A Critical Curriculum on Psychotropic Medications

Module 5

Specific Drug Classes: Use, Efficacy, Safety

“Psychotropic” or “psychoactive” drugs
affect the central nervous system and alter feeling, thinking, and behaving
“Approved use” means...

FDA has reviewed limited data on safety and efficacy for one indication, usually in one population.

A “label” for the drug is established to guide dosage and describe observed side effects.

Fewer than 10% of psychotropic drugs are FDA-approved for any psychiatric use in children.

Focus: Stimulants

Stimulants approved by FDA for pediatric use

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Psychiatric Indication</th>
<th>Age group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall, Adderall XR,</td>
<td>amphetamine, dextroamphetamine</td>
<td>ADHD, narcolepsy</td>
<td>3 +</td>
</tr>
<tr>
<td>Dextrostat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concerta, Ritalin, Daytrana, Metadate Focalin, Focalin XR</td>
<td>methylphenidate, dexamethasone, dextroamphetamine</td>
<td>ADHD</td>
<td>6 +</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>lisdexamfetamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strattera (not considered a stimulant)</td>
<td>atomoxetine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stimulants act quickly

Stimulants change behavior within one hour in 60-70% of children who take them.

Long-term evidence of benefits doubtful

APA Report noted lack of data supporting long-term efficacy or safety.

- Stimulants show minimal efficacy in general life domains of the child, including social and academic success.

Short-term desirable effects of stimulants at usual doses

- Increase alertness and wakefulness
- Induce sense of well-being (euphoria)
- Improve accuracy on brief physical and mental tasks

(Bezchlibnyk-Butler & Jeffries, 2005)

Effects misconstrued as therapeutic in children

- Increased repetitive, persistent behavior
- Decreased exploration and social behavior
- Increased compliance

(Breggin, 1998)

Undesirable behavioral effects of stimulants

- Nervousness, restlessness
- Insomnia
- Agitation
- Depression, “zombie” look
- Irritability, Aggression
- Psychological dependence
- Mania, Psychosis

(Bezchlibnyk-Butler & Jeffries, 2005)

Undesirable physical effects of stimulants

- Increased blood pressure
- Dizziness, headaches
- Palpitations
- Stomach cramps, nausea
- Appetite/weight loss
- Stunted growth
- Cardiac arrest

(Bezchlibnyk-Butler & Jeffries, 2005)

Stunted growth

Decreases in growth averaging ¾” and 6 lbs. without evidence of rebound 3 years after stopping treatment

(Swanson et al., 2007)

Emergency room visits

2,500 children visited ERs in 2004 after taking stimulants for ADHD, most due to accidental overdoses
- 1 in 4 children had heart or blood pressure symptoms including palpitations, chest pain or fainting

(Waters, 2007)
2006: FDA warning on stimulants

- increased risk of sudden death in patients with heart problems
- increased aggression, mania and/or psychotic symptoms (including hallucinations)

The New York Times

Electronic Medication Guide
F.D.A. Strengthens Warnings on Stimulants

Definite risk of tolerance and dependence

Stimulants prescribed to children are Drug Enforcement Administration (DEA) "Schedule II Drugs," indicating a high risk of tolerance and dependence.

RITALIN LA™ is a federally controlled substance (CII) because it can be abused or lead to dependence. Keep RITALIN LA™ in a safe place to prevent misuse and abuse. Selling or giving away RITALIN LA™ may harm others and is against the law.

FDA-approved antidepressants for pediatric use

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Psychiatric Indication</th>
<th>Age group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinequan</td>
<td>doxepin</td>
<td>OCD</td>
<td>12+</td>
</tr>
<tr>
<td>Anafranil</td>
<td>clomipramine</td>
<td>OCD</td>
<td>10+</td>
</tr>
<tr>
<td>Luvox</td>
<td>fluvoxamine</td>
<td>OCD</td>
<td>8+</td>
</tr>
<tr>
<td>Zoloft</td>
<td>sertraline</td>
<td>OCD</td>
<td>6+</td>
</tr>
<tr>
<td>Tofranil</td>
<td>imipramine</td>
<td>Depression, OCD</td>
<td>7+</td>
</tr>
<tr>
<td>Prozac</td>
<td>fluoxetine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Focus: Antidepressants

Meta-analyses of drug vs. placebo studies show 75-82% of the response was duplicated by placebo.
- 57% of studies submitted to FDA failed to show a difference between drug and placebo.

CDC: Antidepressants most prescribed drugs in U.S.

But are they effective?

(Moncrieff et al., 2004; Kirsch et al., 2002; Kirsch & Sapirstein, 1998)
Unimpressive evidence from FDA’s complete adult database

“[I]n 189 trials of 53,048 adult subjects with psychiatric disorders ... Approximately 50% of subjects who received active drug and 40% of subjects who received placebo were designated as responders.”

(Stone & Jones, 2006)

The entire scientific case for antidepressants rests on this 10% difference—which may result from biases in the conduct of clinical trials

FDA analysis of pediatric trials concurs

Only 3 of 15 published and unpublished randomized controlled trials show SSRIs as more effective than placebo in depressed children

None of the studies found drugs better on client- or parent-rated measures

(Laughren, 2004)

No evidence that older antidepressants (tricyclics or MAO inhibitors) have any efficacy with depressed youths

(Somers-Flanagan & Somers-Flanagan, 1996)

Short-term desirable effects at usual doses

- Increased physical activity
- Elevated mood
- Decreased expressions of distress such as crying, hopelessness
- Improved sleep and appetite

(Bezchlibnyk-Butler & Jeffries, 2005)

Undesirable behavioral effects of antidepressants

- Anxiety, nervousness
- Agitation, irritability
- Mood swings, mania
- Aggressiveness
- Thoughts of suicide
- Attempted or actual suicide

(Antonuccio et al., 1999; Preda et al., 2001; Healy, 2003)

Undesirable physical effects of antidepressants

- Gastrointestinal distress (nausea, vomiting, stomach pain, constipation, diarrhea)
- Sexual problems (loss of libido, anorgasmia, erectile dysfunction)
- Sleep disruption (insomnia, hypersomnia)
  - Urinary retention
  - Blurred vision
  - Weight gain
  - Headaches, dizziness

(Antonuccio et al., 1999; Preda et al., 2001; Healy, 2003)
Six clusters of withdrawal effects likely upon abrupt discontinuation of SSRI antidepressants

1. Neurosensory (vertigo, tingling & burning)
2. Neuromotor (tremor, spasms, visual changes)
3. Gastrointestinal (nausea, vomiting, diarrhea, weight loss)
4. Neuropsychiatric (anxiety, depression, crying spells, irritability, suicidal thinking)
5. Vasomotor (heavy sweating, flushing)
6. Other (insomnia, vivid dreaming, fatigue)

(Shatzberg et al., 2006)

Antidepressants double risk of suicidality

2005: FDA issues “black box” warning of “Suicidality in Children and Adolescents”:
“Antidepressants increase the risk of suicidal thinking and behavior (suicidality)”
- (22 RCTs testing 9 antidepressants: 2.3% rate of serious suicidal events among drug-treated children, vs. 1.2% among placebo treated—no completed suicides)

“Activation” syndrome: A more common risk

FDA also warns of increased agitation, irritability, aggression, worsening anxiety, severe restlessness, and other unusual behaviors in youth treated with antidepressants

(Breggin, 2006)

Concern over “prescription cascade”

Continued exposure to the drug can lead to effects misinterpreted as psychiatric symptoms (such as mania), leading to increases in dosage or additional drugs—when reducing or stopping the drug would relieve the patient’s discomfort

(Breggin, 2006)

Focus: Anticonvulsant Drugs

Anticonvulsants on U.S. market (antiepileptics, antiseizure drugs)

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Yr of intro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegretol, Equetro</td>
<td>carbamazepine</td>
<td>1968, 2004</td>
</tr>
<tr>
<td>Neurontin</td>
<td>gabapentin</td>
<td>1993</td>
</tr>
<tr>
<td>Lamictal</td>
<td>lamotrigine</td>
<td>1994</td>
</tr>
<tr>
<td>Depakene, Depakote</td>
<td>valproate</td>
<td>1995</td>
</tr>
<tr>
<td>Topamax</td>
<td>topiramate</td>
<td>1997</td>
</tr>
<tr>
<td>Trileptal</td>
<td>oxcarbazepine</td>
<td>2000</td>
</tr>
</tbody>
</table>

(Breggin, 2006)
Anticonvulsants FDA-approved for pediatric seizure disorders

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Approved Indications</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegretol, Equetro</td>
<td>carbamazepine</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Gabitril</td>
<td>lagabinese</td>
<td>12 +</td>
<td></td>
</tr>
<tr>
<td>Depakote, Depakene</td>
<td>divalproex sodium, valproate</td>
<td>10 +</td>
<td></td>
</tr>
<tr>
<td>Topamax</td>
<td>topiramate</td>
<td>3 +</td>
<td></td>
</tr>
<tr>
<td>Neurontin</td>
<td>gabapentin</td>
<td>2 +</td>
<td></td>
</tr>
<tr>
<td>Lamictal</td>
<td>lamotrigine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trileptal</td>
<td>oxcarbazepine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NO PSYCHIATRIC INDICATIONS

Anticonvulsants widely promoted as “mood stabilizers”

Use started in 1980s-1990s due to dissatisfaction with lithium and antipsychotics in treatment of Bipolar Disorder

Use spread rapidly with the promotion of “mood stabilizer” expression and of Bipolar Disorder diagnosis in children

(Healy, 2006)

The New York Times

Bipolar Illness Soars as a Diagnosis for the Young

40-fold increase in less than a decade

(Moreno et al., 2007)

Polypharmacy without psychotherapy

More than 90% of children diagnosed with Bipolar Disorder received more than 1 psychoactive drug

Less than 40% received psychotherapy

(Moreno et al., 2007)

Scant empirical support

No studies confirm the efficacy and safety of anticonvulsants to treat Bipolar Disorder in children and adolescents

“Despite the frequent use of antiepileptic drugs in the treatment of juvenile bipolar disorder, migraine, and neuropathic pain, the data are insufficient to make recommendations regarding the efficacy of antiepileptics in these conditions in children and adolescents.” (Golden et al., 2006)

(Kowatch et al., 2000, 2005; National Institute of Mental Health, 2000; Ryan, Bhatar and Perel, 1999)
Most trials are open, small, and show limited response in youth

Half of all participants in an open trial of lithium, divalproex, or carbamezepine did not respond to treatment
- 58% received at least one mood stabilizer plus a stimulant, an atypical antipsychotic, or an antidepressant

(Lopez-Larson & Frazier, 2006)

Desired behavioral effects of anticonvulsants

- Reduce aggression and impulsivity
- Calm restlessness and excitability

(Rezchlibnyk-Butler & Jeffries, 2005)

Undesired physical effects of anticonvulsants

- Nausea and dizziness
- Vomiting and abdominal pain
- Headaches and tremors
  - Fatal skin rashes
  - Hypothyroid
  - Blood disorders
- Pancreatitis, liver disease
- Birth defects and menstrual irregularities
- Withdrawal seizures

(Rezchlibnyk-Butler & Jeffries, 2005; Gonzalez-Heydrich et al., 2003)

Birth defects of concern given new patient profiles

Anticonvulsants cross placenta and increase the risk of fetal malformations and cognitive impairments in children exposed in utero
- Highest rates for valproate and carbamazepine

(Adab et al., 2006)
**FDA black-box warnings**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depakote</td>
<td>Liver toxicity (particularly for under 2 yrs of age); birth defects; pancreatitis</td>
</tr>
<tr>
<td>Tegretol</td>
<td>Aplastic anemia and agranulocytosis (severe reduction in white blood cells)</td>
</tr>
<tr>
<td>Lamictal</td>
<td>Serious rash requiring hospitalization; Stevens-Johnson Syndrome for under 16 yrs of age (fatal sores on mucous membranes of mouth, nose, eyes and genitals)</td>
</tr>
<tr>
<td>All anticonvulsants</td>
<td>Suicidal ideation and behavior</td>
</tr>
</tbody>
</table>

**“Atypical” (newer, 2nd generation) antipsychotics on U.S. market**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Yr of intro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozaril</td>
<td>clozapine</td>
<td>1989</td>
</tr>
<tr>
<td>Risperdal</td>
<td>risperidone</td>
<td>1994</td>
</tr>
<tr>
<td>Zyprexa</td>
<td>olanzapine</td>
<td>1996</td>
</tr>
<tr>
<td>Seroquel</td>
<td>quetiapine</td>
<td>1997</td>
</tr>
<tr>
<td>Geodon</td>
<td>ziprasidone</td>
<td>2001</td>
</tr>
<tr>
<td>Abilify</td>
<td>aripiprazole</td>
<td>2002</td>
</tr>
<tr>
<td>Invega</td>
<td>paliperidone</td>
<td>2007</td>
</tr>
</tbody>
</table>

**FDA-approved psychiatric indications of atypicals**

- **Risperdal**: Autism, bipolar mania, schizophrenia
- **Abilify**: Schizophrenia
- **Clozaril**: Treatment resistant schizophrenia
- **Zyprexa**: Bipolar mania, schizophrenia
- **Seroquel**: Adults only
- **Geodon**: Bipolar mania, schizophrenia
- **Symbyax**: Invega

**FDA-approved psychiatric indications of typicals for children**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Psychiatric Indication</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orap</td>
<td>pimozide</td>
<td>Tourette's Disorder (for Haldol non-responders)</td>
<td>12 +</td>
</tr>
<tr>
<td>Haldol</td>
<td>haloperidol</td>
<td>Schizophrenia, Tourette's Disorder</td>
<td>3 +</td>
</tr>
<tr>
<td>Mellaril</td>
<td>thioridazine</td>
<td>Schizophrenia</td>
<td>2 +</td>
</tr>
</tbody>
</table>

Typicals make up less than 5% of FL Medicaid prescriptions of antipsychotics

**“Typical” & “Atypical” antipsychotics**

Since 1950s, antipsychotics were used to treat psychoses, despite high toxicity and limited effectiveness

Newer, expensive “atypical” antipsychotics were heavily promoted in the 1990s as safer and more effective
Yet, newer no better than older...

**New England Journal of Medicine**

2005: largest-ever schizophrenia treatment study finds atypicals neither more effective nor better tolerated than older drug
- 75% of patients quit either drugs within 18 months due to inefficacy or intolerable side effects

(Lieberman et al., 2005)

---

Non-psychotic diagnoses in children treated with atypicals

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% of Florida Medicaid children on antipsychotics (2006)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD / Conduct Disorder</td>
<td>48</td>
</tr>
<tr>
<td>Nonpsychiatric, Anxiety, Other Psychiatric</td>
<td>27</td>
</tr>
<tr>
<td>Bipolar / Depression</td>
<td>13</td>
</tr>
<tr>
<td>Schizophrenia / Psychosis</td>
<td>8</td>
</tr>
<tr>
<td>Autism / Mental Retardation</td>
<td>4</td>
</tr>
</tbody>
</table>

(Florida Times, 2007)

---

“Aggression” said to account for most of the antipsychotic prescribing in children and adolescents

(Patel et al., 2005)

---

But do antipsychotics effectively control aggression?

The latest randomized-controlled trial found placebo more effective than either a typical (haloperidol) or atypical (risperidone) antipsychotic to reduce aggression in patients with intellectual disability

_Trial had no drug company sponsorship_

(Tyrer et al., 2008)

---

“Antipsychotic drugs should no longer be regarded as acceptable routine treatment for aggressive behavior in people with intellectual disability.”

(Tyrer et al., 2008)

---

Few pediatric clinical trials of atypicals for any indication

As of 2006, only a few studies of direct AAP comparisons with placebo

_Most studies are short-term (3-6 weeks) and results favor the funder’s drugs_

(McDonagh et al., 2006)
There are no studies that have shown (atypicals) are safe, or for that matter, that they are effective for children... The bottom line is that the use of psychiatric medications far exceeds the evidence of safety and effectiveness.

Ronald Brown, Chair,
2006 American Psychological Association Task Force on Psychotropic Drug Use in Children

Dopamine-blocking action of all antipsychotics explains
- indifference, sedation, drowsiness, apathy
- reduced spontaneity and affect
- reduced ability to monitor one's state
- increased abnormal movements
- cognitive and motor impairments
- confusion and memory problems
- depression, mood swings, agitation

(Bezchlibnyk-Butler & Jeffries, 2005)

Desirable effects of antipsychotics at usual doses
- suppress psychotic symptoms (delusions, hallucinations, agitation)
- suppress manic symptoms (euphoria, expansiveness, irritability)

(Bezchlibnyk-Butler & Jeffries, 2005)

Effects misconstrued as therapeutic
- increased indifference
- reduced spontaneity and affect
- reduced ability to monitor one's state
- increased compliance with social norms

(Bezchlibnyk-Butler & Jeffries, 2005)

Undesirable behavioral effects of antipsychotics
- Cognitive and motor impairments
- Sedation, drowsiness
- Confusion and memory problems
- Anxiety
- Depression, mood swings
- Abnormal thinking
- Hostility, aggression

(Bezchlibnyk-Butler & Jeffries, 2005)

Undesirable physical effects of antipsychotics
- Weight gain, high blood sugar
- Abnormal movements (all body parts)
- Diabetes
- Cardiac problems
- Liver problems, jaundice
- Neuroleptic malignant syndrome
- Death

(Bezchlibnyk-Butler & Jeffries, 2005; Lindenmayer et al., 2003; Meyer, 2001)
Hormonal dysfunctions

Elevated prolactin levels cause:
- sexual and menstrual disturbances
- infertility
- decreased bone density

(Bezchlibnyk-Butler & Jeffries, 2005; Correll & Carlson, 2006; Patel et al., 2005)

Extrapyramidal symptoms (abnormal movements)

Akathisia: inner distress, rocking, pacing, agitation
Dystonia: sudden, bizarre muscle spasms
Dyskinesia: rhythmic movements of face, mouth and tongue, sometimes of hands and feet
Parkinsonism: rigid muscles, loss of facial expression, unsteady gait, drooling

(Campbell, Rapaport & Simpson, 1999)

Tardive dyskinesia risk highest for typical antipsychotics

Long-lasting abnormal movements affect 12% to 35% of children who receive typical antipsychotics for more than 3 months

(Campbell, Rapaport & Simpson, 1999)

Weight gain and diabetes

50% of patients on antipsychotics gain 20% of their weight (primarily as fat)

Weight gain linked to "metabolic syndrome"

The New York Times

Weight gain and diabetes

50% of patients on antipsychotics gain 20% of their weight (primarily as fat)

Weight gain linked to "metabolic syndrome"

(Campbell, Rapaport & Simpson, 1999)

Neuroleptic malignant syndrome

Can occur with any antipsychotic agent, at any dose, at any time
Symptoms: extreme muscular rigidity, high fever, & altered consciousness
1-2% rate per year
Fatal if untreated

(Bezchlibnyk-Butler & Jeffries, 2005; Silva et al., 1999)

3 atypicals suspected in nearly 4,500 deaths reported to FDA, 1998-2005

Clozaril: 3,277 deaths
Risperdal: 1,093 deaths
Zyprexa: 1,005 deaths

(Moore, Cohen & Furberg, 2007)
**FDA “black-box” warnings**

<table>
<thead>
<tr>
<th>All atypicals</th>
<th>Increased mortality in frail elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozaril</td>
<td>Serious risk of agranulocytosis (severe drop in white blood cells), seizures, myocarditis, and other cardiovascular and respiratory effects</td>
</tr>
<tr>
<td>Seroquel</td>
<td>Risk of suicidality in children and adolescents</td>
</tr>
</tbody>
</table>

"For many adults, and a small number of children, these agents can be an important component of treatment. However, it’s so rare to find an example where evidence-based alternatives were exhausted prior to starting an atypical antipsychotic in a child that I have not found one yet in three years of searching."

Mark E. Helm, MD, MBA
Medical Director, Evidence-Based Prescription Drug Program
University of Arkansas Medical Sciences
College of Pharmacy, 2007

---

**States sue drug makers for illegal marketing of unapproved uses**

States sue drug makers for illegal marketing of unapproved uses to recover money states paid to purchase atypical antipsychotics and the costs of medical care for the people injured by these drugs

(Pringle, 2007; Kesselheim & Avorn, 2007)

---

**Part B**

Lawsuits against drug makers shed light on illegal promotion and serious risks

*The New York Times*
December 8, 2006
Drug Files Show Maker Promoted Unapproved Use
By ALEX BERENSON

---

Patients sue, charging that drug makers did not adequately warn about severe weight gain, pancreatitis, diabetes, and other risks

(Pringle, 2007; Kesselheim & Avorn, 2007)
Zyprexa lawsuits

2007: Several states sue Eli Lilly for downplaying or hiding data linking use of the drug to weight gain and hyperglycemia
- Most of those states’ Medicaid spending on antipsychotics is for Zyprexa

2007: Zyprexa settlements top $1.2 billion, so far

Eli Lilly has paid more than $1.2 billion to settle 30,000+ Zyprexa lawsuits
- The settlements required data on rates of adverse effects be kept secret

(Parsons, 2008)

2008: Feds, Eli Lilly negotiate $1 billion Zyprexa fine

If a deal is reached, it would be the largest fine ever paid by a drug company for breaking the federal laws governing how drugmakers can promote their medicines

The New York Times
Thursday, February 7, 2008
Lilly Considers $1 Billion Fine To Settle Case

2007: Bristol-Myers Squibb pays $515 million over illegal marketing and pricing of Abilify, Serzone, other drugs

Part C
Conclusions and Recommendations

Litigation has
☑ exposed shady practices of pharmaceutical manufacturers
☑ uncovered previously hidden data about adverse events
☑ helped doctors reassess risks and benefits of some drugs and think critically about the available “evidence”

(Kesselheim & Avorn, 2007)
Evidence “poor” for the use of psychotropics in children

- Little or no evidence of efficacy and safety of long-term use of these drugs in children
- Clear evidence of harm and risk of serious adverse events, including death
- Risk-benefit ratio especially poor for antidepressants, anticonvulsants, and antipsychotics

Need to rethink risk-benefit ratio

Risks for adverse events, including death, increase with the number of concomitant drugs administered
Risks for adverse events are higher in children, who are receiving adjusted adult dosages of drugs rarely studied in children

Side effects leading to multiple medications?

After initial medication, side effects may be viewed as mental disorders and drugged, in a “prescribing cascade” of polypharmacy that keeps children at risk with no sign of behavioral improvement

Available evidence does not justify use of psychotropic drugs as first-line treatments for children and adolescents

Reassess all cases?

Given known risks and dearth of valid studies showing benefits, cases of children receiving psychiatric medications should be reassessed
Children are involuntary patients. To support continuing psychotropic drug treatment, rock-solid rationale should be provided in every single case

A Critical Curriculum on Psychotropic Medications

Module 5
The End