SYMPOSIUM

MOVEMENT DISORDER AND ANTIPSYCHOTICS MEDICATION IN CHILDREN AND ADOLESCENT

Ravi Patel
University of California Riverside
Assistant Professor of Psychiatry

Pamela Campbell
SIU Neuroscience Institute
Associate Professor of Psychiatry

Pravesh Deotale
Saint Louis University Missouri
Assistant Professor of Psychiatry
Pamela Campbell, M.D.
SIU Neuroscience Institute
Associate Professor of Psychiatry
Movement Disorders and Atypical Antipsychotics:

• The Nuts and Bolts of How and Why it Happens.
DISCLOSURES FOR PAMELA CAMPBELL M.D.

• Discussions may include off label uses of medications.
• Sub-investigator for an study of Aripiprazole for Adolescent Schizophrenia for Otsuka 2011-13.
• Primary Investigator with Janssen Esketamine Study 2017.
• Primary Investigator with Allergan Fetzima Study 2018.
HOW MANY PEOPLE HAVE SEEN EACH OF THESE WITH ATYPICALS?

• 1) Weight gain
• 2) Tardive Dykinesia
• 3) Symptomatic Prolactinemia
• 4) EPS
• 5) Withdrawal Akathisia
• 6) Withdrawal Dyskinesia
THE DILEMMA

• What sometimes happens when you try to discontinue antipsychotic medications in children?
  • Increased aggression
  • Agitation
  • Restlessness
  • Irritability
  • Increased tantrums
  • Worsening of behavior

• Is this a return of underlying psychopathology or reaction to discontinuing the antipsychotic?
1) A review of current practice for the use of antipsychotics in children and adolescents
2) Overview of theory of movement disorders associated with discontinuation of antipsychotics
3) Suggestions for approaches to discontinuing antipsychotics to minimize risk of withdrawal movement disorder
CONCERNS ABOUT INCREASED FREQUENCY OF USE

• According to a study by Matone, Localio, Huang, dosReis, Feudtner, and Rubin in Health Services Research, between 2002 and 2007, there was a 62% increase in the use of antipsychotic medications in medicaid-enrolled children.

• Other studies had shown increases of 3-6 times the rate of prescription in 1995, when the first atypicals were introduced.

• More recent review of Medicare and Medicaid claims comparing 2004 and 2014 was more reassuring that the trend was stabilizing.
UNSETTLING NEWS

• Recent article in JAMA Psychiatry showed an association between use of higher doses of antipsychotic treatment and unexpected death among children and youth
How Do We Currently Use Antipsychotics in Children and Adolescents?
## Atypical Antipsychotic Dosing in Pediatric Patients

Atypical antipsychotic dosing schedules are guided by the specific indication for use. The FDA-approved indications and dosages for atypical antipsychotics in pediatric patients are provided in the dosing table in the document “Atypical Antipsychotics: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Pediatric Patients.”

## Treatment Guidelines for the Use of Atypical Antipsychotics in Pediatric Patients

The AHRQ hosts a database of treatment guidelines. The AHRQ is a branch of the U.S. Department of Health and Human Services. For information on the available treatment guidelines, search “atypical antipsychotics” or any of the conditions for which an atypical antipsychotic is an indicated treatment in the AHRQ’s National Guideline Clearinghouse at [https://www.guideline.gov](https://www.guideline.gov) on the Internet. Links to some of the guidelines that provide information on the use of atypical antipsychotics in pediatric patients are provided in in Table 1.


• Schizophrenia
• Bipolar disorders, manic
• Autistic Spectrum Disorders
• Tic Disorders

• Disruptive Mood Dysregulation Disorder
• Disruptive Behavior Disorders
• Intermittent Explosive Disorders
• Obsessive Compulsive Disorders
• Trichotillomania
• Eating disorders
• Borderline Behaviors
• Sleep problems
• Bipolar, Type 2
• Psychotic Depression
• Treatment resistant Depression
• Conduct Disorders
• Attention Deficit Hyperactivity Disorder
• Oppositional Defiant Disorder
What Do We Usually Worry About?
TARDIVE DYSKINESIA

• AIMS exams
METABOLIC SYNDROME

• Labwork
• BMI
• Diet, exercise
HYPERPROLACTINEMIA

• Labwork
• Lawyers
• Diet
• Exercise
ANTIPSYCHOTIC WITHDRAWAL SYNDROME (AWS)

• Very little about it in the literature
• Seldom mentioned by clinicians
• Would seem to not be much of an issue.
• Or is it?
CLINICAL OBSERVATION

• Movement disorder secondary to either too rapid discontinuation of antipsychotic or switching antipsychotics is more common than most clinician suspect
Biology of Antipsychotics and AWS
• Atypical Antipsychotics work on a variety of receptors
• Primary focus of treatment are the dopamine and serotonin receptors
• For the purposes of our discussion of movement disorders, we will be focused primarily on the dopamine receptors, primarily D2
DOPAMINE RECEPTORS IN THE BRAIN

• Found predominately in:
  • Mesolimbic-
    • Blockade results in reduction of positive symptoms
    • Stimulation results in reward and reinforcement
  • Mesocortical-
    • Blockade results in secondary negative symptoms
    • Stimulation results in memory dysfunction, reduced motivation
  • Nigrostriatal-
    • Blockade results in EPS, dyskinesia, akathisia
    • Stimulation results in decrease in locomotor activity, parkinsonism
  • Tubero-infundibular-
    • Blockade results in prolactin increase
    • Stimulation results in inhibition of prolactin release
Proposed Mechanism for AWS
D2 receptor
Upregulation

Postsynaptic neuron
Postsynaptic neuron

D2 receptor Antagonist discontinuation
WHAT HAPPENS NEXT?

- Depending on circumstances:
  - Increased aggression
  - Agitation
  - Restlessness
  - Irritability
  - Increased tantrums
  - Worsening of behavior
  - Abnormal movements

- Is this a return of underlying psychopathology or reaction to discontinuing the antipsychotic?
WHAT DETERMINES AWS

- Highly variable depending on many factors:
  - How long patient has been on the antipsychotic
  - How rapidly the antipsychotic is discontinued
  - How potent the D2 blockade is
  - Other medications being taken
  - Underlying predisposition
  - Family support
# EFFECTS OF POTENCY OF D2 BLOCKACE

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Second-generation antipsychotics</th>
<th>First-generation antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor</td>
<td>AMI</td>
<td>ARI</td>
</tr>
<tr>
<td>D₂</td>
<td>1.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.66&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1α&lt;/sub&gt;</td>
<td>&gt;10,000&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2A&lt;/sub&gt;</td>
<td>2,000&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.7&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2C&lt;/sub&gt;</td>
<td>&gt;10,000&lt;sup&gt;c&lt;/sup&gt;</td>
<td>22&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>α₁</td>
<td>7,100&lt;sup&gt;c&lt;/sup&gt;</td>
<td>26&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>α₂</td>
<td>1,600&lt;sup&gt;c&lt;/sup&gt;</td>
<td>74&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>H₁</td>
<td>&gt;10,000&lt;sup&gt;d&lt;/sup&gt;</td>
<td>30&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>M₁</td>
<td>N/A</td>
<td>6,780&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>M₂</td>
<td>N/A</td>
<td>3,510&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>M₃</td>
<td>N/A</td>
<td>4,680&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>M₄</td>
<td>N/A</td>
<td>1,520&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Notes:** Adapted with permission from Correll CU. From receptor pharmacology to improved outcomes: individualizing the selection, dosing, and switching of antipsychotics. *Eur Psychiatry.* 2010;25(Suppl 2):S12–S21. Copyright © 2010, Elsevier Masson SAS. All rights reserved. Data represented as the equilibrium constant (Ki; nM), i.e., nanomolar amount of the antipsychotic needed to block 50% of the receptors in vitro. Therefore, a lower number denotes stronger receptor affinity and binding. Partial agonism. Data from cloned human brain receptors. Data extracted from rat. Data extracted from guinea pig.

**Abbreviations:** AMI, amisulpride; ARI, aripiprazole; ASE, asenapine; CLO, clozapine; HAL, haloperidol; OLA, olanzapine; PALI, paliperidone; PER, perphenazine; QUE, quetiapine; RIS, risperidone; SER, sertindole; ZIP, ziprasidone; N/A, not applicable.
D2 High potency Antagonist discontinuation

Dopamine Reuptake inhibitor

Postsynaptic neuron
GENERAL POINTS

• Antipsychotics have a valuable role in the treatment of children and adolescents
• The pharmacology is complicated, making use in children difficult
• A careful, detailed history is essential in treating children
DISCONTINUING ANTIPSYCHOTICS

• The Bad news: Children may be more vulnerable to upregulation of dopamine receptors than adults- Campbell theory
• The Good news: Children may be more able to down regulate than adults.
• Discontinuing antipsychotics may require very slow tapering over several months or careful preparation of the family.
• This is particularly true with the high potency antipsychotics.
• There seems to be a lower threshold for the high potency antipsychotics.
• (Campbell theory) For risperidone, below 1 mg a day and aripiprasole, below 5 mg a day.
• Use of stimulants may exacerbate withdrawal symptoms by increasing dopamine availability.
• Discontinuing stimulants can precipitate EPS by decreasing dopamine availability.
• Pay attention to all the medications that are being taken.
REFERENCES

- Practice Parameters for the Use of Atypical Antipsychotic Medications in Children and Adolescents (prerelease) American Academy of Child and Adolescent Psychiatry 2015.
The Eyes Do Not See What The Mind Does Not Know - Movement Disorder In Kids Taking Antipsychotics

Pravesh Deotale, M.D.
Assistant Professor of Psychiatry
DISCLOSURE-
I HAVE NO DISCLOSURES...
OBJECTIVES...

• Recognizing and diagnosing movement disorders associated with antipsychotics.
ANTIPSYCHOTICS - HISTORY

LARGACTIL

5 ampollas de 5 cc.

LAsCOTAxO SfS pInAsCuttORS

SOCIETE ANONYMAE CLINIQUE S.A.

S.25
EVOLUTION OF APD
EVOLUTION OF ANTIPSYCHOTICS

1. Haloperidol
2. Seroquel
3. Aripiprazole

Dopamine Receptors
Results - Overall, the children had significant clinical improvement as assessed by the CPRS and CGI. Untoward effects included sedation, increased appetite, and weight gain.

Two of 13 (15.4%) children treated long-term developed mild, reversible withdrawal dyskinesias when risperidone was discontinued. No child developed dyskinesias on risperidone.

Conclusions
Risperidone shows promise as a treatment in autism. However, withdrawal dyskinesias were noted. Further assessment of the risk of risperidone-related dyskinesias is indicated.
Overall rates of drug-induced parkinsonism SGA treatment were low, indicating that the short-term neuromotor adverse effects of SGAs during routine care are not a major clinical problem.

Low rates of drug-induced parkinsonism were found with quetiapine, indicating that youth prone to extrapyramidal adverse effects might benefit from this drug choice.

Beyond SGA choice, drug-induced parkinsonism was associated with higher dose, higher age, and lower baseline functioning:
  • Cautious dosing seems advisable not only in young children but also in adolescents.
  • Cautious dosing seems advisable also in low-functioning youth.

Psychotropic polypharmacy was associated with increased rates of tremor and dyskinesia.
EXTRAPYRAMIDAL SIDE EFFECTS

- Dystonia
- Akathisia
- DIPD
- Tremors

Days………….
Basal Ganglia- Nigrostriatal Pathway

Cerebral Cortex

Striatum

D1 + D2 --

Substantia Nigra

Sun-thalamic Nucleus

Thalamus VA/ VL Nucleus

Globus Pallidus Internal

Globus Pallidus External

Nigrostriatal Pathway
Basal Ganglia- Indirect Pathway

Cerebral Cortex

Striatum

D2 --

Substantia Nigra

Globus Pallidus Internal

Sun-thalamic Nucleus

Thalamus VA/ VL Nucleus

Globus Pallidus External
Increased NA activity from the locus ceruleus.

Blockade of mesocortical dopaminergic pathways

Cerebral Cortex

Striatum

D2 --

Substantia Nigra

Raphe Nucleus

Globus Pallidus External

Sun-thalamic Nucleus

Thalamus VA/ VL Nucleus

Globus Pallidus Internal

Basal Ganglia - Akathisia
Increased dopamine D$_2$ receptor binding after long-term treatment with antipsychotics in humans: a clinical PET study

- This study demonstrates for the first time, using in vivo neuro-receptor imaging, that dopamine D2 receptor binding is increased after long-term treatment with antipsychotics in humans.
- D2 receptor-mediated mechanisms in motor hyperactivity.
Postsynaptic neuron

D2 receptor Antagonist
D2 receptor Upregulation
UNDER-RECOGNITION AND MISDIAGNOSIS OF AKAHTISIA- THE PATIENT FACTORS

1) Mild severity of akathisia,
2) Lack of apparent motor Restlessness,
3) No voluntary expression of inner Restlessness,
4) No clear communication of inner Restlessness,
5) Restlessness in body parts other than the legs,
6) Atypical expressions of inner restlessness,
7) Other prominent psychiatric symptoms, and
8) Absence of other extrapyramidal signs.

UNDER-RECOGNITION AND MISDIAGNOSIS OF AKATHISIA- THE CLINICIAN FACTORS.

1. Emphasis on objective restlessness,
2. Failure to consider akathisia during antipsychotic therapy,
3. Failure to fully implement anti-akathisia treatments in ambiguous cases, and
4. Strict adherence to research diagnostic criteria

This 10-year-old boy was diagnosed with ASD and mood disorder and OCD since the age of 8.

He was seen first at our institution in December of 2012, at which point he demonstrated a variety of motor and phonic tics as well as pronounced obsessive behavior—"in order/just right" “extra sure that things are safe, clean, or right in some way”.
- He had with multiple motor and phonic tics that waxed and waned in nature and severity.
- He emphasized that these movements were purposeful, intended to relieve his restlessness, and they abated completely when he was distracted with a variety of motor tasks.
• He was initially referred for habit reversal therapy but he was unable to participate.
  • Awareness training,
  • Competing response training,
  • Contingency management,
  • Relaxation training, and
  • Generalization training.
He was later tried on guanfacine at maximum dose of 2.5 mg/day but it was discontinued due to sedation and low blood pressure.

In the spring of 2014, he was started on risperidone 0.5 mg/day, and the dosage was gradually increased to 3 mg/day for maximum benefits- Weight gain

In past he was tried on fluoxetine 20 mg/day and sertraline 50 mg/day.

But he became irritable and did not tolerate the medications well.
• Over the next 2 weeks, the dose was reduced at a rate of one third every three days.

  • Risperidone 1 mg two times daily for 3 days
  • Risperidone 0.5 mg two times daily for 3 days
  • Risperidone 0.25 mg two times daily for 3 days

STOP

..Manage his ADHD Anxiety..
CASE - DEVIL'S NIGHT.

• At the beginning of September patient developed a severe restlessness (“this is different”) with a marked inability to remain still.
• This was especially prominent in the sitting position, and he felt better lying and standing.
• He had to walk around to eat and was unable to attend school, losing an entire semester.
• He demonstrated pronounced restlessness and excessive perspiration.
He slept and was sent home with prescription of lorazepam 0.5 mg two times daily.

Mom gave first dose in the morning and in 20 minutes “all hell breaks loose”.

Finally mother called the office and he was given an urgent appointment.
CASE - DIFFERENTIAL DIAGNOSIS

- Anxiety
- Agitation with medical conditions
- The tics of Tourette disorder
- Restless Legs Syndrome (RLS)
DO SOMETHING DOCTOR..

Lets go where it began– we realized that all started when his risperidone was stopped.

So we decided to restart the risperidone– but the question was how much?

We had no idea- mother reported that he was better when he was on risperidone 2 mg/day

With single dose of risperidone 1 mg he reported improvement.

He was maintained on the same dose for 1 month.
WE WANT TO STOP IT- SLOW TAPPER

• How to do it– no literature
• Trial and error—
• We tried- we failed…
• We learned and tied again– we tried slowly..
  • Risperidone 1 mg two times daily for 30 days
  • Risperidone 0.5 mg two times daily for 45 days
  • Risperidone 0.25 mg two times daily for 60 days

STOP
LESSONS..

- They may not present immediately after stopping antipsychotics...
- Presentations can be simple with involvement of single muscle group..
- It can also be complex with multiple dyskinesia...
- They can be voluntary suppressed by the child to avoid embarrassment...
- Simultaneous use of stimulants and Antipsychotics can make it worse...
- No specific guidelines for taper...
- Prevention is the best strategy...
“HOW LONG DOES IT TAKE FOR ANTIPSYCHOTIC TO GET OUT OF MY CHILD SYSTEM?”

DISCONTINUATION OF ANTIPSYCHOTICS IN CHILDREN

Ravi Patel, MD
Child and Adolescent Psychiatrist
Assistant Professor University of California Riverside
Board Certified, American Academy of Neurology and Psychiatry – General Psychiatry, Child and Adolescent Psychiatry
• No relevant financial disclosure
WHY THIS CASE?

- State laws affecting treatment and decisions at times
- Insurance companies changing formularies
- Not having enough access to Child psychiatrist and patients need to seek support from other health providers.
CASE- PLEASE LISTEN AND WATCH!!

- Mr. A is an 8-year-old, boy with multiple hospitalizations in the past
- He was admitted with the chief complaint of “stealing everything under the sun”.
- On face to face eval:
  - could not sit still on the chair. (30 sec test)
  - I walked with him in the hallway: he had difficulty walking straight and was noted to have abnormal choreo-athetoid movement of his extremity, torso, and neck.
REPORTS FROM MOTHER

• could not sit still

• Likes to ride a Go-kart but could not sit still in Go-kart

• At school, he was running half mile

• Teacher noted twitching and lip movements at mouth.
PAST HISTORY

• Diagnosis: ADHD-CT and mood disorder

• NO SA/HA

• Multiple Previous Admissions (7 per report)

• Following up with outpatient psychiatrist and Psychologist (No specific finding).
MEDICATION HISTORY

• Risperidone: which was not working for him.

• Aripiprazole: stopped during previous hospitalization

• Ziprasidone: made him “insane” per mother.

• Olanzapine: caused him a weight gain of 12 lbs and it was stopped in the past.
MEDICATION HISTORY

• Melatonin 5 mg at 2000.

• Had stimulant medication in past: Focalin, Adderall.

• No trial of any antidepressant or mood stabilizer.

• Compliance with Medications: Yes, per mom.

• 4 weeks ago: he was switched from Aripiprazole to Quetiapine
D2 receptor
Upregulation
D2 High potency Antagonist like aripiprazole discontinuation

D2 low potency Antagonist like Quetiapine crossover
D2 High potency Antagonist discontinuation

D2 low potency Antagonist crossover
POTENCY VS. EFFICACY

- **Potency**: Amount of drug required to produce an effect of given intensity.
- **Affinity**: Ability of the drug to bind to a receptor.
- **Efficacy**: Relationship between receptor occupancy and the ability to initiate a response.
## POTENCY OF ANTIPSYCHOTICS

Table III. Receptor binding affinities of antipsychotic agents (empty cells indicate no data)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Inhibition constant (nmol/L)</th>
<th>5-HT&lt;sub&gt;2C&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;2A&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;1A&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;6&lt;/sub&gt;</th>
<th>D&lt;sub&gt;2&lt;/sub&gt;</th>
<th>H&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M&lt;sub&gt;3&lt;/sub&gt;</th>
<th>α&lt;sub&gt;1A&lt;/sub&gt;</th>
<th>α&lt;sub&gt;2A&lt;/sub&gt;</th>
<th>α&lt;sub&gt;2B&lt;/sub&gt;</th>
<th>α&lt;sub&gt;2C&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 000</td>
<td>53</td>
<td>1202</td>
<td>3666</td>
<td>4</td>
<td>1800</td>
<td>10 000</td>
<td>12</td>
<td>1130</td>
<td>480</td>
<td>550</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22.4</td>
<td>8.7</td>
<td>5.57</td>
<td>785.2</td>
<td>0.66</td>
<td>29.7</td>
<td>4677</td>
<td>26</td>
<td>74</td>
<td>102</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Asenapine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.034</td>
<td>0.07</td>
<td>2.7</td>
<td>1.3</td>
<td>1.0</td>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17</td>
<td>5.4</td>
<td>104.8</td>
<td>17</td>
<td>256</td>
<td>12</td>
<td>25</td>
<td>1.64</td>
<td>142</td>
<td>26</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Iloperidone&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14</td>
<td>0.20</td>
<td>33</td>
<td>3.3</td>
<td>12.3</td>
<td>6000</td>
<td>0.31</td>
<td>3.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lurasidone&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.03</td>
<td>6.75</td>
<td></td>
<td>1.68</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>47.9</td>
<td>40.7</td>
<td>10.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.8</td>
<td>2</td>
<td>2063</td>
<td>6.28</td>
<td>34</td>
<td>2</td>
<td>105</td>
<td>115</td>
<td>314.1</td>
<td>81.6</td>
<td>28.8</td>
<td></td>
</tr>
<tr>
<td>Paliperidone&lt;sup&gt;b&lt;/sup&gt;</td>
<td>48</td>
<td>1.21</td>
<td>480</td>
<td>2.8</td>
<td>34</td>
<td>8800</td>
<td>10.1</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 502</td>
<td>101</td>
<td>431.6</td>
<td>1866</td>
<td>245</td>
<td>21</td>
<td>10 000</td>
<td>22</td>
<td>3630</td>
<td>746.6</td>
<td>28.7</td>
<td></td>
</tr>
<tr>
<td>Risperidone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35</td>
<td>0.17</td>
<td>427.5</td>
<td>1188</td>
<td>65</td>
<td>15</td>
<td>10 000</td>
<td>5</td>
<td>150.8</td>
<td>107.6</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13</td>
<td>0.3</td>
<td>76</td>
<td>60.9</td>
<td>9.7</td>
<td>43</td>
<td>10 000</td>
<td>18</td>
<td>160</td>
<td>48</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Kroeze et al.<sup>[49]</sup>
<sup>b</sup> Richelson and Souder<sup>[50]</sup>
<sup>c</sup> Ishibashi et al.<sup>[51]</sup>
### NEUROPHARMACOLOGY AND RECEPTOR BINDING PROFILE
BINDING AFFINITIES OF ATYPICAL ANTIPSYCHOTICS (COMpared with Haloperidol)

<table>
<thead>
<tr>
<th></th>
<th>Haloperidol</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>Quetiapine</th>
<th>Ziprasidone</th>
<th>Aripiprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2 receptors</td>
<td>1.4</td>
<td>130</td>
<td>20</td>
<td>2.2</td>
<td>180</td>
<td>3.1</td>
<td>0.4</td>
</tr>
<tr>
<td>5-HT1A receptors</td>
<td>3,600</td>
<td>140</td>
<td>2,100</td>
<td>210</td>
<td>230</td>
<td>2.5</td>
<td>4.4</td>
</tr>
<tr>
<td>5-HT1B/1D receptors</td>
<td>&gt;5,000</td>
<td>1,700</td>
<td>530</td>
<td>170</td>
<td>&gt;5,100</td>
<td>2</td>
<td>68</td>
</tr>
<tr>
<td>5-HT2A receptors</td>
<td>120</td>
<td>8.9</td>
<td>3.3</td>
<td>0.29</td>
<td>220</td>
<td>0.39</td>
<td>3.4</td>
</tr>
<tr>
<td>5-HT2C receptors</td>
<td>4,700</td>
<td>17</td>
<td>10</td>
<td>10</td>
<td>1,400</td>
<td>1.72</td>
<td>15</td>
</tr>
<tr>
<td>5-HT uptake transporters</td>
<td>1,800</td>
<td>3,900</td>
<td>&gt;15,000</td>
<td>1,400</td>
<td>&gt;18,000</td>
<td>53</td>
<td>98</td>
</tr>
<tr>
<td>NE uptake transporters</td>
<td>5,500</td>
<td>330</td>
<td>2,000</td>
<td>28,000</td>
<td>680</td>
<td>48</td>
<td>2,090</td>
</tr>
</tbody>
</table>

**Binding affinities associated with potential adverse effects (mean pKi, nM)**

<table>
<thead>
<tr>
<th></th>
<th>Haloperidol</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>Quetiapine</th>
<th>Ziprasidone</th>
<th>Aripiprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1 receptors</td>
<td>440</td>
<td>1.8</td>
<td>2.8</td>
<td>19</td>
<td>8.7</td>
<td>47</td>
<td>61</td>
</tr>
<tr>
<td>M1 receptors</td>
<td>1,600</td>
<td>1.8</td>
<td>4.7</td>
<td>2,800</td>
<td>100</td>
<td>5,100</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>±1-adrenoceptors</td>
<td>4.7</td>
<td>4</td>
<td>54</td>
<td>1.4</td>
<td>15</td>
<td>13</td>
<td>57</td>
</tr>
<tr>
<td>±2-adrenoceptors</td>
<td>1,200</td>
<td>33</td>
<td>170</td>
<td>5.1</td>
<td>1,000</td>
<td>310</td>
<td>74</td>
</tr>
</tbody>
</table>

• PET studies: Relationship between D2 receptor occupancy and antipsychotic effects

• D2 receptor occupancy in the ranges of 60% to 75% is associated with antipsychotic efficacy.

• Quetiapine has been shown to occupy approximately 30% of D2 receptors at therapeutic doses

• “Kiss and run”
  • In a series of studies they found that in contrast to other antipsychotics, Quetiapine had a more rapid “run-off”, or rapid dissociation, from D2 receptors

KISS AND RUN
D2 high potency
Antagonist
discontinuation

D2 low potency
Antagonist
crossover

Postsynaptic neuron
• 12 year old girl with ADHD, ODD and Autism

• On Olanzapine - 15 mg PO daily for aggression

• Previous trial of Risperdal - Parents worried about side effects after a few months, Aripiprazole was not covered by insurance at that time

• Following up with PCP who managed medication for 6 years
• Started following patient - continued medication same as patient was doing ok

• After 4 months patient was stable. We had a lengthy discussion about weight gain (total of 16 lb) and patient’s benefit in aggression however, parents requested to stop it.

• Explained in detail about process of discontinuation including withdrawal dyskinesia, experience in reducing medication and possible length of process as well as worsening of behavior and possibility of going back as well as crisis resources in case if needed. Parents and patient both agreed.
PLEASE SLOW DOWN!!!!!

Reduced Olanzapine to 10 mg for 2 weeks

Occasional outbursts, but no more than her baseline

Reduced further to 5 mg for 2 weeks, and then switched to bedtime for 2 weeks (previous experience)

No significant worsening and parents requested to continue taper

Reduced further to 2.5 mg PO bedtime for 4 weeks

STOP (Total 10 weeks)
<table>
<thead>
<tr>
<th>No.</th>
<th>Demographics</th>
<th>Drug taper/stop</th>
<th>Total Time to stop</th>
<th>t 1/2</th>
<th>D2 Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9 yo CM</td>
<td>Aripiprazole</td>
<td>4.5 months</td>
<td>75-94 hrs</td>
<td>0.4</td>
</tr>
<tr>
<td>2</td>
<td>12 yo CF</td>
<td>Olanzapine</td>
<td>2.5 months</td>
<td>21-54 hrs</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>9 yo AAM</td>
<td>Risperidone</td>
<td>2.5 months</td>
<td>3-20 hrs</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>——-</td>
<td>Quetiapine</td>
<td>——-</td>
<td>6 hrs</td>
<td>180 (140-Clozapine)</td>
</tr>
<tr>
<td>4</td>
<td>15 yo CM</td>
<td>Haloperidol</td>
<td>3 months</td>
<td>21-24 hrs</td>
<td>1.4</td>
</tr>
<tr>
<td>5</td>
<td>8 yo CM</td>
<td>Risperidone</td>
<td>9 months</td>
<td>3-20 hrs</td>
<td>2.2</td>
</tr>
<tr>
<td>6</td>
<td>13 yo AF</td>
<td>Abilify</td>
<td>4.2 months</td>
<td>75-94 hrs</td>
<td>0.4</td>
</tr>
</tbody>
</table>
CONCLUSIONS

1. Do not start unless needed.
2. Do not stop during hospitalization.
3. Not to quickly.
4. Not with stimulant.
5. Do not stop during the school.
6. Polypharmacy complicates the taper.
7. Cross taper- careful from high potency to low potency.
QUESTIONS?
REFERENCE

