropine](#), her symptoms did not recur. It was proposed that the addition of [methylphenidate](#) may have unmasked latent extrapyramidal symptoms, a potential side effect of [quetiapine](#) [106].

3.3.9.B.2| Cerebral artery occlusion

a) Cerebral occlusions have occurred in patients receiving [methylphenidate](#) hydrochloride [45].

3.3.9.B.3| Cerebral hemorrhage

a) [Cerebral hemorrhage](#) has occurred in patients receiving [methylphenidate](#) hydrochloride [45].

3.3.9.B.4| Cerebrovascular accident

a) Adults

1) [Stroke](#), sudden death, and [myocardial infarction](#) have occurred in adults taking usual doses of stimulant drugs [39][14][101]. The role of stimulants in adult cases is unknown, however, adults have a greater likelihood than children of having serious structural cardiac abnormalities, [cardiomyopathy](#), serious heart rhythm abnormalities, [coronary artery disease](#), or other serious cardiac problems. Adults with cardiac abnormalities should not be treated with stimulant drugs [39][101]. Perform a thorough history to determine if there is a family history of sudden death or [ventricular arrhythmia](#) and a physical exam to assess the existence of cardiac disease prior to prescribing these drugs to patients [39][14][101]. Patients who develop symptoms of cardiac disease (eg, chest pain, unexplained syncope) during stimulant therapy should receive a prompt cardiac evaluation [39][101].

2) Cerebrovascular accident has occurred in patients receiving [methylphenidate](#) hydrochloride [45].

3) In a retrospective cohort study of 443,198 adults aged 25 to 64 years (mean age 42 years), a slightly reduced risk in the combined primary endpoint of serious cardiovascular events (sudden cardiac death (SCD), acute [myocardial infarction](#) (MI), and [stroke](#)) was observed in those persons currently receiving an ADHD medication compared with nonusers of ADHD medications (adjusted relative risk, 0.83; 95% confidence interval (CI), 0.72 to

0.96). Electronic health records at 4 sites supplied the data for the study populations. Users of ADHD medications (n=150,359; methylphenidate, 45%; amphetamines, 44%; atomoxetine, 8%; or pemoline, 4%) were matched in a 2:1 ratio with persons who had no record of ADHD medication use in the 365 days prior to cohort entry (n=292,839). Each user was matched with 2 nonusers by study site, birth year, sex and calendar year. A total of 1357 cases of MI, 296 cases of SCD, and 575 cases of stroke occurred during the 806,182 person-years of follow-up (median 1.3 years per person) [47].

b) Pediatrics

1) In a retrospective cohort study involving 1,200,438 children and young adults aged 2 to 24 years (mean age 11.1 years) and 2,579,104 person-years of follow up (373,667 person-years of current use of ADHD drugs), there was no significant difference in the combined primary endpoint of serious cardiovascular events (sudden cardiac death, acute myocardial infarction, and stroke) in those who received an ADHD drugs (methylphenidate, dexamethylphenidate, dextroamphetamine, amphetamine salts, atomoxetine, or pemoline) compared with those who did not (adjusted hazard ratio, 0.75; 95% confidence interval (CI), 0.31 to 1.85) [46]. Although this study found no association between the use of ADHD drugs and serious cardiovascular events, the possibility of a small to modest increase in risk cannot be excluded because of the small number of serious cardiovascular events in the children and young adults studied. Patients with serious heart problems or for whom an increase in blood pressure or heart rate would be problematic should not be prescribed stimulant medications. Monitoring for changes in heart rate or blood pressure is recommended in all patients [48].

2) A retrospective, case-controlled study examines the association between stimulant medication, including methylphenidate and unexplained sudden death in healthy children and adolescents. In a collection of data from state vital statistics and surveys across the United States, 564 cases of sudden death in children and adolescents between the ages of 7 to 19 years were matched and compared with 564 youngsters who died as passengers in motor vehicle accidents. The study determined that 1.8% (n=10) of youths who experienced sudden unexplained deaths were taking stimulant medication compared with 0.4% (n=2) of youths in the motor vehicle accident group (odds ratio (OR), 7.4; 95% CI, 1.4 to 74.9; p=0.02). Limitations to this study included the time lag between the youths stimulant medication use and when the data was collected, family recall of information regarding clinical diagnoses, inconsistent postmortem inquiry, and the exclusion of deaths in youth with heart conditions [105].

3.3.9.B.5] Chorea

a) Pediatrics

1) A case of chorea induced by methylphenidate in a 5-year-old boy receiving the drug for hyperactive behavior has been reported . The choreic disorder disappeared 2 months after methylphenidate was discontinued [108].

3.3.9.B.6] Dizziness

a) Incidence: Adult, 6.7%; pediatric, 1.9% [101].

b) In placebo-controlled trials, dizziness was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

c) Adults

1j) Dizziness occurred in 6.7% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=415) compared with 5.2% of adults who received placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

d) Pediatrics

1j) Dizziness occurred in 1.9% of children and adolescent patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=321) compared with 0% of patients who received placebo (n=318), in 4 double-blind, placebo-controlled clinical trials [101].

3.3.9.B.7] Dyskinesia

a) [Dyskinesia](#) has occurred in patients receiving [methylphenidate](#) hydrochloride [45].

b) [Dyskinesia](#) was reported during postmarketing experience with [methylphenidate](#) hydrochloride extended-release tablets [101].

3.3.9.B.8] Gilles de la Tourette's syndrome

a) [Tourette's syndrome](#) has occurred rarely in patients receiving [methylphenidate](#) hydrochloride [45].

b) Pediatrics

1j) Although stimulant therapy was suspected to exacerbate tics, long-term [methylphenidate](#) treatment in this study appeared to be safe and effective in children with ADHD and chronic multiple tic disorder or [Tourette's Syndrome](#). In this 2-year non-blinded, prospective, follow-up study, 32 children (age ranging from 6.1 and 11.9 years) received minimal effective doses of [methylphenidate](#) from a previous trial (mean, 16.5 mg; range, 5 to 40 mg). The children were evaluated in a simulated classroom every 6 months for 2 years for their on-task, fidgeting, worksheet behaviors, and vocal and motor tic frequency. In almost every measure, tics were significantly worse at baseline than placebo (p ranging from less than 0.001 to 0.03). There was no difference in tic condition between placebo and [methylphenidate](#). ADHD behaviors were not significantly different between baseline and placebo, whereas children spent significantly more time on task during the medication conditions than placebo (p less than 0.001). There was no significant difference between children's height and weight when compared to growth table values. Systolic blood pressure and heart rate were significantly increased (p=0.02 and 0.01, respectively), but were considered clinically insignificant. Although this study showed [methylphenidate](#) did not worsen tics in patients with ADHD and [Tourette's syndrome](#), the possibility of individual exacerbation of tic cannot be ruled out [52]. In another study of 19 children with ADHD and [Tourette's syndrome](#), abrupt withdrawal of [methylphenidate](#) and [dextroamphetamine](#) in long-term therapy did not cause worsening of tic severity and frequency [53].

2j) [Tourette's syndrome](#) may be exacerbated or precipitated by the use of stimulant medications for the treatment of [attention deficit disorders](#) in children. Early signs of [Tourette's syndrome](#) or tics are difficult to distinguish from hyperactive and [attention deficit disorder](#) symptoms. Children may therefore mistakenly be treated with stimulant medications ([dextroamphetamine](#), [methylphenidate](#), [pemoline](#)). Stimulants may therefore exacerbate the severe motor and phonic tics requiring discontinuation of the stimulants and possible institution of [haloperidol](#) therapy. In patients diagnosed as having an [attention deficit disorder](#), clinical evaluation for tics and [Tourette's syndrome](#) in the children and their families should precede the use of stimulant medication. In children with no symptoms of

[Tourette's syndrome](#) but with a familial history, stimulants should be used very cautiously. The use of stimulants is contraindicated in children with [Tourette's syndrome](#). If tics occur during stimulant treatment, stimulant therapy should be discontinued [50].

3.3.9.B.9] Headache

a) Incidence: Adult, 22.2% [101]; pediatric, up to 12% [39][45]

b) Adults

1) Headache occurred in 22.2% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=415) compared with 15.6% of patients who received placebo (n=212), in 2 double-blind, placebo-controlled clinical trials [101].

c) Pediatrics

1) Headache occurred in 12% of pediatric patients treated with [methylphenidate](#) hydrochloride extended-release (dose range, 20 mg to 60 mg/day) for ADHD (n=188) compared with 8% of patients receiving placebo (n=190) in pooled analysis of 3 clinical trials of up to 4 weeks' duration [39].

2) In a 4-week titration period leading up to a placebo-controlled, double-blind, parallel-group study, greater than 5% of children aged 6 to 12 years experienced headache while receiving [methylphenidate](#) hydrochloride extended-release capsules (dose range, 10 to 40 mg) [45].

3.3.9.B.10] Insomnia

a) Incidence: Adult, 12.3% [101]; pediatric, 2.8% to 5% [14][45][101][39]

b) In placebo-controlled trials, insomnia was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving [methylphenidate](#) products [14].

c) Adults

1) Insomnia was reported in 12.3% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=415) compared with 6.1% of patients who received placebo (n=212), in 2 double-blind, placebo-controlled clinical trials; [initial insomnia](#) was reported in 4.3% of patients who received [methylphenidate](#) hydrochloride extended-release tablets compared with 2.8% of patients who received placebo[101].

d) Pediatrics

1) Insomnia occurred in 5% of pediatric patients treated with [methylphenidate](#) hydrochloride extended-release (dose range, 20 mg to 60 mg/day) for ADHD (n=188) compared with 2% of patients who received placebo (n=190) in pooled analysis of 3 clinical trials of up to 4 weeks' duration [39].

2) In a placebo-controlled cross-over trial (n=45), [initial insomnia](#) was among the most commonly reported events occurring 2% of children (6 to 12 years) receiving [methylphenidate](#) extended release oral suspension compared with 0% with placebo [14].

3) Insomnia, including [initial insomnia](#), was reported in 2.8% of children and adolescents with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=321)

compared with 0.3% of patients who received placebo (n=318), in 4 double-blind, placebo-controlled clinical trials [101].

4) In a 4-week titration period leading up to a placebo-controlled, double-blind, parallel-group study, greater than 5% of children aged 6 to 12 years experienced insomnia while receiving methylphenidate hydrochloride extended-release capsules (dose range, 10 to 40 mg). During the study, insomnia was reported in 3.1% of children receiving methylphenidate therapy (n=65), compared with 0% of children receiving placebo (n=71) [45].

3.3.9.B.11] Lethargy

a) Lethargy has been reported in clinical trials [101].

b) Pediatrics

1) In a 4-week titration period leading up to a placebo-controlled, parallel-group study, lethargy was a reason for discontinuation of methylphenidate hydrochloride extended-release capsules (dose range, 10 to 40 mg) in children with ADHD [45].

3.3.9.B.12] Migraine

a) Pediatrics

1) In a 4-week titration period leading up to a placebo-controlled, parallel-group study, migraine was a reason for discontinuation of methylphenidate hydrochloride extended-release (dose range, 10 to 40 mg) in children with ADHD [45].

3.3.9.B.13] Motion sickness

a) Incidence: Pediatric, 2% [14]

b) Pediatrics

1) In a placebo-controlled cross-over trial (n=45), motion sickness was among the most commonly reported events occurring 2% of children (6 to 12 years) receiving methylphenidate extended release oral suspension compared with 0% with placebo [14].

3.3.9.B.14] R.I.N.D. syndrome

a) Reversible ischemic neurological deficit has been reported with methylphenidate hydrochloride use in postmarketing surveillance [39].

3.3.9.B.15] Seizure

a) For patients with a prior history of seizures, prior EEG abnormalities without seizures, and very rarely patients without a history of seizures and no prior EEG evidence of seizures, stimulants may lower the convulsive threshold. Discontinue methylphenidate hydrochloride use in the presence of seizures [39][45][101].

b) Convulsions and grand mal convulsions were reported during postmarketing experience [14][101].

c) Pediatrics

1) Children with ADHD who have normal EEGs have minimal risk for seizures should they receive stimulant therapy for ADHD (methylphenidate, dextroamphetamine, or combination amphetamine and dextroamphetamine (Adderall(R))). However, children with epileptiform EEGs may have considerable risk for eventual seizure, although the occurrence of seizure may

or may not be attributable to use of the stimulant. These conclusions were based on a study of 234 children without known [epilepsy](#) who were diagnosed with ADHD. All had EEGs prior to parental choosing of stimulant treatment or foregoing stimulant treatment for their children's ADHD. Overall, 36 children (15.4%) demonstrated epileptiform abnormalities compared with 198 with normal EEGs. Of the 36 with abnormalities, 30 received stimulant treatment for ADHD. Three of the 30 who received stimulant therapy experienced seizures (p less than 0.03), including a 9-year-old girl, a 7-year-old boy, and a 6-year-old boy. The girl was treated uneventfully with [methylphenidate](#) for 12 months, then 2 months after withdrawal of [methylphenidate](#) experienced a 4-minute generalized tonic-clonic seizure. Her EEG revealed a nonfocal epileptiform abnormality. Of the 2 boys, the first experienced a 2-minute generalized tonic [clonic seizure](#) with focal onset 3 years after starting [methylphenidate](#). The second boy had an episode at 10 months after initiation of [methylphenidate](#); he was heard to fall and was unresponsive with upward eye deviation for 2 minutes. EEGs of both boys had shown rolandic spikes, a focal epileptiform abnormality. One child who had a normal EEG had a seizure 6 weeks after beginning [methylphenidate](#) [49].

2j) Use of [methylphenidate](#) appears to be safe and effective to treat ADHD in children with [epilepsy](#) who are seizure free, while receiving antiepileptic drugs, before starting [methylphenidate](#) therapy. However, caution is warranted for those children still having seizures while receiving antiepileptic drugs [107].

3.3.9.B.16] Somnolence

- a) Drowsiness has occurred in patients receiving [methylphenidate](#) hydrochloride [45].
- b) Somnolence has been reported in clinical trials [101].

3.3.9.B.17] Tic

- a) Incidence: Pediatric, 1% to 9% [101][14]
- b) Numerous case reports have demonstrated tics either starting or worsening of tics after [methylphenidate](#), [pemoline](#) or [dextroamphetamine](#) use. There is no correlation between stimulant dosages (high or low) or duration of treatment, and tic development. Tics have developed or worsened over days, months, even years. Many of the patients who developed tics years later were within the age range where tics frequently begin spontaneously, so it is unknown if disease onset was independent of stimulant use. The highest risk for tic exacerbation appears to be in susceptible patients who are treated with stimulant medication early in life and/or for a long duration. Investigators have noted that in those patients without a prior history of tics, discontinuing the stimulant decreased tic severity but did not necessarily completely resolve the condition [54][55][50]; [56][57][58][59][60].
- c) Pediatrics

1j) In a placebo-controlled cross-over trial (n=45), tics were among the most commonly reported events occurring 2% of children (6 to 12 years) receiving [methylphenidate](#) extended release oral suspension compared with 0% with placebo [14].

2j) The cumulative incidence of onset of new tics was 9% in children after 27 months of treatment with [methylphenidate](#) hydrochloride extended-release tablets in a long-term uncontrolled study (n=432). The cumulative incidence of onset of new tics was 1% in children after treatment with [methylphenidate](#) hydrochloride extended-release tablets for up to 9 months (mean treatment duration, 7.2 months), in an uncontrolled study (n=682) [101].

3j) The incidence of tics emergence was 7.8% in children treated with stimulant medication (methylphenidate, dextroamphetamine, or pemoline) for ADHD, based on a retrospective chart review (n=555). These stimulant medications were initiated only in children if they were free of tics and without a history of tics according to the practice of the settings in which the study was performed. Tics developed in 8.3% of subjects treated with methylphenidate, 6.3% treated with dextroamphetamine, and 7.7% treated with pemoline. Onset of tics was unrelated to dose or duration of stimulant therapy. Mean age of subjects was 11 years. A significant correlation occurred between younger age and development of tics. As the authors noted, these children may have developed tics, regardless of treatment with the medications in question [51].

4j) One group of investigators evaluated 1500 children who received methylphenidate in the treatment of minimal brain dysfunction to study the incidence of tics following the drugs administration. The authors found that the incidence of tics developing or worsening was 1.3% (20 patients). The types of tics described included eyelid, facial muscle, head, jaw, neck, limb and trunk tics. The author noted that the development of tics had no relation to dose or duration of therapy and that in most patients discontinuing the drug resulted in resolution of the tics [59]. In contrast, another study [55] found that stimulant medications aggravated existing tics in 13% to 33% of patients.

3.3.9.B.18] Tremor

a) Incidence: Adult, 2.7% [101]

b) In placebo-controlled trials, tremor was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

c) Adults

1j) Tremor occurred in 2.7% of adult patients with ADHD who received methylphenidate hydrochloride extended-release tablets (n=415) compared with 0.5% of patients who received placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

3.3.9.B.19] Vertigo

a) Incidence: 1.7% to 2% or greater [14][101]

b) In placebo-controlled trials, vertigo was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

c) Adults

1j) Vertigo was reported in 1.7% of adult patients with ADHD who received methylphenidate hydrochloride extended-release tablets (n=415) compared with 0% of patients who received placebo (n=212), in 2 double-blind, placebo-controlled clinical trials [101].

3.3.10] Ophthalmic Effects

3.3.10.A] Methylphenidate

3.3.10.A.1] Blurred vision

a) Blurring of vision has been reported [44].

3.3.10.A.2] Disorder of accommodation

- a) Difficulties with accommodation have been reported [44].

3.3.10.A.3] Photophobia

a) A 7-year old boy developed photophobia following administration of methylphenidate 35 mg/day for treatment of attention-deficit hyperactive disorder (ADHD). Within days of diagnosis and initiation of treatment, the patient felt irritated by light, especially extremely bright lighting. The patient reported hating sunlight or excessive light and an inability to adjust to lighting which sometimes led to headaches. The patient and his family had no history of albinos or migraine headaches, and there was no history of head trauma. The patient did not wear contact lenses. Treatment with methylphenidate was discontinued 3 times within one year and each time the sensitivity to light subsided immediately. Methylphenidate was reinitiated 3 months after discontinuation and sensitivity to light was immediately reported [83].

3.3.10.A.4] Visual disturbance

- a) Incidence: rare [44]
b) Rarely, symptoms of visual disturbances have been experienced [44].

3.3.10.B] Methylphenidate Hydrochloride**3.3.10.B.1] Blurred vision**

- a) Incidence: 1.7% to 2% or greater [14][101]
b) Stimulant treatment may cause blurred vision and difficulties with accommodation [39][45].
c) In placebo-controlled trials, blurred vision was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].
d) Visual impairment was also reported during postmarketing experience with methylphenidate hydrochloride extended-release tablets[101]
e) Adults

1) Blurred vision was reported in 1.7% of adult patients with ADHD who received methylphenidate hydrochloride extended-release tablets (n=415) compared with 0.5% of patients who received placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

3.3.10.B.2] Diplopia

- a) Diplopia was reported during postmarketing experience with methylphenidate hydrochloride extended-release tablets [101].

3.3.10.B.3] Pain in eye

- a) Incidence: Pediatric, 2% [14]
b) Pediatrics

1) In a placebo-controlled cross-over trial (n=45), eye pain was among the most commonly reported events occurring 2% of children (6 to 12 years) receiving methylphenidate extended release oral suspension compared with 0% with placebo [14].

3.3.12] Psychiatric Effects

3.3.12.A] Methylphenidate

3.3.12.A.1] Labile affect

a)] Incidence: 6% [44]

b)] Mild affect lability occurred in 6% of patients treated with transdermal methylphenidate compared with 0% of patients treated with placebo during clinical trials (n=183). Of the 6 patients who experienced affect lability, symptoms were characterized as increased emotionally sensitive, emotionality, emotional instability, emotional lability, and intermittent emotional lability [44].

3.3.12.A.2] Mania

a)] In a review of 49 randomized, controlled pediatric ADHD clinical trials involving psychostimulant medications (atomoxetine hydrochloride, methylphenidate hydrochloride, modafinil and dexamethylphenidate hydrochloride), the rate of psychosis/mania events in pediatric subjects receiving an active drug was 1.48 (95% CI 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of psychosis or mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years of age or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset [87].

3.3.12.A.3] Psychotic disorder

a)] In a review of 49 randomized, controlled pediatric ADHD clinical trials involving psychostimulant medications (atomoxetine hydrochloride, methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pediatric subjects receiving active drug was 1.48 (95% CI 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of psychosis or mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset [87].

- b) Exacerbation of [psychosis](#) (behavior disturbance and thought disorder) has occurred during clinical experience with [methylphenidate](#) [44].

3.3.12.B] [Methylphenidate](#) Hydrochloride

3.3.12.B.1] Aggressive behavior

- a) Incidence: Adult, 1.7% [101]
b) Aggressive behavior has been reported in clinical trials and in the postmarketing surveillance of [methylphenidate](#) hydrochloride. Patients should be monitored for aggressive behavior when starting [methylphenidate](#) therapy for ADHD [39][45][101].
c) Adult

- 1) Aggression was reported in 1.7% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release (n=415) compared with 0.5% of patients who received placebo (n=212), in 2 double-blind, placebo-controlled clinical trials [101].

3.3.12.B.2] Agitation

- a) Incidence: Adult, 2.2% [101]
b) In placebo-controlled trials, agitation was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving [methylphenidate](#) products [14].
c) Adults

- 1) Agitation was reported in 2.2% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=415) compared with 0.5% of patients who received placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

3.3.12.B.3] Anxiety

- a) Incidence: Adult, 8.2% [101]
b) In placebo-controlled trials, anxiety was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving [methylphenidate](#) products [14].
c) Adults

- 1) Anxiety was reported in 8.2% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=415) compared with 2.4% of patients on placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

d) Pediatrics

- 1) In a 4-week titration period leading up to a placebo-controlled, parallel-group study, anxiety was a reason for discontinuation of [methylphenidate](#) extended-release (dose range, 10 to 40 mg) in children with ADHD [45].

3.3.12.B.4] Depression

- a) Incidence: Adult, 1.7% to 3.9% [101]
b) Adults

1J) Depressed mood was reported in 3.9% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=415) compared with 1.4% of patients who received placebo (n=212), in 2 double-blind, placebo-controlled clinical trials [101].

2J) Depression was reported in 1.7% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=415) compared with 0.9% of patients who received placebo (n=212), in 2 double-blind, placebo-controlled clinical trials [101].

cJ) Pediatrics

1J) Transient depressed mood has occurred in patients receiving [methylphenidate](#) hydrochloride. In a 4-week titration period leading up to a placebo-controlled, parallel-group study, depression was a reason for discontinuation of [methylphenidate](#) hydrochloride extended-release (dose range, 10 to 40 mg) in children with ADHD. During the study, 1.5% (1 of 65) of patients discontinued [methylphenidate](#) therapy due to depression [45].

3.3.12.B.5] Disorientated

aJ) Disorientation has been reported during postmarketing experience with [methylphenidate](#) hydrochloride extended-release tablets [101].

3.3.12.B.6] Feeling angry

aJ) Anger has been reported in clinical trials of [methylphenidate](#) hydrochloride extended-release tablets [101].

bJ) Pediatrics

1J) In a 4-week titration period leading up to a placebo-controlled, parallel-group study, anger was a reason for discontinuation of [methylphenidate](#) hydrochloride extended-release in 1.2% (2 of 161) of children with ADHD [45].

3.3.12.B.7] Feeling nervous

aJ) Incidence: Adult, 3.1% [101]

bJ) In placebo-controlled trials, nervousness was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving [methylphenidate](#) products [14].

cJ) Nervousness commonly occurs in patients receiving [methylphenidate](#) hydrochloride [45].

dJ) Adults

1J) Nervousness was reported in 3.1% of adult patients with ADHD who received [methylphenidate](#) hydrochloride extended-release tablets (n=415) compared with 0.5% of patients who received placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

3.3.12.B.8] Hallucinations

aJ) Hallucinations, including auditory and visual hallucinations, have been reported during postmarketing experience with [methylphenidate](#) hydrochloride extended-release tablets [101].

bJ) An 11-year-old boy developed visual hallucinations 3 years after starting immediate-release [methylphenidate](#) for ADHD. The patient initially presented with attention deficit, distractibility,

hyperactivity, and impulsivity before 6 years of age. At the age of 7 years, the diagnosis of ADHD was established, and at age 8 years, oral methylphenidate-immediate-release 0.5 mg/kg twice daily (30 mg daily) was started. The dose was maintained for 3 years with significant improvement in symptoms. Therapy was discontinued each summer and was associated with recurrence of symptoms and impaired adaptive functioning. During treatment, the patient had no complaints of side effects until age 11 when he presented with an episode of complex visual hallucinations. The patient described dramatic violent scenes involving people shooting guns in his bedroom before going to bed and occasionally during the day after taking methylphenidate. Physical and neurological examinations, visual acuity, standard laboratory workup, and drug screening were all within normal limits. Psychiatric comorbidities were ruled out and sleep EEG was normal. Family history consisted of mother presenting with seasonal affective disorder and binge eating disorder. Methylphenidate was discontinued with complete resolution of symptoms, and atomoxetine 60 mg daily was started. During the 24-month follow-up period, no further hallucinations occurred [117].

3.3.12.B.9] Hypomania

a) Pediatrics

- 1) In a 4-week titration period leading up to a placebo-controlled, parallel-group study, hypomania was a reason for discontinuation of methylphenidate extended-release (dose range, 10 to 40 mg) in children with ADHD [45].

3.3.12.B.10] Irritability

a) Incidence: Adult, 5.8% [101]

- b) In placebo-controlled trials, irritability was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

c) Adults

- 1) Irritability was reported in 5.8% of adult patients with ADHD who received methylphenidate hydrochloride extended-release tablets (n=415) compared with 1.4% of patients who received placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

3.3.12.B.11] Labile affect

a) Incidence: Adult, 1.4% [101]; pediatric, 9% [14]

- b) In placebo-controlled trials, affect lability was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

c) Adults

- 1) Affect lability was reported in 1.4% of adult patients with ADHD who received methylphenidate hydrochloride extended-release tablets (n=415) compared with 0.9% of patients who received placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

d) Pediatrics

- 1) In a placebo-controlled cross-over trial (n=45), affect lability was among the most commonly reported events occurring in 9% of children (6 to 12 years) receiving methylphenidate extended-release oral suspension compared with 2% with placebo [14].

3.3.12.B.12] Mania

a) Stimulants may induce mixed/[manic episodes](#) in patients with comorbid [bipolar disorders](#). Exercise caution when using stimulants in these patients [39][14][45][101].

b) Stimulants may cause treatment-emergent psychotic or manic symptoms (eg, hallucinations, delusional thinking, mania) in patients without a history of mania or psychotic illness [39][14]. In a pooled analysis of multiple short-term, placebo-controlled studies, these types of symptoms occurred in approximately 0.1% of patients treated with stimulants (4 of 3482) compared with 0% in placebo-treated patients [39][45][101].

c) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving psychostimulant medications ([atomoxetine](#) hydrochloride, [methylphenidate](#) hydrochloride, [modafinil](#), and dextromethylphenidate hydrochloride), the rate of [psychosis](#)/mania events in pediatric subjects receiving active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of [psychosis](#) or mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of [psychoses](#) or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years old or younger, and approximately 90% of cases involved no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications ([methylphenidate](#) hydrochloride, [atomoxetine](#) hydrochloride, and mixed salts of a single entity [amphetamine](#) product) included in the analysis; in many cases, a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset [87].

d) [Methylphenidate](#) was associated with mania in a 10-year-old boy who was treated for severe hyperactivity. The patient received increasing doses up to 45 mg daily, which resulted in [manic episodes](#) during the third week of treatment; withdrawal of the drug resulted in improvement over 2 days and [lithium](#) carbonate therapy was initiated. This patient had a positive family history for bipolar illness [115].

3.3.12.B.13] Obsessive-compulsive disorder

a) High-dose [methylphenidate](#) was associated with obsessive-compulsive symptoms in a 10-year-old girl. The patient had a history of ADHD, for which she was receiving [methylphenidate](#) (doses increased gradually to 90 mg/day), [sertraline](#) (50 mg nightly), and [clonidine](#) (0.025 mg nightly). For 2 years, the child was uncontrollably stealing from peers, teachers, neighbors, and stores; she told her mother that she was unable to control her urge to steal. The dose of [methylphenidate](#) was tapered to 30 mg/day. Her stealing became less frequent but continued on an occasional basis. She was hospitalized so [methylphenidate](#) could be withdrawn under observation; [sertraline](#) was also discontinued. No major signs of ADHD were observed after [methylphenidate](#) withdrawal; stealing episodes were further reduced. At 1-year follow-up, she was free of stealing [116].

3.3.12.B.14] Psychotic disorder

a) Stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with psychiatric conditions [45], including [psychotic disorder](#) [39].

b) Stimulants may cause treatment-emergent psychotic or manic symptoms (eg, hallucinations, delusional thinking, mania) in patients without a history of mania or psychotic illness [39][14]. In a pooled analysis of multiple short-term, placebo-controlled studies, these types of symptoms occurred

in approximately 0.1% of patients treated with stimulants (4 of 3482) compared with 0% in placebo-treated patients [39][45][101]. Toxic psychosis has occurred in patients receiving methylphenidate hydrochloride [45]. Hallucinations, including auditory and visual hallucinations, have been reported during postmarketing experience with methylphenidate hydrochloride extended-release tablets [101].

c) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving psychostimulant medications (atomoxetine hydrochloride, methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pediatric subjects receiving active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of psychosis or mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset [87].

3.3.12.B.15] Restlessness

a) Incidence: Adult, 3.1% [101]

b) In placebo-controlled trials, restlessness was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

c) Adults

1) Restlessness was reported in 3.1% of adult patients with ADHD who received methylphenidate hydrochloride extended-release tablets (n=415) compared with 0% of patients who received placebo (n=212) in 2 double-blind, placebo-controlled clinical trials [101].

3.3.12.B.16] Stuttering

a) Stuttering has been temporally associated with the use of pemoline (9.375 mg/day) and methylphenidate (5 mg/day) on 2 separate trials in a 3-year-old girl. The stuttering stopped with the discontinuation of each drug [114].

3.3.12.B.17] Suicidal behavior

a) Suicidal behavior, including completed suicide, has been reported with methylphenidate hydrochloride use in postmarketing surveillance [39].

3.3.12.B.18] Volubility

a) Logorrhea has been reported during postmarketing experience with methylphenidate hydrochloride extended-release tablets [101].

3.3.14] Reproductive Effects

3.3.14.A] Methylphenidate**3.3.14.A.1] Priapism**

a) Cases of painful and prolonged penile erections (ie, more than 4 hours) and priapism have been reported with methylphenidate use following dose increases, with longer than usual dosing intervals, and after temporary or permanent drug withdrawal. Some cases required surgical intervention. Inform male patients of the signs and symptoms of priapism and the need for immediate medical evaluation if the condition occurs [31].

b) In an FDA analysis, 15 cases of priapism associated with methylphenidate were reported over a 15-year period, with the majority of affected patients under age 18 (median age, 12.5 years; range, 8 to 33 years). Some cases required inpatient care, including surgical treatment in 2 patients (ie, shunt placement, needle aspiration of the corpus cavernosum). Priapism developed following methylphenidate withdrawal in 4 cases. Priapism resolved after the drug was restarted in some patients [88]

3.3.14.B] Methylphenidate Hydrochloride**3.3.14.B.1] Priapism**

a) Cases of painful and prolonged penile erections (ie, more than 4 hours) and priapism have been reported with methylphenidate use following dose increases, with longer than usual dosing intervals, and after temporary or permanent drug withdrawal. Some cases required surgical intervention. Inform male patients of the signs and symptoms of priapism and the need for immediate medical evaluation if the condition occurs [43].

b) In an FDA analysis, 15 cases of priapism associated with methylphenidate were reported over a 15-year period, with the majority of affected patients under age 18 (median age, 12.5 years; range, 8 to 33 years). Some cases required inpatient care, including surgical treatment in 2 patients (ie, shunt placement, needle aspiration of the corpus cavernosum). Priapism developed following methylphenidate withdrawal in 4 cases. Priapism resolved after the drug was restarted in some patients [88]

3.3.15] Respiratory Effects**3.3.15.A] Nasal congestion**

1) Incidence: 6% [44]

2) Nasal congestion occurred in 6% of patients treated with transdermal methylphenidate compared with 1% of patients treated with placebo during a 7-week study (n=183) [44].

3.3.15.B] Nasopharyngitis

1) Incidence: 5% [44]

2) Nasopharyngitis occurred in 5% of patients treated with transdermal methylphenidate compared with 2% of patients treated with placebo during a 7-week study (n=183) [44].

3.3.16] Other**3.3.16.A] Methylphenidate****3.3.16.A.1] Drug dependence**

a) Marked tolerance and psychological dependence with varying degrees of abnormal behavior have been experienced in patients who chronically abused methylphenidate. Frank psychotic episodes can occur, particularly with parenteral abuse. Risk factors are a history of drug dependence or alcoholism. Withdrawing methylphenidate in a patient who has abused it may lead to severe depression. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up [44]

b) Among children with attention deficit disorder treated with methylphenidate, no strong conclusive evidence exists correlating the long-term use of methylphenidate with the occurrence of adult drug abuse.

c) Ingestion of high doses (doses above those normally recommended) of methylphenidate for extended periods of time may result in tolerance to the euphoric effect and psychological dependence. Dependence on methylphenidate may be characterized as compulsive drug use and varying degrees of abnormal behavior. Intravenous administration of methylphenidate has been reported to produce dependence in patients receiving doses of 30 to 100 mg/day for 14 days. Severe depression and amphetamine-like withdrawal symptoms including irritability, boisterousness, belligerence, anxiety, muscular aches, chills, tremors, sleep disturbances, lethargy, exhaustion, and suicidal ideations may occur during methylphenidate withdrawal. Withdrawal therapy usually consists of adjunctive neuroleptic and/or antidepressant therapy along with abrupt or gradual methylphenidate withdrawal. The gradual tapering of methylphenidate doses in dependent individuals may not alter the severity or duration of withdrawal symptoms. Further studies are needed to justify any advantage of gradual compared with abrupt drug withdrawal. Chronic ingestion of this drug may result in toxic psychosis. Multiple organ failure including hepatic, renal, pancreatic, and pulmonary toxicity, may occur following intravenous or intraarterial injection of crushed methylphenidate tablets [89][90][91][92][93][94][95][96][97][98][99][100].

3.3.16.A.2] Viral disease

a) During an open-label study (n=191) of 40 months duration with transdermal methylphenidate worn for 12 hours daily, viral infection occurred in 28% of subjects [44].

3.3.16.B] Methylphenidate Hydrochloride

3.3.16.B.1] Dead - sudden death

a) Sudden death has been associated with stimulant treatment at usual doses in adults and in pediatric patients with structural cardiac abnormalities or other serious heart problem [39][101]. Methylphenidate hydrochloride extended-release capsules are contraindicated in patients with angina, cardiac arrhythmias, heart failure, or recent myocardial infarction [39]. Stimulants should not be used in patients with cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems; in pediatric patients with known serious structural cardiac abnormalities; or in adults with structural cardiac abnormalities or coronary artery disease. [39][101]

3.3.16.B.2] Drug tolerance

a) Two double-blind, randomized, crossover trials evaluating the effectiveness of various drug delivery profiles of methylphenidate demonstrated acute tolerance to methylphenidate may exist in the treatment of children with ADHD. In Study 1 (n=38), 3 methylphenidate delivery patterns (twice-daily, flat, and ascending) and placebo were compared. The twice-daily dosing with immediate-release methylphenidate was designed to produce typical school day peak and trough concentrations. The flat regimen was intended to provide an initial peak followed by a uniform methylphenidate concentration throughout the day. The ascending regimen produced an increasing methylphenidate level from a low-

drug concentration early in the morning to a high-drug concentration by the end of the day. The flat delivery pattern was significantly less efficacious for measures of efficacy than the twice daily regimen in the afternoon, which suggests that acute tolerance to sustained methylphenidate concentrations may be emerging throughout the day. In Study 2, 32 children were assigned 3 treatments profiles (3 times daily, ascending, and placebo) where the timing of the middle bolus of the 3-times daily regimen was either 9:30 AM or 1:30 PM after the 7:30 am dose. Only small increases in efficacy were measured in the 9:30-AM regimen after the second dose compared with large increases in efficacy in the 1:30-PM regimen following the second dose. Following the administration of the third bolus dose in each regimen, a larger increase in efficacy was observed in the 9:30 AM regimen compared with small increases in efficacy for the 1:30-PM regimen. The interpretation of these patterns suggests a consistency with the tolerance hypothesis. The results of Study 1 and Study 2 support the hypothesis that acute tolerance may contribute to the reduced efficacy of sustained-release drug delivery compared with immediate-release drug delivery of methylphenidate [118].

3.3.16.B.3] Fatigue

a) Fatigue has been reported in clinical trials of methylphenidate hydrochloride extended-release tablets in placebo-controlled, double-blind clinical trials. Fatigue was also reported during open-label studies [101].

b) Pediatrics

1) In a 4-week titration period leading up to a placebo-controlled, parallel-group study, fatigue was a reason for discontinuation of methylphenidate hydrochloride extended release (dose range, 10 to 40 mg) in children with ADHD [45].

3.3.16.B.4] Fever

a) Incidence: Pediatric, 2.2% [101]

b) Hypersensitivity reactions including fever have occurred in patients receiving methylphenidate hydrochloride [45].

c) In placebo-controlled trials, pyrexia was among commonly reported events occurring at an incidence rate at least twice that of placebo and in at least 2% of children, adolescents, and adults with ADHD receiving methylphenidate products [14].

d) Pediatrics

1) Pyrexia was reported in 2.2% of child and adolescent patients with ADHD who received methylphenidate hydrochloride extended-release tablets (n=321) compared with 0.9% of patients who received placebo (n=318) in 4 double-blind, placebo-controlled clinical trials [101].

3.3.16.B.5] Neuroleptic malignant syndrome

a) Neuroleptic malignant syndrome (NMS) has occurred very rarely in patients receiving methylphenidate. Most patients were receiving concomitant therapy for NMS. In a case report, a 10-year-old male patient who received methylphenidate for 18 months experienced an NMS-like event within 45 minutes after receiving his first dose of venlafaxine [45].

3.4] Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (All Trimesters)

a)) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential [risk to the fetus](#).

2)) Australian Drug Evaluation Committee's (ADEC) Category: B2

a)) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3)) Crosses Placenta: Unknown

4)) Clinical Management

a)) Although a causal relationship between [methylphenidate](#) and [teratogenic effects](#) has not been found, the safe use of [methylphenidate](#) during pregnancy has yet to be confirmed. In a population-based study, no significantly increased risk of cardiac or other major [congenital malformations](#) was seen with first-trimester [methylphenidate](#) exposure (n=222) when compared with unexposed cohorts (n=2220) in adjusted analyses [148]. Until additional data are available, caution should be exercised with the use of [methylphenidate](#) in pregnant women.

5)) Literature Reports

a)) In a population-based study, no significantly increased risk of cardiac or other major [congenital malformations](#) was seen with first-trimester [methylphenidate](#) exposure (n=222) when compared with unexposed cohorts (n=2220) in adjusted analyses. Rates of major malformations and cardiac malformations in both groups were comparable to rates reported in a random sample of unexposed pregnancies. Other pregnancy complications (ie, [spontaneous abortion](#), [preterm birth](#), low birthweight, neonatal complications, postnatal neurodevelopmental effects) were not studied [148].

b)) There are few reports of outcomes after inadvertent exposure during pregnancy. Adequate studies to establish safe use of [methylphenidate](#) during pregnancy have not been conducted [146]. One source describes a series of women (n=11) who used [methylphenidate](#) (dose unspecified) during the first 4 months of pregnancy; no [birth defects](#) or other abnormalities were reported in any of the infants and all 11 were considered normal [149]. A later report [150] discussed the outcomes of another 38 women who used [methylphenidate](#) during pregnancy. Although infants in these reports were more likely to be premature, growth retarded, and to show signs of neonatal withdrawal, no increase in congenital abnormalities was identified; however, this number is so small that no pattern or estimate of risk can be determined at this time.

B)) Breastfeeding

1)) Micromedex Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) It is not known whether [methylphenidate](#) is excreted into human breast milk and the potential for adverse effects in the nursing infant from exposure to the drug are unknown. Given the drug's low molecular weight of approximately 270, transfer into milk would be expected.

3) Literature Reports

a) No reports describing the use of [methylphenidate](#) during human lactation or measuring the amount, if any, of the drug detected in milk have been located.

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

3.5.1.A] [Amitriptyline](#)

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [141][142]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [143]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [144]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [145]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [132][133][134][135]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [132][133][134].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [82].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [136].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [137][135].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [138].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [139]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [140].

3.5.1.B] [Amoxapine](#)

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [141][142]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [143]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [144]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [145]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [132][133][134][135]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [132][133][134].

- b)) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [82].
- c)) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [136].
- d)) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [137][135].
- e)) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [138].
- f)) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [139]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [140].

3.5.1.C] Brofaromine

- 1)) Interaction Effect: [hypertensive crisis](#) (headache, palpitation, and neck stiffness)
- 2)) Summary: Coadministration of [methylphenidate](#) and a monoamine oxidase inhibitor may result in [hypertensive crisis](#), which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. [Hypertensive crisis](#) associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of [methylphenidate](#) with monoamine oxidase inhibitors is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].
- 3)) Severity: contraindicated
- 4)) Onset: rapid
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concurrent use of monoamine oxidase inhibitors and [methylphenidate](#) is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7)) Probable Mechanism: unknown

3.5.1.D] Bupropion

- 1)) Interaction Effect: increased risk of seizure
- 2)) Summary: Both [buPROPion](#) and [methylphenidate](#) may lower the seizure threshold[128][129], especially in patients with a seizure history with or without prior EEG abnormalities [129]. Concomitant use of [buPROPion](#) and [methylphenidate](#) may result in an increased risk of seizures. Extreme caution is advised

with concomitant therapy. If a seizure occurs, discontinue both [buPROPion](#) and [methylphenidate](#) therapy [128][129]; do not attempt to restart any form of [buPROPion](#) [128].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised with concomitant use of [buPROPion](#) and [methylphenidate](#), as this may result in an increased risk of seizures[128][129], especially in patients with a seizure history and with or without prior EEG abnormalities [129]. Discontinue both [buPROPion](#) and [methylphenidate](#) therapy if a seizure occurs [128][129]; do not attempt to restart any form of [buPROPion](#) [128].

7) Probable Mechanism: additive lowering of the seizure threshold

3.5.1.E] [Carbamazepine](#)

1) Interaction Effect: loss of [methylphenidate](#) efficacy

2) Summary: Two case reports describe the loss of [methylphenidate](#) efficacy after [carbamazepine](#) therapy was introduced. Carbamazepine is an inducer of cytochrome P450 enzymes, a pathway involved in [methylphenidate](#) metabolism. Although [methylphenidate](#) plasma concentrations are not routinely measured, they may be helpful in patients receiving [carbamazepine](#) who are showing no benefits or side effects from [methylphenidate](#)[126][127].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Clinicians should monitor patient response to [methylphenidate](#) therapy when [carbamazepine](#) is initiated. Monitoring of plasma [methylphenidate](#) levels may also be helpful. Doses of [methylphenidate](#) may need to be increased to maintain efficacy.

7) Probable Mechanism: induction by [carbamazepine](#) of cytochrome P450 3A4-mediated [methylphenidate](#) metabolism

8) Literature Reports

a) A 7-year-old male with severe [mental retardation](#) and [attention deficit disorder](#) was failing to respond to [methylphenidate](#) 20 mg every four hours and [thiothixene](#) 10 mg daily. Other drug therapy included [carbamazepine](#) 1000 mg daily to control [grand mal epilepsy](#). After five days of confirmed medication compliance, plasma levels of [methylphenidate](#) were measured two hours after the morning dose. No trace of either psychotropic agent or of their metabolites could be found. Doses were increased to [methylphenidate](#) 30 mg every four hours and [thiothixene](#) 20 mg daily with no evidence of efficacy or side effects. Both agents were then discontinued [124].

b) Attention deficit/hyperactivity disorder (ADHD) was being treated with [methylphenidate](#) 20 mg three times daily in a 13-year-old female. Because of mood lability and significant impulsivity, [carbamazepine](#) was introduced at 200 mg daily. The strict two-hour peak [methylphenidate](#) and ritalinic acid serum level was 5.3 ng/mL (normal range 5 to 20 ng/mL) at this time. ADHD symptoms began to worsen as the [carbamazepine](#) dose was increased to 800 mg daily. Six weeks after the start of combination therapy, the patient's [methylphenidate](#) and ritalinic acid strict two-hour peak blood level had decreased to 4.2 ng/mL. A month later, the [carbamazepine](#) dose was increased to 1000 mg daily with a steady-state blood level of 11.2 mcg/mL. Despite an increase in her [methylphenidate](#) dose to 35 mg three times daily, her [methylphenidate](#) and ritalinic acid peak level had further decreased to 2.4 ng/mL. After another two months, her [carbamazepine](#) dose was 1200 mg daily with a steady-state blood level of 11.5 mcg/mL, and [methylphenidate](#) was increased to 60 mg three times daily to regain the benefit from the drug that she had experienced before the initiation of [carbamazepine](#) [125].

3.5.1.F] Citalopram

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with [methylphenidate](#). Additionally, when initiating or discontinuing [methylphenidate](#), the SSRI dose may need to be adjusted as needed[123].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of [methylphenidate](#) and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing [methylphenidate](#) therapy[123].
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by [methylphenidate](#)

3.5.1.G] Clomipramine

- 1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#)[141][142]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [143]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [144]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [145]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation[132][133][134][135]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports
 - a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [132][133][134].
 - b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [82].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [136].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [137][135].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [138].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [139]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [140].

3.5.1.H) Clorgyline

1) Interaction Effect: [hypertensive crisis](#) (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of [methylphenidate](#) and a monoamine oxidase inhibitor may result in [hypertensive crisis](#), which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. [Hypertensive crisis](#) associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of [methylphenidate](#) with monoamine oxidase inhibitors is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and [methylphenidate](#) is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.I) Clovoxamine

1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations

2) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with [methylphenidate](#). Additionally, when initiating or discontinuing [methylphenidate](#), the SSRI dose may need to be adjusted as needed[123].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of [methylphenidate](#) and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing [methylphenidate](#) therapy[123].

7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by [methylphenidate](#)

3.5.1.J) [Desipramine](#)

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#)[141][142]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [143]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [144]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [145]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation[132][133][134][135]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [132][133][134].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [82].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [136].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [137][135].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [138].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [139]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [140].

3.5.1.K] Dicumarol

1) Interaction Effect: an increased risk of bleeding

2) Summary: [Methylphenidate](#) may increase the hypoprothrombinemic effect of dicumarol[121]. Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of coumarin anticoagulants, such as dicumarol. Downward dose adjustments of dicumarol may be necessary when it is used concurrently with [methylphenidate](#). Additionally, coagulation times should be closely monitored, when initiating or discontinuing [methylphenidate](#), and should be reassessed periodically during concurrent therapy. Dicumarol dose adjustments may be made as necessary in order to maintain the desired level of [anticoagulation](#) [82].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [methylphenidate](#) and dicumarol may increase dicumarol levels due to inhibition of dicumarol metabolism by [methylphenidate](#). In patients receiving oral [anticoagulant therapy](#), the prothrombin time ratio or [international normalized ratio](#) (INR) should be closely monitored with the addition and withdrawal of treatment with [methylphenidate](#), and should be reassessed periodically during concurrent therapy. Adjustments of the dicumarol dose may be necessary in order to maintain the desired level of [anticoagulation](#).

7) Probable Mechanism: inhibition of dicumarol metabolism

3.5.1.L] Donepezil

1) Interaction Effect: reduced seizure threshold

2) Summary: Seizure threshold lowering effects have been associated with [donepezil](#)[122]. Use extreme caution when prescribing [donepezil](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Seizure threshold lowering effects have been associated with [donepezil](#)[122]. Use extreme caution when prescribing [donepezil](#) with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, [theophylline](#), systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually.

7) Probable Mechanism: unknown

3.5.1.M] Dothiepin

- 1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#) [141][142]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [143]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [144]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [145]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation [132][133][134][135]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [132][133][134].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [82].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [136].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [137][135].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [138].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [139]. However, a systemic review of stimulants in the treatment of

depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [140].

3.5.1.N] Doxepin

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#)[141][142]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [143]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [144]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [145]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation[132][133][134][135]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [132][133][134].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [82].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [136].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [137][135].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two

weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [138].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [139]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [140].

3.5.1.O) Escitalopram

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with [methylphenidate](#). Additionally, when initiating or discontinuing [methylphenidate](#), the SSRI dose may need to be adjusted as needed[123].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of [methylphenidate](#) and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing [methylphenidate](#) therapy[123].
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by [methylphenidate](#)

3.5.1.P) Femoxetine

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with [methylphenidate](#). Additionally, when initiating or discontinuing [methylphenidate](#), the SSRI dose may need to be adjusted as needed[123].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of [methylphenidate](#) and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing [methylphenidate](#) therapy[123].
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by [methylphenidate](#)

3.5.1.Q) Fluoxetine

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI

may be necessary when it is used concurrently with [methylphenidate](#). Additionally, when initiating or discontinuing [methylphenidate](#), the SSRI dose may need to be adjusted as needed[123].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of [methylphenidate](#) and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing [methylphenidate](#) therapy[123].

7J) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by [methylphenidate](#)

3.5.1.RJ [Fluvoxamine](#)

1J) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations

2J) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with [methylphenidate](#). Additionally, when initiating or discontinuing [methylphenidate](#), the SSRI dose may need to be adjusted as needed[123].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of [methylphenidate](#) and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing [methylphenidate](#) therapy[123].

7J) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by [methylphenidate](#)

3.5.1.SJ [Fosphenytoin](#)

1J) Interaction Effect: increased [phenytoin](#) plasma concentrations

2J) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of anticonvulsants, such as [phenytoin](#). Downward dose adjustments of [phenytoin](#) may be necessary when it is used concurrently with [methylphenidate](#). Additionally, serum [phenytoin](#) levels may need to be monitored when initiating or discontinuing [methylphenidate](#) and [phenytoin](#) dose adjusted as necessary[82].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [methylphenidate](#) and [phenytoin](#) may increase [phenytoin](#) levels due to inhibition of [phenytoin](#) metabolism by [methylphenidate](#). Consider a decrease in [phenytoin](#) dose when these agents are coadministered. Additionally, consider monitoring serum [phenytoin](#) concentrations when initiating or discontinuing [methylphenidate](#) and adjust [phenytoin](#) dose if necessary.

7J) Probable Mechanism: inhibition of [phenytoin](#) metabolism by [methylphenidate](#)

3.5.1.TJ [Furazolidone](#)

1J) Interaction Effect: [hypertensive crisis](#) (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of [methylphenidate](#) and a monoamine oxidase inhibitor may result in [hypertensive crisis](#), which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. [Hypertensive crisis](#) associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of [methylphenidate](#) with monoamine oxidase inhibitors is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and [methylphenidate](#) is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.U] [Imipramine](#)

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#)[141][142]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [143]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [144]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [145]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation[132][133][134][135]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [132][133][134].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [82].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [136].

d) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation [137][135].

e) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine [138].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [139]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [140].

3.5.1.V) Ioflupane I 123

1) Interaction Effect: interference with ioflupane I 123 imaging

2) Summary: The ioflupane component of ioflupane I 123 binds to the dopamine transporter allowing for striatal dopamine transport visualization using single photon emission computed tomography (SPECT) brain imaging. Because methylphenidate binds with high affinity to the dopamine transporter, there is the potential for interference with ioflupane I 123 imaging. It is unknown whether discontinuing methylphenidate prior to ioflupane I 123 administration may minimize this interference[120]. The potential for imaging interference should be considered when administering ioflupane I 123 to patients who are already receiving methylphenidate.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of ioflupane I 123 and methylphenidate may result in interference with ioflupane I 123 imaging. It is unknown whether discontinuing methylphenidate prior to ioflupane I 123 administration may minimize the interference[120]. Consider the potential for imaging interference when administering ioflupane I 123 to patients who are already receiving methylphenidate.

7) Probable Mechanism: unknown

3.5.1.W) Iproniazid

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of methylphenidate with monoamine oxidase inhibitors is contraindicated. If methylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. If methylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.X] Isocarboxazid

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of methylphenidate with monoamine oxidase inhibitors is contraindicated. If methylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. If methylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.Y] Lazabemide

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of methylphenidate with monoamine oxidase inhibitors is contraindicated. If methylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. If methylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.Z] Linezolid

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of methylphenidate with monoamine oxidase inhibitors is contraindicated. If methylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and [methylphenidate](#) is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.AA] Lofepramine

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#)[141][142]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [143]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [144]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [145]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation[132][133][134][135]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [132][133][134].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [82].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [136].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [137][135].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two

weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [138].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [139]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [140].

3.5.1.AB] Moclobemide

- 1) Interaction Effect: [hypertensive crisis](#) (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of [methylphenidate](#) and a monoamine oxidase inhibitor may result in [hypertensive crisis](#), which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. [Hypertensive crisis](#) associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of [methylphenidate](#) with monoamine oxidase inhibitors is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and [methylphenidate](#) is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

3.5.1.AC] Nefazodone

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with [methylphenidate](#). Additionally, when initiating or discontinuing [methylphenidate](#), the SSRI dose may need to be adjusted as needed[123].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take a selective serotonin reuptake inhibitor (SSRI). Concomitant use of [methylphenidate](#) and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing [methylphenidate](#) therapy[123].
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by [methylphenidate](#)

3.5.1.AD] Nialamide

- 1) Interaction Effect: [hypertensive crisis](#) (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of [methylphenidate](#) and a monoamine oxidase inhibitor may result in [hypertensive crisis](#), which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. [Hypertensive crisis](#) associated with monoamine oxidase inhibitors has been

fatal[119]. The concomitant administration of [methylphenidate](#) with monoamine oxidase inhibitors is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and [methylphenidate](#) is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.AE] [Nortriptyline](#)

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#)[141][142]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [143]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [144]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [145]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation[132][133][134][135]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [132][133][134].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [82].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [136].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation

of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [137][135].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [138].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [139]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [140].

3.5.1.AF] Opipramol

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#)[141][142]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [143]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [144]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [145]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation[132][133][134][135]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [132][133][134].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [82].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [136].

d)) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation [137][135].

e)) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine [138].

f)) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [139]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [140].

3.5.1.AG] Pargyline

1)) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2)) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of methylphenidate with monoamine oxidase inhibitors is contraindicated. If methylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].

3)) Severity: contraindicated

4)) Onset: rapid

5)) Substantiation: theoretical

6)) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. If methylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7)) Probable Mechanism: unknown

3.5.1.AH] Paroxetine

1)) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations

2)) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with methylphenidate. Additionally, when initiating or discontinuing methylphenidate, the SSRI dose may need to be adjusted as needed[123].

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use caution when prescribing methylphenidate to patients who take a selective serotonin reuptake inhibitor (SSRI). Concomitant use of methylphenidate and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing methylphenidate therapy[123].

7J) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by methylphenidate

3.5.1.AI] Phenelzine

1J) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2J) Summary: Coadministration of methylphenidate and a monoamine oxidase inhibitor may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of methylphenidate with monoamine oxidase inhibitors is contraindicated. If methylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].

3J) Severity: contraindicated

4J) Onset: rapid

5J) Substantiation: theoretical

6J) Clinical Management: The concurrent use of monoamine oxidase inhibitors and methylphenidate is contraindicated. If methylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7J) Probable Mechanism: unknown

3.5.1.AJ] Phenobarbital

1J) Interaction Effect: increased phenobarbital plasma concentrations

2J) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of anticonvulsants, such as phenobarbital. Downward dose adjustments of phenobarbital may be necessary when it is used concurrently with methylphenidate. Additionally, serum phenobarbital levels may need to be monitored when initiating or discontinuing methylphenidate and phenobarbital dose adjusted as necessary[82].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of methylphenidate and phenobarbital may increase phenobarbital levels due to inhibition of phenobarbital metabolism by methylphenidate. Consider a decrease in phenobarbital dose when these agents are coadministered. Additionally, consider monitoring serum phenobarbital concentrations when initiating or discontinuing methylphenidate and adjust phenobarbital dose if necessary.

7J) Probable Mechanism: inhibition of phenobarbital metabolism by methylphenidate

3.5.1.AK] Phenytoin

1J) Interaction Effect: increased phenytoin plasma concentrations

2J) Summary: Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of anticonvulsants, such as phenytoin. Downward dose adjustments of phenytoin may be necessary when it is used concurrently with methylphenidate. Additionally, serum phenytoin levels may need to be monitored when initiating or discontinuing methylphenidate and phenytoin dose adjusted as necessary[82].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of methylphenidate and phenytoin may increase phenytoin levels due to inhibition of phenytoin metabolism by methylphenidate. Consider a decrease in phenytoin

dose when these agents are coadministered. Additionally, consider monitoring serum [phenytoin](#) concentrations when initiating or discontinuing [methylphenidate](#) and adjust [phenytoin](#) dose if necessary.

7) Probable Mechanism: inhibition of [phenytoin](#) metabolism by [methylphenidate](#)

3.5.1.AL] [Primidone](#)

- 1) Interaction Effect: increased [primidone](#) plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of anticonvulsants, such as [primidone](#). Downward dose adjustments of [primidone](#) may be necessary when it is used concurrently with [methylphenidate](#). Additionally, serum [primidone](#) levels may need to be monitored when initiating or discontinuing [methylphenidate](#) and [primidone](#) dose adjusted as necessary[82].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [methylphenidate](#) and [primidone](#) may increase [primidone](#) levels due to inhibition of [primidone](#) metabolism by [methylphenidate](#). Consider a decrease in [primidone](#) dose when these agents are coadministered. Additionally, consider monitoring serum [primidone](#) concentrations when initiating or discontinuing [methylphenidate](#) and adjust [primidone](#) dose if necessary.
- 7) Probable Mechanism: inhibition of [primidone](#) metabolism by [methylphenidate](#)

3.5.1.AM] [Procarbazine](#)

- 1) Interaction Effect: [hypertensive crisis](#) (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of [methylphenidate](#) and a monoamine oxidase inhibitor may result in [hypertensive crisis](#), which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. [Hypertensive crisis](#) associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of [methylphenidate](#) with monoamine oxidase inhibitors is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and [methylphenidate](#) is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

3.5.1.AN] [Protriptyline](#)

- 1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation
- 2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#)[141][142]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [143]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [144]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [145]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).
- 3) Severity: moderate

- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation[132][133][134][135]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).
- 7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
- 8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as [desipramine](#) or [protriptyline](#) results in sustained increases in d-amphetamine concentration in the brain [132][133][134].

b) Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of some tricyclic antidepressants, such as [imipramine](#), [clomipramine](#), or [desipramine](#) [82].

c) A 55-year-old female patient was maintained on [imipramine](#) 350 mg daily for several years, with [imipramine](#) plus [desipramine](#) blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with [fenfluramine](#) 20 mg three times daily, the patient fell asleep while driving. The [imipramine](#) plus [desipramine](#) level was 704 mcg/L. [Fenfluramine](#) may have inhibited the CYP450 isoenzyme responsible for metabolizing [imipramine](#) [136].

d) Concomitant administration of tricyclic antidepressants and [methylphenidate](#) can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the [methylphenidate](#) usually results in the blood pressure returning to normotensive levels; reinstitution of the [methylphenidate](#) resulted in further blood pressure elevation [137][135].

e) Fifteen patients with DSM-III [major depression](#), who failed to respond to treatment with [desipramine](#) given for at least four weeks, were given [fenfluramine](#) 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, [fenfluramine](#) more than doubled steady-state plasma levels of [desipramine](#) [138].

f) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [139]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [140].

3.5.1.AO] [Rasagiline](#)

- 1) Interaction Effect: [hypertensive crisis](#) (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of [methylphenidate](#) and a monoamine oxidase inhibitor may result in [hypertensive crisis](#), which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. [Hypertensive crisis](#) associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of [methylphenidate](#) with monoamine oxidase inhibitors is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].

- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and [methylphenidate](#) is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

3.5.1.AP] [Selegiline](#)

- 1) Interaction Effect: [hypertensive crisis](#) (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of [methylphenidate](#) and a monoamine oxidase inhibitor may result in [hypertensive crisis](#), which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. [Hypertensive crisis](#) associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of [methylphenidate](#) with monoamine oxidase inhibitors is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and [methylphenidate](#) is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
- 7) Probable Mechanism: unknown

3.5.1.AQ] [Sertraline](#)

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with [methylphenidate](#). Additionally, when initiating or discontinuing [methylphenidate](#), the SSRI dose may need to be adjusted as needed[123].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of [methylphenidate](#) and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing [methylphenidate](#) therapy[123].
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by [methylphenidate](#)

3.5.1.AR] [Toloxatone](#)

- 1) Interaction Effect: [hypertensive crisis](#) (headache, palpitation, and neck stiffness)
- 2) Summary: Coadministration of [methylphenidate](#) and a monoamine oxidase inhibitor may result in [hypertensive crisis](#), which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. [Hypertensive crisis](#) associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of [methylphenidate](#) with monoamine oxidase inhibitors

is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and [methylphenidate](#) is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.AS] [Tranlycypromine](#)

1) Interaction Effect: [hypertensive crisis](#) (headache, palpitation, and neck stiffness)

2) Summary: Coadministration of [methylphenidate](#) and a monoamine oxidase inhibitor may result in [hypertensive crisis](#), which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. [Hypertensive crisis](#) associated with monoamine oxidase inhibitors has been fatal[119]. The concomitant administration of [methylphenidate](#) with monoamine oxidase inhibitors is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days [82].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and [methylphenidate](#) is contraindicated. If [methylphenidate](#) is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.AT] [Trimipramine](#)

1) Interaction Effect: [hypertension](#), other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and [amphetamine](#) administration has been reported to result in enhanced [amphetamine](#) effects from the release of [norepinephrine](#)[141][142]. A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted [143]. Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When [amphetamine](#) analogs are being used to treat [obesity](#), it should be noted that TCAs frequently lead to moderate weight gain [144]. False positive urine tests for [amphetamines](#) have been reported during therapy with some TCAs [145]. Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects ([hypertension](#) and [dysrhythmias](#)).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [amphetamines](#) and tricyclic antidepressants or other sympathomimetic agents could lead to [hypertension](#), increased cardiovascular effects, or CNS stimulation[132][133][134][135]. Use caution if such therapy is warranted. Monitor the patient closely for [hypertension](#) and [dysrhythmias](#).

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) [Amphetamines](#) may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as

desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain [132][133][134].

b)) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine [82].

c)) A 55-year-old female patient was maintained on imipramine 350 mg daily for several years, with imipramine plus desipramine blood levels ranging from 218 mcg/L to 145 mcg/L. After four weeks of treatment with fenfluramine 20 mg three times daily, the patient fell asleep while driving. The imipramine plus desipramine level was 704 mcg/L. Fenfluramine may have inhibited the CYP450 isoenzyme responsible for metabolizing imipramine [136].

d)) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation [137][135].

e)) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine [138].

f)) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy [139]. However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression [140].

3.5.1.AU] Tyrosine

- 1)) Interaction Effect: increased adverse effects
- 2)) Summary: Tyrosine prolonged the effect of methylphenidate in rats[131].
- 3)) Severity: moderate
- 4)) Onset: rapid
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Caution is advised if tyrosine and methylphenidate are used together. Monitor the patient for increased side effects of methylphenidate.
- 7)) Probable Mechanism: not specified
- 8)) Literature Reports

a)) Exogenous tyrosine supplementation prolonged the effect of methylphenidate (MPD) in rats. Simultaneous infusion of tyrosine 100 micromoles and MPD into the nucleus accumbens of Sprague-Dawley rats resulted in potentiation and prolongation of the MPD effect. Potentiation was noted during the final 20 minutes of infusion when dopamine concentrations already declined during the MPD-alone experiment and peaked 40 minutes after the maximum MPD effect was observed [130].

3.5.1.AV] Warfarin

- 1) Interaction Effect: increased [warfarin](#) plasma concentrations and an increased risk of bleeding
- 2) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of coumarin anticoagulants, such as [warfarin](#). Downward dose adjustments of [warfarin](#) may be necessary when it is used concurrently with [methylphenidate](#). Additionally, coagulation times should be closely monitored, when initiating or discontinuing [methylphenidate](#), and should be reassessed periodically during concurrent therapy. [Warfarin](#) dose adjustments may be made as necessary in order to maintain the desired level of [anticoagulation](#)[82].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [methylphenidate](#) and [warfarin](#) may increase [warfarin](#) levels due to inhibition of [warfarin](#) metabolism by [methylphenidate](#). Consider a decrease in [warfarin](#) dose when these agents are coadministered. Additionally, monitor coagulation times when initiating or discontinuing [methylphenidate](#) and adjust [warfarin](#) dose if necessary.
- 7) Probable Mechanism: inhibition of [warfarin](#) metabolism by [methylphenidate](#)

3.5.1.AW] Zimeldine

- 1) Interaction Effect: increased selective serotonin reuptake inhibitor plasma concentrations
- 2) Summary: Human pharmacologic studies have demonstrated that [methylphenidate](#) may inhibit the metabolism of selective serotonin reuptake inhibitors (SSRIs). Downward dose adjustments of the SSRI may be necessary when it is used concurrently with [methylphenidate](#). Additionally, when initiating or discontinuing [methylphenidate](#), the SSRI dose may need to be adjusted as needed[123].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing [methylphenidate](#) to patients who take an selective serotonin reuptake inhibitor (SSRI). Concomitant use of [methylphenidate](#) and an SSRI may cause elevated SSRI plasma concentrations. Consider a decrease in the dose of SSRI when these agents are coadministered. Additionally, consider adjusting the SSRI dose if necessary when initiating or discontinuing [methylphenidate](#) therapy[123].
- 7) Probable Mechanism: inhibition of selective serotonin reuptake inhibitor metabolism by [methylphenidate](#)

3.5.2] Drug-Food Combinations

3.5.2.A] Ethanol

- 1) Interaction Effect: additive CNS effects
- 2) Summary: Coadministration of [methylphenidate](#) with alcohol may exacerbate the CNS adverse effects of [methylphenidate](#), and alcohol may cause a more rapid release of the dose of extended-release formulations of [methylphenidate](#). In 2 in vitro studies, the majority of [methylphenidate](#) extended-release oral doses were released within the first hour of exposure to 40% alcohol concentrations[36][35]. Advise patients to avoid consuming alcohol during [methylphenidate](#) therapy [35].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [methylphenidate](#) with alcohol may exacerbate the CNS adverse effects of [methylphenidate](#). Alcohol may cause a more rapid release of the dose of extended-release formulations of [methylphenidate](#). Advise patients to avoid consuming alcohol during [methylphenidate](#) therapy[35][36].

7) Probable Mechanism: rapid dissolution of extended-release formulation of [methylphenidate](#) by alcohol

8) Literature Reports

a) An in vitro study of the effects of 40% alcohol concentrations on [methylphenidate](#) extended release 60 mg oral metabolism found that 84% of the dose was released within the first hour of alcohol exposure [36]. In a similar in vitro study, 98% of [methylphenidate](#) extended-release 40 mg oral was released within the first hour of exposure to concentrations of 40% alcohol [35]. Both sets of study results were considered representative of other capsule strengths [36][35].

3.5.5] Intravenous Admixtures

3.5.5.1] Drugs

3.5.5.1.A] [Amobarbital](#)

1) Incompatible

a) [Methylphenidate](#) (incompatible with [amobarbital](#); conditions not specified) [284]

3.5.5.1.B] [Dextran](#)

1) Compatible

a) Dextran 70 6% in [Dextrose](#) 5% in water with [methylphenidate](#) 30 mg/L, physically compatible for 24 hours; conditions not specified [277][278]

b) Dextran 70 6% in [Sodium chloride](#) 0.9% with [methylphenidate](#) 30 mg/L, physically compatible for 24 hours; conditions not specified [277][278]

3.5.5.1.C] [Methohexital](#)

1) Incompatible

a) [Methohexital](#) (barbiturates physically incompatible with [methylphenidate](#); drug concentrations and conditions not specified) (Kramer, 1971)

3.5.5.1.D] [Pentobarbital](#)

1) Incompatible

a) [Pentobarbital](#) (barbiturates physically incompatible with [methylphenidate](#); drug concentrations and conditions not specified) (Kramer, 1971)

3.5.5.1.E] [Phenobarbital](#)

1) Incompatible

a) [Methylphenidate](#) 1 mL, reconstituted, with [phenobarbital](#) 1 mL, reconstituted, both added to Sterile water for injection 5 mL, precipitate formation was reported within 2 hours; exact drug concentrations not specified [281]

b) [Phenobarbital](#) barbiturates physically incompatible with [methylphenidate](#); drug concentrations and conditions not specified (Kramer, 1971)

3.5.5.1.F] Procainamide**1) Compatible**

- a) **Methylphenidate** 1 mL, reconstituted, with **procainamide** 1 mL, reconstituted, both added to Sterile water for injection 5 mL, visually compatible for 2 hours [280].

3.5.5.1.G] Procaine**1) Compatible**

- a) **Procaine** (0.1% in **Sodium chloride** 0.9% with **methylphenidate** 30 mg/L physically compatible; conditions not specified) [282]
- b) **Methylphenidate** (30 mg/L with **procaine** 1 g/L physically compatible in **Sodium chloride** 0.9%; conditions not specified) [283]

3.5.5.1.H] Secobarbital**1) Incompatible**

- a) **Secobarbital** (barbiturates physically incompatible with **methylphenidate**; drug concentrations and conditions not specified) (Kramer, 1971)

3.5.5.1.I] Thiopental**1) Incompatible**

- a) **Thiopental** (barbiturates physically incompatible with **methylphenidate**; drug concentrations and conditions not specified) (Kramer, 1971)
- b) **Methylphenidate** (incompatible with barbiturates; conditions not specified) [279]

3.5.5.2] Solutions**3.5.5.2.A] ALKALINE SOLUTIONS****1) Incompatible**

- a) Alkaline solutions (physically incompatible with **methylphenidate**; conditions not specified) (Kramer, 1971)

3.5.5.2.B] Dextrose 10% in lactated Ringer's injection**1) Compatible**

- a) **Methylphenidate** 30 mg/L is physically compatible with **Dextrose** 10% in lactated Ringer's injection; conditions not specified (Kirkland et al, 1961)

3.5.5.2.C] Dextrose 10% in Ringer's injection**1) Compatible**

- a) **Methylphenidate** 30 mg/L is physically compatible with **Dextrose** 10% in Ringer's injection; conditions not specified [285]

3.5.5.2.D] Dextrose 10% in Sodium chloride 0.9%**1) Compatible**

a) **Methylphenidate** 30 mg/L is physically compatible with **Dextrose** 10% in **Sodium chloride** 0.9%; conditions not specified [285].

3.5.5.2.E] DEXTROSE 10% in water**1) Compatible**

a) **Methylphenidate** 30 mg/L is physically compatible with **Dextrose** 10% in water; conditions not specified [285].

3.5.5.2.F] Dextrose 2.5% in half-strength lactated Ringer's injection**1) Compatible**

a) **Methylphenidate** 30 mg/L is physically compatible with **Dextrose** 2.5% in half-strength lactated Ringer's injection; conditions not specified [285]

3.5.5.2.G] Dextrose 2.5% in half-strength Ringer's injection**1) Compatible**

a) **Methylphenidate** 30 mg/L is physically compatible with **Dextrose** 2.5% in half-strength Ringer's injection; conditions not specified [285]

3.5.5.2.H] Dextrose 2.5% in Sodium chloride 0.45%**1) Compatible**

a) **Methylphenidate** 30 mg/L is physically compatible with **Dextrose** 2.5% in **Sodium chloride** 0.45%; conditions not specified [285].

3.5.5.2.I] Dextrose 2.5% in Sodium chloride 0.9%**1) Compatible**

a) **Methylphenidate** 30 mg/L is physically compatible with **Dextrose** 2.5% in **Sodium chloride** 0.9%; conditions not specified [285].

3.5.5.2.J] DEXTROSE 2.5% in water**1) Compatible**

a) **Methylphenidate** 30 mg/L is physically compatible with **Dextrose** 2.5% in water; conditions not specified [285].

3.5.5.2.K] DEXTROSE 20% in water**1) Compatible**

a) **Methylphenidate** 30 mg/L is physically compatible with **Dextrose** 20% in water; conditions not specified [285].

3.5.5.2.L] Dextrose 5% in lactated Ringer's injection**1) Compatible**

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in lactated Ringer's injection; conditions not specified [285]

3.5.5.2.M] Dextrose 5% in Ringer's injection**1) Compatible**

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in Ringer's injection; conditions not specified [285]

3.5.5.2.N] Dextrose 5% in sodium chloride 0.225%**1) Compatible**

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in sodium chloride 0.225%; conditions not specified [285].

3.5.5.2.O] Dextrose 5% in Sodium chloride 0.45%**1) Compatible**

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in Sodium chloride 0.45%; conditions not specified [285].

3.5.5.2.P] Dextrose 5% in Sodium chloride 0.9%**1) Compatible**

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in Sodium chloride 0.9%; conditions not specified [285].

3.5.5.2.Q] DEXTROSE 5% in water**1) Compatible**

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 5% in water; conditions not specified [285].

3.5.5.2.R] DEXTROSE 50% in water**1) Compatible**

a) Methylphenidate 30 mg/L is physically compatible with Dextrose 50% in water; conditions not specified [285].

3.5.5.2.S] FRUCTOSE 10%**1) Compatible**

a) Fructose 10% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

b) **Methylphenidate** (30 mg/L in FRUCTOSE 10% or FRUCTOSE 10% IN **SODIUM CHLORIDE** 0.9% physically compatible; conditions not specified) [286]

3.5.5.2.T] FRUCTOSE 10% IN SODIUM CHLORIDE 0.9%

1) Compatible

a) Fructose 10% in **sodium chloride** 0.9% (with **methylphenidate** 30 mg/L physically compatible; conditions not specified) [282]

b) **Methylphenidate** (30 mg/L in FRUCTOSE 10% or FRUCTOSE 10% IN **SODIUM CHLORIDE** 0.9% physically compatible; conditions not specified) [286]

3.5.5.2.U] Invert sugar 10%

1) Compatible

a) Invert sugar 10% (with **methylphenidate** 30 mg/L physically compatible; conditions not specified) [282]

b) **Methylphenidate** (30 mg/L in Invert sugar 10% physically compatible; conditions not specified) [287]:

3.5.5.2.V] Invert sugar 10% in sodium chloride 0.9%

1) Compatible

a) Invert sugar 10% in **sodium chloride** 0.9% (with **methylphenidate** 30 mg/L physically compatible; conditions not specified) [282]

b) **Methylphenidate** (30 mg/L in Invert sugar 10% in **sodium chloride** 0.9% physically compatible; conditions not specified) [287]:

3.5.5.2.W] Invert sugar 5%

1) Compatible

a) Invert sugar 5% (with **methylphenidate** 30 mg/L physically compatible; conditions not specified) [282]

b) **Methylphenidate** (30 mg/L in Invert sugar 5% physically compatible; conditions not specified) [287]:

3.5.5.2.X] Invert sugar 5% in sodium chloride 0.9%

1) Compatible

a) Invert sugar 5% in **sodium chloride** 0.9% (with **methylphenidate** 30 mg/L physically compatible; conditions not specified) [282]

b) **Methylphenidate** (30 mg/L in Invert sugar 5% in **sodium chloride** 0.9% physically compatible; conditions not specified) [287]:

3.5.5.2.Y] IONOSOL(R) B IN DEXTROSE 5%

1) Compatible

a) Ionosol(R) B in dextrose 5% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.Z] Ionosol(R) D, modified in invert sugar 10%**1) Compatible**

a) Ionosol(R) D, modified in invert sugar 10% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AA] IONOSOL(R) DCM**1) Compatible**

a) Ionosol(R) DCM (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AB] IONOSOL(R) DCM IN DEXTROSE 5%**1) Compatible**

a) Ionosol(R) DCM in dextrose 5% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AC] IONOSOL(R) D IN DEXTROSE 10%**1) Compatible**

a) Ionosol(R) D in dextrose 10% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AD] Ionosol(R) D in invert sugar 10%**1) Compatible**

a) Ionosol(R) D in invert sugar 10% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AE] IONOSOL(R) G IN DEXTROSE 10%**1) Compatible**

a) Ionosol(R) G in dextrose 10% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AF] IONOSOL(R) G IN INVERT SUGAR 10%**1) Compatible**

a) Ionosol(R) G in invert sugar 10% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AG] IONOSOL(R) K IN INVERT SUGAR 10%

1) Compatible

a) Ionosol(R) K in invert sugar 10% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AH] IONOSOL(R) MB IN DEXTROSE 5%**1) Compatible**

a) Ionosol(R) MB in dextrose 5% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AI] IONOSOL(R) PSL**1) Compatible**

a) Ionosol(R) PSL (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282] al.

3.5.5.2.AJ] Ionosol(R) T in dextrose 5%**1) Compatible**

a) Ionosol(R) T in dextrose 5% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AK] LACTATED RINGER'S INJECTION**1) Compatible**

a) Lactated Ringer's injection (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AL] RINGER'S INJECTION**1) Compatible**

a) Ringer's injection (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AM] SODIUM CHLORIDE 0.45%**1) Compatible**

a) SODIUM CHLORIDE 0.45% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AN] SODIUM CHLORIDE 0.9%**1) Compatible**

a) SODIUM CHLORIDE 0.9% (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AO] SODIUM CHLORIDE 3%

1) Compatible

- a) SODIUM CHLORIDE 3%** (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AP] SODIUM CHLORIDE 5%**1) Compatible**

- a) SODIUM CHLORIDE 5%** (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]

3.5.5.2.AQ] SODIUM LACTATE 1/6 M**1) Compatible**

- a) Sodium lactate 1/6 M** (with methylphenidate 30 mg/L physically compatible; conditions not specified) [282]
- b) Methylphenidate** (30 mg/L in Sodium lactate 1/6 M physically compatible; conditions not specified) [288]

4.0] Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

[Comparative Efficacy / Evaluation With Other Therapies](#)

4.1] Monitoring Parameters**A) Methylphenidate****1) Therapeutic****a) Physical Findings**

- 1) Improvement in symptoms of attention deficit hyperactivity disorder (ADHD) indicates efficacy.**
- 2) Periodically reassess the need for long-term methylphenidate treatment by temporarily withdrawing therapy and monitoring for recurrence of behavioral symptoms [29].**

2) Toxic**a) Laboratory Parameters**

- 1) Monitor CBC with differential, including platelet counts periodically during prolonged therapy [29].**

b) Physical Findings

1j) Monitor for the development of underlying disorders or severe depression during withdrawal from chronic therapeutic use or abusive use [29].

2j) The American Academy of Pediatrics (AAP) does not recommend the routine use of ECGs or routine subspecialty cardiology evaluations (which were previously recommended by the American Heart Association [AHA] scientific statement to detect cardiac conditions that might place the child at risk for sudden cardiac death [SCD]) before initiating stimulant therapy to treat attention-deficit/hyperactivity disorder ADHD in most children. The APA cited specific reasons for changing the recommendation including: lack of evidence establishing a relationship between stimulant drugs used to treat ADHD and SCD, the frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher than that in the general population of children, and lack of cost-effective analysis to support ECG screening or special evaluation by pediatric cardiologist [162]. Based on the AAP and the AHA consensus statements, the following cardiac monitoring recommendations have been established to assist clinicians in the evaluation of children treated with stimulant drugs, including methylphenidate, for ADHD [162][163]:

- Conduct a thorough examination prior to initiating methylphenidate therapy for a diagnosis of ADHD. Special attention should be given to symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determine current use of any other prescription or over-the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical findings associated with Marfan syndrome, and signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac disease during initial visit or at follow up visits, and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up visits.
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 1 to 3 months, and at follow up visits every 6 to 12 months. Increases in blood pressure and heart rate have been reported with stimulant use.

3j) Screen patients with depressive symptoms for the risk of bipolar disorder before therapy initiation [29].

4j) Monitor for new or worsening aggressive behavior or hostility when initiating therapy [29].

5j) Observe for signs and symptoms of peripheral vasculopathy (eg, Raynaud's phenomenon) during treatment and if needed, conduct further evaluation (eg, rheumatology referral) [29].

6j) Assess growth determinations (body weight and height) periodically [29].

Bj) Methylphenidate Hydrochloride

1) Therapeutic**a) Attention Deficit Hyperactivity Disorder (ADHD)**

1) Improvement in symptoms of attention deficit hyperactivity disorder (ADHD) indicates efficacy.

2) Periodically reassess the need for continued methylphenidate treatment by temporarily withdrawing therapy and monitoring for recurrence of behavioral symptoms and their severity [39][14][15][164].

b) Narcolepsy

1) Decreased frequency of narcoleptic attacks indicates efficacy.

2) Toxic**a) Laboratory Parameters**

1) Monitor CBC, differential, and platelet counts periodically during prolonged therapy [39][32][25][34][33][165][27].

b) Physical Findings

1) Monitor for the development of underlying disorders or severe depression during withdrawal from chronic therapeutic use or abusive use [39].

2) The American Academy of Pediatrics (AAP) does not recommend the routine use of ECGs or routine subspecialty cardiology evaluations (which were previously recommended by the American Heart Association [AHA] scientific statement to detect cardiac conditions that might place the child at risk for sudden cardiac death [SCD]) before initiating stimulant therapy to treat attention-deficit/hyperactivity disorder (ADHD) in most children. The APA cited specific reasons for changing the recommendation including: lack of evidence establishing a relationship between stimulant drugs used to treat ADHD and SCD, the frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher than that in the general population of children, and lack of cost-effective analysis to support ECG screening or special evaluation by pediatric cardiologist [162]. Based on the AAP and the AHA consensus statements, the following cardiac monitoring recommendations have been established to assist clinicians in the evaluation of children treated with stimulant drugs, including methylphenidate, for ADHD [162][163]:

- Conduct a thorough examination prior to initiating methylphenidate therapy for a diagnosis of ADHD. Special attention should be given to symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determine current use of any other prescription or over-the-counter medications.

- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical findings associated with Marfan syndrome, and signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac disease during initial visit or at follow up visits, and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up visits.
- Blood pressure and heart rate should be evaluated at baseline, during routine followup within 1 to 3 months, and at follow up visits every 6 to 12 months. Increases in blood pressure and heart rate have been reported with stimulant use.

3j) Screen patients for risk factors for developing a manic episode prior to treatment [39][14].

4j) Monitor patients shortly after initiating treatment for new or worsening aggressive behavior or hostility [39].

5j) Observe for signs and symptoms of peripheral vasculopathy (eg, Raynaud's phenomenon) during treatment and if needed, conduct further evaluation (eg, rheumatology referral) [39].

6j) Assess growth determinations (body weight and height) periodically during therapy [39][14][32][25][34][33][165][27].

4.2] Patient Instructions

Aj) **Methylphenidate** (Absorbed through the skin)

Methylphenidate

Treats **attention deficit hyperactivity disorder** (ADHD).

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use if you had an **allergic reaction** to **methylphenidate**. Do not use if you have **glaucoma**, muscle tics, or a history of **Tourette syndrome**.

How to Use This Medicine:

Patch

Your doctor will tell you how many patches to use, where to apply them, and how often to apply them. Do not use more patches or apply them more often than your doctor tells you to.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one. The patch is usually placed on your hip. When you put on a new patch, do not put it on the same place you wore the last one.

Open the medicine pouch carefully. Do not cut or tear the patch itself. Do not use a patch that is cut or torn. Do not touch the sticky side, because you will get medicine on your skin.

Wash your hands with soap and water before and after applying a patch.

Do not put the patch over burns, cuts, or irritated skin. Make sure the skin area is clean, dry, cool, and free of powder, oil, or lotion before you apply the patch. Press down on the patch for 30 seconds to make sure it sticks.

If a patch comes off, put on a new one in a different spot on the same hip. Remove the new patch at the same time that you would have removed the old one.

Never wear 2 patches at the same time.

Do not wear patches for longer than 9 hours a day total. If you put on a new patch because one fell off, the total time for both patches should still be less than 9 hours. Use the chart that comes with the patient instructions to help you keep track of how long to wear the patch. Take the patch off by slowly [peeling](#) it back. Use [mineral oil](#) or petroleum jelly if needed to make the patch less sticky.

The patch might come off if you go swimming or take a bath or shower.

Missed dose: If you forget to apply the patch at the usual time, you may apply it later in the day. Remove it at the time you normally would, so you do not have side effects later than usual (such as trouble sleeping that night).

Store the patches at room temperature in a closed container, away from heat, moisture, and direct light. Do not store in the refrigerator or freezer.

Throw any used patch away so that children or pets cannot get to it. There is still enough medicine in a used patch to make a child or pet sick. Fold the patch in half with the sticky sides together and flush it down the toilet. Then wash your hands with soap and water. When you stop treatment or the patches expire, take each patch out of its pouch and flush each patch down the toilet.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Do not use this medicine if you have used an MAO inhibitor (MAOI) in the past 14 days.

Some foods and medicines can affect how [methylphenidate](#) works. Tell your doctor if you are also using cold or allergy medicine, blood pressure medicine, a blood thinner (such as [warfarin](#)), medicine for seizures (such as [phenobarbital](#), [phenytoin](#), [primidone](#)), or medicine to treat depression (such as [citalopram](#), [clomipramine](#), [desipramine](#), [fluoxetine](#), [imipramine](#), [sertraline](#)).

Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have [heart disease](#), heart rhythm problems, blood vessel or circulation problems, [high blood pressure](#), skin problems, or seizures. Tell your doctor if you have depression, anxiety, agitation, [bipolar disorder](#), mental illness, or a history of drug or alcohol dependence. Also tell your doctor if you or anyone in your family has tried to commit suicide or talked about suicide.

This medicine may cause the following problems:

- Sudden death in people who already have serious heart problems
- Heart or blood vessel problems, including [heart attack](#) or [stroke](#) in adults
- Slow growth in children
- Blood circulation problem in the fingers or toes, such as [Raynaud phenomenon](#)

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.

This medicine may make you feel dizzy or drowsy or have trouble seeing. Do not drive or do anything else that could be dangerous until you know how this medicine affects you.

Do not expose the patch to direct heat, such as a hair dryer, heating pad, electric blanket, water bed, or hot tub.

Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments. Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

- [Allergic reaction](#): Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
- Blurred vision or changes in vision

Chest pain that may spread to your arms, jaw, back, or neck, trouble breathing, nausea, unusual sweating
Erection of the penis that is painful or lasts longer than 4 hours
Extreme energy, mood or mental changes, confusion, restlessness, trouble sleeping, unusual thoughts or behavior
Fast, slow, pounding, or uneven heartbeat
Seeing, hearing, or feeling things that are not there
Seizures, tremors, twitching
Severe skin redness, swelling, itching, or blistering where the patch is worn
Sores, coldness, numbness, or color changes on your fingers or toes

If you notice these less serious side effects, talk with your doctor:

Mild trouble sleeping, feeling irritable
Mild nausea, vomiting, stomach pain, loss of appetite, weight loss
Mild redness or itching where a patch was applied

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B)) Methylphenidate (By mouth)

Methylphenidate

Treats ADHD. Also treats [narcolepsy](#).

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an [allergic reaction](#) to [methylphenidate](#), or if you have [glaucoma](#), an [overactive thyroid](#), muscle tics, or a history of [Tourette syndrome](#).

How to Use This Medicine:

Long Acting Capsule, Liquid, Long Acting Suspension, Tablet, Chewable Tablet, Long Acting Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

Chewable tablet: Drink at least 8 ounces of water or other liquid when you take the tablet.

Chewable tablet, immediate-release tablet, or oral liquid: Take the medicine 30 to 45 minutes before meals. Take the last dose of the day before 6 PM if you have problems falling asleep.

Extended-release capsule: Take your medicine in the morning before breakfast. Swallow it whole with water or other liquid. If you cannot swallow the capsule whole, you may open it and mix the medicine with a tablespoonful of applesauce. Swallow this mixture right away then drink some water.

Extended-release tablet: Take your medicine in the morning. Swallow it whole with water or other liquid. Do not crush, break, or chew it.

Extended-release suspension: Take the medicine in the morning. Shake the bottle well for at least 10 seconds before you measure each dose. Measure the dose with the dispenser that comes with the medicine.

Oral liquid: Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup. If you take the extended-release tablet, part of the tablet may pass into your stools. This is normal and is nothing to worry about.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Throw away any unused mixed extended-release suspension after 4 months.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Do not use this medicine if you have used an MAO inhibitor (MAOI) within the past 14 days.

Some medicines can affect how [methylphenidate](#) works. Tell your doctor if you are using any of the following:

[Guanethidine](#), [phenylbutazone](#)

Antacids or stomach medicine

Blood pressure medicine

Blood thinner (including [warfarin](#))

Medicine to treat depression (including [clomipramine](#), [desipramine](#), [imipramine](#))

Medicine to treat seizures (including [phenobarbital](#), [phenytoin](#), [primidone](#))

Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have [heart](#) or [blood vessel disease](#), heart rhythm problems, [high blood pressure](#), [phenylketonuria](#), [thyroid problems](#), or a history of seizures, [heart attack](#), or [stroke](#). Tell your doctor if you or anyone in your family has a history of depression, mental health problems, or drug or alcohol abuse.

This medicine may cause the following problems:

Serious heart or blood vessel problems, including [heart attack](#) and [stroke](#)

Unusual changes in behavior or mood

Peripheral vasculopathy (a blood circulation problem)

Slow growth in children

Painful or prolonged erection

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.

This medicine may make you dizzy or cause blurred vision. Do not drive or do anything else that could be dangerous until you know how this medicine affects you.

If you need surgery, tell the doctor who treats you that you are using this medicine. Medicines used during surgery can increase your blood pressure when used this medicine.

Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

[Allergic reaction](#): Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Blurred vision or vision changes

Chest pain that may spread, trouble breathing, nausea, unusual sweating

Extreme energy or restlessness, confusion, agitation, unusual moods or behaviors

Fast, slow, pounding, or uneven heartbeat

Lightheadedness, dizziness, fainting

Seeing, hearing, or feeling things that are not there

Seizure

Numb, cold, pale, or painful fingers or toes

Painful erection or an erection that lasts longer than 4 hours

If you notice these less serious side effects, talk with your doctor:

Dry mouth, nausea, stomach pain

Loss of appetite, weight loss

Trouble sleeping

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3] Place In Therapy

A) Oral and transdermal [methylphenidate](#) are primarily used as an adjunct to the treatment of [attention deficit disorder](#) with hyperactivity (ADHD) in children 6 years of age or older (oral) and in children and adolescents 6 to 17 years of age (transdermal) [1][123][12][33][34]. Children who exhibit ADHD-like symptoms that are secondary to environmental factors and/or other primary psychiatric disorders (including [psychosis](#)) may not be candidates for use of stimulants such as [methylphenidate](#) [1]. The FDA's Psychopharmacologic Drugs Advisory Committee recommends that transdermal [methylphenidate](#) be used after oral forms have been considered. The committee is concerned with the unknown risks of sensitization of the topical form [170]. Patients who develop a contact sensitization to transdermal [methylphenidate](#) might not be able to take [methylphenidate](#) in any form [1]. [Methylphenidate](#) has also been successful in the treatment of [narcolepsy](#).

B) Sustained-release [methylphenidate](#) (MSR) therapy for cognitive impairment in HIV-1-infected substance abusers resulted in significant improvement on composite neuropsychological test performance when compared to placebo treatment in a pilot study. However, when used as a treatment for [cognitive deficits](#), MSR failed to confirm superiority over placebo [171].

C) Other potential therapeutic uses of [methylphenidate](#) include treatment of depression, chronic pain, [brain tumors](#), [syncope](#), [traumatic brain injury](#), [dementia](#), and cocaine abuse [172][173][174][175][176][177][178][179][180][181].

4.4] Mechanism of Action / Pharmacology

A) [Methylphenidate](#)

1) Mechanism of Action

a) [Methylphenidate](#) is a mild central nervous system stimulant; the drug has similar pharmacological properties as the [amphetamines](#), with predominantly central activity and minimal effects on the cardiovascular system. Although its exact mechanism of action is not known, [methylphenidate](#) is thought to activate the brainstem arousal system, cortex, and subcortical structures including the thalamus to produce its stimulant effect. The mechanism by which [methylphenidate](#) exerts its behavioral effects in children has not been determined [44].

B) [Methylphenidate](#) Hydrochloride

1) Mechanism of Action

a) [Methylphenidate](#) is a mild central nervous system stimulant; the drug has similar pharmacological properties as the [amphetamines](#), with predominantly central activity and minimal effects on the cardiovascular system. Although its exact mechanism of action is not known, [methylphenidate](#) is thought to activate the brainstem arousal system, cortex, and subcortical structures including the thalamus to produce its stimulant effect. The mechanism by which [methylphenidate](#) exerts its behavioral effects in children has not been determined [156].

4.5] Therapeutic Uses

4.5.A] [Methylphenidate](#)

4.5.A.1] [Attention deficit hyperactivity disorder](#)

FDA Labeled Indication

a) Overview

FDA Approval: Adult, no; **Pediatric, yes (6 to 17 years)**

Efficacy: Pediatric, Effective

Recommendation: Pediatric, Class IIb

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Indication

Transdermal [methylphenidate](#) is indicated to improve symptoms of ADHD in pediatric patients 6 to 12 years and adolescents 13 to 17 years [1].

Evidence

Transdermal [methylphenidate](#) delivered once daily for 9 hours effectively improved behavior and reduced symptoms of ADHD compared with placebo in randomized trials. Long-term effects (greater than 7 weeks) in children have not been established [1][2].

c) Pediatric:

1) Adolescents 13 to 17 years

a) [Methylphenidate](#) transdermal system was superior to placebo for the treatment of ADHD symptoms during a randomized, double-blind trial. Subjects received placebo (n=72) or flexible doses of [methylphenidate](#) (n=145) at 10 mg, 15 mg, 20 mg, or 30 mg for 9 hours daily during a 5-week dose-optimization phase, followed by a 2-week maintenance phase. Symptomatic improvement was significantly better with [methylphenidate](#) than with placebo. [Methylphenidate](#) was associated with higher incidences of decreased appetite (25.5% vs 1.4%), irritability (11% vs 6.9%), nausea (9.7% vs 2.8%), and insomnia (6.2% vs 2.8%) compared with placebo [1].

2) Children 6 to 12 years

a) Transdermal [methylphenidate](#) (MTS) worn 9 hours daily produced optimal ADHD treatment results compared with placebo (PTS) during a randomized, double-blind trial. After an open-label dose optimization phase, 57 boys and 22 girls (mean age, 9.1 years) were randomized to receive 1 of 4 daily doses of MTS or placebo. Most patients (78%) were optimized to the MTS patch delivering 16 mg or 20 mg over 9 hours. After 1 week, patients crossed over to the opposite treatment. All patients attended 2 days of simulated classroom. From 2 through 12 hours after patch application, behavior and school performance improved more with MTS than with PTS across all clinician assessment scales. The incidence of any adverse effect was 30% in the MTS group versus 22.5% in the PTS group; anorexia was 2.5% versus 0%, and nausea was 3% versus 0% [2].

4.5.B) [Methylphenidate](#) Hydrochloride

4.5.B.1| Attention deficit hyperactivity disorder

FDA Labeled Indication

a)| Overview

FDA Approval: Adult, yes (up to 65 years, [Methylin](#)(TM), [Quillivant XR](#)(TM), [Ritalin](#)(R), [Ritalin SR](#)(R), and [Concerta](#)(R)); **Pediatric, yes (6 years and older)**

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b)| Summary:

Indication

[Methylphenidate](#) hydrochloride is indicated to improve symptoms of ADHD in adults and in pediatric patients 6 to 17 years [14][10][11][15][12].

Evidence (Adult)

[Methylphenidate](#) extended-release (ER) demonstrated efficacy and produced significant ADHD symptom improvements compared with placebo in randomized trials [13][16].

Evidence (Pediatric)

Extended-release [methylphenidate](#) demonstrated equivalent efficacy to immediate-release [methylphenidate](#) given 3 times daily and was superior to placebo in randomized trials involving pediatric patients 6 to 16 years with ADHD [17][18][19].

The combination of [methylphenidate](#) and [clonidine](#) appears to be better than monotherapy with either agent alone in ADHD with tics [20].

c)| Adult:

1)| Extended-release (ER) [methylphenidate](#) produced significant symptom improvements in adults with ADHD compared with placebo during a randomized, double-blind trial. After a 2-week washout period, patients received placebo (n=118) or [methylphenidate](#) ER (n=241) starting at 10 mg/day, with titrations to 60 mg/day divided into 2 doses per day. The minimum maintenance dose after 5 weeks was 20 mg/day. At week 24, the mean daily dose was 41.2 mg. A 30% reduction in inattention, hyperactivity, hot temper, affect lability, emotional overreactivity, disorganization, and impulsivity at week 24 was achieved in 61% of the [methylphenidate](#) ER group compared with 42% in the placebo group. A significant elevation in heart rate occurred during the titration phase in the [methylphenidate](#) ER group [16].

2)| The efficacy of [methylphenidate](#) extended-release (ER) tablets ([Concerta](#)(R)) was demonstrated in patients 18 to 65 years with ADHD in 2 randomized, double-blind studies. The first was a 7-week dose-titration study that randomized 226 patients to placebo or to [methylphenidate](#) ER at an initial dose of 36 mg/day. Incremental increases of 18 mg/day were allowed, based on tolerability, to 108 mg/day. A significant improvement from baseline scores was associated with [methylphenidate](#) ER compared with placebo. The second was a 5-week, fixed-

dose study that randomized 401 patients to [methylphenidate](#) ER 18, 36, or 72 mg/day or placebo. Improvement in symptoms was significant at all doses of [methylphenidate](#) compared with placebo [13].

d) Pediatric:

1) Monotherapy - Extended Release

a) In an open-label study, once-daily OROS [methylphenidate](#) ([Concerta\(R\)](#)) maintained effectiveness for up to 2 years in 407 children 6 to 13 years with ADHD. Patients received OROS [methylphenidate](#) 18, 36, or 54 mg once daily, based on the dose established in a previous efficacy or [pharmacokinetic study](#). Doses could be adjusted up or down in 18-mg increments throughout the trial depending on clinical response and adverse events. Patients were allowed to have medication reduced or stopped for weekends or nonschool days and to take medication holidays. Efficacy values from parents/caregivers for symptom control increased from 87% at month 3 to 95% at the end of the study. Investigator assessment for the second treatment year ranged from 91% to 95%. Parent satisfaction was high with 86% reporting being pleased, very pleased, or extremely pleased with OROS [methylphenidate](#) at the time of last observation. The majority of reported adverse events were mild; 282 participants (69.3%) reported at least 1 adverse event possibly related to OROS [methylphenidate](#) (headache, insomnia, decreased appetite, abdominal pain, and tics). Only slight changes in blood pressure and heart rate occurred throughout the study, with the only significant increase in systolic blood pressure [17].

b) In a small 2-week, randomized, double-blind study in 45 children 6 to 12 years, [methylphenidate](#) extended-release oral suspension 20 to 60 mg daily was superior to placebo in improving ADHD symptom scores. The [methylphenidate](#) dose was titrated during a 4- to 6-week open-label dose-optimization period. Patients received the optimized dose or placebo for 2 weeks, then crossed over to the other treatment arm. Patients were assessed at the end of each week at 0.75, 2, 4, 8, 10 and 12 hours postdose. Results from the first week showed lower scores (indicating superior symptom control) in the [methylphenidate](#) arm compared with the placebo arm at all time points assessed at the end of the first week (week 2 data not provided). The most commonly reported adverse events were affect lability, excoriation, [initial insomnia](#), tic, decreased appetite, vomiting, motion sickness, eye pain, and rash [14].

c) A 3-week course of once-daily [methylphenidate](#) ([Metadate CD\(R\)](#)) given in the morning was well tolerated and significantly improved symptoms of ADHD through the afternoon compared with placebo in a double-blind trial involving 321 children 6 to 16 years. A controlled delivery formulation was used; approximately 30% of the dose was immediate-release and 70% was extended-release. Subjects were randomized to placebo or to [methylphenidate](#) every morning; dosing started at 20 mg and was titrated to effect (maximum 60 mg/day), with the mean dose reaching 40.7 mg/day at the end of the study. Teacher-rated symptom scores dropped from 12.7 to 4.9 (indicating efficacy) in the MPH group after 3 weeks, compared with a reduction from 11.5 to 10.3 in the placebo group. The mean morning score was reduced to 4.8 and the mean afternoon score to 5.4, showing that MPH had a sustained effect throughout the day. Parent ratings demonstrated a similar pattern to the teacher ratings. Investigators classified 64% of the MPH group as responders (moderate or marked improvement) compared with 27% of the placebo group. The most common adverse effects were headache, anorexia, abdominal pain, and insomnia. No serious adverse effects were reported in either group [18].

d) A 4-week course of **Concerta(R)** (extended-release **methylphenidate** [OROS]) was shown to be more effective than placebo, and had similar efficacy to immediate-release **methylphenidate** (IR MPH) in a double-blind trial involving 277 children 6 to 12 years with ADHD. Enrollees were assigned 1 of 3 dose schedules, based on a predetermined optimized dose: (1) OROS 18 mg once daily or IR MPH 5 mg 3 times daily; (2) OROS 36 mg once daily or IR MPH 10 mg 3 times daily; or (3) OROS 54 mg once daily or IR MPH 15 mg 3 times daily. Subjects were randomized to OROS, IR MPH, or placebo. Average total daily dose was 29.5 mg/day for those taking the immediate-release form and 34.3 mg/day for those taking the extended-release form. Ratings scales completed by teachers and parents showed equivalent efficacy for extended-release and immediate-release **methylphenidate**. No serious adverse events occurred during the study. More children in the 2 active treatment groups were rated as eating less than usual compared with the control group, and 5 patients reported tics (4 on placebo and 1 on IR MPH) [19].

2) Monotherapy - Immediate Release

a) The racemic mixture of L and D-amphetamine (**Adderall(R)**) was at least as effective as **methylphenidate** (**Ritalin(R)**) in the treatment of ADHD, and was more effective at 4 to 5 hours postadministration (beyond expected duration of action) in a small double-blind study of children with ADHD (mean age, 9.6 years). Patients were randomized to **methylphenidate** 10 mg, 17.5 mg, **Adderall(R)** 7.5 mg, 12.5 mg, or placebo twice a day (at 7:45 am and 12:15 pm) for 24 days. Teachers and counselors rated subjects' behavior throughout the day and at times beyond the expected duration of action (noon and 5 pm). Parents rated behavior at the end of the day and in the evening. When compared with placebo, **Adderall(R)** and **methylphenidate** significantly improved behaviors and classroom measures. Drug effects were significantly affected by time. **Adderall(R)** consistently resulted in higher effect size (ES) than **methylphenidate** and higher doses consistently resulted in higher ES than lower doses. **Adderall(R)** was also significantly more effective than **methylphenidate** at midday and end of day. The ES of both drugs dropped at midday and steadily increased in the afternoon, suggesting a reduction of the afternoon dose. Adverse effects were reported more frequently with **Adderall(R)** but did not preclude the use of both medications. Only 1 patient was eliminated from the study due to exacerbation of his motor tic condition [21].

b) Acute tolerance to **methylphenidate** may exist in the treatment of children with ADHD and may contribute to the reduced efficacy of sustained-release drug delivery compared with immediate-release drug delivery of **methylphenidate**, according to 2 small double-blind trials. In the first, 3 **methylphenidate** delivery patterns were compared with placebo: twice-daily dosing with immediate-release **methylphenidate**, flat dosing, and ascending dosing. The flat delivery was significantly less efficacious than the twice-daily regimen in the afternoon, which suggests that acute tolerance to sustained **methylphenidate** concentrations may be emerging throughout the day. In the second, children were assigned to placebo or to 3-times-daily or ascending dosing; the timing of the middle bolus of the 3-times-daily regimen was either 9:30 am or 1:30 pm after the 7:30 am dose. Only small increases in efficacy were measured in the morning regimen after the second dose compared with large increases in efficacy in the afternoon regimen following the second dose. Following the administration of the third bolus **dose in each regimen**, a larger increase in efficacy was observed in the morning regimen compared with small increases in efficacy for the afternoon regimen [22].

3) Use In Patients With [Tourette Syndrome](#) Or Tics

a) In a study of 136 children 7 to 14 years with ADHD and tics, [methylphenidate](#) (MPH) in combination with [clonidine](#) provided greater symptomatic improvement in ADHD without causing worsening of tics than either drug alone. A significant treatment effect was observed for [clonidine](#) and for MPH, and either [clonidine](#) or MPH was more effective than placebo. Subjects were randomized to placebo, [clonidine](#) alone, MPH alone, or combination [clonidine](#)/MPH. Average daily doses were 0.25 mg for [clonidine](#) alone, 0.28 mg for [clonidine](#) given with MPH, 25.7 mg for MPH alone, and 26.1 mg for MPH given with [clonidine](#). Worsening of tics was reported in 9 patients receiving [clonidine](#) alone, 8 receiving MPH alone, 6 receiving combination [clonidine](#)/MPH, and 7 receiving placebo. Compared with placebo, severity of tics decreased in all active treatment groups. Study medications were well tolerated, except for sedation in 48% of those receiving [clonidine](#). The authors observed that [clonidine](#) seemed to be most helpful for impulsivity and hyperactivity; MPH appeared most helpful for inattentiveness [20].

4.5.B.2] [Cataplexy - Narcolepsy](#)

See Drug Consult reference: [NARCOLEPSY AND CATAPLEXY - DRUG THERAPY](#)

4.5.B.3] [Fatigue, Cancer-related](#)

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category A

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Evidence

A meta-analysis showed that [methylphenidate](#) or [dexmethylphenidate](#), compared with placebo, significantly improved cancer-related fatigue scores in 3 randomized studies that used the Functional Assessment of [Cancer](#) Therapy-Fatigue subscale, but not in 2 that used the Brief Fatigue Inventory. More patients who received either drug reported vertigo, anxiety, anorexia, and nausea [3].

Guideline

Psychostimulants (eg, [methylphenidate](#)) or other wakefulness agents (eg, [modafinil](#)) may be beneficial in patients receiving active treatment or who have advanced disease. Effectiveness in patients who are disease-free after active treatment is unknown [4].

c) Adult:

1j) A systematic review identified 5 randomized, double-blind studies with a total enrollment of 498 patients with cancer-related fatigue [3] that compared methylphenidate [5][6][7] or dexmethylphenidate [8][9] with placebo. Patients had a variety of cancers, including breast, prostate, and brain, and received various dosages (see table). All were good quality studies [3]. Methylphenidate or dexmethylphenidate produced a significantly lower score on the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) subscale compared with placebo score (mean difference, -3.13), according to meta-analysis (3 studies, 269 patients). A subgroup analysis of the FACT-F studies showed a significant difference between dexmethylphenidate and placebo in the 8-week study (123 patients; mean difference, -3.7), but no significant difference in the 2 studies of methylphenidate or dexmethylphenidate of 4 weeks or less (146 patients). Meta-analysis of 2 studies (148 patients) that used the Brief Fatigue Inventory showed no significant difference between methylphenidate or dexmethylphenidate and placebo. Methylphenidate or dexmethylphenidate did not significantly improve depression (2 studies, 132 patients) or cognition (2 studies, 184 patients). Adverse effects were reported in 4.9% of patients who received methylphenidate or dexmethylphenidate and in 1.6% who received placebo [3].

Table: Drug Dosage

Study	Drug	Dosage
Moraska et al, 2010	methylphenidate	Target dose of 54 mg over 8 weeks in a 4-week study
Roth et al, 2010	methylphenidate	A maximum of 30 mg over 6 weeks
Bruera et al, 2006	methylphenidate	5 mg every 2 hours as needed (maximum, 20 mg/day)
Lower et al, 2009	dexmethylphenidate	5 mg twice daily for 8 weeks (maximum, 50 mg/day)
Butler et al, 2007	dexmethylphenidate	Target dose of 15 mg twice daily during and for 8 weeks of radiotherapy

4.5.B.4| Narcolepsy

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (immediate release formulations and Ritalin(R)-SR only); Pediatric, yes (6 years and older, immediate release formulations and Ritalin(R)-SR only)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Indication

Methylphenidate is indicated for the treatment of narcolepsy in adults and children 6 years or older [10][11][12][15].

Evidence

Methylphenidate 60 mg/day improved ability to stay awake, subjective rating of symptom severity, and quantity of performance in a small study in adults with **narcolepsy** [26].

c) Adult:

1) **Methylphenidate** 60 mg/day was associated with improved ability to stay awake, subjective rating of symptom severity, and quantity of performance in a small, crossover study in adults with **narcolepsy**. Patients (n=13; mean age 50.7 years) progressed through 3 **methylphenidate** doses in a randomized manner, receiving **methylphenidate** 10 mg, 30 mg, and 60 mg/day (divided 3 times daily, with doses at morning, noon, and afternoon) for 1 week. Maintenance of wakefulness test (MWT), Wilkinson Addition Test (WAT), Digit-Symbol Substitution Test (DSST), and a symptom severity questionnaire were performed on the seventh day of each dose level. **Methylphenidate** 60 mg/day significantly improved MWT performance, increased the number of DSST problems attempted, and improved subjective sleepiness and overall symptoms compared with baseline. **Methylphenidate** 30 mg/day significantly increased the number of DSST problems attempted compared with baseline. **Methylphenidate** 10 mg/day significantly improved MWT performance compared with baseline. There were no changes in WAT performance or improvement in **cataplexy** with **methylphenidate** therapy [26].

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] **Amphetamine**4.6.A.1] **Attention deficit hyperactivity disorder**

a) SUMMARY: In comparative studies, **Adderall(R)** (combination **AMPHETAMINE/DEXTROAMPHETAMINE**) and **METHYLPHENIDATE** showed similar efficacy in the treatment of attention deficit hyperactive disorder in children. **METHYLPHENIDATE** requires twice daily dosing compared to **Adderall's** once daily doses.

b) The racemic mixture of L- and D-amphetamine (**ADDERALL(R)**) was at least as effective as **methylphenidate** (**RITALIN(R)**) in the treatment for **attention deficit hyperactivity disorder** (ADHD), and was more effective at 4 to 5 hours post-administration (beyond **methylphenidate's** expected duration of action). In this within-subject, double-blind, placebo-controlled, crossover study, 25 children with ADHD (mean age 9.6 years) were given **methylphenidate** 10 milligram (mg), 17.5 mg, **Adderall(R)** 7.5 mg, 12.5 mg, and placebo twice a day (at 7:45 a.m. and 12:15 p.m.) in a randomized manner every day for 24 days. Teachers and counselors rated their behavior throughout the day and at times beyond **methylphenidate's** expected duration of action (noon and 5 p.m.). Parents rated them at the end of the day and in the evening for possible rebound effects. When compared to placebo, **Adderall(R)** and **methylphenidate** significantly improved in-school behaviors (p less than 0.0001 and 0.001, respectively), classroom measures (p less than 0.0001), recess violations (p less than 0.0001), and after-school behaviors (p less than 0.0001). Drug effects were significantly affected by time (p less than 0.01). **Adderall(R)** consistently resulted in higher effect size (ES) than **methylphenidate** and higher doses consistently resulted in higher ES than lower doses. **Adderall(R)** was also significantly more effective than **methylphenidate** at midday and end of day (p less than 0.05). The ES of both drugs dropped at midday and steadily increased in the afternoon, implicating the possibility of reducing the afternoon dose. Side effects were reported more frequently with **Adderall(R)** but did not preclude the use of both medications. Only 1 patient was eliminated from the study due to exacerbation of his motor tic condition. Further studies are needed to evaluate the possibility of once daily dosing of **Adderall(R)**, and to compare the efficacy of **methylphenidate** to D-amphetamine [193].

c) Once-daily Adderall(R) (combination [AMPHETAMINE/DEXTROAMPHETAMINE](#)) appeared to be as effective as twice-daily [METHYLPHENIDATE](#) in the treatment of attention deficit hyperactive disorder in children aged 6 to 12 years, according to a double-blind, placebo-controlled, cross-over study (n=21). Also, a mid-afternoon dose of either Adderall or [methylphenidate](#) (MPH) produced better evening behavior than placebo as determined by parental ratings, although either active treatment tended to induce loss of appetite and sleep difficulties. In a randomized manner every day for 24 study-days, children received each day 1 of 7 treatment protocols: (1) MPH 0.3 milligram/kilogram (mg/kg) at 7:30, 11:30, and 15:30; (2) MPH 0.3 mg/kg at 7:30 and 11:30 and MPH 0.15 mg/kg at 15:30; (3) MPH 0.3 mg/kg at 7:30; (4) Adderall 0.3 mg/kg at 7:30 and 15:30; (5) Adderall 0.3 mg/kg at 7:30 and Adderall 0.15 mg/kg at 15:30; (6) Adderall 0.3 mg/kg at 7:30; or (7) placebo. While twice-daily MPH 0.3 mg/kg did not differ significantly from single morning-dose Adderall 0.3 mg/kg, single morning-dose MPH 0.3 mg/kg produced less significant effects than either once-daily Adderall 0.3 mg/kg or twice-daily MPH 0.3 mg/kg. Morning only MPH began to lose its effectiveness approximately 6.5 hours later. Evening behavior was rated better after MPH 0.3 mg/kg than 0.15 mg/kg. With Adderall, no evening differences were seen after mid-afternoon doses of either 0.3 or 0.15 mg/kg. Children showed differential responses to the 2 drugs. Overall, 25% responded more positively to MPH, 37% responded more positively to Adderall, and 38% responded equally well to both medications. For a few of those responding more positively to MPH, one dose of MPH was sufficient to carry them all day and into the evening. Fifty percent of those responding more positively to Adderall needed only once-daily dosing of the drug [194].

4.6.B] [Atomoxetine Hydrochloride](#)

4.6.B.1] [Attention deficit hyperactivity disorder](#)

a) During a 6-week, multicenter, parallel-group, randomized, double-dummy study of pediatric patients (age, 6 to 16 years) with ADHD (n=516), osmotically-released [methylphenidate](#) was associated with a significantly higher response rate compared with [atomoxetine](#) or placebo. Eligible patients had baseline symptom severity of at least 1.5 SD greater than United States age and gender norms per the ADHD Rating Scale IV - Parent Version: Investigator-Administered and -Scored. Patients with [bipolar disorder](#), seizures, a psychotic illness, [pervasive developmental disorder](#), or who received concomitant psychoactive medications were excluded, as were patients with anxiety or tic disorders (due to the relative contraindication for use of osmotically-released [methylphenidate](#)). Prior treatment with stimulants was allowed if the patient had experienced at least some improvement in ADHD signs and symptoms without intolerable adverse effects. Patients were randomized in a 3:3:1 ratio to treatment with either [atomoxetine](#) (n=222), osmotically-released [methylphenidate](#) (n=220), or placebo (n=74). The initial dose of [atomoxetine](#) was 0.8 mg/kg/day, administered as a divided twice-daily dose, with titration allowed as clinically indicated to 1.2 mg/kg/day on day 5 and to 1.8 mg/kg/day (not an approved dose) at the week 6 visit. Osmotically-released [methylphenidate](#) was initiated at 18 mg/day with increases to 36 mg and 54 mg allowed at the week 1 and week 3 visits, respectively. Response was defined as a decrease from baseline of 40% or more in total ADHD rating scale score (investigator-administered and -scored) at week 6. In the intent-to-treat analysis of the response rates for the active treatments (primary endpoint), the osmotically-released [methylphenidate](#) group had a statistically superior response rate compared with the [atomoxetine](#) group (56% vs 45%; p=0.02; number needed to treat (NNT), 9). Mean change from baseline in the total ADHD rating score was -16.9 +/- 13.1 in the osmotically-released [methylphenidate](#) group and -14.4 +/- 12.7 in the [atomoxetine](#) group. The 95% CI for the difference in the response rates was -21% to -2%, which was not within the protocol-specified margin of noninferiority for [atomoxetine](#) of 15%. At week 6, both active treatment groups had significantly higher response rates compared with placebo ([atomoxetine](#) vs placebo, 45% vs 24%, respectively; p=0.003; NNT, 5; osmotically-released [methylphenidate](#) vs placebo, 56% vs 24%, respectively; p less than or equal to 0.001; NNT, 3). The mean final administered dose of [atomoxetine](#) was 1.45 mg/kg/day (53 mg/day), which was slightly higher than the currently approved

labeled dose of 1.4 mg/kg/day. The mean final administered dose of osmotically-released methylphenidate was 39.9 mg/day. In the crossover phase, 178 of 180 patients who completed 6 weeks of treatment with osmotically-released methylphenidate were switched to atomoxetine using the same dosage titration schedule as was used in the original 6-week phase of the trial and without a washout period. The response rate to atomoxetine crossover treatment was 43% in the 70 patients who had not responded to osmotically-released methylphenidate in the original trial. Overall, 34% of patients responded to either treatment with atomoxetine or with osmotically-released methylphenidate, but not both, 44% responded to both treatments, and 22% did not respond to either treatment [200].

4.6.C] Clonidine

4.6.C.1] Attention deficit hyperactivity disorder

a) In children with attention deficit hyperactive disorder (ADHD) and TICS (both by DSM-IV criteria), CLONIDINE alone, METHYLPHENIDATE (MPH) alone, or combination CLONIDINE/MPH provided symptomatic improvement in ADHD without causing worsening of tics; however, CLONIDINE/MPH combination therapy provided the greatest benefit. This finding emanated from a double-blind, multi-center trial in children 7 to 14 years of age (n=136). Subjects were randomized to placebo (n=32), clonidine alone starting at 0.1 milligram (mg)/day (n=34), MPH alone starting at 5 mg/day (n=37), or combination clonidine/MPH (n=33). Average daily doses were 0.25 mg for clonidine alone, 0.28 mg for clonidine given with MPH, 25.7 mg for MPH alone, and 26.1 mg for MPH given with clonidine. Based on the primary endpoint (Conners Abbreviated Questionnaire-Teacher), a significant treatment effect was observed for clonidine (compared to no clonidine; p=0.002), and for MPH (compared to no MPH; p=0.003), and either clonidine or MPH was more effective than placebo (both p=0.02). However, the greatest improvement on symptomatic ratings was seen with combination clonidine/MPH (p less than 0.0001 compared to placebo). Worsening of tics was reported in 9 receiving clonidine alone, 8 receiving MPH alone, 6 on combination clonidine/MPH, and 7 receiving placebo. Compared with placebo, severity of tics decreased in all active treatment groups according to the Yale Global Tic Severity Scale, the Global Tic Rating Scale, and the Tic Symptom Self-Report. Study medications were well tolerated except for sedation caused by clonidine; 48% of those receiving clonidine reported this side effect. The authors observed that clonidine seemed to be most helpful for impulsivity and hyperactivity, while MPH appeared most helpful for inattentiveness [182].

b) An open pilot study compared oral and transdermal clonidine to methylphenidate in attention deficit disorder with hyperactivity [183]. Clonidine was equivalent to methylphenidate (MPH). Both were more effective than placebo. In another study, MPH acted preferentially in children with major attention-deficit and moderate hyperactivity. In ADHD children with symptoms of hyperarousal, hyperactivity, and aggression, clonidine is advocated [184].

4.6.D] Dexmethylphenidate

4.6.D.1] Attention deficit hyperactivity disorder

a) No comparisons with methylphenidate have been published, and data released by the manufacturer have not emphasized comparative efficacy, although this data is available. In a completed 4- week, placebo-controlled study described in the package insert [185], dexmethylphenidate 5 to 20 milligrams (mg) daily was compared to methylphenidate 10 to 40 mg daily (each in two divided doses) in patients with ADHD (n=132, 6 to 17 years of age). Patients included had all subtypes of ADHD (combined type, inattentive type, hyperactive-impulsive type). Dexmethylphenidate was reported to provide significantly greater improvement of symptom scores from baseline on the Swanson, Noland, and Pelham (SNAP)-ADHD rating scale compared to placebo (mean change, -0.7 versus -0.2). Although methylphenidate was the comparator, no results for methylphenidate were provided.

b) In manufacturer releases, apparently referring to the same package insert trial described above, the efficacy and safety of [dexmethylphenidate](#) were reported similar to [methylphenidate](#) (Anon, 2001)[186]. Earlier releases also did not indicate a significant difference in efficacy between the two drugs [187][188], although they were carefully prepared to avoid this conclusion.

c) One manufacturer release suggested a longer duration of action of [dexmethylphenidate](#) in ADHD; in this study, control of symptoms with [dexmethylphenidate](#) was reportedly seen at all time points, but there was failure of [methylphenidate](#) to control symptoms at the last measurements (5.5 to 6.5 hours postdose) [187]. However, the duration of action of [methylphenidate](#) was not given, precluding assessment of the duration of [methylphenidate](#) relative to [dexmethylphenidate](#). The duration of [dexmethylphenidate](#) in this trial was similar to that of [methylphenidate](#) in other studies (4 to 6 hours), suggesting this difference is small. No study has provided comparative improvements in symptom scores from baseline, or statistical comparisons at all time points.

d) Available studies have not indicated a more favorable adverse- effect profile for [dexmethylphenidate](#) compared to [methylphenidate](#) [188]; (Anon, 2001).

4.6.E] [Dextroamphetamine](#)

4.6.E.1] [Attention deficit hyperactivity disorder](#)

a) SUMMARY: In comparative studies, Adderall(R) (combination [AMPHETAMINE/DEXTROAMPHETAMINE](#)) and [METHYLPHENIDATE](#) showed similar efficacy in the treatment of attention deficit hyperactive disorder in children. [METHYLPHENIDATE](#) requires twice daily dosing compared to Adderall's once daily doses.

b) The racemic mixture of L- and D-amphetamine (ADDERALL (R)) was at least as effective as [methylphenidate](#) (RITALIN (R)) in the treatment for [attention deficit hyperactivity disorder](#) (ADHD), and was more effective at 4 to 5 hours post-administration (beyond [methylphenidate's](#) expected duration of action). In this within-subject, double-blind, placebo-controlled, crossover study, 25 children with ADHD (mean age 9.6 years) were given [methylphenidate](#) 10 milligram (mg), 17.5 mg, Adderall (R) 7.5 mg, 12.5 mg, and placebo twice a day (at 7:45 a.m. and 12:15 p.m.) in a randomized manner every day for 24 days. Teachers and counselors rated their behavior throughout the day and at times beyond [methylphenidate's](#) expected duration of action (noon and 5 p.m.). Parents rated them at the end of the day and in the evening for possible rebound effects. When compared to placebo, Adderall(R) and [methylphenidate](#) significantly improved in-school behaviors (p less than 0.0001 and 0.001, respectively), classroom measures (p less than 0.0001), recess violations (p less than 0.0001), and after-school behaviors (p less than 0.0001). Drug effects were significantly affected by time (p less than 0.01). Adderall(R) consistently resulted in higher effect size (ES) than [methylphenidate](#) and higher doses consistently resulted in higher ES than lower doses. Adderall(R) was also significantly more effective than [methylphenidate](#) at midday and end of day (p less than 0.05). The ES of both drugs dropped at midday and steadily increased in the afternoon, implicating the possibility of reducing the afternoon dose. Side effects were reported more frequently with Adderall(R) but did not preclude the use of both medications. Only 1 patient was eliminated from the study due to exacerbation of his motor tic condition. Further studies are needed to evaluate the possibility of once daily dosing of Adderall(R), and to compare the efficacy of [methylphenidate](#) to D-amphetamine [197].

c) Once-daily Adderall(R) (combination [AMPHETAMINE/DEXTROAMPHETAMINE](#)) appeared to be as effective as twice-daily [METHYLPHENIDATE](#) in the treatment of attention deficit hyperactive disorder in children aged 6 to 12 years, according to a double-blind, placebo-controlled, cross-over study (n=21). Also, a mid-afternoon dose of either Adderall or [methylphenidate](#) (MPH) produced better evening behavior than placebo as determined by parental ratings, although either active treatment tended to induce loss of appetite and sleep difficulties. In a randomized manner every day for 24 study-days, children received each day 1 of 7 treatment protocols: (1) MPH 0.3 milligram/kilogram (mg/kg) at 7:30, 11:30, and 15:30; (2) MPH 0.3 mg/kg at 7:30 and 11:30 and MPH 0.15 mg/kg at 15:30; (3) MPH 0.3 mg/kg at

7:30; (4)Adderall 0.3 mg/kg at 7:30 and 15:30; (5)Adderall 0.3 mg/kg at 7:30 and Adderall 0.15 mg/kg at 15:30; (6)Adderall 0.3 mg/kg at 7:30; or (7)placebo. While twice-daily MPH 0.3 mg/kg did not differ significantly from single morning-dose Adderall 0.3 mg/kg, single morning-dose MPH 0.3 mg/kg produced less significant effects than either once-daily Adderall 0.3 mg/kg or twice-daily MPH 0.3 mg/kg. Morning only MPH began to lose its effectiveness approximately 6.5 hours later. Evening behavior was rated better after MPH 0.3 mg/kg than 0.15 mg/kg. With Adderall, no evening differences were seen after mid-afternoon doses of either 0.3 or 0.15 mg/kg. Children showed differential responses to the 2 drugs. Overall, 25% responded more positively to MPH, 37% responded more positively to Adderall, and 38% responded equally well to both medications. For a few of those responding more positively to MPH, one dose of MPH was sufficient to carry them all day and into the evening. Fifty percent of those responding more positively to Adderall needed only once-daily dosing of the drug [198].

d) In a direct, double-blind, cross-over comparison of adverse effect profiles, both **DEXTROAMPHETAMINE** 0.15 milligram/kilogram (mg/kg) twice daily and **METHYLPHENIDATE** 0.3 mg/kg twice daily were well-tolerated in 125 children with **attention deficit disorder** (mean age 8.7 years). The only adverse effects reported more frequently during drug therapy than at baseline were appetite suppression (both drugs) and insomnia (**dextroamphetamine** only). The mean severity of adverse effects was significantly higher in the **dextroamphetamine** group. However, only 1.6% of children in each group had to discontinue therapy because of adverse effects [109].

4.6.F] **Lithium**

4.6.F.1] **Attention deficit hyperactivity disorder**

a) In a preliminary randomized, double-blind, crossover study, **lithium** and **methylphenidate** had comparable efficacy and side effect profiles in ADULTS with attention-deficit/hyperactivity disorder (ADHD). Adult patients (n=32) met the Diagnostic and Statistical Manual of Mental Disorders Fourth edition (DSM-IV) criteria for ADHD at age 7 years and at the time of the study. Patients were randomly assigned to receive either **methylphenidate** (MPH) or **lithium** for the first 8 weeks of the study, and then switch to the other 8-week treatment arm after a 2-week washout period. For the MPH arm, patients received an initial oral dose of 10 milligrams (mg) once daily for the first 2 weeks; the daily dose was increased by 10 mg every 2 weeks, as tolerated, for the 8 week duration of the study arm. For the **lithium** arm, the initial oral dose was 300 mg once daily for 2 weeks; the daily dose was increased by 300 mg, as tolerated, every 2 weeks for the 8 week duration of the study arm. After the first 2 weeks of the study arm, **lithium** and MPH administration was twice daily. At the end of the 8-week study arm, the average daily doses of MPH and **lithium** carbonate were 38.9 mg and 1173 mg, respectively. Twenty-three patients completed both arms of the study; 9 patients dropped out due to side effects (4 of 9), lack of perceived benefit (4 of 9), or relocation to another country (1 of 9). The rate of improvement of ADHD, as assessed by a 30% or more reduction in the Conners' Adult ADHD Rating Scale sum score of Learning Problems, Hyperactivity, and Impulsivity, was 48% for the MPH arm and 37% for the **lithium** arm. When evaluating only the patients that completed both arms of the study, the improvement rate was 47% and 43% for the MPH and **lithium** arms, respectively. Side effects included headache, diarrhea, nausea, chest discomfort, and **orthostatic hypertension**. A limitation of the study was the presence of a substantial arm effect, in which the improvements during the first arm were maintained during the second arm. In addition, the study had small number of patients and lacked a placebo arm. However, there was no significant sequence by arm interaction, suggesting that MPH and **lithium** had comparable efficacy [196].

4.6.G] **Pemoline**

4.6.G.1] **Attention deficit hyperactivity disorder**

a) In a retrospective chart review (n=485), **METHYLPHENIDATE** (MPD) and **PEMOLINE** (PEM) were both effective for treatment of attention deficit hyperactive disorder (ADHD) and **attention deficit disorder** (ADD) (DSM- IV) in children 4 to 18 years of age; however, good or excellent responses to treatment were shown by more PEM-treated than MPD-treated patients (PEM 225 of 245 (92%); MPD 168 of 240 (70%); p value not specified). The rating scale for treatment efficacy ranged from 1 to 4; 1-poor or no response; 2-initially good but not sustained; 3-good, sustained response; and 4-excellent. Mean efficacy ratings for the MPD and PEM groups were 2.7 and 3.5, respectively. Most frequent adverse effects were anorexia and irritability for the MPD group and insomnia and irritability for the PEM group. The rates of drug discontinuation for lack of efficacy were 32% in the MPD group and 10% in the PEM group. Discontinuations due to adverse effects were higher in the PEM group (22% compared with 5% for MPD). No abnormalities in liver function were reported for either group. Standard doses were 1.44 milligrams/kilogram (mg/kg) for PEM given once daily and 0.4 mg/kg for MPD given once daily for the sustained-release form and in 2 or 3 divided doses daily for the immediate-release form. The sustained-release form of MPD was associated with greater efficacy than the immediate-release form [190].

4.6.G.2] Fatigue

a) A 6-week course of an oral psychostimulant medication, **METHYLPHENIDATE** or **PEMOLINE**, reduced the level of fatigue in patients positive for HIV; quality of life also tended to improve with **methylphenidate** (MPH) and **PEMOLINE** (PEM) therapy, and drug-induced side effects were mild. Enrollees had a score of at least 5 on a 10-point scale for persistent fatigue. MPH (n=53) was initiated at 7.5 milligrams (mg) twice daily with possible titration to 60 mg/day (mean end-of-study dose 51 mg/day); PEM (n=45) was started at 18.75 mg twice daily with maximum titration to 150 mg/day (mean end-of-study dose 96 mg/day). At 6 weeks, total scores on the Piper Fatigue Scale (patient-rated) were significantly improved among MPH- and PEM-treated subjects compared with placebo (p=0.04). Also, on the patient-rated visual analog scale for fatigue (VAS-F), the energy subscore was significantly higher for those receiving MPH or PEM (p=0.02). No significant differences were found on any outcome measurement comparing MPH and PEM. Significant correlations were found between improvement in fatigue and better quality of life. Five patients dropped out due to side effects (MPH (2), PEM (2), control (1)). Only jitteriness and hyperactivity were experienced significantly more often by those on MPH or PEM than those on placebo [191].

4.6.G.3] Narcolepsy

a) One group of investigators studied the efficacy of **methylphenidate**, **pemoline**, and **protriptyline** in the treatment of **narcolepsy** and reported preliminary data. Six subjects received **methylphenidate** at dosages of 10 milligrams (mg), 30 mg, and 60 mg/day (1 week at each dosage). Seven subjects received **pemoline** at dosages of 18.75 mg, 56.25 mg, and 112.5 mg/day (1 week at each dosage). Two subjects received **protriptyline** at dosages of 10 mg, 30 mg, and 60 mg/day and two subjects received **protriptyline** dosages of 10 mg, 20 mg, and 40 mg/day (1 week at each dosage). The orders of dosage levels were randomized from patient to patient. Nine healthy subjects with no sleep disorder received placebos and served as controls. Preliminary data suggest that **methylphenidate** significantly improves the ability of the narcoleptic to stay awake, **pemoline** seems to improve ability to perform, and **protriptyline** does not significantly alter the ability to stay awake or perform. More data are needed to confirm these findings, and further studies are planned [192].

4.6.H] Protriptyline

4.6.H.1] Narcolepsy

a) **Protriptyline** did not improve either the ability to stay awake or perform tasks in a double-blind, parallel (by drug), crossover (by dose) study [189]. Three dose levels of 3 drugs were compared in the

treatment of [narcolepsy](#) in 17 patients. The drugs were [pemoline](#) (18.75, 56.25, and 112.5 milligrams (mg)/day), [methylphenidate](#) (10, 30, or 60 mg/day) and [protriptyline](#) (10, 30, and 60 mg/day). [Methylphenidate](#) improved the ability to stay awake and perform tasks. [Pemoline](#) improved the ability to perform tasks, but not to stay awake.

4.6.I] [Thioridazine](#)

1) Adverse Effects

a) One group of investigators reported a controlled study of [methylphenidate](#) and [thioridazine](#) in improving cognitive and motor performance in intellectually subaverage children. Twenty-seven children with subaverage IQs participated in a double-blind, placebo-controlled, cross-over study comparing [methylphenidate](#) (0.4 milligrams/kilogram/day and [thioridazine](#) (1.75 milligrams/kilogram/day). The children were tested for IQ performance, breadth of attention, and performance on a series of electronically-controlled cognitive-motor tests. [Methylphenidate](#) improved accuracy on a memory task, reduced omission errors on an attentional task, and reduced seat movements on two tasks. [Thioridazine](#) had no significant effects in improving cognitive-motor performance. It did not produce deleterious effects on IQ performance when subjects received reinforcers for correct answers. [Thioridazine](#) at the given dose did not adversely effect performance on any of the cognitive-motor performance tests [195].

4.6.J] [Venlafaxine Hydrochloride](#)

4.6.J.1] [Attention deficit hyperactivity disorder](#)

a) [Venlafaxine](#) was similar to [methylphenidate](#) for the treatment ADHD in pediatric patients in a randomized, double-blind, comparison trial (n=38). Eligible outpatients had confirmed ADHD (DSM-IV-text revision criteria and Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime diagnostic interview) and at least 1.5 standard deviations above normal for patient age and gender on the ADHD Rating Scale-IV (ADHD-RS-IV) School Version total and/or subscale scores. Patients were equally randomized to receive [venlafaxine](#) (n=19; mean age, 9.42 +/- 2.19 years; 74% male) or [methylphenidate](#) (n=19; mean age, 9.57 +/- 1.86 years; 68% male) for 6 weeks. The study regimens were based on weight: [venlafaxine](#) 50 mg orally daily (weight less than 30 kg) to 75 mg daily (weight greater than 30 kg) and [methylphenidate](#) 20 mg/day or 30 mg/day, respectively. Both treatments were titrated up during the first 2 to 3 weeks ([venlafaxine](#), week 1: 25 mg once a day; week 2: 25 mg in the morning and midday; and if needed for week 3: 25 mg in the morning, 25 mg midday, and 25 mg at 4 PM; [methylphenidate](#), week 1: 5 mg in the morning and 5 mg at midday; week 2: 10 mg in the morning and 10 mg at midday; and if needed for week 3: 10 mg in the morning, 10 mg at midday, and 10 mg at 4 PM). All patients were Persian and had newly diagnosed combined subtype ADHD. While both treatment arms demonstrated statistically significant within-group improvement in Parent and Teacher ADHD-RS-IV from baseline to 6 weeks (p less than 0.001), there was no significant difference between [venlafaxine](#) and [methylphenidate](#) in the change in mean Parent and Teacher ADHD-RS-IV from baseline to 6 weeks (primary outcome; intent-to-treat). At 6 weeks, change in the mean Parent ADHD-RS-IV scores from baseline was -14.15 +/- 7.01 for [venlafaxine](#) and -16.63 +/- 8.59 for [methylphenidate](#) (difference, p=0.33). Similarly at 6 weeks, change in the mean Teacher ADHD-RS-IV from baseline was -13.05 +/- 4.77 for [venlafaxine](#) and -15.31 +/- 8.13 for [methylphenidate](#) (difference, p=0.3). Adverse events were tolerable and mild to moderate in severity and were not significantly different except for insomnia (10.52% vs 52.63%) and headaches (15.78% vs 57.89%) in the [venlafaxine](#) and [methylphenidate](#) arms, respectively. The most commonly reported events were abdominal pain, somnolence, and restlessness [199].

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