Notes on Common Medications Used in Child Behaviour and Learning Management

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ADHD PHARMACOTHERAPY

CURRENT PRACTICE RECOMMENDATIONS

American Academy of Pediatrics (AAP) recommendations vary by age

i) Children aged 4-5 years

- treat first with parent- and/or teacher-administered behavioral therapy (AAP Strong Recommendation, Evidence Quality A)

- consider methylphenidate **only** if behavioral interventions do not lead to improvement and if there is moderate-to-severe functional disturbance (AAP Recommendation, Evidence Quality B)

ii) Children aged 6-11 years

- FDA-approved medications (AAP Strong Recommendation, Evidence Quality A)
  - best evidence for stimulants
  - sufficient but less strong evidence for the following (in order of best evidence)
    - atomoxetine
    - extended-release guanfacine
    - extended-release clonidine (Writer's note: In CANADA-Immediate release only available)
- parent- or teacher-based behavioral therapy (AAP Strong Recommendation, Evidence Quality B)
- NOTE: Combination of pharmacotherapy & behavioral therapy is strongly preferred

iii) Adolescents aged 12-18 years,

- FDA-approved medications (AAP Strong Recommendation, Evidence Quality A)
- behavioral therapy (AAP Recommendation, Evidence Quality C)

NOTE: Medication management with or without behavior treatment appears to improve ADHD symptoms compared to behavior treatment alone or standard care (level 2 [mid-level] evidence)

- pharmacologic treatment of children with ADHD associated with improved family quality of life (level 2 [mid-level] evidence)

- medication use reported to improve academic achievement in elementary school children with ADHD (level 3 [lacking direct] evidence)

Canadian Psychiatric Societies-Choosing Wisely Canada statement:

"Thirteen Things Physicians and Patients Should Question" June 2, 2015
http://www.choosingwiselycanada.org/recommendations/psychiatry/ (Accessed Sept 12, 2015)

(NOTE: Recommendations are compiled from the Canadian Academy of Child and Adolescent Psychiatry (CACAP), Canadian Academy of Geriatric Psychiatry (CAGP), Canadian Psychiatric Association)

> *"Do not use atypical antipsychotics as first-line intervention for Attention Deficit Hyperactivity Disorder (ADHD) with disruptive behavior disorders"*

Treatment of ADHD should include adequate education of patients and their families, behavioral interventions, psychological treatments and educational accommodations first. If this approach is not sufficient, stimulant medication and a behavioral analysis to ensure appropriate support from the parent and classroom are indicated. The

use of alpha 2 agonists (such as guanfacine) and atomoxetine should be considered before using atypical antipsychotics (such as risperidone) in children with disruptive behavior disorders (oppositional defiant disorder, conduct disorder).

"Do not use psychostimulants as a first-line intervention in preschool children with ADHD"

Preschool children with ADHD need to be assessed for other neurodevelopmental disorders and consideration given to environmental stressors such as neglect, abuse or exposure to domestic violence. Treatment also includes adequate education and support of parents followed by advice on behavioral management and community placement.

Pharmacotherapy Overview

(Reference: Dynamed"Medications for attention deficit hyperactivity disorder (ADHD) in children")

i)Stimulants are first-line treatment for ADHD

While stimulant treatment for ADHD in childhood might be associated with growth delay (level 2 [mid-level] evidence) it appears not to be associated with long-term growth outcomes (level 2 [mid-level] evidence)

ii)First-line therapy from methylphenidate group (methylphenidate) or amphetamine group, both FDA approved for ADHD in children > 6 years old and adolescents

- long-acting formulation preferred in children ≥ 16 kg (35.3 lbs)
- use short-acting formulation in children < 16 kg (35.3 lbs) and consider as adjunct to long-acting medication (for example, late in day for homework or after-school activities)
- long-acting and short-acting formulations of methylphenidate appear equally effective for improving symptoms in children and adolescents (level 2 [mid-level] evidence)
- most stimulants are controlled substances (due to potential for substance abuse), but stimulant therapy in childhood associated with reduced risk for subsequent drug and alcohol use disorders (level 2 [mid-level] evidence)

- stimulant medications for ADHD may not be associated with increased risk for serious cardiovascular events in children and adolescents, but screening electrocardiogram (ECG) has been suggested before starting stimulant medications in children
  - screening ECG considered reasonable by American Heart Association (AHA) (AHA Class IIa, Level C)
  - screening ECG not recommended by AAP (AAP Option, Evidence quality D)

a) In **preschool children** with ADHD, methylphenidate may be associated with reduced symptoms (level 2 [mid-level] evidence)

b) In **school-aged children** with ADHD

- short-acting methylphenidate appears effective for treating ADHD in short-term trials (level 2 [mid-level] evidence)
- dextroamphetamine and amphetamine (Adderall, Adderall XR) appear effective (level 2 [mid-level] evidence)

- lisdexamfetamine (Vyvanse) appears to reduce ADHD symptoms in children (level 2 [mid-level] evidence) but no evidence that lisdexamfetamine offers any therapeutic advantage over other amphetamines
- modafinil may be as effective as methylphenidate in children with ADHD (level 2 [mid-level] evidence), but not FDA approved for ADHD

c) In **adolescents** with ADHD

- extended-release methylphenidate once daily may improve ADHD (level 2 [mid-level] evidence) and may reduce driving errors in adolescents with ADHD (level 2 [mid-level] evidence)
- lisdexamfetamine reduces symptoms in adolescents with moderate-to-severe ADHD (level 1 [likely reliable] evidence), and improvements maintained at 52 weeks (level 2 [mid-level] evidence)

iii)Non-stimulant medications are second-line treatment for ADHD; usually used if stimulant medication ineffective or poorly tolerated

- atomoxetine (Strattera)
  - may be first choice in children with significant anxiety or history of substance abuse
  - appears effective in reducing ADHD symptom scores in children and may be as effective as methylphenidate in reducing core ADHD symptoms in children and adolescents (level 2 [mid-level] evidence)

- antidepressants and anxiolytics may be more effective than placebo, but benefit unclear compared with stimulants

- alpha 2 adrenergic agonists may be used as monotherapy or as adjunct to stimulants (i.e. clonidine, guanfacine XR)
  - alpha-2 agonists may improve ADHD symptoms in children (level 2 [mid-level] evidence)
  - guanfacine extended-release formulation (Intuniv XR) may improve ADHD symptoms in children but may increase risk for adverse events (level 2 [mid-level] evidence)

- carbamazepine may improve ADHD symptoms in children and adolescents (level 2 [mid-level] evidence), but appears much less effective than clonidine for treating ADHD in children (level 2 [mid-level] evidence)

iv)Mineral supplementation

- zinc sulfate as monotherapy or as adjunct to methylphenidate may improve some ADHD symptoms (level 2 [mid-level] evidence)

- iron supplementation may improve ADHD symptoms and severity in children with ADHD **and** low serum ferritin levels (level 2 [mid-level] evidence)

v)Follow-up and medication adjustment

- periodic follow-up suggested every 1-3 weeks for initial dose titration then every 3-6 months

- n-of-1 trials may affect individual management decisions by informing patient-specific efficacy in children with ADHD

NOTE: Guidelines disagree regarding screening electrocardiogram (ECG) before starting medications for ADHD in children, including atomoxetine

- screening ECG considered reasonable by American Heart Association (AHA) (AHA Class IIa, Level C)

- screening ECG not recommended by American Academy of Pediatrics (AAP) (AAP Option, Evidence quality D)

PHARMACOTHERAPY AND PRESCRIBING INFORMATION

Stimulant Medications

1)Methylphenidate:

Mechanism of Action:
Mild CNS stimulant; blocks the reuptake of norepinephrine and dopamine into presynaptic neurons; appears to stimulate the cerebral cortex and subcortical structures similar to amphetamines

- Immediate-release oral formulations - Ritalin, Methylphenidate, generic (Onset of Action ~2 hours)
- Extended-release oral formulations – Concerta (Onset of Action 1-2hrs), Biphentin (Onset <1hr), Ritalin-SR (Onset of Action 4-7 hrs), generic

  Note: Methylphenidate is part of the College of Physicians and Surgeons of Alberta Triplicate Prescription Program (TPP) and requires to be written on a Triplicate prescription—EXCEPT Concerta brand.

Begin with recommended starting dose and titrate medication based on response and tolerance

- Children aged 3-5 years
  - consider starting with 2.5 mg or 0.25 mg/kg orally daily (**no evidence to support specific dosing**)
  - increase dose slowly at weekly intervals
    - consider doubling daily dosage each week until 2 mg/kg/day once or twice daily is reached
    - **no evidence to support specific dosing intervals or maximum dose**

- Children ≥ 6 years old and adolescents
  - conventional formulations
    - start with 5 mg orally twice daily, before breakfast and lunch
    - increase dose at weekly intervals by 5-10 mg/day, based on response and tolerance (maximum 60 mg/day)
    - administer daily dose in 2 or 3 divided doses

  - extended-release formulations
    - Ritalin SR- start with 20 mg orally once daily in morning (alternative is 10 mg once daily orally when lower initial dose is appropriate), increase dose at weekly intervals by 10 mg/day (maximum 60 mg/day)
    - Concerta - start with 18 mg orally once daily in morning; if inadequate response, increase at weekly intervals up to 54 mg/day in children aged 6-12 years, or 72 mg in children aged 13-17 years (maximum 2 mg/kg/day in adolescents)

- Consult Pharmacist or physician for information on dosing when switching from 1 formulation to another (for example, from conventional to extended release)

Cautions with use

- contraindicated if marked anxiety, agitation, glaucoma, motor tics (controversial), monoamine oxidase (MAO) inhibitors within 14 days
- tolerance and psychological dependence may occur with chronic abuse
- psychotic episodes can occur, especially with parenteral abuse
- sudden death and cardiovascular disease has been reported
- possible lowering of seizure threshold

- Common adverse effects include insomnia, headache, nervousness, abdominal pain, nausea, vomiting, anorexia, weight loss, affect lability, tic

2)Amphetamines:

- FDA approved for ADHD in children, adolescents, and adults
- Amphetamines have high potential for abuse and diversion, a controlled substance

Mechanism of Action:
Amphetamines are noncatecholamine, sympathomimetic amines that promote release of catecholamines (primarily dopamine and norepinephrine) from their storage sites in the presynaptic nerve terminals. A less significant mechanism may include their ability to block the reuptake of catecholamines by competitive inhibition

NOTE: dextroamphetamine (Dexedrine IR) is only medication with FDA approval for treatment of ADHD in children aged < 6 years

Available as:

- dextroamphetamine and amphetamine in immediate, extended-release, and fixed-combination extended-release formulations - **Adderall XR**
- dextroamphetamine in immediate, extended-release, and fixed-combination extended release formulations - , **Dexedrine spansules and IR tablets**
- lisdexamfetamine in immediate-release oral capsules – **Vyvanse**

Dosing

i) Dextroamphetamine immediate-release (Dexedrine IR tablets) Time to peak serum levels: ~3 hrs

- doses > 40 mg/day rarely needed
- children aged 3-5 years - start with 2.5 mg orally once daily in early morning, increase dose at weekly intervals by 2.5 mg/day until optimal response achieved
- children ≥ 6 years old – start with 5 mg orally once or twice daily, increase dose at weekly intervals by 5 mg/day until optimal response achieved
- add noon dose if effect does not last through school day
- add 4 PM dose if needed
- increasing morning dose may extend duration
- limit individual doses to < 10 mg in children < 25 kg (55 lbs)

ii) Dextroamphetamine extended-release (Dexedrine Spansule) Time to peak serum levels: ~8 hrs

- usually taken once daily, but twice daily dosing may be beneficial for some patients
- children aged 3-5 years - initiate and titrate dose with IR tablets; substitute extended-release formulation once daily (at same total daily dose) only if daily intake is divisible by 5
- children ≥ 6 years old and adults - start with 5-10 mg orally once daily, increase dose at weekly intervals by 5 mg/day

iii) Fixed-combination extended-release formulation (Adderall XR, contains both amphetamine and dextroamphetamine) Time to peak serum levels : 7hrs

- children aged 6-12 years - start with 10 mg orally once daily (alternative is 5 mg once daily when lower initial dose is appropriate), increase dose at weekly intervals by 5-10 mg/day (maximum 30 mg/day)
- adolescents aged 13-17 years - start with 10 mg orally once daily, increase to 20 mg once daily after 1 week if symptoms not adequately controlled; no evidence that doses > 20 mg/day provide additional benefit

iv)Lisdexamfetamine dimesylate(Vyvanse)

Time to peak serum levels: T_{max}: Lisdexamfetamine: ~1 hour; Dextroamphetamine: ~3.5 hours

Mechanism of Action:

Lisdexamfetamine dimesylate is a prodrug that is converted to the active component dextroamphetamine (a noncatecholamine, sympathomimetic amine). Amphetamines are noncatecholamine, sympathomimetic amines that cause release of catecholamines (primarily dopamine and norepinephrine) from their storage sites in the presynaptic nerve terminals. A less significant mechanism may include their ability to block the reuptake of catecholamines by competitive inhibition.

- initially 30 mg once daily in morning
- may adjust in 10-20 mg increments weekly
- maximum 70 mg once daily in morning
- may swallow whole or dissolve contents of capsule in water immediately before taking; do not subdivide capsule contents
- available in immediate-release oral capsules (20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg)

Cautions with amphetamines

- amphetamines have high potential for abuse and diversion, controlled substance
- misuse of amphetamines may cause sudden death and serious cardiovascular adverse events
- contraindicated if symptomatic cardiovascular disease, hyperthyroidism, moderate-to-severe hypertension, glaucoma, advanced atherosclerosis, monoamine oxidase (MAO) inhibitor use within 14 days, agitation, history of drug abuse
- serious adverse events reported include sudden death, stroke, myocardial infarction, psychotic symptoms, manic symptoms, seizures, exacerbation of tics
- common adverse effects include decreased appetite, insomnia, abdominal pain

Nonstimulant Medications

Atomoxetine (Strattera)
Time to peak plasma levels: 1-2 hours

Mechanism of Action
Selectively inhibits the reuptake of norepinephrine (Ki 4.5 nM) with little to no activity at the other neuronal reuptake pumps or receptor sites.

- Not first-line treatment, usually used if stimulant medication ineffective or poorly tolerated
- May be first choice in children with significant anxiety or history of substance abuse
- Onset of treatment effect may be days to weeks, and optimum effect may not be achieved at 4-6 weeks
- Drug Class: Selective norepinephrine reuptake inhibitor (SNRI); not a controlled substance (unlike stimulant medications for ADHD)
- FDA approved for treatment of ADHD in children > 6 years old and adults
- available in oral capsules (10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg)
- Reduce dose by 50% if moderate hepatic impairment and by 75% if severe hepatic impairment

Dosing

- Give orally once daily in morning, or twice daily in equally divided doses, without regard to meals

- Children and adolescents ≤ 70 kg (154 lbs)
  - start with about 0.5 mg/kg/day
  - increase after 3 days to target dose 1.2 mg/kg/day (maximum 100 mg/day or 1.4 mg/kg/day, whichever is less)
  - doses > 1.2 mg/kg/day not shown to have additional benefit

- Children and adolescents > 70 kg (154 lbs)
  - start with 40 mg/day
  - increase after 3 days to target dose 80 mg/day
  - if suboptimal response after 2-4 additional weeks, may increase dose to maximum 100 mg/day
  - doses > 100 mg/day not shown to have additional benefit

Cautions and adverse events:

- contraindicated if patient has angle-closure glaucoma or has taken monoamine oxidase (MAO) inhibitors within prior 2 weeks
- increased risk of suicidal thinking reported in children and adolescents
- sudden death and cardiovascular disease reported
- psychotic symptoms reported
- atomoxetine metabolized by cytochrome P450 2D6 so drug levels and risk of side effects may be increased by 2D6 inhibitors such as fluoxetine, paroxetine, quinidine
- rarely reported serious adverse effects include severe hepatic injury, hypersensitivity reactions, priapism, urinary retention, and exacerbation of Raynaud's phenomenon
- Common adverse effects in children include dyspepsia, nausea, vomiting, fatigue, dizziness

PHARMACOTHERAPY MONITORING

Reference: Dynamed "Medications for attention deficit hyperactivity disorder (ADHD) in children

- Follow-up frequency determined by symptom severity, impact of comorbid conditions, treatment response, and level of impairment with peers or in home, school, and work settings

- close follow-up by phone or visit is needed during and directly after medication trial or dose increase for first several weeks to assess response and titrate dose
    - titrate dose every 1-3 weeks until any of:
        - target ADHD symptoms remit
        - further dose increase contraindicated due to adverse events
        - maximum drug dose is reached
        - NOTE: response to atomoxetine may not be evident for up to 4-6 weeks
    - consider alternate or additional medication if trial unsuccessful or side-effects not tolerated
    - schedule visit after medication trial to review care plan; follow-up visit recommended ≤ 6 weeks after starting stimulant medication
- follow-up when client on optimal dose includes :
    - visits 2-4 times per year in uncomplicated ADHD (greater frequency in patients with significant comorbid conditions)
    - weekly visits for severe dysfunction or complications
    - monitoring height and weight throughout treatment due to concern for possible growth reduction associated with stimulant use
    - assessment of need for continued treatment
        - continue treatment for persistent symptoms responding to current medication
        - consider alternate or complementary medications if symptoms no longer controlled or side-effects not tolerated
        - consider stopping medication if patient stable and doing well
            - try discontinuing medication for 1-4 weeks with close monitoring
            - schedule trial of discontinuation during period of few transitions and demands (for example, avoid beginning of school year, testing periods, or during complicated projects)
    - anticipatory guidance on short- and long-term goals, academic and organizational skills, behavior management, and availability of additional resources
- issues to consider discussing during follow-up visits
    - current medication doses, timing, benefits, side effects, coverage priorities, duration of effect, adherence
    - parent and teacher observations or behavior ratings
    - functioning in and outside the home including family and peer relationships
    - school performance
    - perception of ADHD and self-esteem
    - in older children and adolescents:
        - increased driving, smoking, drug and other substance abuse risks in adolescents with ADHD
        - prescription medication misuse by patient or others
        - transitioning to adult care

DEBUNKING CONCERNS

i) Efficacy (pharmacologic treatment):

- **Pharmacologic treatment may provide control of ADHD symptoms while being well-tolerated long-term (≥ 12 months) in children ≥ 6 years old with ADHD (level 2 [mid-level] evidence)**
    - Reference - AHRQ Comparative Effectiveness Review 2011 Oct:44

- **Medication management with or without behavior treatment appears to improve ADHD symptoms compared to behavior treatment alone or standard care in children with combined type ADHD (level 2 [mid-level] evidence)**
    - Reference - Multimodal Treatment Study of Children with ADHD (Arch Gen Psychiatry 1999 Dec;56(12):1073 full-text), editorial can be found in Arch Gen Psychiatry 1999 Dec;56(12):1097, commentary can be found in Arch Gen Psychiatry 2001 Dec;58(12):1184 and Pediatrics 2000

Apr;105(4 Pt 1):863

- **Persistent though diminished benefit seen at 24 month follow-up, but not at 36 month follow-up of original patients compared to behavior treatment alone or standard management (level 2 [mid-level] evidence)**
    - Reference - Pediatrics 2004 Apr;113(4):754
    - Commentary can be found in Pediatrics 2004 Aug;114(2):514
    - Consistent use of medication in 14-24 months of follow-up associated with maintenance of efficacy in reduced symptom scores; but also decreased height and weight change (Pediatrics 2004 Apr;113(4):762
    - At 36 months all groups still had symptom improvement from baseline but significant differences between groups on any measure no longer apparent in follow-up of 579 (83%) of original subjects (J Am Acad Child Adolesc Psychiatry 2007 Aug;46(8):989)

- **Stimulant treatment for ADHD in childhood might decrease risk of cumulative psychiatric morbidity (level 2 [mid-level] evidence)**
    - Reference - Pediatrics 2009 Jul;124(1):71

- **Pharmacologic treatment of children with ADHD may be associated with improved family quality of life (level 2 [mid-level] evidence)**
    - Reference - J Child Adolesc Psychopharmacol 2009 Oct;19(5):511

- **Medication use reported to improve academic achievement in elementary school children with ADHD (level 3 [lacking direct] evidence)**
    - Reference - Pediatrics 2009 May;123(5):1273

- **Stimulant treatment may be associated with reduced risk of being held back for ≥ 1 grade level in children with ADHD (level 2 [mid-level] evidence)**
    - Reference - J Dev Behav Pediatr 2007 Aug;28(4):274

ii) Cautions and adverse effects

Most common adverse effects:

- most common adverse effects associated with stimulant use include appetite suppression, abdominal pain, headaches, irritability, and sleep disturbance
- adverse effects typically are dose-dependent

a) Appetite suppression:

- **Stimulant medications may decrease appetite in children with ADHD (level 2 [mid-level] evidence)**
    - Reference - Pediatrics 1997 Oct;100(4):662
    - Commentary can be found in Am Fam Physician 1998 Feb 1;57(3):544

b) Cardiovascular concerns:

- Obtain cardiology consultation if patient has known structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems because of sympathomimetic effects of stimulant medication and/or atomoxetine

- **Stimulant medications for ADHD may not be associated with increased risk for serious cardiovascular events in children and adolescents (level 2 [mid-level] evidence)**

- Reference - BMC Cardiovasc Disord 2012 Jun 9;12:41
- Reference - N Engl J Med 2011 Nov 17;365(20):1896
- Reference - Pediatrics 2011 Jun;127(6):1102
- Reference - Am J Psychiatry 2009 Sep;166(9):992
- Editorial can be found in Am J Psychiatry 2009 Sep;166(9):955
- Commentary can be found in Am J Psychiatry 2010 Feb;167(2):213-4
- Reference - BMJ 2012 Jul 18;345:e4627

Guidelines disagree regarding screening electrocardiogram (ECG) before starting medications for attention deficit hyperactivity disorder (ADHD) in children

- **American Heart Association (AHA) considers screening ECG before starting medications for ADHD in children a reasonable option (AHA Class IIa, Level C)**

  Rationale

  - rare association of sudden cardiac death with stimulant drugs presumed to be in predisposed patients
  - stimulant drug monographs generally state drug should not be used in children with serious cardiac problems

  Screening to identify risk factors for heart disease should include:

  - patient history including fainting or dizziness, seizures, rheumatic fever, chest pain or shortness of breath with exercise, unexplained change in exercise tolerance, palpitations, increased heart rate, extra or skipped heart beats, high blood pressure, heart murmur (other than innocent or functional murmur) or history of other heart problems, intercurrent viral illness with chest pains or palpitations, current medications and health supplements (AHA Class I, Level C)

  - Family history of sudden or unexplained death at young age, sudden death during exercise, "heart attack" or event requiring resuscitation before age 35 years, cardiac arrhythmia, cardiomyopathy, long QT syndrome, short QT syndrome, Brugada syndrome, Wolff-Parkinson-White syndrome, or Marfan syndrome (AHA Class I, Level C)

  - Physical exam, including evaluation for abnormal heart murmur, hypertension, arrhythmia, tachycardia, and physical findings suggestive of Marfan's syndrome (AHA Class I, Level C)

  - Baseline ECG (may repeat after age 12 years if baseline ECG conducted prior to age 12 years) (AHA Class IIa, Level C)

- Reasonable to check history, physical examination, and ECG for children already taking stimulants (AHA Class IIa, Level C)

- Drugs for which ECG on first visit is considered reasonable include methylphenidate, amphetamines, atomoxetine, clonidine, guanfacine, desipramine, imipramine, and bupropion (AHA Class IIa, Level C)

- Reference - Circulation 2008 May 6;117(18):2407
  Correction in Circulation 2009 Aug 18;120(7):e55

- **American Academy of Pediatrics (AAP) does not recommend routine ECG prior to treatment with stimulant medications in children with ADHD (AAP Option, Evidence quality D)**

        - AAP finds no compelling evidence of increased risk for sudden death in children treated for ADHD
        - physicians encouraged to carefully assess all children for cardiac abnormalities by reviewing history and physical assessments (AAP Recommendation, Evidence quality C)
        - Reference - AAP policy statement on cardiovascular monitoring and stimulant drugs for ADHD (Pediatrics 2008 Aug;122(2):451)

- **FDA safety review of association between stimulants and sudden death in children**
    - authors of study above funded by FDA and National Institute of Mental Health conclude possible association between stimulant medication use and sudden death in healthy children
    - FDA does not agree with conclusion due to various methodologic limitations including
        - significant time lag between date of deaths and data collection
        - circumstance of death may have influenced family or caregiver recall of medication use at time of death
        - postmortem inquiry more likely in case of sudden unexplained death than death due to blunt force trauma
        - low frequency of stimulant use reported in both cases and controls
        - rate of untreated ADHD not determined for either group
        - ADHD itself could not be excluded as risk factor for sudden death
    - FDA believes this study should not serve as basis to stop stimulant medications in children
    - Reference - FDA Press Release 2009 Jun 15, FDA MedWatch 2009 Jun 15

- **Stimulant medication might increase heart rate but not blood pressure in children with ADHD (level 3 [lacking direct] evidence)**
    - Reference - Am J Psychiatry 2012 Feb;169(2):167
    - Editorial can be found in Am J Psychiatry 2012 Feb;169(2):112

c) Psychiatric concerns:

- **Psychosis or mania may be adverse effects of stimulant and non-stimulant medications for ADHD**
    - Reference - Pediatrics 2009 Feb;123(2):611 full-text

d) Substance abuse:

- **Stimulant therapy in childhood associated with reduced risk for subsequent drug and alcohol use disorders (level 2 [mid-level] evidence)**
    - Reference - Pediatrics 2003 Jan;111(1):179

e) Growth delay:

- Stimulant therapy may be associated with short-term growth delay in children, but appears not to affect long-term growth outcomes

- Growth delay reported to typically attenuate with time and/or disappear after ceasing medication

- **Stimulant therapy might be associated with slight growth delay (level 2 [mid-level] evidence)**
    - Reference - Arch Dis Child 2005 Aug;90(8):801

- **Stimulant therapy for ADHD may not be not associated with long-term growth deficits (level 2 [mid-level] evidence)**
    - Reference - J Pediatr 2010 Oct;157(4):635 f

f) Visual effects

- Rare ocular side effects mentioned include accommodation disturbance, blurred vision, dry eye syndrome, eye pain (children), mydriasis (Reference-Lexi-comp: Methylphenidate, dextroamphetamine)

- Atomoxetine: Opthalmic: Blurred vision, conjunctivitis, mydriasis (Ref: Lexi-comp); (no adverse effects listed in Micromedex)

- Methylphenidate: Frequency not defined (Ref: Lexi-comp); blurred vision 1.7-2% or greater (Ref: Micromedex)

- Monitoring of ophthalmic adverse effects is warranted for stimulant medications.

Writer's comments:
"Blurred vision" are noted included in the adverse effects profile of many ADHD medications and may be due to post-market case-reports that have emerged but at the moment do not demonstrate significant causal evidence.

An example case report from China discusses a 10-year-old boy who was diagnosed with ADHD and had received methylphenidate hydrochloride, 60 mg/day for 2 years. He presented with blurred vision. Best-corrected visual acuity was 6/60 in both eyes. Ocular examinations revealed intraocular pressure (IOP) of 30 mmHg under medication, dense posterior subcapsular opacity of lens, pale disc with advanced cupping, and marked constriction of visual field. Despite maximal anti-glaucomatous medication, IOP still could not be controlled. The patient then received combined cataract and glaucoma surgery. Visual acuity improved and IOP was within normal limits in both eyes postoperatively. The mechanism remains unclear. Doctors should be aware of the possible ocular side effects of methylphenidate.

  - Reference- Journal of the Chinese Medical Association: JCMA. 69(12):589-90, 2006 Dec

NOTE: Contraindications in the Canadian labelling of methylphenidate prescribing for ADHD in patient's with glaucoma.

Neurophysiology

- Nervous system side effects have frequently included tic. Convulsions and migraine have also been reported. Dizziness, drowsiness, dyskinesia, and Tourette's syndrome have been reported rarely. Neuroleptic malignant syndrome (NMS) and reversible ischemic neurological deficit have been reported very rarely--most reported cases of neuroleptic malignant syndrome (NMS) involved patients who were treated concomitantly with other drugs associated with NMS
  (References: Drug monographs of stimulant medications)

- Meta-analysis of controlled trials does not support an association between new onset or worsening of tics and psychostimulant use. Clinicians may want to consider rechallenging children who report new onset or worsening of tics with psychostimulant use, as these symptoms are much more likely to be coincidental rather than caused by psychostimulants
  (Reference: J Am Acad Child Adolesc Psychiatry. 2015 Sep;54(9):728-36

- **methylphenidate, alpha-agonists, or desipramine may improve attention-deficit/hyperactivity disorder (ADHD) and possibly reduce tics in children with ADHD and comorbid tic disorder**
  - Reference - J Am Acad Child Adolesc Psychiatry 2009 Sep;48(9):884
    Cochrane Database Syst Rev 2011 Apr 13;(4):CD007990 including 8 of the same trials

g) Other adverse events:

- priapism reported to be rare adverse event associated with methylphenidate (15 cases), amphetamines (4 cases), and atomoxetine (1 case) in systematic review of case reports
    - Reference: Ann Pharmacother 2014 Oct;48(10):1350

Management of adverse effects

For adverse effects associated with stimulants

- Anorexia, weight loss, stomach ache
    - take medication with or after meals
    - have high calorie breakfast and snacks after school or at bedtime
    - use stimulant medication only for high-priority needs
    - referral to dietitian

- Insomnia
    - allow "wind-down time" after school
    - give dose earlier in day, or eliminate afternoon or evening doses
    - switch to short-acting formulation
    - try adjunctive medications such as clonidine or antidepressants

- Rebound irritability or moodiness (usually 4-5 hours after dose; phenomenon may be result of natural mood variability)
    - overlap stimulant doses
    - step-down dosing
    - switch to long-acting formulation, or combine short- and long-acting formulations
    - administer immediate-release stimulant in afternoon (typically smaller than morning doses)

- Generalized irritability, dysphoria, or agitation
    - consider timing of symptoms, such as peak withdrawal
    - reduce dose, or change to long-acting formulation
    - consider alternative stimulant or adjunctive medication
    - consider comorbid disorder

- tics
    - if mild and infrequent, continue medication and monitor for worsening
    - discuss benefit vs. risk of continuing stimulant treatment
    - consider nonstimulant alternatives (i.e. guanfacine, clonidine)

- headache
    - adjust timing of medication dose
    - decrease dose with gradual return to therapeutic dose
    - try long-acting formulation or alternative medication

- linear growth impairment
    - decrease stimulant intake by using only for high-priority needs or taking weekend/vacation drug holidays
    - consider alternative medication

ADMINSTRATION TIPS

atomoxetine (*Strattera*)	*Capsule*: recommended to be swallowed whole but can be opened if necessary: caution GI irritation, eye contact and inhalation
dextroamphetamine IR (*Dexedrine*)	*Tablet*: may be cut, crushed or chewed
dextroamphetamine SR (*Dexedrine Spansule*)	*Spansule*: may be opened and contents sprinkled on soft foods
lisdexamfetamine (*Vyvanse*)	*Capsule*: May be opened and contents dissolved in water
methylphenidate IR (generics, *Ritalin*)	*Tablet*: may be cut, crushed or chewed
methylphenidate SR (generics, *Ritalin SR*)	*Tablet*: do not crush or chew tablet - will no longer be sustained release
methylphenidate CR (*Biphentin*)	*Capsule*: may be opened and sprinkled on soft foods
methylphenidate bilayer CR (*Concerta*)	*Tablet*: do not cut, crush or chew - will destroy controlled release bilayer
mixed amphetamines SR (*Adderall XR*)	*Capsule*: may be opened and sprinkled on soft foods

ANTIPSYCHOTIC PHARMACOTHERAPY

CURRENT PRACTICE RECOMMENDATIONS

For children and adolescents (Reference: Dynamed "Antipsychotics")

- second-generation (atypical) antipsychotic agents appear no more effective than first-generation (typical) agents for children and adolescents with early-onset schizophrenia and schizoaffective disorder (level 2 [mid-level] evidence)
- clozapine may be more effective than olanzapine in children and adolescents with refractory schizophrenia (level 2 [mid-level] evidence)

Canadian Psychiatric Societies-Choosing Wisely Canada statement:

"Thirteen Things Physicians and Patients Should Question" June 2, 2015
http://www.choosingwiselycanada.org/recommendations/psychiatry/ (Accessed Sept 12, 2015)

"Do not use atypical antipsychotics as a first-line intervention for insomnia in children and you".

Recent research confirms a dramatic increase in the use of atypical antipsychotics with subsequent side-effects including obesity, which is already a major health issue. It is prudent to pursue nonpharmacological measures first, such as behavioral modifications and ensuring good sleep hygiene (such as eliminating daytime napping and shutting off electronics an hour before bedtime). If these interventions are not successful, then consider short-term use of melatonin.

"Do not use atypical antipsychotics [risperidone] as a first-line intervention for Attention Deficit Hyperactivity Disorder (ADHD) with disruptive behaviour disorders"

Treatment of ADHD should include adequate education of patients and their families, behavioral interventions, psychological treatments and educational accommodations first. If this approach is not sufficient, stimulant medication and a behavioral analysis to ensure appropriate support from the parent and classroom is indicated. The use of alpha 2 agonists (such as guanfacine) and atomoxetine should be considered before using atypical antipsychotics (such as risperidone) in children with disruptive behavior disorders (oppositional defiant disorder, conduct disorder).

"Do not routinely use antipsychotics to treat primary insomnia in any age group"

Second-generation antipsychotics (SGAPs), such as olanzapine and quetiapine, have sedative properties, and are often prescribed off-label for complaints of insomnia. These drugs carry significant risk of potential side-effects including weight gain and metabolic complications, even at low doses used to treat insomnia. In patients with dementia, they can also potentially cause serious side-effects of increased risk of cerebrovascular event and increased risk of death.

"Do not routinely prescribe high-dose or combination antipsychotic treatment strategies in the treatment of schizophrenia"

High-dose and combination strategies involving atypical antipsychotics (AAPs) are used in clinical practice for patients with schizophrenia who are inadequately controlled with one or more AAPs used at standard doses. A recent meta-analysis found no clinically significant improvements in patients with schizophrenia who were inadequately controlled on standard-dose antipsychotics when treated with combination or high-dose AAPs. In terms of safety, no clinically significant differences were evident between combination or high-dose therapy in comparison with standard-dose monotherapy.

PHARMACOTHERAPY & PRESCRIBING INFORMATION

NOTE: Pediatric Approved Indications and Doses (Reference: RxFiles 9th Edition)

TYPICAL ANTIPSYCHOTICS

i) **Chlorpromazine** (oral 10mg, 25mg, 50mg, 100mg, 200mg; injection 25mg/mL)

Onset of Action: (oral) 30-60 minutes
Maximum antipsychotic effect: 6 weeks to 6 months
Duration: (oral) 4-6 hours

Mechanism of Action:
Chlorpromazine is an aliphatic phenothiazine antipsychotic which blocks postsynaptic mesolimbic dopaminergic receptors in the brain; exhibits a strong alpha-adrenergic blocking effect and depresses the release of hypothalamic and hypophyseal hormones; believed to depress the reticular activating system, thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis
Dosing:

- Schizophrenia: ≤6 months 0.5-1mg/kg po/IM/IV every 4-6 hours
- MAX Dose <22.7kg = 40mg/d, 22.7-45.5kg = 75mg/d

ii)**Haloperidol** (oral 0.5mg, 1mg, 2mg, 5mg, 10mg, 20mg; injection 2mg/mL; Depot 50mg/mL)

Mechanism of Action:
Haloperidol is a butyrophenone antipsychotic which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors in the brain; depresses the release of hypothalamic and hypophyseal hormones; believed to depress the reticular activating system thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis

Dosing:

- Schizophrenia: >3yr 0.25-0.5mg/d po divided 2-3x/day, increased every 5-7 day; usual 0.05-0.15/kg/day MAX 0.15mg/kg/day
- Tourette's: >3y 0.05-0.75mg/kg/d po divided 2-3x/day

iii)**Thioridazine** (oral 10mg, 25mg, 50mg, 100mg)

Mechanism of Action:
Thioridazine is a piperidine phenothiazine which blocks postsynaptic mesolimbic dopaminergic receptors in the brain; also has activity at serotonin, noradrenaline, and histamine receptors (Fenton, 2007).

Dosing:

- Behavioral problems: 2-12 year 10mg po divided 2-3 times per day; >12 years- adult dosing

ATYPICAL ANTIPSYCHOTICS

i)**Pimozide** (Oral 1mg, 2mg)

Onset of action: within 1 week
Maximum effect: 4-6 weeks
Duration of effect: variable

Mechanism of Action:
Pimozide, a diphenylbutylperidine conventional antipsychotic, is a potent centrally-acting dopamine-receptor antagonist resulting in its characteristic neuroleptic effects

Dosing

- Tourette's: ≤12yr 0.05mg/kg po at bedtime, increase every 3 days; usual 2-4mg/day;
- MAX 10mg/day or 0.2mg/kg/day; >12yr adult dosing

ii)**Aripiprazole** (oral 2mg, 5mg, 10mg, 15mg, 20mg, 30mg)

Onset of Action: Initial 1-3 weeks

Mechanism of Action:
Aripiprazole is a quinolinone antipsychotic which exhibits high affinity for D_2, D_3, 5-HT_{1A}, and 5-HT_{2A} receptors; moderate affinity for D_4, 5-HT_{2C}, 5-HT_7, alpha$_1$ adrenergic, and H_1 receptors. It also possesses moderate affinity for the serotonin reuptake transporter; has no affinity for muscarinic (cholinergic) receptors. Aripiprazole functions as a partial agonist at the D_2 and 5-HT_{1A} receptors, and as an antagonist at the 5-HT_{2A} receptor.

Dosing

- Autism irritability: ≥6 year start 2 mg po daily, target 5-10mg po daily, MAX 15mg po daily
- Bipolar mixed/mania: ≥13 yr 2mg po daily, target 10mg daily, MAX 30mg po OD (NOTE: FDA labelling ≥10 years)
- Schizophrenia: ≥15 year, start 2mg po daily, target 10mg po daily, MAX 10-30mg po daily (NOTE: FDA labelling ≥13years)

iii)**Olanzapine (**oral 2.5mg, 5mg, 7.5mg, 10mg; oral dispersible 5mg, 10mg, 15mg, 20mg; Injection 10mg)

Time to peak serum concentration: oral (peds 10-18 years n=8) 4.7 ± 3.7 hr (Grothe, 2000)

Mechanism of Action:
Olanzapine is a second generation thienobenzodiazepine antipsychotic which displays potent antagonism of serotonin 5-HT_{2A} and 5-HT_{2C}, dopamine D_{1-4}, histamine H_1, and alpha$_1$-adrenergic receptors. Olanzapine shows moderate antagonism of 5-HT_3 and muscarinic M_{1-5} receptors, and weak binding to GABA-A, BZD, and beta-adrenergic receptors. Although the precise mechanism of action in schizophrenia and bipolar disorder is not known, the efficacy of olanzapine is thought to be mediated through combined antagonism of dopamine and serotonin type 2 receptor sites.

Dosing:

- Bipolar mixed/mania ≥13 year start 2.5-5mg po od, target 10mg po od, MAX 20mg/day
- Schizophrenia ≥13 year start 2.5-5mg po od, target 10mg po od, MAX 20mg po od

iv)**Paliperidone** (Extended release 24 hr tablet 1.5mg, 3mg, 6mg, 9mg)

Mechanism of Action:
Paliperidone is considered a benzisoxazole atypical antipsychotic as it is the primary active metabolite of risperidone. As with other atypical antipsychotics, its therapeutic efficacy is believed to result from mixed central serotonergic and dopaminergic antagonism. The addition of serotonin antagonism to dopamine antagonism (classic neuroleptic mechanism) is thought to improve negative symptoms of psychoses and reduce the incidence of extrapyramidal side effects. Similar to risperidone, paliperidone demonstrates high affinity to α_1, D_2, H_1, and 5-HT_{2C} receptors, and low affinity for muscarinic and 5-HT_{1A} receptors. In contrast to risperidone, paliperidone displays nearly 10-fold lower affinity for α_2 and 5-HT_{2A} receptors, and nearly three- to fivefold less affinity for 5-HT_{1A} and 5-HT_{1D}, respectively

Dosing:

- Schizophrenia: ≥12 year start 3mg po od,

Target

- <51kg: 3-6mg/day; MAX <51kg 6mg/day
- ≥51kg: 3-12mg/day; MAX ≥51kg 12mg/day

v)**Quetiapine**
(oral 25mg, 50mg, 100mg, 200mg, 300mg, 400mg; 24 hr ER tab 50mg, 150mg, 200mg, 300mg, 400mg)

Time to peak serum concentration: ages 12-17: Immediate release: 0.5-3 hours (McConville, 2000)

Mechanism of Action:
Quetiapine is a dibenzothiazepine atypical antipsychotic. It has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 (5-HT_2) antagonism. It is an antagonist at multiple neurotransmitter receptors in the brain: Serotonin 5-HT_{1A} and 5-HT_2, dopamine D_1 and D_2, histamine H_1, and adrenergic $alpha_1$- and $alpha_2$-receptors; but appears to have no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors. Norquetiapine, an active metabolite, differs from its parent molecule by exhibiting high affinity for muscarinic M1 receptors.

Antagonism at receptors other than dopamine and 5-HT_2 with similar receptor affinities may explain some of the other effects of quetiapine. The drug's antagonism of histamine H_1-receptors may explain the somnolence observed. The drug's antagonism of adrenergic $alpha_1$-receptors may explain the orthostatic hypotension observed.

Dosing

- Bipolar Mania ≥10 year start 25mg po BID, target 400-600mg/day po divided 2-3 times per day
- Schizophrenia ≥13 year start 25mg po BID, target 400-800mg/day po divided 2-3 times per day

vi)**Risperidone**
(oral 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg; dispersible tab 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg; solution 1mg/mL)

Mechanism of Action:
Risperidone is a benzisoxazole atypical antipsychotic with mixed serotonin-dopamine antagonist activity that binds

to 5-HT_2-receptors in the CNS and in the periphery with a very high affinity; binds to dopamine-D_2 receptors with less affinity. The binding affinity to the dopamine-D_2 receptor is 20 times lower than the 5-HT_2 affinity. The addition of serotonin antagonism to dopamine antagonism (classic neuroleptic mechanism) is thought to improve negative symptoms of psychoses and reduce the incidence of extrapyramidal side effects. $Alpha_1$, $alpha_2$ adrenergic, and histaminergic receptors are also antagonized with high affinity. Risperidone has low to moderate affinity for 5-HT_{1C}, 5-HT_{1D}, and 5-HT_{1A} receptors, weak affinity for D_1 and no affinity for muscarinics or $beta_1$ and $beta_2$ receptors

Dosing:

- Autism irritability:
  - ≥5 year & <20kg start 0.25mg/day, target 0.5mg/day, MAX 1mg/day
    ≥5 year& ≥20kg start 0.5mg/day, target 1mg/day, MAX 2.5mg/day (>45kg 3mg/day)

- Bipolar mania/mixed: ≥10 year start 0.5mg/day, target 2.5mg/day

- Schizophrenia: ≥13 year start 0.5mg/day, target 3mg/day

ADVERSE EFFECTS

- cardiovascular adverse effects
  - antipsychotics associated with increased risk for cardiac arrest, sudden cardiac death and ventricular arrhythmias (level 2 [mid-level] evidence)
  - all antipsychotics may be associated with increased risk for stroke (level 2 [mid-level] evidence)
  - antipsychotics may be associated with increased risk for venous thromboembolism (level 2 [mid-level] evidence)

- metabolic adverse effects
  - weight gain varies; highest with olanzapine and clozapine, lowest with haloperidol (level 2 [mid-level] evidence)
  - management of weight gain
    - metformin and/or lifestyle intervention is effective for prevention of antipsychotic-associated weight gain (level 1 [likely reliable] evidence)
    - cognitive-behavioral therapy or nutritional counseling may be effective for weight loss and prevention of weight gain in patients taking antipsychotics (level 2 [mid-level] evidence)
  - atypical antipsychotics may be more likely to induce diabetes than typical antipsychotics (level 2 [mid-level] evidence)
  - atypical or typical antipsychotics associated with increased risk of hyperglycemia in elderly patients with diabetes (level 2 [mid-level] evidence)
- sedation more likely with clozapine, quetiapine or zotepine than haloperidol, and less likely with aripiprazole (level 2 [mid-level] evidence)
- antipsychotics may increase risk of extrapyramidal side effects (level 2 [mid-level] evidence)
  - highest risk with haloperidol or chlorpromazine (level 2 [mid-level] evidence)
  - risk may be higher with risperidone than olanzapine which may be higher than quetiapine (level 2 [mid-level] evidence)
- neuroleptic malignant syndrome (NMS) (rare)

- dopamine antagonists may be associated with small increased risk of breast cancer (level 2 [mid-level] evidence)

EVALUATION OF LITERATURE

Aripiprazole appears effective in acute treatment of adolescents with schizophrenia (level 2 [mid-level] evidence)

- most common adverse events with aripiprazole were extrapyramidal symptoms, akathisia, tremor, somnolence
- Reference - Am J Psychiatry 2008 Nov;165(11):1432, editorial can be found in Am J Psychiatry 2008 Nov;165(11):1369

Clozapine appears more effective than olanzapine in children and adolescents with refractory schizophrenia (level 2 [mid-level] evidence)

- based on 8-week randomized trial in 25 children and adolescents aged 7-16 years with schizophrenia resistant to at least 2 prior antipsychotics
- Reference - Arch Gen Psychiatry 2006 Jul;63(7):721

Atypical antipsychotics may be as effective as typical antipsychotics with different adverse event profiles in adolescents with psychosis (level 2 [mid-level] evidence)

- Reference - Cochrane Database Syst Rev 2013 Oct 15;(10):CD009582

Clozapine, olanzapine, and risperidone may be more effective than haloperidol in children and young adults with schizophrenia (level 2 [mid-level] evidence)

- Reference - AHRQ Comparative Effectiveness Review 2012 Feb:39

Insufficient evidence to evaluate efficacy of antipsychotic medication for childhood-onset schizophrenia

- Reference - Cochrane Database Syst Rev 2007 Jul 18;(3):CD004027 (Metabolic adverse effects:

Atypical antipsychotics associated with weight gain (level 2 [mid-level] evidence)

- Note: olanzapine and quetiapine each associated with significant increase from baseline in mean
  - total cholesterol
  - triglycerides
  - non-high-density lipoprotein (HDL) cholesterol
  - ratio of triglycerides to HDL cholesterol
- Note: risperidone associated with significantly increased triglycerides (from baseline)
- Reference - JAMA 2009 Oct 28;302(16):1765

Metabolic and cardiovascular adverse events associated with antipsychotics in children and adolescents

- compared to controls, antipsychotic use associated with higher prevalence of
  - obesity
  - type 2 diabetes
  - cardiovascular conditions
  - orthostatic hypotension
- risks higher for patients using multiple antipsychotics compared to those on monotherapy
- Reference - Arch Pediatr Adolesc Med 2008 Oct;162(10):929

Haloperidol may increase risk of extrapyramidal symptoms compared to olanzapine or risperidone but may decrease weight gain compared to olanzapine in children and young adults (level 2 [mid-level] evidence)

- Reference - AHRQ Comparative Effectiveness Review 2012 Feb:39:

Metformin may reduce weight gain in children and adolescents taking atypical antipsychotics

- Reference - Am J Psychiatry 2006 Dec;163(12):2072

ANTIDEPRESSANT PHARMACOTHERAPY

SUMMARY

Canadian Psychiatric Societies-Choosing Wisely Canada statement:

"Thirteen Things Physicians and Patients Should Question" June 2, 2015
http://www.choosingwiselycanada.org/recommendations/psychiatry/ (Accessed Sept 12, 2015)

"Do not use SSRIs as the first-line intervention for mild to moderately depressed teens"

Evidence clearly indicates that antidepressant medication is less effective in children and adolescents up to the age of 17 years and first-line treatment for this group should include cognitive behavioral therapy or interpersonal psychotherapy. Attention should always be focused on children's and teens' environmental safety and adequate parental support to avoid missing cases of neglect or abuse. Following this, a first-line intervention should be psychoeducation on the importance of regular sleep, diet and exercise to ensure healthy, age-appropriate developmental support.

i)Antidepressants:

- suggested dosing from manufacturer for fluoxetine for children ≥ 8 years old is 10 mg or 20 mg daily with goal of 20 mg daily at end of 1 week, or goal of 10 mg for children with lower weight
- SNRI and TCA antidepressants may be more appropriate than SSRIs for patients with melancholic depression
- Canadian psychiatric societies, including Canadian Academy of Child and Adolescent Psychiatry (CACAP) and Canadian Psychiatric Association (CPA), recommend against using selective serotonin reuptake inhibitors (SSRIs) as the first-line intervention for mild to moderately depressed teens (Choosing Wisely Canada 2015 Jun 2)

ii)Efficacy:

- **antidepressants that appear to increase remission include fluoxetine, sertraline, escitalopram, and venlafaxine; and venlafaxine may also increase suicide-related outcomes (level 2 [mid-level] evidence)**
  - Reference - Cochrane Database Syst Rev 2012 Nov 14;(11):CD004851
- **SSRIs and other second generation antidepressants appear to increase response rates but may have small risk of suicidal ideation in children and adolescents with depression (level 2 [mid-level] evidence)**
  - based on systematic review with inadequate assessment of trial quality
  - Reference - JAMA 2007 Apr 18;297(15):1683
- **TCAs do not appear to increase remission but may modestly improve symptoms of depression in adolescents (level 2 [mid-level] evidence); limited evidence to evaluate efficacy in children**
  - adverse effects of TCAs included vertigo, orthostatic hypotension, tremor, and dry mouth
  - Reference - Cochrane Database Syst Rev 2013 Jun 18;(6):CD002317
- **fluoxetine may improve response and remission rates in children and adolescents with major depressive disorder (level 2 [mid-level] evidence)**
  - Reference - Arch Gen Psychiatry 2012 Jun;69(6):572

iii)Safety and adverse events:

- **use of antidepressants in adolescents controversial due to concerns about suicidality**

    - FDA recommends not using paroxetine (Paxil) in children and adolescents because of no evidence of efficacy and possible increased risk of suicidal thinking and suicide attempts (FDA Press Release 2007 May 2)
    - most SSRIs (citalopram, escitalopram, paroxetine, sertraline, venlafaxine) discouraged in children by United Kingdom Committee on Safety and Medicines (BMJ 2004 Jan 3;328(7430):3
    - FDA added **BLACK BOX WARNING** to antidepressants to note increased risk of suicidal thinking and behavior in children and adolescents in short-term studies of major depressive disorder and other psychiatric disorders (FDA Press Release 2004 Oct 15)
    - summary of FDA deliberations on antidepressant use in pediatric patients can be found in Pediatrics 2005 Jul;116(1):195 full-text, editorials can be found in Pediatrics 2005 Jul;116(1):231
    - review of antidepressant drugs and suicide risk in children and adolescents can be found in Pediatr Drugs 2014 Apr;16(2):115
- **antidepressants might be associated with increased self-harm and suicide-related events in children and adolescents, but evidence limited (level 2 [mid-level] evidence)**
    - based on systematic review with inadequate quality assessment
    - systematic review of 16 randomized placebo-controlled trials of newer antidepressants (paroxetine, citalopram, mirtazapine, sertraline, venlafaxine, fluoxetine) in 2,741 children and adolescents
    - data obtained from United Kingdom Committee on Safety of Medicines review in 2003 and authors did not provide information about randomization, allocation concealment or treatment discontinuation rates
    - no completed suicides in any patient
    - combined outcome of any self-harm or suicide-related event was higher with active drug than placebo (4.8% vs. 3%, NNH 55)
    - no statistically significant findings for individual outcomes of suicidal thoughts, self-harm, or suicide attempts
    - no statistically significant findings for combined outcomes for any individual drug except venlafaxine (7.7% vs. 0.6%, NNH 14)
    - Reference - Br J Psychiatry 2006 Nov;189:393 full-text
- **SSRIs associated with increased risk of attempted or completed suicide in adolescents, but decreased risk in adults (level 2 [mid-level] evidence)**
    - Reference - CMAJ 2009 Feb 3;180(3):291
- **higher dose of SSRIs associated with increased risk of self-harm in patients aged 10-24 years (level 2 [mid-level] evidence)**
    - Reference - JAMA Intern Med 2014 Jun;174(6):899,
- **suicide risk not associated with type of antidepressant used in children and adolescents (level 2 [mid-level] evidence)**
    - Reference - Pediatrics 2014 Feb;133(2):204
    - Reference - Pediatrics 2010 May;125(5):876 full-text, editorial can be found in Pediatrics 2010 May;125(5):1064 full-text
- **venlafaxine extended-release may be associated with increased suicidality in children (level 2 [mid-level] evidence)**
    - Reference - Arch Gen Psychiatry 2006 Mar;63(3):332
- **early phase of antidepressant treatment for major depressive episode associated with suicide attempts in children (level 2 [mid-level] evidence)**
    - based on nested case-control study
    - study used Medicaid administrative data on outpatients treated for major depressive episode
    - 51 children aged 6-18 years were compared to 239 matched controls
    - in first 120 days of treatment antidepressants associated with increased suicide attempts in children (OR 2.08, p = 0.03)
    - Reference - J Clin Psychiatry 2008 Mar;69(3):425

iv)Long-term therapy:

NICE guidelines recommend antidepressants be continued ≥ 6 months after remission in responsive patients

- **continuation or maintenance treatment with antidepressants may reduce risk of relapse in children and adolescents with depressive disorder (level 2 [mid-level] evidence)**
    - Reference - Cochrane Database Syst Rev 2012 Nov 14;(11):CD007504

v)Other medications for depression in children and adolescents:

- **omega-3 fatty acid 1,000 mg daily might be associated with reduced depression scores in children with depression (level 2 [mid-level] evidence)**
    - Reference - Am J Psychiatry 2006 Jun;163(6):1098