

Child Psychopharmacology *Antipsychotics for Aggression - Can We Do Better?*

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Objectives

- Appropriately and fully evaluate child and adolescents with aggressive behavior and consider treatment alternatives to atypical antipsychotics
- Ensure that antipsychotic medications are used in child and adolescent populations according to evidence-based guidelines
- Decrease disparities in use of antipsychotics in youth by restricting their use to cases that fall under FDA guidelines, or for cases with a robust evidence base, or when alternative treatments have failed

Case #1

7 year old Hispanic male interviewed with adoptive mother

- History of mild developmental delay; biological mom in jail and has history of drug use and possible bipolar disorder
- Concern about aggressive and defiant behavior since entering preschool at age 3
- Tends to get irritable easily, agitated, restless
- Patient "shuts down" when he gets upset and refuses to do work. No friends in school because he throws tantrums and is aggressive nearly daily

Case #1 (continued)

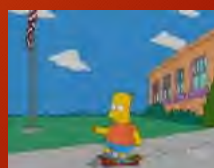
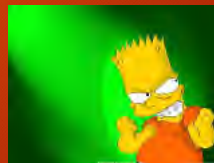
- Has run away from class, climbed over fence, tried to walk home when upset; police involved at one point.
- Grades are average even with a lot of academic support. Mom reports that at home he is hyper at times; he is inattentive, has difficulty listening, staying on task, distracted easily but she is unsure if this is worse than for other 7 -year old boys.
- Seems to enjoy some social interaction; no OCD-like symptoms; normal interests for age.
- Sleeps well, good appetite, good energy level.
- Current stressors: 7-month old adoptive brother at home for past 3 months, change in school this year to special education program

What is the problem?

CSGs/NCQHA Hedis measures

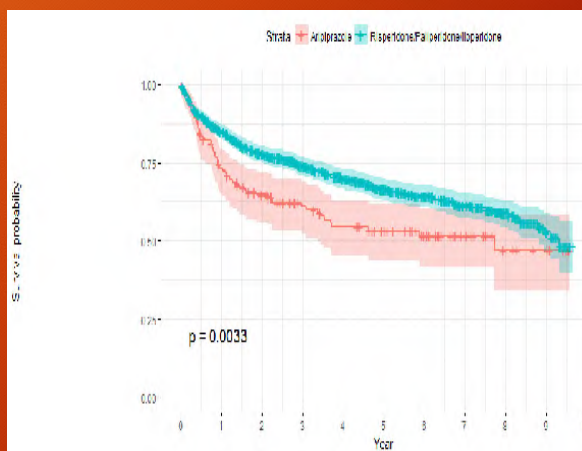
- Use of Multiple Concurrent Antipsychotics in Children and Adolescents (APC)
- Metabolic Monitoring for Children and Adolescents on Antipsychotics (APM)
- Use of First-Line Psychosocial Care for Children and Adolescents on Antipsychotics (APP)

- Correll et al, 2009:
- ~11 weeks of treatment, youth 4-19 years old:
 - Olanzapine +8.5kg
 - Quetiapine +6.1kg
 - Risperidone +5.3 kg
 - Aripiprazole +4.4 kg



What is the problem?

- Kaiser Permanente Southern California patients, age 2-11 (unpublished data)



What is the problem?

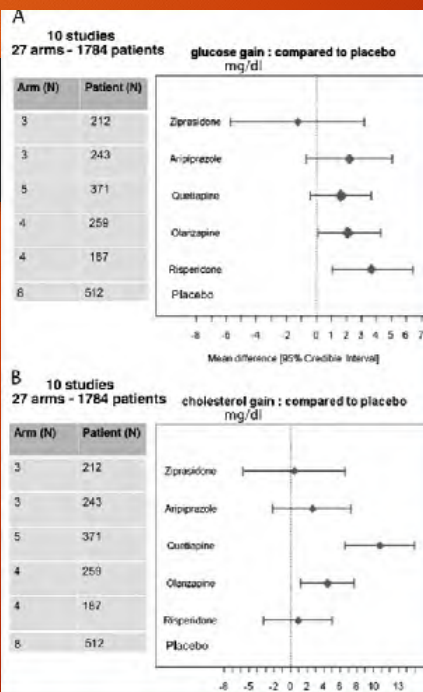
- Correll et al. 2009 (~11 weeks):

Glucose, mg/dL		
Aripiprazole	0.54 (-2.85 to 3.93)	.76
Olanzapine	3.14 (0.69 to 5.59)	.02
Quetiapine	2.64 (-0.65 to 5.93)	.12
Risperidone	1.14 (-0.84 to 3.12)	.26
Untreated	0.69 (-4.84 to 6.22)	.81

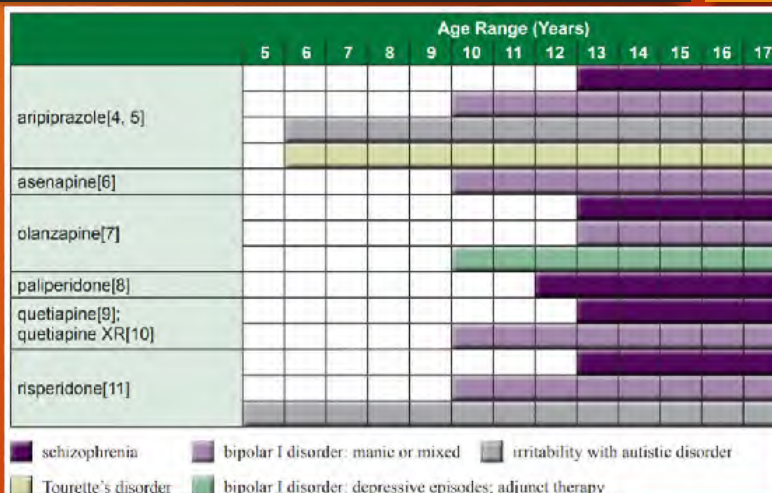
LDL cholesterol, mg/dL		
Aripiprazole	7.38 (0.77 to 13.99)	.05
Olanzapine	11.54 (3.97 to 19.11)	.004
Quetiapine	3.88 (-3.37 to 11.13)	.30
Risperidone	0.21 (-4.14 to 4.56)	.92
Untreated	2.99 (-5.18 to 11.16)	.49

What is the problem?

- Cohen et al. 2012 (3-12 weeks):



FDA approved uses for atypical antipsychotics



FDA-approved medications

Chlorpromazine: ages 1-12

- for severe behavioral problems “marked by combativeness and/or explosive hyperexcitable behavior”

Factor I (Irritability, Agitation, Crying)

2. Injures self
4. Aggressive to other patients and staff
8. Screams inappropriately
10. Temper tantrums
14. Irritable (“grizzly” & “whiny”)
19. Yells at inappropriate times
25. Depressed mood
29. Demands must be met immediately
34. Cries over minor annoyances and hurts
36. Mood changes quickly
41. Cries and screams inappropriately
47. Stomps feet while banging objects or slamming doors
50. Deliberately hurts himself/herself
52. Does physical violence to self
57. Throws temper tantrums when he/she does not get own way

FDA-approved medications

Haloperidol: ages 3-12

- “For the treatment of severe behavioral problems associated with oppositional defiant disorder or other disruptive behavioral disorders, or for the treatment of attention-deficit hyperactivity disorder (ADHD) in pediatric patients who show excessive motor activity with accompanying conduct disorders.”

Irritability associated with autism

- Risperidone (5 and up)
- Aripiprazole (6 and up)

Alternative (“off-label”) treatments for aggression

- TOSCA trial (6-12 years old, mostly boys with ADHD and severe aggression and defiance)
 - Parent Training (weekly for 9 weeks) + stimulant (MTP OROS or AMP XR)
 - Added risperidone or placebo after 3 weeks, until week 9
- Results: 60% of patient improved significantly in the placebo group
 - Risperidone group: ODD symptoms improved for parents - effect size 0.27, ADHD symptoms improved for teachers - effect size 0.61

Alternative (“off-label”) treatments for aggression

- However, reduced effects of risperidone by week 21, and nonsignificant difference by week 52
 - Also had higher prolactin, more weight gain and GI upset
- *Alternative conclusion:* majority of benefit is from parent training and treatment of ADHD with stimulant medication

Alternative (“off-label”) treatments for aggression

Disruptive Mood Dysregulation Disorder

- Intended as an alternative to “bipolar disorder” overdiagnosis in children and adolescents
 - Chronic irritability is associated with development of Major Depressive Disorder (not bipolar)
- Angry/irritable mood daily, 3 or more temper outbursts weekly for 12+ months

Alternative (“off-label”) treatments for aggression

- No RCTs yet for specific treatment recommendations
 - Valproate may help with mood lability, temper tantrums, aggression
 - Fluoxetine, bupropion may help with aggression
 - Clonidine and guanfacine show benefit for aggression

Alternative (“off-label”) treatments for aggression

- Autism Spectrum Disorders -Irritability
 - N-acetylcysteine showed large effect size (0.7), similar to risperidone (0.9) and aripiprazole (0.8)
 - Clonidine showed moderate effect size (0.6)
 - Methylphenidate showed moderate effect size (0.6)
 - Venlafaxine showed smaller effect size (0.4), and citalopram (0.1)

Alternative ways to look at “aggression” as a symptom

- *Impulsive* - high arousal, anger, fear, responsive to perceived threat vs. *nonimpulsive* - low arousal, goal-oriented, rewarded
- Reactive/impulsive actions associated with ADHD and anxiety

Alternative ways to look at “aggression” as a symptom

- *Consider stimulants, nonstimulants, SSRIs, hydroxyzine*
- Proactive/nonimpulsive actions associated with conduct disorder, environmental influences (parenting, school setting)
- *Focus on psychotherapy, family and school interventions*

Case #1 revisited

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Case #1 Revisited (continued)

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Case #1 Revisited (continued)

- Sleeps well, good appetite, good energy level.
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Case #1 Revisited

- Patient was screened with teacher and parent Conners' for ADHD
 - Met criteria for combined type
- Responded well to treatment with stimulant
 - A2 agonist added to help with early morning and afternoon/evening behavior

Case #1 Revisited

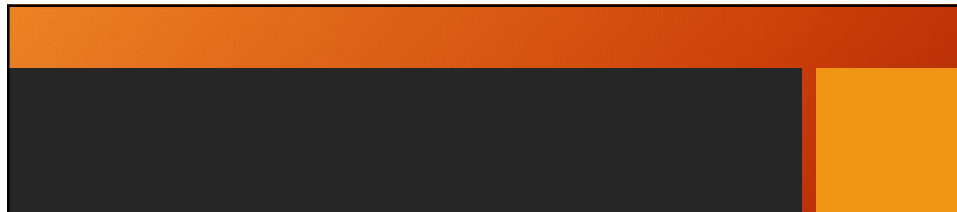
- After about 1 year, patient was started on SSRI for anxiety symptoms and since has had only minor episodes of verbal aggression
- Continues in therapy and has been able to implement more adaptive coping skills
 - Mother has been more consistent with parenting strategies

Summary


- Atypical antipsychotics are commonly used to treat disruptive behavior in children and teenagers
- There are growing concerns about metabolic abnormalities with use of these medications, including new governmental policies to attempt to reduce their use
- Usually these medications are being used off-label
- In many cases, there may be safer and effective alternatives for pharmacologic treatment of disruptive behavior, including evaluation and treatment of other comorbid conditions

Case #2

- 3 year old girl presenting with several episodes per day of uncontrollable screaming and “losing control”.
- Severe insomnia, having trouble falling asleep and waking up in the middle of the night screaming uncontrollably.
- Grandmother reports extreme hyperactivity during the day and daily fighting with her sister. Child will not allow grandmother to bathe her or help her with activities of daily living.



- Developmental assessment shows typically developing child
- Average cognition
- In the office, child was well behaved and showed typical level of activity



- Patient had been removed from mother's care at 2.5 years old.
- Mother with history of substance abuse.
- Child was exposed to drug dealing at home. Many of the deals happened in the middle of the night.
- Exposed to sexual activity
- History of being taken out of mother's care in the middle of the night.
- Mother visitations were extremely inconsistent

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- Grandmother reports extreme hyperactivity during the day severe fighting with her sister. Child not, allowing grandmother to bather or help her with activities of daily living.
- Grandmother has video of her severe behaviors

- Developmental assessment shows typically developing child.
- Average cognition.
- In office child was well behaved, typical level of activity

Brief History

- Patient had been removed from mother's care at 2.5 years old.
- Mother with history of substance abuse.
- Child was exposed to drug dealing at home. Many of the deals happened in the middle of the night.
- Exposed to sexual activity
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Medication Trials

- Guanfacine attempted for 6 months. Symptoms improved but persisted
- Clonidine attempted for 1 year. Symptoms improved but persisted
- Fluoxetine attempted for one month, it caused hyper alertness and increased level of activity.

- Risperidone attempted and it helped with symptoms. However symptoms were never completely controlled.
- After one year of risperidone child developed hypertriglyceridemia and hypercholesterolemia. Weight jumped from 40th% to 85th %.
- Risperidone was weaned down and child was placed on clonidine again.
- Behaviors on clonidine were similar to when on risperidone.

Discussion questions



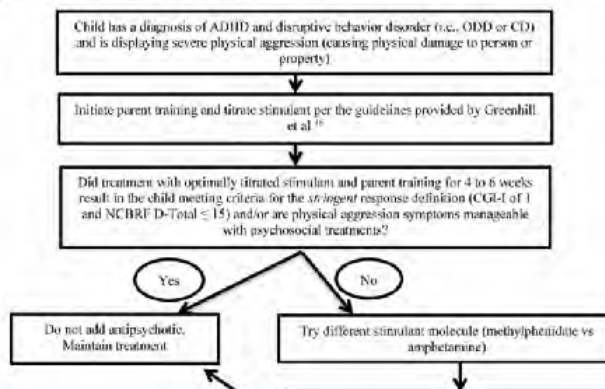
Consider in your discussion:

1. What are the symptoms that can be targeted for treatment?
2. What additional information is needed to clarify diagnosis and appropriate treatment targets?
3. In addition to therapy, what psychotropic medication may be helpful to treat this patient?

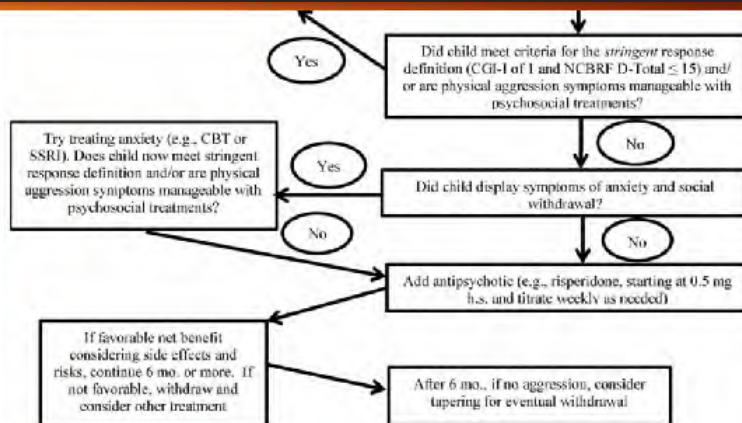
Once done discussing these questions, please review Part 2 of the case and then we'll have a volunteer from each table report out.

Barterian et al, 2017

FIGURE 2 Potential treatment algorithm for children with severe physical aggression. Note: Clinicians should weigh adverse reactions into their cost-benefit analysis. ADHD = attention-deficit/hyperactivity disorder; CBT = cognitive-behavioral therapy; CD = conduct disorder; CGI-I = Clinical Global Impression-Improvement (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change); D-total = disruptive behavior total; NCBRF = Nisonger Child Behavior Report Form; ODD = oppositional defiant disorder; SSRI = selective serotonin reuptake inhibitor.



Barterian et al, 2017 continued



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Self-Assessment Questions

Self-Assessment Questions

1. Which of the following medications are FDA-approved for the treatment of irritability in children with autism?

- A. Aripiprazole and risperidone
- B. Risperidone and quetiapine
- C. Risperidone and olanzapine
- D. Risperidone and haloperidol
- E. Haloperidol and perphenazine

2. A 6-year-old normally developing boy is brought to your office for an evaluation. He has been increasingly aggressive at home and at school with family and peers, including punching his teacher, leading to a suspension. His parents are pleading for any help you can provide. Practice guidelines recommend first-line treatment for aggression in children should be:

- A. Behavioral therapy
- B. Atypical antipsychotic
- C. SSRI
- D. A2 agonist
- E. Psychostimulant

3. Pharmacotherapy of aggression in children and adolescents with autism is most effective when:

- A. There is aggressive behavior in multiple settings
- B. The behavior is unresponsive to behavioral intervention
- C. The aggression is impulsive and uncontrolled
- D. All of the above

4. Which of the following medications is FDA-approved for treatment of severe behavioral problems “marked by combativeness and/or explosive hyperexcitable behavior” in young children?

- A. Chlorpromazine
- B. Risperidone
- C. Quetiapine
- D. Aripiprazole
- E. Olanzapine

5. For disruptive behavior disorders comorbid with ADHD in normally developing children, which of the following medications was found to be most effective for reducing aggression?

- A. Risperidone
- B. Quetiapine
- C. Valproic Acid
- D. Methylphenidate
- E. Lithium