“The day the child realizes that all adults are imperfect, he becomes an adolescent; the day he forgives them, he becomes an adult; the day he forgives himself, he becomes wise.”

Alden Nowlan, poet (1933-1983)
Antipsychotics

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Adolescent Inpatient Unit,
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Assistant Professor, Department of Psychiatry,
University of Toronto

Disclosures

Every effort was made to ensure the accuracy of these slides.
If there are errors, omissions, and/or suggestions for future,
please let the course directors know.

Acknowledgments

Thank you to previous contributors to this presentation:
Dr. Daniel Gorman
Dr. Corine Carlisle
Dr. John Langley

Learning Objectives

• Understand when and how to use antipsychotics in children and youth
• Understand the risk of side effects and strategies to monitor individuals on antipsychotic medication
Outline

• Historical perspective
• Indications & clinical use
• Pharmacodynamics & pharmacokinetics
• Efficacy: Schizophrenia, bipolar disorder, autism spectrum, aggression and disruptive behaviour
• Adverse effects
• Contraindications & drug interactions
• Monitoring
• Dosing
• Clozapine

Clinical Uses in Children and Youth

• Schizophrenia and other primary psychotic disorders
• Mood disorders with psychotic features
• Aggression in youth with disruptive behaviour disorders, especially CD
• Disruptive behaviour and agitation in individuals with Developmental Delay, Autism, or traumatic brain injury
• Eating disorders
• Tic disorders
• Delirium
• Insomnia

References

1) Clinical Handbook of Psychotropic Drugs for Children and Adolescents. 3rd Ed. (Elbe, Bezchlibnyk-Butler, Virani, Procysyn (EDS.) Antipsychotic Chapter (p.119-202).

2) Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications (Stephen Stahl)
   Chapter 5: Antipsychotic Agents

“Typical” or “First-Generation” Antipsychotics (FGAs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Chemical Class</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
<td>Butyrophenone</td>
<td>Tablet, liquid, IM, IV, depot</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Loxapine</td>
<td>Dibenzoxazepine</td>
<td>Tablet, liquid, IM</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Orap</td>
<td>Diphenylbutylpiperidine</td>
<td>Tablet</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Largactil</td>
<td>Aliphatic</td>
<td>Tablet, liquid, IM, supp</td>
</tr>
<tr>
<td>Trifluperazine</td>
<td>Stelazine</td>
<td>Piperazine</td>
<td>Tablet, liquid, IM</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>Clopixol, Acuphase</td>
<td>Thianthrene</td>
<td>Tablets, IM, depot</td>
</tr>
</tbody>
</table>

Historical Perspective

1950 Charpenter developed Chlorpromazine, looking for a new anesthetic
1952 Delay and Deniker observed that Chlorpromazine “quieted” psychosis
1957 Haloperidol
1960s Clozapine
1989 Clozapine
1993 Risperidone
1997 Olanzapine, Quetiapine
2001 Ziprasidone
2002 Aripiprazole
2006 Paliperidone PO
2009 Paliperidone IM (q1mo)
2009 Asenapine (Saphris)
2013 Lurasidone (Latuda)
2015 Cariprazine (Vraylar) – FDA Sept 2015 - not available in Canada as of August 2017
2015 Amisulpride – available in Europe since 1990s
2015 Paliperidone IM (q3mo)
2015 Brexpiprazole (Rexulti) - FDA Sept 2015, Health Canada May 2017

- (partial D2 agonist, partial serotonin agonist (1A)/antagonist (2A))
FGA Approved Pediatric Uses

**FGA (U.S.)**  
Health Canada

<table>
<thead>
<tr>
<th>Chlorpromazine</th>
<th>FDA (≥ 6 months)</th>
<th>Health Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis, dementia, depression, anxiety, and agitation (≥ 6 months)</td>
<td>Not approved for use in children (≥ 6 months)</td>
<td>Not approved for use in children (≥ 6 months)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Haloperidol</th>
<th>FDA (≥ 3 years)</th>
<th>Health Canada</th>
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<tr>
<td>Psychosis, dementia, depression, anxiety, and agitation (≥ 3 years)</td>
<td>Not approved for use in children (≥ 3 years)</td>
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</table>

<table>
<thead>
<tr>
<th>Fluphenazine</th>
<th>FDA (≥ 12 years)</th>
<th>Health Canada</th>
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</thead>
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<tr>
<td>Psychosis, dementia, depression, anxiety, and agitation (≥ 12 years)</td>
<td>Not approved for use in children (≥ 12 years)</td>
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<table>
<thead>
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<th>Loxapine</th>
<th>FDA (≥ 12 years)</th>
<th>Health Canada</th>
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<td>Not approved for use in children (≥ 12 years)</td>
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</table>

<table>
<thead>
<tr>
<th>Pimozide</th>
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<tr>
<td>Psychosis, dementia, depression, anxiety, and agitation (≥ 12 years)</td>
<td>Not approved for use in children (≥ 12 years)</td>
<td>Not approved for use in children (≥ 12 years)</td>
</tr>
</tbody>
</table>

FGA: Pharmacodynamics

- **FGAs are powerful long-acting D2 antagonists that act throughout the brain.**
- **D2 antagonism…**
  - in mesolimbic pathways is thought to be responsible for cognitive side effects
  - in nigrostriatal pathways causes EPS
- **Other side effects of FGAs are caused by the blockade of histaminic, muscarinic, and α-adrenergic receptors.**

<table>
<thead>
<tr>
<th>Equivalent oral dose (mg)</th>
<th>Potency</th>
<th>Dose range (mg)</th>
<th>Sedation</th>
<th>Autonomic (e.g., anticholinergic)</th>
<th>EPS</th>
<th>Approved age for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>10-100</td>
<td>3-100</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>≥ 6 months</td>
</tr>
<tr>
<td>Loxapine</td>
<td>15</td>
<td>Medium</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>≥ 3 years</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>10</td>
<td>High</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>≥ 12 years</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>8-15</td>
<td>High</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>≥ 16 years</td>
</tr>
<tr>
<td>Pimozide</td>
<td>1-2</td>
<td>High</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>≥ 16 years</td>
</tr>
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</table>

Relative Potency of Selected FGAs

<table>
<thead>
<tr>
<th>Receptor Binding Profiles of Selected FGAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block D&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>CPZ</td>
</tr>
<tr>
<td>---</td>
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<tr>
<td>+++</td>
</tr>
</tbody>
</table>

FGA Classification by Potency

- **High-potency (e.g., haloperidol)**
  - Less sedating, less anticholinergic, more likely to cause EPS
- **Mid-potency (e.g., loxapine)**
  - Intermediate with respect to sedation, anticholinergic side effects, and EPS
- **Low-potency (e.g., chlorpromazine)**
  - More sedating, more anticholinergic, less likely to cause EPS
FGA Pharmacokinetics

- Information about the pharmacokinetics of FGAs is derived mainly from studies in adults.
- FGAs are well absorbed when given orally, but they undergo extensive first-pass metabolism.
- Oral administration generally leads to a peak plasma level in 1-4 hours.

FGA Pharmacokinetics (cont.)

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Metabolized by</th>
<th>Source of Information</th>
<th>Plasma Level</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>1A2, 2D6, 3A4</td>
<td>Lee, 1983; Tsuchiya, 2010</td>
<td>100-200 mg; 10 nmol/L</td>
<td>Tablet, IM, Oral Solution</td>
</tr>
<tr>
<td>Loxapine</td>
<td>1A2, 2D6, 3A4</td>
<td>Gold, 1972</td>
<td>15-30 mg</td>
<td>Tablet</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>1A2, 2D6, 3A4</td>
<td>Cooper, 1980</td>
<td>4-8 mg</td>
<td>Tablet</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>1A2, 2D6, 3A4</td>
<td>Cooper, 1980</td>
<td>1-50 mg</td>
<td>Tablet</td>
</tr>
</tbody>
</table>

FGA Pharmacokinetics (cont.)

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"Atypical" or "Second-Generation" Antipsychotics (SGAs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Chemical Class</th>
<th>Dosage Forms</th>
</tr>
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<tbody>
<tr>
<td>Risperidone</td>
<td>Risperdal, Risperdal M-Tab, Risperdal Consta</td>
<td>Benzisoxazole</td>
<td>Tablet, IM, Oral Solution</td>
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<tr>
<td>Olanzapine</td>
<td>Zyprexa, Zyplar, Zypral XR</td>
<td>Thienobenzodiazepine</td>
<td>Tablet, IM</td>
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<tr>
<td>Quetiapine</td>
<td>Seroquel IR, Seroquel XR</td>
<td>Dibenzothiazepine</td>
<td>Tablet</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Zeldox</td>
<td>Benzothiazolpyrazepane</td>
<td>Tablet</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Solian</td>
<td>Benzamid</td>
<td>Tablet</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Saphris</td>
<td>Dibenzoxepinopyridine</td>
<td>Tablet</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Latuda</td>
<td>Benzisothiazol</td>
<td>Tablet</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Clozaril</td>
<td>Dibenzodiazepine</td>
<td>Tablet, IM</td>
</tr>
</tbody>
</table>
Stahl's Essential Psychopharmacology Fig 10.14

Stahl, 2008

What Makes an Antipsychotic Atypical?

Adding 5HT2A Antagonist / Inverse Agonist Actions

Stahl's Essential Psychopharmacology Fig 10.45

Stahl, 2008

What Makes an Antipsychotic Atypical?

D2 Partial Agonist Actions (DPA)

Stahl, 2008

Canadian Institute for Health Information -2015

Care for Children and Youth With Mental Disorders

Report May 2015

“Third-Generation” Antipsychotics

<table>
<thead>
<tr>
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<th>Trade Name</th>
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<tr>
<td>Brexpiprazole</td>
<td>Rexulti</td>
<td></td>
<td>Tablet, IM</td>
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</tbody>
</table>

Stahl, 2008


<table>
<thead>
<tr>
<th>Year</th>
<th>Antipsychotics</th>
<th>Mood and Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007–2008</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>2008–2009</td>
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<td>29</td>
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<tr>
<td>2009–2010</td>
<td>27</td>
<td>29</td>
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<tr>
<td>2010–2011</td>
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<td>29</td>
</tr>
<tr>
<td>2011–2012</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>2012–2013</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>2013–2014</td>
<td>27</td>
<td>29</td>
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</tbody>
</table>

Population estimates: Statistics Canada, Demography Division.


Includes claims data for Manitoba, Saskatchewan and British Columbia (see the Technical Notes).

Rate is per 100,000.

MAOI: Monoamine oxidase inhibitor.

SSRI: Selective serotonin reuptake inhibitor.

Notes


<table>
<thead>
<tr>
<th>Year</th>
<th>Antipsychotics</th>
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</tr>
</thead>
<tbody>
<tr>
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</tbody>
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Population estimates: Statistics Canada, Demography Division.


Includes claims data for Manitoba, Saskatchewan and British Columbia (see the Technical Notes).

Rate is per 100,000.

MAOI: Monoamine oxidase inhibitor.

SSRI: Selective serotonin reuptake inhibitor.

Notes
Pharmacodynamics

- The mechanism of action of SGAs remains unclear, and each SGA has a different receptor binding profile
- In general, however, SGAs possess a low affinity for dopamine D2 receptors compared with the FGAs, and a high affinity for serotonin receptors, especially serotonin 5-HT2A

Pharmacokinetics

- The PK of SGAs have not been well characterized in children and adolescents, but a small number of pediatric PK studies have been conducted (Pichini et al., 2009)
- Oral SGAs are:
  - Readily absorbed from the GI tract
  - Highly lipophilic
  - Highly protein bound
  - Metabolized in the liver by CYP450 enzymes
Highlights

• Aggression, not psychosis most common target symptom for SGAs
• Evidence supports use of clozapine for treatment refractory schizophrenia
• Risperidone has the most amount of evidence for use in children and adolescents

Recommendations:

1. Prior to the initiation of and during treatment with an AAA, the general guidelines that pertain to the prescription of psychotropic medications should be followed [CS].
2. When selecting any AAA for use in a child or adolescent, the clinician should follow the most current available evidence in the scientific literature [CS].
3. Due to the specific risks associated with the use of AAAs, additional factors to address, prior to the initiation of treatment with the AAAs, include obtaining a personal and family history of diabetes and hyperlipidemia, seizures and cardiac abnormalities, as well as any family history of previous response or adverse events associated with AAAs [CS].

4. Dosing of the AAAs should follow the “start low and go slow” approach and seek to find the lowest effective dose, recognizing that dosing may differ based on the targeted symptoms and patient diagnosis [CG].

5. Target dosing should be supported by the current literature and will vary depending on the condition being treated [CG].

6. If side effects do occur, a trial at a lower dose should be considered; however, certain side effects may preclude further treatment with the specific AAA [CG].

7. The use of multiple psychotropic medications in refractory patients may, at times, be necessary but has not been studied rigorously and clinicians should proceed with caution [OP].

8. The simultaneous use of multiple AAAs has not been studied rigorously and generally should be avoided [NE].

9. After the failure of one AAA the selection of an alternative medication may include consideration of another AAA and/or a medication from a different class of drugs [OP].

10. The acute and long-term safety of these medications in children and adolescents has not been fully evaluated and therefore careful and frequent monitoring of side effects should be performed [CG].

11. BMI should be obtained at baseline and monitored at regular intervals throughout treatment with an AAA [CS].

12. Careful attention should be given to the increased risk of developing diabetes with the use of AAA, and blood glucose levels and other parameters should be obtained at baseline and monitored at regular intervals [CS].

13. In those patients with significant weight changes and/or a family history indicating high risk, lipid profiles should be obtained at baseline and monitored at regular intervals [CG].

14. Measurements of movement disorders utilizing structured measures, such as the Abnormal Involuntary Movement Scale, should be done at baseline and at regular intervals during treatment and during tapering of the AAA [CS].
15. Due to limited data surrounding the impact of AAAs on the cardiovascular system, regular monitoring of heart rate, blood pressure and EKG changes should be performed [CG].
16. Although there is a relationship between AAA use and elevations of prolactin, the current state of evidence does not support the need for routine monitoring of prolactin levels in asymptomatic youths [OP].

17. Due to drug-specific risks, additional monitoring should be considered for specific AAAs [CG].
18. The limited long-term safety and efficacy data warrants careful consideration, before the initiation of medication, of the planned duration of the medication trial [CG].
19. Abrupt discontinuation of a medication is not recommended [CS].
Efficacy: Schizophrenia

Childhood Schizophrenia: Background

• Childhood schizophrenia used to be clustered with other syndromes (including autism) as part of a broad construct of “childhood psychoses”

• “Childhood psychoses” were defined by developmental delays in language, perception, and motor skills

• Delusions and hallucinations were not required criteria

Schizophrenia (DSM 5)

• A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
  • 1. Delusions.
  • 2. Hallucinations.
  • 3. Disorganized speech (eg, frequent derailment or incoherence)
  • 4. Grossly disorganized or catatonic behavior.
  • 5. Negative symptoms (ie, diminished emotional expression or avolition).

Childhood Schizophrenia: Definitions

• “Childhood onset schizophrenia” (COS) or “very early onset schizophrenia” (VEOS):
  – Onset of psychotic symptoms before age 13
  – Considered “quite rare” (at most 1% of individuals with schizophrenia)
  – Generally has an insidious onset

• “Early onset schizophrenia” (EOS):
  – Onset of psychotic symptoms before age 18
  – Rate of illness onset sharply during adolescence:
    20-40% of patients with schizophrenia have their first psychotic symptoms before age 20
  – Onset may be acute or insidious
23 recommendations:
- First Episode Psychosis
- Early Post Acute Period
- Subsequent Acute Episodes of Psychosis or Schizophrenia
- Hospital Care
- Management of Acute Aggression or Agitation
- Promoting Recovery and Providing Possible Future Care in Primary Care
- Interventions for Children and Young People Whose Illness Has Not Responded Adequately to Treatment


#3 Antipsychotic medication should be offered once diagnosis is confirmed


#4 Choosing an antipsychotic:
- Lack of evidence for differences in
  - Efficacy
  - Clinical superiority (except clozapine)
  - Generation (1st, 2nd, 3rd)
  - Mode of administration


#4 Choosing an antipsychotic:
Consider the following possible side effects when making a choice:
- Metabolic (weight gain, diabetes)
- Extrapyramidal (akathisia, dyskensia, dystonia)
- Cardiovascular (QTc prolongation)
- Hormonal (prolactin increase)
- Other (subjective experience, drug interactions)


#10 Combined antipsychotics not recommended, except briefly for medication changes

#13 Probably best to stay on medication 1-2 years to avoid risk of relapse

#23 Treatment Refractory Schizophrenia
- Adequate doses of 2 different antipsychotics for 6-8 weeks each
- Offer clozapine


• AACAP: Practice Parameter for the Assessment and Treatment of Children and Adolescents with Schizophrenia
  • www.jaacap.org
  • 52(9), p 976, September 2013
  • 10 Recommendations
Recommendation #4

- Antipsychotic medication is the primary treatment for schizophrenia spectrum disorders in children and adolescents

Recommendation #5

- Ongoing medication therapy should be provided to most youth with schizophrenia to improve functioning and prevent relapse
  - Maintain regular physician contact to monitor symptom course, side effects, medication adherence
  - After a prolonged remission, a small number of individuals may be able to discontinue antipsychotics without reemergence of psychotic symptoms
  - Periodic monitoring still recommended

Recommendation #6

- Some youth with schizophrenia spectrum disorders may benefit from adjunctive medication treatments to address side effects of the antipsychotic agent or to alleviate associated symptomatology (e.g., agitation, mood instability, depression, explosive outbursts).

Recommendation #8

- Baseline and follow-up monitoring of symptoms, side effects, and laboratory tests should be performed as indicated
  - AACAP - Practice Parameter for Use of Atypical Antipsychotic Medication in Children and Adolescents
  - CAMESA – Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (camesaguideline.org)

- Baseline assess the patient’s and/or family history of obesity, diabetes, cardiovascular disease, dyslipidemia, hypertension
- Assess and document the patient’s body mass index at baseline, at 4, 8, and 12 weeks, and at least every 3 months thereafter, or more often as indicated
- Assess and document the patient’s fasting glucose, fasting lipid profile, and blood pressure at baseline and after 3 months of treatment. If the results are normal after 3 months of treatment, glucose and blood pressure monitoring is recommended annually. If the lipid profile is normal after 3 months, follow-up monitoring is recommended at least every 5 years.
Kumar et al., 2013. Atypical antipsychotics for psychosis in adolescents.

13 studies included in Analysis

Kumar 1996

Kumar 2008

Sikich 2004

Sikich 2008

Swadi 2010

Xiong 2004
Xiong Y. Comparison study of childhood schizophrenia treated with risperidone and chlorpromazine. Guizhou Medical Journal 2004;28(8):697–8

Xiong 2007

Kumar et al., Cochrane Database of Systemic Reviews. 2013; 10.

Authors Main Findings:

"No convincing evidence suggests that atypical antipsychotic medications are superior to typical medications for the treatment of adolescents with psychosis. However, atypical antipsychotic medications may be more acceptable to young people because fewer symptomatic adverse effects are seen in the short term.

Little evidence is available to support the superiority of one atypical antipsychotic medication over another, but side effect profiles are different for different medications.

Treatment with clozapine, risperidone and chlorpromazine is often associated with weight gain. Aripiprazole is not associated with increased prolactin or with dyslipidaemia.

Adolescents may respond better to standard-dose as opposed to lower-dose risperidone, but for aripiprazole and ziprasidone, lower doses may be equally effective.

Future trials should ensure uniform ways of reporting."
Schizophrenia and Related Psychosis:

“Compared with placebo, SGAs as a class probably increase response rates, decrease slightly (not clinically significant for many patients) negative and positive symptoms, and improve slightly global impressions of improvement, severity, and functioning. Many outcomes for individual drug comparisons were of low or insufficient strength of evidence.”

• Strength of evidence:
  High = “will”
  Moderate = “probably/likely”
  Low = “may/appears to”
  Insufficient = “not known”

• Magnitude of effects:
  Clinically important = “increase/improve/decrease/worsen”
  Small = “slightly increase/improve/decrease/worsen”

TEOSS Study

• Sikich et al., 2008:
  “Treatment of Early-Onset Schizophrenia Spectrum Disorders”
  Federally funded, 8-week, double-blind RCT of RISP vs. OLZ vs. molindone (MOL) in 119 youth (8-19 years old) with EOSS (schizophrenia or schizoaffective disorder) and moderate to severe psychotic symptoms
**TEOSS: Methods**

- **Antipsychotic doses:**
  - RISP: 0.5-6 mg/day (mean=2.8 mg)
  - OLZ: 2.5-20 mg/day (mean=11.4 mg)
  - MOL: 10-140 mg/day (mean=59.9 mg), plus benztropine 1 mg/day

- **Primary outcome:**
  - Responder status based on the CGI and the PANSS and the ability to tolerate 8 weeks of treatment

- **Secondary outcomes:**
  - PANSS (positive/negative subscale & total scores); BPRS-Children; Child and Adolescent Functional Assessment Scale

**TEOSS: Efficacy Results**

- **Response rates:**
  - RISP (46%) = OLZ (34%) = MOL (50%)

- **No group differences on any secondary outcome measures**

- **No group differences in the time course of treatment discontinuation**

**TEOSS: Adverse Event Results**

- Overall, frequent adverse events included sedation, irritability, and anxiety

- Overall, few and generally mild EPS were observed

- **Group differences in adverse events:**
  - RISP: significantly more constipation and ↑ prolactin
  - OLZ: significantly greater ↑ in appetite/weight, lipids, AST/ALT, and insulin
  - MOL: significantly more akathisia

- **QTC:**
  - Significantly ↑ with OLZ (+11.2 msec), but not with RISP (+0.5 msec) or MOL (+1.2 msec)

- **TEOSS: Weight Gain**

  - Changes in weight and BMI differed significantly among all 3 groups:
    - RISP: +3.7 kg; +6.8 percentile in BMI
    - OLZ: +6.1 kg; +10.8 percentile in BMI
    - MOL: no weight change; -2.3 percentile in BMI

  - Random assignment to OLZ was stopped by NIMH based on interim data that showed greater ↑ in weight with OLZ compared to RISP and MOL, without evidence of greater efficacy

**TEOSS: Conclusions**

- "RISP and OLZ did not demonstrate superior efficacy over MOL for treating early-onset schizophrenia and schizoaffective disorder"

- "Adverse effects were frequent but differed among medications"

- "The results question the nearly exclusive use of SGAs to treat early-onset schizophrenia and schizoaffective disorder"

- "The safety findings related to weight gain and metabolic problems raise important public health concerns, given the widespread use of SGAs in youth for nonpsychotic disorders"

---

**Efficacy: Bipolar Disorder**

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Bipolar Disorder

“Compared with placebo, SGAs probably decrease mania, decrease depression symptoms slightly, and improve symptom severity and global functioning to a small extent. SGAs (and aripiprazole alone) probably increase response and remission rates versus placebo for manic/mixed phases. Quetiapine likely makes little or no difference in depression.”

Pillay et al., AHRQ Comp Effect Review # 184. March 2017

Tarr G et al. 2011

- Systematic review and meta-analysis
- Comparative efficacy and acceptability of mood stabilizer and second generation antipsychotic monotherapy for acute mania.
- 9 RCT studies, 1631 patients, comparing MS with SGA

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**Treatment of Early Age Mania (TEAM) Study**

- Geller B et al. 2012. NIMH funded study
- Question: Which medication to give first to antimanic medication-naïve patients?
- 279 clients age 6-15 with DSM-IV mania/mixed episode of at least 4 consecutive weeks
- 5 sites
- Co-morbid ADHD, ODD, and CD allowed
- Stable maintenance stimulant therapy allowed

**TEAM Study (cont.)**

- AEs: Increased weight, BMI, prolactin with RIS vs. LI and DVP (p<.001)
- Significantly higher discontinuation rates in LI arm
- "RIS is significantly more efficacious than LI or DVP in the initial management of mania in children but it is associated with adverse effects such as weight gain and hyperprolactinemia that raise concern for long-term treatment"

**PBD DB RC Trials: Summary 2011**

- RISP, OLZ, ARI, and QUE each superior to PBO for mania in youth 10-17 years old
- SGAs produce faster improvement than MS and may be better tolerated
- SGAs becoming first line for treatment of mania
- For studies with two dosage arms, low dose was equally effective as higher dose
- Strong need for maintenance trials

**Efficacy: Autism Spectrum Disorder**


Autism Spectrum Disorders

“Compared with placebo, SGAs as a class probably decrease irritability, and decrease slightly lethargy/social withdrawal, stereotypy, and inappropriate speech; they likely increase response rates and (slightly) clinical severity. It is likely that aripiprazole and risperidone decrease irritability.”

Pillay et al., AHRQ Comp Effect Review # 184. March 2017

Compared with placebo, SGAs as a class probably decrease conduct problems and aggression. Risperidone alone likely decreases hyperactivity in children with a primary diagnosis of conduct disorders or with ADHD but not responding to stimulants.

Pillay et al., AHRQ Comp Effect Review # 184. March 2017

Efficacy: ADHD, Disruptive, Impulse-Control and Conduct Disorders


11 RCTs for antipsychotics included in analysis

Relevant Main findings:
- There is moderate-quality evidence that risperidone has a moderate-to-large effect on conduct problems and aggression in youth with subaverage IQ and ODD, CD, or DBD-NOS, with and without ADHD.
- There is high-quality evidence that risperidone has a moderate effect on disruptive and aggressive behaviour in youth with average IQ and ODD or CD, with and without ADHD.
Low/Insufficient Strength of Evidence

- Tic Disorders
- OCD
- Depression
- Eating Disorders
- Behavioral Issues

Pillay et al., AHRQ Comp Effect Review # 184. March 2017

Extrapyramidal Side Effects

- Acute and tardive dystonias
  - Symptoms include shuffling gait, rigidity, cogwheeling, bradykinesia, tremor, and “rabbit syndrome” (perioral tremor)
- Akathisia
  - The risk of TD and WD with FGAs may be higher in children than in adults

FGA Adverse Effects

<table>
<thead>
<tr>
<th>Allergic</th>
<th>Acute</th>
<th>Urticaria, photosensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic</td>
<td>Orthostatic hypotension, sexual dysfunction</td>
<td></td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Dry mouth, dry eyes, nasal congestion, blurred vision, urinary retention, constipation</td>
<td></td>
</tr>
<tr>
<td>CVS</td>
<td>Sinus tachycardia, ↑ QTc &amp; torsades de pointe (especially with pimozide), sudden death</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>EPS, dyskinesias (tardive and withdrawal), sedation, ↓ seizure threshold, cognitive dulling, NMS</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>↑ prolactin, hyperglycemia, hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Blood dyscrasias, e.g., mild and transient leukopenia (agranulocytosis is rare)</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>↓ LFTs, jaundice</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>↓ appetite, weight gain, hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Cataracts and pigmented retinopathy, especially with phenothiazines</td>
<td></td>
</tr>
</tbody>
</table>

Anticholinergic Toxicity

- "Red as a beet, dry as a bone, blind as a bat, mad as a hatter, and hot as a hare":
  - Refers to the symptoms of flushing, dry skin and mucous membranes, mydriasis with loss of accommodation, altered mental status, and fever
- Additional peripheral manifestations include:
  - ↑ HR, ↑ BP, ↓ bowel sounds, functional ileus, urinary retention, tremulousness, and myoclonic jerking
- Additional CNS manifestations include:
  - Ataxia, confusion, delirium, hallucinations, seizures, coma, respiratory failure, and CV collapse

Treatment of EPS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tremor</th>
<th>Rigidity</th>
<th>Dystonia</th>
<th>Akathisia</th>
<th>Akinesia, rigidity</th>
<th>↓ facial expression</th>
<th>↓ seizure threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benztropine</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Biperiden</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Propranolol</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Procyclidine</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

- not established; + some effect (20% response); ++ mod effect (20-50% response); +++ good effect (>50% response)
Neuroleptic Malignant Syndrome

• Associated with use of “neuroleptics,” including SGAs as well as FGAs
• Defined by fever, autonomic dysfunction, muscular rigidity, and mental status changes
• Lab abnormalities may include ↑ CK, leukocytosis, and ↓ serum iron
• Clinically indistinguishable from catatonia
• Risk of NMS is estimated to be 0.05-2% among patients treated with antipsychotics, and about twice as high in males as in females
• It has been suggested that high-potency antipsychotics and rapid dose escalation ↑ the risk of NMS
• Mortality rate of full-blown NMS is ~10%

Contraindications

• Hypersensitivity to the drug (cross-sensitivity between FGAs in the same chemical class may occur)
• Severe CNS depression from any cause
• History of spastic disorders or Parkinson’s disease
• History of seizures
• Lesions of the basal ganglia or other subcortical brain damage
• Circulatory collapse
• Bone marrow depression

SGA Adverse Effects

Weight Gain Trajectories with OLZ, CLZ & RISP

Weight Gain Trajectories with OLZ, CLZ & RISP

Reference: Correll et al., 2006

Pillay et al., AHRQ Comp Effect Review # 184. March 2017

Reference: Fleischhaker et al., 2008

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Risk of Tardive Dyskinesia

- A recent review & meta-analysis suggests that the risk of TD with SGAs in children and adolescents is relatively low (Correll & Kane, 2007):
  - Among 783 youth in 10 studies, 3 new cases of TD emerged during long-term treatment with SGAs for up to 3 years (2 with Risp, 1 with Que)
  - TD rate with SGAs: crude=0.38%, annualized=0.42%
  - In the 2 cases with information, the TD resolved within weeks after antipsychotic discontinuation
- Limitations include:
  - Small sample size of studies with SGAs other than Risp
  - Use of relatively low doses

Selected Drug Interactions for Each SGA

- Risperidone:
  - Carbamazepine ↓ RISP levels
  - RISP ↑ VPA levels

- Olanzapine:
  - Carbamazepine ↓ OLZ levels
  - Diazepam and ethanol may potentiate the orthostatic hypotension observed with OLZ

- Quetiapine:
  - Carbamazepine, phenytoin, barbiturates, rifampin, and glucocorticoids all ↓ QUE levels
  - VPA ↑ QUE levels
  - QUE ↓ lorazepam levels

Drug Interactions: All SGAs

- CYP450 interactions (see slide 40)
- Cigarette smoking may ↓ SGA levels through induction of CYP450 enzymes (especially 1A2)
- Given the primary CNS effects of SGAs, exercise caution when combining them with other centrally acting drugs or alcohol
- SGAs may potentiate the hypotensive effects of antihypertensive agents
- SGAs may antagonize the effects of levodopa and dopamine agonists

Contraindications

- All SGAs: hypersensitivity to the agent
- Ziprasidone:
  - History of QT prolongation (including congenital long QT syndrome)
  - Recent acute myocardial infarction
  - Uncompensated heart failure
  - Concomitant medication that prolongs the QT interval
Selected Drug Interactions for Each SGA (cont.)

- Ziprasidone:
  - Carbamazepine ↓ ZIP levels
  - As ZIP and Li are each associated with cardiac conduction changes, the combination may further ↑ the risk of arrhythmias

- Clozapine:
  - Caution with benzodiazepines (possibly ↑ risk of CV collapse and cardiac/respiratory arrest)
  - CLZ may potentiate the anticholinergic effects of atropine-type drugs
  - Administration of epinephrine should be avoided in the treatment of CLZ-induced hypotension because of a possible reverse epinephrine effect

CAMESA
- Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children
- Camesaguideline.org

SGA Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose (mg/day)</th>
<th>Usual Dose Range (mg/day)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>2 mg</td>
<td>5-30 mg</td>
<td>Only SGA approved by Health Canada for any indication in youth</td>
</tr>
<tr>
<td>Clozapine</td>
<td>12.5 mg</td>
<td>50-900 mg</td>
<td>WBC monitoring required</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1.25-5 mg</td>
<td>5-20 mg</td>
<td>Given its adverse effect profile, other SGAs should be tried first</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>3 mg</td>
<td>3-12 mg</td>
<td>Paliperidone (9-hydroxy-risperidone) is the major active metabolite of risperidone</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>12.5-50 mg</td>
<td>150-800 mg</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.125-0.5 mg</td>
<td>0.25-6 mg</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>20-40 mg</td>
<td>40-160 mg</td>
<td></td>
</tr>
</tbody>
</table>

Choosing an Atypical

- Consider the evidence that supports the use of the different SGAs for the pediatric indication in question
- RIS is the best studied SGA in children and adolescents
- Consider the side effect profiles of the different SGAs
- Consider the patient’s individual characteristics, as certain side effects may be more problematic for some patients than for others (e.g., weight gain)

CAMESA
- Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children
- Camesaguideline.org
Dosing: General Principles

- SGA doses for treating aggression, tics, and OCD symptoms (augmenting SSRIs) are generally lower than for treating psychosis or mania
- When treating EOS/VEOS, be patient: an adequate SGA trial takes ≥6 weeks at the maximum tolerated dose
- Careful, systematic, adequate, and sequential trials of single agents is generally preferable to treatment with multiple agents simultaneously

Kane et al., 1988

- Definition of treatment-resistance:
  - 3 periods of treatment in last 5 years with agents from at least 2 different chemical classes at doses > 1000mg CPZ for six weeks without significant symptomatic relief
  - No period of good functioning within the preceding 5 years
- 268 patients who did not improve DB randomized to clozapine (up to 900 mg/d) or CPZ (up to 1800 mg/d) for six weeks
- Results: 30% of clozapine patients and 4% of CPZ patients classified as "responders"

Kumra et al., 1996

- 6 week DB randomized trial of clozapine and HAL in 21 youth (mean age 14) with schizophrenia nonresponsive to typical neuroleptics
- Clozapine “strikingly superior” on all measures of psychosis, including positive and negative symptoms
- Side effects: neutropenia and seizures

Clozapine

- Introduced in Europe in 1971
- Withdrawn by manufacturer in 1975 secondary to cases of agranulocytosis
- Reintroduced in US in 1989 for treatment-resistant schizophrenia
- The first atypical antipsychotic

CLZ vs. OLZ

- In double-blind RCTs, CLZ was found to be more efficacious than OLZ (Shaw et al., 2006; Kumra et al., 2008) for both positive and negative symptoms in treatment-resistant EOS/VEOS
- However, CLZ was associated with considerable adverse effects, especially:
  - Neutropenia, seizures and EEG abnormalities, ↑ appetite and weight gain, metabolic abnormalities, hypertension and tachycardia, hypersalivation, and enuresis
Agid et al., 2007

- CAMH First Episode Treatment Algorithm: Patients receive 2 trials of atypical antipsychotics followed by clozapine as early as 25 weeks
- Case series: 123 patients; 93 (76%) responded to first antipsychotic; 7 (23%) of remaining 30 patients responded to second trial
- 13 of remaining 23 agreed to clozapine; 9 refused clozapine and remained on same drug
- 10 (73%) of 13: robust response to clozapine (BPRS, CGI) compared to 9 who remained on same drug

Extra Monitoring: Clozapine

- Because of the risk of granulocytopenia and agranulocytosis:
  - Must have normal WBC+diff prior to starting CLZ
  - Must check WBC+diff at least weekly for the first 26 weeks of CLZ treatment, and at least once every 2 weeks thereafter
  - Must check WBC+diff at least weekly for 4 weeks after stopping CLZ
  - See CPS for detailed guidelines about what to do if WBC or ANC ↓, or if patient develops symptoms that might suggest infection

Contraindications

- Clozapine:
  - Myeloproliferative disorders
  - Uncontrolled epilepsy
  - Paralytic ileus
  - History of clozapine-induced agranulocytosis or severe granulocytopenia
  - Severe CNS depression or comatose states from any cause
  - Concomitant medication that can cause agranulocytosis or otherwise suppress bone marrow function (e.g., carbamazepine)

Clozapine: Conclusions

- Most effective medication for treatment-refractory cases of EOS for short-term and maintenance therapy
- Significant side effect profile: neutropenia, seizure risk, weight gain and metabolic abnormalities
- 3rd-line medication after 2 failed trials of atypical antipsychotics

Extra Monitoring: Clozapine

- Because of the risk of tachycardia and hypotension:
  - Monitor VS very closely, particularly with dose changes
- Because of the risk of seizures:
  - Consider baseline and on-drug EEG
- Because of 30 post-marketing reports of myocarditis, including 17 fatalities:
  - Consider the possibility of myocarditis if the patient develops unexplained fatigue, dyspnea, tachypnea, fever, chest pain, or EKG abnormalities

Suggested Dosing: Clozapine

- Start 12.5 mg/day
- Titrate every other day by 12.5-25 mg increments
- Initial target dose: 300-450 mg/day
- Subsequent dose ↑ of up to 100 mg may be made once or twice weekly to a maximum of 900 mg/day
- Dosing is BID or QHS
- Cautious titration and divided dosing are necessary to minimize the risks of hypotension, seizure, and sedation
### FGA Approved Pediatric Uses

<table>
<thead>
<tr>
<th></th>
<th>FDA (U.S.)</th>
<th>Health Canada</th>
</tr>
</thead>
</table>
| **Chlorpromazine**  | • Severe behaviour problems (≥6 months)  
                      • Psychosis (≥6 months)  
                      Possible indications:  
                      • Severe ADHD  
                      • Severe agitation or explosive aggression in PDD/autism | • Psychotic disorders  
                      • Prevention and treatment of nausea & vomiting  
                      • Adjunct in the treatment of tetanus  
                      • Intractable hiccups  
                      • Nausea, vomiting and restlessness/anxiety associated with attacks of acute intermittent porphyria  
                      • *Children with acute illnesses such as viral infections, CNS infections or dehydration may be more susceptible to dystonic reactions to phenothiazines.* |
| **Haloperidol**     | • Psychotic disorders (≥3 years)  
                      • Tourette’s syndrome (≥3 years)  
                      • Explosive aggression (≥3 years) after failure of psychosocial interventions | • Psychotic disorders (e.g., schizophrenia), acute agitation, delirium, acute mania, and Tourette’s syndrome; also used as antiemetic and in the treatment of intractable hiccups  
                      • *Safety and efficacy have not been established for children under 3 years of age* |
| **Trifluoperazine** | Psychotic disorders (≥6 years)  
                      • Psychotic disorders including schizophrenia  
                      • Prevention or treatment of nausea & vomiting  
                      • *Children may be more susceptible to extrapyramidal reactions than adults, particularly if they have acute infectious illnesses or are dehydrated. Use lower doses in children and monitor therapy closely.* |
### FGA: Approved Pediatric Uses (cont.)

<table>
<thead>
<tr>
<th></th>
<th>FDA (U.S.)</th>
<th>Health Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pimozide</strong></td>
<td>• Severe Tourette's syndrome in patients (&gt;12 years) who have not responded to standard therapy</td>
<td>• Not approved for use in the pediatric age group</td>
</tr>
<tr>
<td><strong>Fluphenazine</strong></td>
<td>• Psychotic disorders (≥ 12 years)</td>
<td>• Psychotic disorders (≥12 years)</td>
</tr>
<tr>
<td><strong>Molindone</strong></td>
<td>• No longer available</td>
<td>• Not available in Canada</td>
</tr>
</tbody>
</table>
| **Loxapine**         | • Safety and effectiveness of Loxapine in pediatric patients have not been established  
                      | • Not approved for use in children (<16 years)                           | • Not recommended for use in children (<16 years)                  
                      |                                                                             | • Children are more prone to adverse effects including EPS, TD (up to 51%), sedation, weight gain, hyperprolactinemia |
| **Thioridazine**     | Thioridazine was withdrawn from both the U.S. and Canadian markets in 2005 because of the risk of cardiac arrhythmias. Previously, it was approved in the U.S. for children with schizophrenia who are unresponsive to other agents; and in Canada for children with anxiety, tension, difficulties with concentration, sleep disturbances, and behavioral disorders such as agitation, hyperactivity, or aggressiveness. |
# Relative Potency of Selected FGAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equivalent oral dose (mg)</th>
<th>Potency</th>
<th>Dose range (mg)</th>
<th>Sedation</th>
<th>Autonomic (Anti-α, anti-Ach)</th>
<th>EPS</th>
<th>Approved age for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>100</td>
<td>Low</td>
<td>10-1000</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>≥6 months</td>
</tr>
<tr>
<td>Loxapine</td>
<td>15</td>
<td>Medium</td>
<td>5-100</td>
<td>++</td>
<td>+/++</td>
<td>+++/+++</td>
<td>≥16 years</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>10</td>
<td>Medium</td>
<td>2-64</td>
<td>++</td>
<td>+</td>
<td>+++/+++</td>
<td>≥12 years</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>2</td>
<td>High</td>
<td>0.25-10</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>≥16 years</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2</td>
<td>High</td>
<td>0.25-15</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>≥3 years</td>
</tr>
<tr>
<td>Pimozide</td>
<td>1-2</td>
<td>High</td>
<td>0.25-10</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>≥12 years</td>
</tr>
</tbody>
</table>
# Receptor Activity & Clinical Effects

## TABLE 2
Adverse and Therapeutic Effects of Antipsychotic Receptor Occupancy and Withdrawal

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Occupancy</th>
<th>Rebound/Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine $H_1$</td>
<td>Anxiolytic, sedation, weight gain, anti-EPs/akathisia</td>
<td>Agitation, insomnia, anxiety, EPs</td>
</tr>
<tr>
<td>$\alpha_1$-Adrenergic</td>
<td>Postural hypotension, dizziness, syncope</td>
<td>Tachycardia, hypertension</td>
</tr>
<tr>
<td>Muscarinic M$_1$ (central)</td>
<td>Memory, cognition, anti-EPs/akathisia</td>
<td>Agitation, confusion, anxiety, insomnia</td>
</tr>
<tr>
<td>Muscarinic M$_{2-4}$ (peripheral)</td>
<td>Dry mouth, constipation, urinary retention</td>
<td>Diarrhea, diaphoresis</td>
</tr>
<tr>
<td>Dopamine D$_2$</td>
<td>Antipsychotic, antimanic, antiaggressive, EPSs/akathisia, tardive dyskinesia, prolactin increase, sexual or reproductive system dysfunction</td>
<td>Psychosis, mania, agitation, akathisia, withdrawal dyskinesia</td>
</tr>
<tr>
<td>Serotonin 5-HT$_{1A}$ (partial agonism)</td>
<td>Anxiolytic, antidepressant, anti-EPs/akathisia (?)</td>
<td>EPs/akathisia</td>
</tr>
<tr>
<td>Serotonin 5-HT$_{2A}$</td>
<td>Anti-EPs/akathisia</td>
<td>EPs/akathisia</td>
</tr>
<tr>
<td>Serotonin 5-HT$_{2c}$</td>
<td>Increased appetite/weight (?)</td>
<td>Decreased appetite (?)</td>
</tr>
</tbody>
</table>

*Note: EPs = extrapyramidal symptoms.*

Reference: Correll, 2008

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<table>
<thead>
<tr>
<th></th>
<th>Bioavailability</th>
<th>Protein Binding</th>
<th>T½ (h)</th>
<th>T_max (h) with oral dosing</th>
<th>D&lt;sub&gt;2&lt;/sub&gt; Occupancy (with corresponding dose &amp; plasma level)</th>
<th>5-HT&lt;sub&gt;2A&lt;/sub&gt; Occupancy (with corresponding dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>25-65%</td>
<td>95-99%</td>
<td>16-30</td>
<td>?</td>
<td>78-80% (100-200 mg; 10 nmol/L)</td>
<td>?</td>
</tr>
<tr>
<td>Loxapine</td>
<td>33%</td>
<td>?</td>
<td>8-30</td>
<td>1-3</td>
<td>60-80% (15-30 mg)</td>
<td>58-75% (10-30 mg) 75-90% (&gt;30 mg)</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>25%</td>
<td>91-92%</td>
<td>9-21</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>1-50%</td>
<td>90-99%</td>
<td>13-58</td>
<td>&lt;1</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Haldol</td>
<td>40-80%</td>
<td>92%</td>
<td>12-36</td>
<td>2-6</td>
<td>75-89% (4-6 mg; 6-13 nmol/L)</td>
<td>?</td>
</tr>
<tr>
<td>Pimozide</td>
<td>15-50%</td>
<td>97%</td>
<td>29-55</td>
<td>?</td>
<td>77-79% (4-8 mg)</td>
<td>?</td>
</tr>
</tbody>
</table>
# FGAs and CYP450

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Metabolized By:</th>
<th>Inhibits:</th>
<th>Examples of Psychotropic Drugs That Interact</th>
</tr>
</thead>
</table>
| Chlorpromazine | 1A2 (+/-), **2D6**, 3A4 | 1A2, 2D6, 3A4 (+/-), 2C9 (+/-), 2C19, 2E1 | Fluoxetine (2D6)  
Paroxetine (2D6)  
Sertraline (3A4)  
Carbamazepine (3A4) |
| Loxapine      | 1A2, 2D6, 3A4   | —         | Benadryl (2D6)  
Propranolol (1A2, 2D6, 2C19)  
Zopiclone (1A2, 2C9, 3A4)  
Valproate (2A6, 2C9, 2C19) |
| Perphenazine  | 1A2, **2D6**, 3A4, 2C9, 2C19 | 1A2 (+/-), **2D6**, 3A4, 2C9, 2C19 | Quetiapine (3A4)  
Benztropine (2D6) |
<p>| Haloperidol   | 1A2 (+/-), <strong>2D6</strong>, (<strong>3A4</strong>) | <strong>2D6</strong>, 3A4 | |
| Pimozide      | 1A2 (+/-), <strong>3A4</strong> | <strong>2D6</strong>, 3A4 | |</p>
<table>
<thead>
<tr>
<th></th>
<th>FDA (U.S.)</th>
<th>Health Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risperidone</strong></td>
<td>• Schizophrenia</td>
<td>• Schizophrenia and related psychotic disorders</td>
</tr>
<tr>
<td></td>
<td>• Bipolar mania or mixed episodes (monotherapy</td>
<td>• Bipolar mania</td>
</tr>
<tr>
<td></td>
<td>or combined with Li or VPA)</td>
<td>• Symptomatic management of inappropriate behaviour in severe dementia</td>
</tr>
<tr>
<td></td>
<td>• Maintenance treatment in bipolar disorder</td>
<td>• None</td>
</tr>
<tr>
<td><strong>Olanzapine</strong></td>
<td>• Schizophrenia</td>
<td>• Schizophrenia</td>
</tr>
<tr>
<td></td>
<td>• Bipolar mania or mixed episodes (monotherapy</td>
<td>• Bipolar mania or mixed episodes (10-17 years)</td>
</tr>
<tr>
<td></td>
<td>or combined with Li or VPA)</td>
<td>• Bipolar mania or mixed episodes (10-17 years)</td>
</tr>
<tr>
<td></td>
<td>• Maintenance treatment in bipolar disorder</td>
<td>• Bipolar mania or mixed episodes (10-17 years)</td>
</tr>
<tr>
<td><strong>Quetiapine</strong></td>
<td>• Schizophrenia</td>
<td>• Schizophrenia</td>
</tr>
<tr>
<td></td>
<td>• Bipolar mania (monotherapy or combined with</td>
<td>• Schizophrenia</td>
</tr>
<tr>
<td></td>
<td>Li or VPA)</td>
<td>• Bipolar mania</td>
</tr>
<tr>
<td></td>
<td>• Bipolar depression</td>
<td>• Bipolar mania and related psychotic disorders</td>
</tr>
<tr>
<td></td>
<td>• Maintenance treatment of bipolar I disorder</td>
<td>• None</td>
</tr>
<tr>
<td></td>
<td>as adjunct to Li or VPA</td>
<td>• None</td>
</tr>
<tr>
<td></td>
<td>• Adjunct to antidepressants for acute treatment of MDD</td>
<td>• Schizophrenia</td>
</tr>
<tr>
<td><strong>Ziprasidone</strong></td>
<td>• Schizophrenia</td>
<td>• Schizophrenia</td>
</tr>
<tr>
<td></td>
<td>• Bipolar mania or mixed episodes (monotherapy</td>
<td>• Schizophrenia</td>
</tr>
<tr>
<td></td>
<td>or adjunct to Li or VPA)</td>
<td>• Bipolar mania</td>
</tr>
<tr>
<td></td>
<td>• Maintenance treatment in bipolar disorder</td>
<td>• Bipolar mania</td>
</tr>
<tr>
<td></td>
<td>• Adjunct to antidepressants for acute treatment of MDD</td>
<td>• Bipolar depression</td>
</tr>
<tr>
<td><strong>Aripiprazole</strong></td>
<td>• Schizophrenia</td>
<td>• Schizophrenia</td>
</tr>
<tr>
<td></td>
<td>• Bipolar mania or mixed episodes (monotherapy</td>
<td>• Schizophrenia</td>
</tr>
<tr>
<td></td>
<td>or adjunct to Li or VPA)</td>
<td>• Bipolar mania</td>
</tr>
<tr>
<td></td>
<td>• Maintenance treatment in bipolar disorder</td>
<td>• Bipolar mania and related psychotic disorders</td>
</tr>
<tr>
<td></td>
<td>• Adjunct to antidepressants for acute treatment of MDD</td>
<td>• None</td>
</tr>
<tr>
<td><strong>Lurasidone</strong></td>
<td>• Schizophrenia</td>
<td>• Schizophrenia</td>
</tr>
<tr>
<td></td>
<td>• Depressive Episodes of Bipolar I Disorder</td>
<td>• Schizophrenia</td>
</tr>
<tr>
<td><strong>Asenapine</strong></td>
<td>• Treatment-resistant schizophrenia</td>
<td>• Schizophrenia and Bipolar Disorder</td>
</tr>
<tr>
<td></td>
<td>• Reducing the risk of recurrent suicidal behaviour in schizophrenia or schizoaffective disorder</td>
<td>• None</td>
</tr>
<tr>
<td><strong>Clozapine</strong></td>
<td>• Treatment-resistant schizophrenia</td>
<td>• Treatment-resistant schizophrenia</td>
</tr>
<tr>
<td></td>
<td>• Reducing the risk of recurrent suicidal behaviour in schizophrenia or schizoaffective disorder</td>
<td>• None</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>$T_{\text{max}}$ (hrs)</th>
<th>Effect of Food on Absorption</th>
<th>$T_{\frac{1}{2}}$ (hrs)</th>
<th>CYP450 substrate</th>
<th>CYP450 inhibition</th>
<th>CYP450 induction</th>
</tr>
</thead>
</table>
| Risperidone    | A: 2   
               | C: 1  | None | A: 17  
               | C: 3 | 2D6, 3A4 | – | – |
| Olanzapine     | A: 5-8  
               | C: 5  | None | A: 33  
               | C: 37 | 1A2, 2D6 | – | – |
| Quetiapine     | A: 2*  
               | C: 1.5 | Mild ↑ in extent of absorption | A: 6-7  
               | C: 4 | 3A4 | – | – |
| Ziprasidone    | A: 6-8  
               | C: 5  | ↑ extent of absorption up to 2x | A: 6-10  
               | C: 3.5 | 3A4 | – | – |
| Aripiprazole   | A: 3-5  
               | C: ? | No effect on extent of absorption, but ↓ rate | A: 75-146  
               | C: ? | 2D6, 3A4 | – | – |
| Clozapine      | A: 2.5  
               | C: ? | None | A: 12  
               | C: ? | 1A2, 2D6, 3A4 | – | – |

*6 hours for extended-release quetiapine (Seroquel XR)

A=adult; C=child/adolescent

References: CPS & PDR (adult parameters); Pichini et al., 2009 (child/adolescent parameters)
<table>
<thead>
<tr>
<th>Category</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic</td>
<td>Urticaria, photosensitivity</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Orthostatic hypotension, sexual dysfunction</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Dry mouth, dry eyes, nasal congestion, blurred vision, urinary retention, constipation</td>
</tr>
<tr>
<td>CVS</td>
<td>Sinus tachycardia, ↑ QTc &amp; torsades de pointe (especially with pimozide), sudden death</td>
</tr>
<tr>
<td>CNS</td>
<td>EPS, dyskinesias (tardive and withdrawal), sedation, ↓ seizure threshold, cognitive dulling, NMS</td>
</tr>
<tr>
<td>Endocrine</td>
<td>↑ prolactin, hyperglycemia, hypoglycemia</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Blood dyscrasias, e.g., mild and transient leukopenia (agranulocytosis is rare)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>↑ LFTs, jaundice</td>
</tr>
<tr>
<td>Metabolic</td>
<td>↑ appetite, weight gain, hyperlipidemia</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Cataracts and pigmentary retinopathy, especially with phenothiazines</td>
</tr>
</tbody>
</table>
EPS: Time Course

A = Dystonic reactions
B = Akathisia
C = Akinesia, rigidity, ↓ facial expression
D = Tremors
E = Tardive and withdrawal dyskinesias
## Treatment of EPS

<table>
<thead>
<tr>
<th></th>
<th>Tremor</th>
<th>Rigidity</th>
<th>Dystonia</th>
<th>Akinesia</th>
<th>Akathisia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benztropine</strong></td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Biperiden</strong></td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Propranolol</strong></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Lorazepam</strong></td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Procyclidine</strong></td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

**ORAL:** 0.5-3 mg/dose; up to max of 6 mg/day  
**IM/IV:** 1-2 mg; may repeat once in adolescents

**ORAL:** 2-8 mg/day  
**ORAL:** 2-8 mg/kg or 10 mg tid; up to max of 60 mg/day  
**IM:** 0.025-0.05 mg/kg/dose

- not established; + some effect (20% response); ++ mod effect (20-50% response); +++ good effect (>50% response)

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**Table 2**

Comparative overview of side-effect profiles of second-generation antipsychotic medications in children and adolescents

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Aripiprazole</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>0/+</td>
<td>0</td>
<td>+/a</td>
</tr>
<tr>
<td>Acute EPS</td>
<td>+/a</td>
<td>0</td>
<td>+/a</td>
<td>0</td>
<td>+/a</td>
<td>+/a</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0/+b</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>0/+b</td>
</tr>
<tr>
<td>↑ Lipids</td>
<td>0/+b</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>0/+b</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0/+</td>
<td>++</td>
<td>0/+</td>
<td>0/+</td>
<td>0/+</td>
<td>0/+</td>
</tr>
<tr>
<td>Orthostasis</td>
<td>0/+</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>↑ Prolactin</td>
<td>0/↓</td>
<td>0</td>
<td>+/c</td>
<td>0</td>
<td>+/a</td>
<td>+/a</td>
</tr>
<tr>
<td>↑ QTc interval</td>
<td>0/+c</td>
<td>+/c</td>
<td>0/+c</td>
<td>+/c</td>
<td>+/c</td>
<td>+/c</td>
</tr>
<tr>
<td>Sedation</td>
<td>0/+</td>
<td>+++</td>
<td>++</td>
<td>++/e</td>
<td>+</td>
<td>0/+</td>
</tr>
<tr>
<td>Seizures</td>
<td>0/+</td>
<td>+/a</td>
<td>0/+</td>
<td>0/+</td>
<td>0/+</td>
<td>0/+</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>0/+b</td>
<td>0</td>
<td>0/+d</td>
<td>0/+d</td>
<td>0/+d</td>
<td>0/+b</td>
</tr>
<tr>
<td>Weight gain</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Abbreviations:*  
↑, increased; ↓, decreased; 0, none; 0/+, minimal; +, mild; ++, moderate; ++++, severe.

- **a** Dose-related effect.
- **b** Insufficient long-term data to determine the risk fully.
- **c** Relevance for the development of torsade de points not established.
- **d** Less than 1% per year in adults that were often pretreated with first-generation antipsychotics.
- **e** More sedating at lower doses.

**Reference:** Correll et al., 2006
Weight Gain Trajectories with OLZ, CLZ & RISP

Fig. 1 Mean proportional weight change with standard deviation during the 45 weeks of study

Fig. 2 Mean change of body mass index standardized scores (BMI-SDS) with standard deviation during the 45 weeks of study

Reference: Fleischhaker et al., 2008
# SGA Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose (mg/day)</th>
<th>Usual Dose Range (mg/day)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>2 mg</td>
<td>5-30 mg</td>
<td>Only SGA approved by Health Canada for any indication in youth</td>
</tr>
<tr>
<td>Clozapine</td>
<td>12.5 mg</td>
<td>50-900 mg</td>
<td>WBC monitoring required</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1.25-5 mg</td>
<td>5-20 mg</td>
<td>Given its adverse effect profile, other SGAs should be tried first</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>3 mg</td>
<td>3-12 mg</td>
<td>Paliperidone (9-hydroxy-risperidone) is the major active metabolite of risperidone</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>12.5-50 mg</td>
<td>150-800 mg</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.125-0.5 mg</td>
<td>0.25-6 mg</td>
<td>Should be dosed BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Capsules should not be cut, and the smallest available is 20 mg</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>20-40 mg</td>
<td>40-160 mg</td>
<td>Should be dosed BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Capsules should not be cut, and the smallest available is 20 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consider ECG monitoring</td>
</tr>
</tbody>
</table>