Advanced Child Psychopharmacology

Course Director:
Daniel Gorman, MD, FRCPC

Associate Directors:
Elia Abi-Jaoude, MSc, MD, FRCPC
Amy Cheung, MD, FRCPC
John Langley, MD, FRCPC

“Learning without thought is labour lost; thought without learning is perilous.”
Confucius

• The course promotes “advanced” knowledge of child psychopharmacology
• The course was initially designed for child psychiatry residents, but since July 2007 it has been offered to core residents as well
• The course assumes prior knowledge of:
  – The major psychiatric disorders of childhood
  – Psychopharmacology for adults

• The level of detail in this course may induce somnolence, nausea, headache, akathisia, anxiety, irritability, agitation, hallucinations, and sexual dysfunction
• Core residents may be at greater risk than child psychiatry residents for these adverse effects
• If you experience any of these adverse effects, consult your program director

Introductory Seminar:
“Kids Aren’t Little Adults”

Learning Objectives
1. Appreciate that child psychopharmacology differs from adult psychopharmacology
2. Explain how drug pharmacokinetics differ in children compared to adults
3. Summarize the evidence supporting the efficacy of psychotropic medications in youth, and describe concerns about adverse effects in this population
4. Discuss the meanings that psychotropic medication may have for children, parents, and clinicians

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Outline

• Introductory comments
• Clinical vignettes
• Importance of child development
• Pharmacodynamic considerations
• Pharmacokinetic considerations
• Evidence for efficacy in child psychopharmacology
• Concerns about adverse effects

Outline (cont.)

• Principles of “conservative prescribing” (not just for kids!)
• The meaning of medication for children and parents
• Clinician attitudes about using medication in children

Comment #1

Comment #2
“He’s the best physician who knows the worthlessness of the most medicines.”

Benjamin Franklin

“To write prescriptions is easy, but to come to an understanding with people is hard.”

Franz Kafka, “The Country Doctor”

Comment #3

“Kids Aren’t Little Adults”

• When considering psychotropic medication for a child or adolescent, be cautious about extrapolating from adult studies or practices
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Negative Placebo-Controlled Trials of TCAs for Pediatric Depression

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- Petti et al., 1982 (IMI)
- Kashani et al., 1984 (AMI)
- Preskorn et al., 1987 (IMI; equivocal)
- Geller et al., 1989 (NT)
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- Boulos et al., 1991 (DMI)
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- Kutcher et al., 1994 (DMI)
- Puig-Antich et al., 1987 (IMI)
- Klein et al., 1998 (DMI)
- Birmaher et al., 1996 (AMI)
- Kye et al., 1996 (AMI; equivocal)
- Keller et al., 2001 (IMI)

A total of >500 children and adolescents were included in these trials

Legend: TCA=tricyclic antidepressant, AMI=amitriptyline, IMI=imipramine, NT=nortriptyline, DMI=desipramine

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Clinical Vignettes

1. The Good
2. The Sad
3. The Ugly

Child Psychopharmacology: Developmental Factors

- Need to distinguish between “target symptoms” and behaviours that are normal for the child’s stage of development, e.g.,
  - ADHD symptoms vs. normal distractibility/restlessness
  - OCD symptoms vs. normal rituals and superstitions
- Need to consider conditions in children that you may not be used to considering in adults, e.g.,
  - ADHD
  - Learning disabilities
  - Developmental disorders

Developmental Factors (cont.)

- Psychiatric conditions may present differently in children and adolescents vs. adults, e.g.,
  - Bipolar disorder
  - Depressive disorders
  - PTSD
- Treatment decisions must be informed by an understanding of the developmental course of psychiatric disorders in childhood, e.g.,
  - Tourette syndrome
  - ADHD

Developmental Factors (cont.)

- Untreated symptoms can have a negative influence on children’s developing internal representations of themselves and others
- Untreated symptoms can impair children’s ability to cope with normal developmental challenges (e.g., self-regulatory, learning, social, romantic)

Developmental Factors (cont.)

- Children may not be reliable reporters of the benefits or side effects of medication
- Pharmacological effects may vary considerably at different developmental stages:
  - CNS/pharmacodynamic factors
  - Physiological/pharmacokinetic factors

Pharmacodynamics

- The CNS undergoes substantial developmental change during childhood and adolescence
- Developmental changes in neurotransmitter systems can influence both therapeutic and adverse effects of psychotropic medications

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Pharmacodynamics (cont.)

- Examples that may relate to developmental changes in neurotransmitter systems:
  - **Dopamine system**: children and adolescents appear to have an ↑ risk of dystonic reactions with antipsychotics compared to adults.
  - **Serotonin system**: prepubertal children appear to be at ↑ risk of activating side effects from SSRIs compared to adults.
  - **Noradrenergic system**: immaturity of noradrenergic pathways may explain, at least in part, why TCAs are less effective for depression in children and adolescents than in adults.

Pharmacokinetics

- Many PK similarities exist between adults and children, e.g., age-independent genetic influences on protein binding, metabolism, and elimination.
- Nonetheless, youth display unique PK properties compared to adults, and PK differences also exist between infants, children, and adolescents.
- PK differences can be especially dramatic around puberty, when hormonal factors can influence plasma drug concentrations.

Pharmacokinetic Domains

- Absorption
- Distribution
- Metabolism
- Elimination

Absorption

- Little information is available regarding the effect of age on the absorption of psychotropic medications.
- Nonetheless, oral absorption is generally similar in older infants and children compared to adults (Pichini et al., 2009).

Distribution

- \( \text{Cp} = \frac{D}{V_d} \)
  - plasma concentration of drug = amount of drug absorbed ÷ volume of distribution.
- Two factors that change with development have an influence on drug distribution:
  1. Fat stores
  2. Body water (total & extracellular)

Proportion of Body Fat

- Highest in the first year of life, followed by a steady decrease during early/middle childhood, until an increase occurs prepubertally.
Proportion of Body Fat (cont.)

- Developmental changes in the proportion of body fat substantially influence the Vd of highly lipophilic drugs (including most antidepressants and antipsychotics):
  - Lower proportion of body fat → smaller Vd
  - Higher proportion of body fat → larger Vd

- For lipophilic drugs, the lower proportion of body fat in (middle) childhood results in a smaller Vd, and thus higher plasma drug concentrations (other factors being equal and adjusting the dose for weight)

Proportion of Body Water

- Proportion of body water (total and extracellular) is high in infancy and decreases with age (Pichini et al., 2009), influencing the Vd of drugs primarily distributed in body water (e.g., lithium):
  - Higher proportion of body water → larger Vd
  - Lower proportion of body water → smaller Vd

- For drugs primarily distributed in body water, the higher proportion of body water in childhood results in a larger Vd, and thus lower plasma drug concentrations (other factors being equal and adjusting the dose for weight)

Metabolism

- Most psychotropic drugs undergo:
  - Extensive biotransformation in the liver
  - Both phase I and phase II reactions

- Phase I reactions include hydroxylation, reduction, and hydrolysis, and are catalyzed by hepatic microsomal enzymes (CYP450 system)

- Phase II reactions involve conjugation by glucuronic acid and may occur in almost any organ

Metabolism: Clinical Comments

- For drugs that are not metabolized, developmental changes in metabolism are irrelevant (e.g., lithium, gabapentin)

- Drugs that undergo phase II but not phase I reactions are metabolized at the same rate in children (>3-4 years) as in adults, so adjusting the dose for weight may be particularly important (e.g., lorazepam, oxazepam, temazepam, lamotrigine)

Developmental Changes in Phase I & II Reactions

- Phase I:
  - CYP450 enzyme activity develops in the fetal period and infancy, increases in childhood to above adult levels, and then declines after puberty to adult levels
  - The greater CYP450 activity during childhood results in lower plasma drug concentrations (other factors being equal and adjusting the dose for weight)

- Phase II:
  - Glucuronide formation reaches adult levels by age 3-4 years, so after that the efficiency of phase II reactions does not vary with age (Pichini et al., 2009)

Metabolism: Clinical Comments (cont.)

- Both phase I and phase II reactions are susceptible to inhibition or induction by other drugs

- Examples:
  - Phase I: fluoxetine increases atomoxetine and risperidone levels through CYP2D6 inhibition
  - Phase II: valproate increases lamotrigine levels through inhibition of glucuronidation
Elimination

• The kidney is the most important organ for drug elimination

• GFR is much lower in newborns, but reaches adult values age 6-12 months (Picchini et al., 2009)

• “Clearance” refers to the efficiency of drug removal

Elimination (cont.)

• Children usually have lower absolute clearance than adults because of their smaller body size (Vitiello, 2008)

• However, evidence is mixed on whether children have higher (Vitiello et al., 1988) or the same (Findling et al., 2010) weight-adjusted clearance compared to adults

• Aside from the issue of clearance, children have relatively more body water and less adipose tissue than adults, and consequently they accumulate lipophilic drugs to a lesser extent and eliminate them faster (Vitiello, 2008)

Elimination in Children vs. Adults (Vitiello, 2008)

Children have relatively more kidney parenchyma relative to body size

Greater weight-adjusted clearance

Children have relatively more body water and less adipose tissue

Less accumulation of lipophilic drugs

Faster drug elimination

Shorter time to plasma peak

Shorter half-life

Note: Countered by Findling et al., 2010

Pediatric PK: Bottom Line

• Children tend to have higher rates of metabolism and elimination than adults (Vitiello, 2008; Anderson & Holford, 2008/2009)

• Consequently, children generally require higher weight-adjusted doses of most medications to achieve similar blood levels as adults

Pediatric PK: Bottom Line (cont.)

• However, pharmacokinetics are highly variable in children and not readily predictable based on adult information (Rodriguez et al., 2008)

• Therefore, although body weight may often be used as a general guideline for pediatric dosing, the appropriate dose of a psychotropic medication for a child should be determined empirically and cautiously (“Start low, go slow”)

Efficacy

• Although the child psychopharmacology evidence base is still limited relative to the adult literature, it has grown markedly over the past 2 decades

• Double-blind, placebo-controlled (DBPC) trials have now been conducted in youth for the major classes of psychotropic medication:
  – Stimulants
  – Antidepressants
  – Antipsychotics
  – Certain anticonvulsants (oxcarbazepine, valproate)
Efficacy (cont.)

- Furthermore, federally funded landmark trials have evaluated pharmacotherapy for most of the common psychiatric disorders in childhood:
  - ADHD (MTA, 1999)
  - Tourette syndrome (TSSG, 2002)
  - ASD (RUPP, 2002; RUPP, 2005; STAART, 2009)
  - Major depression (TADS, 2004; TORDIA, 2008)
  - OCD (POTS, 2004)
  - Other anxiety disorders (CAMS, 2008)
  - Schizophrenia (TEOSS, 2008)
  - Bipolar disorder (TEAM, 2012)

- With regard to the major medication classes, the pediatric evidence is generally strongest for stimulants, intermediate for SSRIs and antipsychotics, and weakest for lithium and anticonvulsants.

- Although evidence for short-term efficacy may be strong for certain medications and indications in youth, evidence supporting the long-term benefits of pharmacotherapy is sparse.

- As in the adult literature, most studies of psychotropic medication in youth are funded by the pharmaceutical industry.

Influence of Pharma

"It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of The New England Journal of Medicine."


“Off-Label” Prescribing

- Although many psychotropic medications are now approved by the FDA for pediatric use, few have pediatric approval from Health Canada.

- For example, Health Canada has not approved any SSRI for use in youth, and the only atypical antipsychotic that it has approved in youth is aripiprazole (to treat schizophrenia [≥15 years] and bipolar I manic/mixed episodes [≥13 years]).

- Consequently, the pediatric use of most psychotropic medications in Canada is “off-label,” and it is important to discuss this issue when obtaining informed consent.

Adverse Effects

- For most psychotropic drugs, risks and adverse effects—especially long-term ones—have not been well studied in youth.

- Youth may be at higher risk than adults for adverse effects, e.g.,
  - Weight gain, sedation, and EPS with antipsychotics
  - Activation and suicidality with SSRIs

- Therefore, greater caution and increased monitoring are generally required in youth.

Adverse Effects (cont.)

- Youth may experience adverse effects that you are not used to thinking about in adults, e.g.,
  - Enuresis with risperidone (Herguner & Mukaddes, 2008)

- Cognitive side effects and sedation can interfere with learning and academic performance.

- Weight gain can have a negative influence on a child or adolescent’s fragile self-esteem.
Adverse Effects (cont.)

- Youth may be more susceptible to the cardiac effects of medications:
  - ECG monitoring is indicated when using TCAs, lithium, and arguably antipsychotics in children
- Some medications may affect growth (e.g., stimulants)
- Hormonal side effects (e.g., hyperprolactinemia caused by antipsychotics) may affect sexual development and bone density

Principles of “Conservative Prescribing” (Schiff et al., Arch Intern Med, 2011)

1. Think beyond drugs:
   - Seek nondrug alternatives first
   - Consider potentially treatable underlying causes of problems rather than just treating the symptoms with a drug
   - Look for opportunities for prevention rather than focusing on treating symptoms or advanced disease
   - Use the test of time as a diagnostic and therapeutic trial whenever possible

“Conservative Prescribing” (cont.)

2. Practice more strategic prescribing:
   - Use only a few drugs and learn to use them well
   - Avoid frequent switching to new drugs without clear, compelling evidence-based reasons
   - Be skeptical about individualized therapy
   - Whenever possible, start treatment with only one drug at a time

“Conservative Prescribing” (cont.)

3. Maintain heightened vigilance regarding adverse effects:
   - Have a high index of suspicion for adverse drug effects
   - Educate patients about possible adverse effects to ensure that they are recognized as early as possible
   - Be alert to clues that you may be treating or risking withdrawal symptoms

“Conservative Prescribing” (cont.)

4. Approach new drugs and new indications cautiously and skeptically:
   - Learn about new drugs and new indications from trustworthy, unbiased sources
   - Do not rush to use newly marketed drugs
   - Be certain that the drug improves actual patient-centred clinical outcomes rather than just treating or masking a surrogate marker
   - Be vigilant about indications creep
   - Do not be seduced by elegant molecular pharmacology or drug physiology
   - Beware of selective reporting of studies

“Conservative Prescribing” (cont.)

5. Work with patients for a shared agenda:
   - Do not uncritically succumb to patients’ requests for drugs, especially those they have heard advertised
   - Avoid mistakenly prescribing additional drugs for refractory problems, failing to appreciate the potential for patient nonadherence
   - Avoid repeating prescriptions for drugs that previously were unsuccessful or caused an adverse reaction
   - Discontinue treatment with drugs that are not working or are no longer needed
   - Work with patients’ desires to be conservative with medications

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“Conservative Prescribing” (cont.)

6. Consider longer-term, broader effects:
   – Think beyond short-term beneficial drug effects to consider longer-term benefits and risks
   – Look for opportunities to improve prescribing systems, changes that can make prescribing and medication use safer

Meaning of Medication for Children

• Taking medication may make children feel:
  – Sick, defective, stupid, crazy
  – Embarrassed, stigmatized, worried about being teased or bullied
  – Scared, anxious
  – Punished, controlled
  – Like they’re not “themselves”
  – Without internal resources to manage their emotions or behaviour

Meaning of Medication for Children (cont.)

• Children can also experience medication as empowering and beneficial:
  – An 8-year-old boy with ADHD said that when he takes dextroamphetamine, “I feel refreshed … like I have a new life!”
  – A 14-year-old boy presented with Tourette syndrome, ADHD, social anxiety, depression, and passive SI. He said that taking methylphenidate has been “great” because he now feels better about himself and his mood has improved. He also no longer feels suicidal.

Meaning of Medication for Children (cont.)

• It is important to talk to children (as well as their parents) about medication, and explore what meaning it has for them
  • While the meaning of medication is highly individual, it also depends on the child’s age and cognitive abilities
  • Piaget’s stages of cognitive development (preoperational, concrete operations, formal operations) are a useful framework for anticipating the meaning that medication may have for a child (the following examples are taken from Pruett et al., 2011, in Pediatric Psychopharmacology, 2nd ed.)

Preoperational

• One boy liked “the little mines I swallow. They have codes stamped on them for each little monster inside me that they’re going to blow up today.”

Concrete Operations

• Upon reading the label of her medication, one girl realized that she was getting hundreds of milligrams and it was only helping a little. She concluded that she must be much sicker than she had thought.
Formal Operations

• “I know I’m less depressed and irritable. My boyfriend says I’m easier to take, but I’m not sure this is really me. I feel like this poser [posing as another]. Like, every time I take my pills it reminds me that I’m this fuck-up who can’t manage her feelings on her own. I hated feeling suicidal, but hey, maybe that’s more me.”

Meaning of Medication for Parents

Recommended medication for a child may elicit a variety of feelings and reactions from parents:

<table>
<thead>
<tr>
<th>Scared about harming their child</th>
<th>vs.</th>
<th>Hopeful about helping their child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guilty or ashamed for being “bad parents”</td>
<td>vs.</td>
<td>Relieved that they’re not “bad parents”</td>
</tr>
<tr>
<td>Angry that the clinician wants to “drug” their child instead of offering a psychosocial treatment</td>
<td>vs.</td>
<td>Less willing to consider psychosocial factors that may be contributing to the child’s difficulties</td>
</tr>
</tbody>
</table>

Meaning of Medication for Parents (cont.)

<table>
<thead>
<tr>
<th>Criticized personally through identification with the child (“like father, like son” or “chip off the old block”)</th>
<th>vs.</th>
<th>Eager to provide their child with treatment that was not made available to them</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worried about extinguishing something positive about the child’s personality (e.g., the child’s “charm” or “spark”)</td>
<td>vs.</td>
<td>An expectation that medication will solve all the child’s problems</td>
</tr>
</tbody>
</table>

Clinician Attitudes About Medication

Various factors may make clinicians reluctant or hasty to prescribe psychotropic medications for children:

<table>
<thead>
<tr>
<th>Reluctant</th>
<th>Hasty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive fear of causing harm</td>
<td>Minimization of risks and side effects</td>
</tr>
<tr>
<td>Minimization of the impairment caused by the child’s mental illness</td>
<td>Wish to stamp out symptoms without considering impairment</td>
</tr>
<tr>
<td>Lack of knowledge regarding evidence</td>
<td>Lack of knowledge regarding evidence</td>
</tr>
<tr>
<td>Lack of experience</td>
<td>“Cowboy” attitude</td>
</tr>
</tbody>
</table>

Clinician Attitudes (cont.)

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<tr>
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<tbody>
<tr>
<td>Fear of parents’ reaction to a recommendation of pharmacotherapy</td>
<td>Overwhelmed by parents’ affect (e.g., desperation, anger)</td>
</tr>
<tr>
<td>Fear of pathologizing the child</td>
<td>Unwilling to explore psychosocial factors</td>
</tr>
<tr>
<td>Use of medication in children is experienced as overly harsh (defence against one’s own aggressive impulses?)</td>
<td>Frustration with the child or parent (acting out of angry feelings?)</td>
</tr>
<tr>
<td>View drugs as a “quick fix”</td>
<td>Anxious for a “quick fix”</td>
</tr>
<tr>
<td>Identity as a psychotherapist</td>
<td>Identity as a pharmacologist</td>
</tr>
</tbody>
</table>

Words of Wisdom from and for Clinicians

• “Be brave.”
  – John Walkup, MD

• “Be cautious.”
  – Elizabeth Guthrie, MD

• “Be thoughtful.”
  – Alice Charach, MD

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