**Advanced Child Psychopharmacology**

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“Reports that say that something hasn't happened are always interesting to me, because as we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns -- the ones we don't know we don't know. And if one looks throughout the history of our country and other free countries, it is the latter category that tend to be the difficult ones”

- Donald Henry Rumsfeld

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**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 children and adolescents, and describe concerns about adverse effects in this population
4. Discuss the meanings that psychotropic medication may have for children, parents, and clinicians
Outline

• Three introductory comments
• Importance of child development
• Pharmacodynamics
• Pharmacokinetics
• Evidence for efficacy in child psychopharmacology
• Concerns about adverse effects
• The meaning of medication for children and parents
• Clinician attitudes about using medication in children

Comment #1

We are all biased

Comment #2

It's not about medications

“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
Comment #3

*Be very cautious of ‘facts’*

“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

- Kramer et al., 1981 (AMI)
- Petti et al., 1982 (IMI)
- Kashani et al., 1984 (AMI)
- Preskorn et al., 1987 (IMI; equivocal)
- Geller et al., 1989 (NT)
- Geller et al., 1990 (NT)
- Hughes et al., 1990 (?)

Positive Placebo-Controlled Trials of TCAs for Pediatric Depression

- Boulos et al., 1991 (DMI)
- Geller et al., 1992 (NT)
- Kutcher et al., 1994 (DMI)
- Puig-Antich et al., 1987 (IMI)
- Klein et al., 1996 (DMI)
- Birmaher et al., 1998 (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

Child Psychopharmacology: Developmental Factors

- Need to distinguish between “target symptoms” and behaviors 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, ODD
  - Learning disabilities (LD)
  - Developmental disorders

Developmental Factors (cont.)

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

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Developmental Trajectory

- Full, mature function

Age 18 (or 24)

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 medications
  - Timing (e.g., sense of time)
- Pharmacological effects may vary considerably at different developmental stages:
  - CNS / pharmacodynamic factors
  - Physiological / pharmacokinetic factors

Pharmacodynamics

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

Pharmacodynamics (cont.)

- Examples that may relate to developmental changes in neurotransmitter systems:
  - Dopamine system: compared to adults, children and adolescents appear to have a higher risk of dystonic reactions with antipsychotics
  - Serotonin system: compared to adults, prepubertal children appear to have a higher risk of activating side effects from SSRIs
  - 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

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Pharmacokinetic Domains

- Absorption
- Distribution
- Metabolism
- Elimination

Kids vs. adults?

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

\[ C_p = \frac{D}{V_d} \]
- 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 pre-pubertally

Proportion of Body Fat (cont.)

- Developmental changes in the proportion of body fat substantially influence the Vd of highly lipophilic drugs (inc. 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, but mainly in the liver

**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; thereafter the efficiency of phase II reactions *does not* vary with age (Pichini et al., 2009)

**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, lamotrigine)

**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, risperidone, and aripiprazole levels through CYP2D6 inhibition. Fluvoxamine is a strong inhibitor of CYP1A2, CYP2CX, and CYP3AX
  - **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 by age 6-12 months* (Picchini et al., 2009)
- “*Clearance*” refers to the efficiency of drug removal, i.e., the theoretical volume of blood that is totally cleared of drug per unit time

**Elimination (cont.)**

- Children 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
- In addition, recall that children have relatively more body water and less adipose tissue, hence they accumulate lipophilic drugs to a lesser extent (Vitiello, 2008)
Elimination in Children vs. Adults (Vitiello, 2008)

- Children have relatively more kidney parenchyma relative to body size
- Greater weight-adjusted clearance
- Less accumulation of lipophilic drugs
- Faster drug elimination
- Shorter time to plasma peak
- Shorter half-life

Note: Countered by Findling et al., 2010

Faster drug elimination

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”)

Use of Psychotropic Medications in U.S. Youths (6-17 Years)


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 been conducted in children and adolescents for the major classes of psychotropic medication:
  - Stimulants and non-stimulant ADHD medications
  - Antidepressants
  - Antipsychotics
  - Certain anticonvulsants (e.g., oxcarbazepine, VPA)
  - Lithium

Efficacy (cont.)

- Furthermore, federally funded landmark trials have evaluated pharmacotherapy for most of the common psychiatric conditions in childhood:
  - ADHD (MTA, 1999)
  - TS (TSSG, 2002)
  - ASD (RUPP, 2002; RUPP, 2005; STAART, 2009)
  - MDD (TADS, 2004; TORDIA, 2008)
  - OCD (POTS, 2004; POTS II, 2011)
  - Other anxiety disorders (CAMs, 2008)
  - Schizophrenia (TEOSS, 2008)
  - Bipolar disorder (TEAM, 2012; CoLT, 2015)
  - Aggression associated with ADHD (TOSCA, 2014)
Efficacy (cont.)

- The pediatric evidence for efficacy is generally:
  - **Strongest** for stimulants
  - **Intermediate** for SSRIs and antipsychotics
  - **Weakest** for lithium and anticonvulsants
- Although evidence for **short-term** efficacy may be strong for certain medications and indications in children and adolescents, evidence supporting the **long-term** benefits of pharmacotherapy is sparse
- Most studies of psychotropic medications, both in children and adults 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

- Many psychotropic medications are now approved by the **FDA** for pediatric use.
- Only ADHD medications and a few others have pediatric approval from **Health Canada**:
  - No approval of any SSRI for use in children / adolescents.
  - The only approved atypical antipsychotic 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 children and adolescents
- Children and adolescents may be at higher risk than adults for adverse effects, e.g.:
  - **Weight gain** and **sedation** with antipsychotics (Correll et al., 2010)
  - **Activation** and **suicidality** with SSRIs (Bridge et al., 2007; Stone et al., 2009)
- Therefore, greater caution and **increased monitoring** are generally required in youth

Adverse Effects (cont.)

- Children and adolescents may experience adverse effects that you are not used to thinking about in adults or in children, e.g.,
  - Enuresis with risperidone (Herguner & Mukaddes, 2008)
  - Priapism with stimulants
- 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.)

- Children may be more susceptible to the **cardiac effects of medications**:
  - ECG monitoring is indicated when using **TCAs**, **lithium**, and possibly 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
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 behavior

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 TS, 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 with children (and their parents) about the **meaning** that medication has for them
• While the meaning is highly individual, it also depends on age and **developmental stage**
• Piaget’s 4 stages of cognitive development 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.)

Pre-operational (2nd Stage)

• 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.”
• One girl was happy to swallow her clonazepam, but no other medication, because her first initial “K” was “cut into it for me.”

Concrete Operational (3rd Stage)

• 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 Operational (4th Stage)

• “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 screw-up who can’t manage her feelings on her own. I hated feeling suicidal, but hey, maybe that’s more me.”

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Meaning of Medication for Parents
Recommending medication for a child may elicit a variety of feelings and reactions from parents:

| Scared about harming their child | vs. | Hopeful about helping their child |
| Guilty or ashamed for being “bad parents” | vs. | Relieved that they’re not “bad parents” |
| Angry that the clinician wants to “drug” their child instead of offering a psycho-social treatment | vs. | Less willing to consider psycho-social factors that may be contributing to the child’s difficulties |

Feeling criticized personally through identification with the child (“like father, like son” or “chip off the old block”) vs. Eager to provide their child with treatment that was not made available to them

Worried about extinguishing something positive about the child’s personality (e.g., the child’s “charm” or “spark”) vs. An expectation that medication will solve all the child’s problems

Clinician Attitudes About Medication
Various factors may make clinicians reluctant or hasty to prescribe psychotropic medications for children:

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<th>Reluctant</th>
<th>Hasty</th>
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<tbody>
<tr>
<td>1. Excessive fear of causing harm</td>
<td>1. Minimization of risks and side effects</td>
</tr>
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<td>2. Minimization of the impairment caused by the child’s mental illness</td>
<td>2. Wish to stamp out symptoms without considering impairment</td>
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<td>3. Lack of knowledge regarding evidence</td>
<td>3. Lack of knowledge regarding evidence</td>
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<td>4. Lack of experience</td>
<td>4. “Cowboy” attitude</td>
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<td>5. Feeling pressured by the parents</td>
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<td>6. Fear of parents’ reaction to a recommendation of pharmacotherapy</td>
<td>6. Overwhelmed by parents’ affect (e.g., desperation, anger)</td>
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<td>7. Fear of pathologizing the child</td>
<td>7. Unwilling to explore psychosocial factors</td>
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<td>8. Use of medication in children is experienced as overly harsh (defence against one’s own aggressive impulses?)</td>
<td>8. Frustration with the child or parent (acting out of angry feelings?)</td>
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<td>9. View drugs as a “quick fix”</td>
<td>9. Anxious for a “quick fix”</td>
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<tr>
<td>10. Identity as a psychotherapist</td>
<td>10. Identity as a pharmacologist</td>
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Words of Wisdom from and for Clinicians

• “Be brave.”
  – John Walkup, MD

• “Be cautious.”
  – Elizabeth Guthrie, MD

• “Be thoughtful.”
  – Alice Charach, MD