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Antipsychotics and Mood Stabilizers in children and adolescents

What we will cover today

- FDA Status
- Informed consent
- Medications
- Non-medication treatments
- Ways to engage the prescriber
- Interactive discussion/questions using ‘Chat’ function

What does FDA approval mean

- The FDA has decided the benefits outweigh the potential risks
  - FDA= Food and Drug Administration
- No drug is entirely risk-free
- Research and testing must show that the benefits of the drug for a particular condition outweigh the risks to patients of using the item

‘Off-Label’ Medications

- We prescribe medications that are **‘off-label’**
- This means they are not FDA approved
- The importance is to describe that the use is ‘off-label’ when obtaining informed consent to treat with medications
  - ‘Off-label’ does not mean bad
  - In Child Psychiatry many medication treatments are off label

Informed Consent

- Informed Consent
  - The information about treatment that needs to be communicated to the guardian in order to get consent to treat
  - Important that this process is interactive
  - Appropriate for guardian to get questions answered in order to feel confident about treatment

Elements of Informed Consent

- **Elements of Informed consent**
  - Purpose of proposed treatment (expected outcome)
  - Risk and benefit of treatment
  - Alternatives for treatment
    - Including non-medication options
  - Risks and benefit of alternative medications
  - Risk and benefit of not receiving treatment
  - FDA status of medication options
  - Possible side effects (aka: adverse drug reactions or ADR's)

Antipsychotic Medications

First Generation Antipsychotics (FGA)

- Chlorpromazine
- Fluphenazine
- Haloperidol
- Loxapine
- Perphenazine
- Pimozide
- Thioridazine
- Thiothixene
- Trifluoperazine

Second Generation Antipsychotics (SGA)

- Aripiprazole
- Asenapine
- Brexpiprazole
- Cariprazine
- Clozapine
- Iloperidone
- Lurasidone
- Olanzapine
- Paliperidone
- Quetiapine
- Risperidone
- Ziprasidone

FGA: Approved Indications

	Schizophrenia	Tourette's	Severe Behavioral Problems
Chlorpromanzine			6 mo - 12 yrs
Haloperidol		≥ 3 yrs	"children"
Perphenazine	≥ 12 yrs		
Pimozide		≥ 12 yrs	
Thiothixene	≥ 12 yrs		
Trifluoperazine	≥ 12 yrs		

SGA: Approved Indications

	Schizo	BPD, Mania	BPD, Mixed	BPD, Maint	ASD, Agitation
Aripiprazole	13-17 yrs	10-17 yrs	10-17 yrs		6-17 yrs
Asenapine		10-17 yrs	10-17 yrs		
Lurasidone	13-17 yrs				
Olanzapine	13-17 yrs	13-17 yrs	13-17 yrs		
Paliperidone	12-17 yrs				
Quetiapine	13-17 yrs	10-17 yrs		10-17 yrs	
Risperidone	≥ 13 yrs	≥ 10 yrs		≥ 10 yrs	≥ 5 yrs

Schizo = Schizophrenia; BPD = Bipolar Disorder Type I; ASD = Autism Spectrum Disorder; Maint = Maintenance therapy

Antipsychotics

- First generation—aka typical antipsychotics are the older antipsychotics
  - Higher risk of Extrapyramidal Symptoms (EPS)
- Second generation—aka atypical antipsychotics are the newer antipsychotics
  - Higher risk of metabolic syndrome
  - **Used more commonly than first generation**

SGA Safety and Adverse Effects

- Children and adolescents appear to be more susceptible to a number of side effects caused by antipsychotic medications
  - Sedation, withdrawal dyskinesia, endocrine abnormalities, age-inappropriate weight gain, and other metabolic side effects
- Safety and tolerability data are still sparse
- Even fewer long-term safety studies exist to evaluate the distal risks/benefits

Correll CU. *J Am Child Adolesc Psychiatry.* 2008;47
Vitiello B. *European Neuropsychopharmacology.* 2009

SGA Side Effects

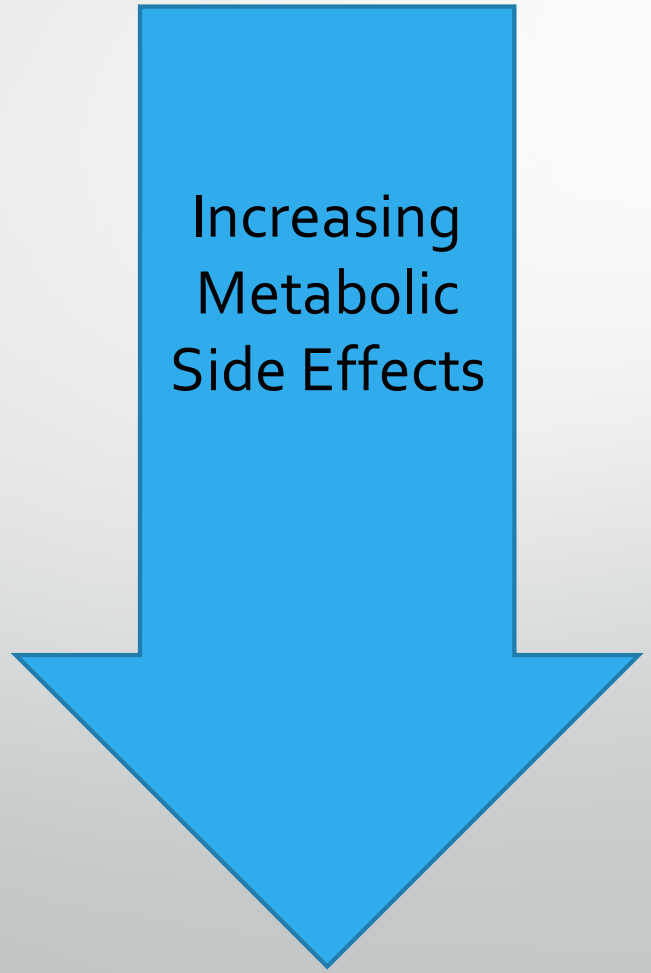
- Sedation
- Stomach upset
- Nausea
- Constipation
- Prolactin elevation
  - Risperidone
  - Paliperidone
- Cardiovascular
  - QTc prolongation
    - Quetiapine

- Extrapyramidal Symptoms (EPS)
  - Akathisia
  - Tardive Dyskinesia
  - Pseudoparkinsonism
  - Dystonic Reaction

- Metabolic Effects
  - Weight gain
  - Lipid abnormalities
  - Glucose intolerance

SGA Side Effects

- Aripiprazole
- Lurasidone
- Asenapine
- Risperidone
- Paliperidone
- Quetiapine
- Olanzapine



Antipsychotic Side Effects

- EPS
  - **Akathisia**-feeling of internal motor restlessness
  - **Tardive dyskinesia-**-involuntary muscle movements in the lower face and distal extremities
  - **Pseudoparkinsonism**-drug-induced parkinsonism (rigidity, bradykinesia, tremor, masked facies, shuffling gait, stooped posture, sialorrhoea, and seborrhea)
    - greater risk in the elderly
  - **Dystonia**-muscle spasm of neck, jaw, back, extremities, eyes, throat, and tongue
    - highest risk in young men

Antipsychotic Side Effects

- **Metabolic Syndrome**
  - obesity
  - abnormal glucose and lipid metabolism
    - elevated glucose
    - elevated lipids
  - clozapine and olanzapine associated with the highest metabolic risk

Antipsychotic Side Effects

- **Neuroleptic Malignant Syndrome**
  - **Rare** and **life-threatening** neurological disorder caused by antipsychotic
  - Symptoms
    - muscle rigidity
    - fever
    - autonomic instability
    - cognitive changes such as delirium
    - associated with elevated plasma creatine phosphokinase

*ADA Monitoring protocol for patients on SGAs**

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status

Diabetes Care 2004; 27: 596-601.

AACAP Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents

https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx

AACAP Findings (2011)

Indications	Cloz	Risp	Olanz	Quet	Zipras	Aripip
Schizophrenia	+++	+++	++++	++++	+	++++
Bipolar Disorder	++	+++	+++	++++	+++	+++
Aggression	++	+++	+++	++	+	+
Autism Irritability	+	++++	+++	+	+	++++
Tourettes		++++	+		+++	
Eating Disorder			+			
Long-Term Safety		+		+		

Cloz = Clozapine; Risp = Risperidone; Olanz = Olanzapine; Zipras = Ziprasidone; Aripip = Aripiprazole

AACAP Conclusions (Antipsychotics)

- There exists a paucity of methodologically rigorous studies evaluating the use of SGAs in children and adolescents
- Evidence is strongest in supporting use of SGA for schizophrenia and bipolar
- Evidence for use with disruptive behavior disorders is much less robust except in youths with autism

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American Psychiatric Association

Five Things Physicians and Patients Should Question

1 Don't prescribe antipsychotic medications to patients for any indication without appropriate initial evaluation and appropriate ongoing monitoring.

Metabolic, neuromuscular and cardiovascular side effects are common in patients receiving antipsychotic medications for any indication, so thorough initial evaluation to ensure that their use is clinically warranted, and ongoing monitoring to ensure that side effects are identified, are essential. "Appropriate initial evaluation" includes the following: (a) thorough assessment of possible underlying causes of target symptoms including general medical, psychiatric, environmental or psychosocial problems; (b) consideration of general medical conditions; and (c) assessment of family history of general medical conditions, especially of metabolic and cardiovascular disorders. "Appropriate ongoing monitoring" includes re-evaluation and documentation of dose, efficacy and adverse effects; and targeted assessment, including assessment of movement disorder or neurological symptoms; weight, waist circumference and/or BMI; blood pressure; heart rate; blood glucose level; and lipid profile at periodic intervals.

2 Don't routinely prescribe two or more antipsychotic medications concurrently.

Research shows that use of two or more antipsychotic medications occurs in 4 to 35% of outpatients and 30 to 50% of inpatients. However, evidence for the efficacy and safety of using multiple antipsychotic medications is limited, and risk for drug interactions, noncompliance and medication errors is

5 Don't routinely prescribe antipsychotic medications as a first-line intervention for children and adolescents for any diagnosis other than psychotic disorders.

Recent research indicates that use of antipsychotic medication in children has nearly tripled in the past 10 to 15 years, and this increase appears to be disproportionate among children with low family income, minority children and children with externalizing behavior disorders (i.e., rather than schizophrenia, other psychotic disorders and severe tic disorders). Evidence for the efficacy and tolerability of antipsychotic medications in children and adolescents is inadequate and there are notable concerns about weight gain, metabolic side effects and a potentially greater tendency for cardiovascular changes in children than in adults. Additional information on medication use in children and adolescents.

and monitoring plan to assess outcome, side effects, metabolic status and discontinuation, if appropriate, is also critical. The evidence base for use of atypical antipsychotics in preschool and younger children is limited and therefore further caution is warranted in prescribing in this population.

Controversial Issues

- Use of **antipsychotics for treatment of anger** or aggression
  - Common practice at times
  - Off label with exception of irritability/aggression associated with autism
  - Aggression as a symptom can be present in multiple disorders
- Use of **more than one antipsychotic**

Aggression

- Aggression is **typically defined** as hostile or violent behavior or attitudes toward another; readiness to attack or confront
- Aggressive behavior is **not uncommon** during childhood and adolescence
- Aggression is also an **important associated feature** of many psychiatric disorders
- Persistent aggression is associated with many negative outcomes later in life, including social isolation, criminal behavior, and low socioeconomic status and unemployment (Buchmann et al., 2013)

Aggression

- Aggression falls in the category of externalizing behaviors, among impulsive, hyperactive, and delinquent behaviors.
- Subtypes and Categories of Aggression (Connor 2002)
  - Overt and Covert
  - Reactive and Proactive
  - Instrumental and Hostile
  - Predatory and Affective
  - Offensive and Defensive
  - Relational
- Given the significant impact of aggression on individual and family outcomes, it is imperative to properly diagnose and seek targeted intervention efforts

Potential Diagnoses for Symptom of Aggression

- Oppositional Defiant Disorder
- Conduct Disorder
- Attention-Deficit/Hyperactivity Disorder
- Substance Use Disorders
- Depression
- Disruptive Mood Dysregulation Disorder
- Post-Traumatic Stress Disorder
- Autism Spectrum Disorder
  - Ex: In a study of children and adolescents with Autism Spectrum Disorder, 68% demonstrated aggression to a caregiver and 49% to non-caregivers (Kanne & Mazurek 2011).

Assessment and Treatment of Aggression

- A **thorough assessment** (clinical interview, assessment tools, psychological evaluation) to provide diagnostic clarification to guide treatment planning and recommendations.
- Determining **diagnosis** will have significant impact on treatment.
- In general, Cognitive Behavioral Therapy **(CBT)** is the primary evidence-based individual therapy intervention for addressing aggression and many disorders with aggression as a symptom. **Problem-Solving Skills Training** also has proven efficacy (Eyberg, Nelson, & Boggs, 2008)

Mood Stabilizers

Traditional Mood Stabilizers: Approved Indications

	Seizure Disorders	BPD, Mania	BPD, Maint
Carbamazepine	All ages		
Divalproex	≥ 10 yrs		
Lamotrigine	≥ 2 yrs (adjunct)		
Lithium		≥ 12 yrs	≥ 12 yrs

BPD = Bipolar Disorder; Maint = Maintenance therapy

Mood Stabilizer Side Effects

- All commonly cause
  - Sedation
  - Nausea
  - Stomach upset
  - Dizziness
  - Weight gain
- Risk of birth defects
- Lithium
  - Tremor
  - Increased thirst/urination
  - Acne
- Valproate/Divalproex
  - Elevated LFTs
    - Most concerning in children < 10 yrs.
  - Decreased platelets
- Carbamazepine
  - Elevated LFTs
  - Hyponatremia
  - Rare:
    - **Stevens-Johnson Syndrome**
    - Agranulocytosis

Mood Stabilizer Monitoring

	Lithium	Valproate	Carbamazepine
Drug level	Q wk until stable Q 3-6 mo	5-7 d Q 6-12 mo	5-7 days and/or 1 mo Q 6-12 mo
CBC with Diff	Baseline, annually	Baseline, 2 wk, Q 6-12 mo	Baseline Q 2 wk x 2 mo Q 3-6 mo
LFTs	n/a	Baseline, 2 wk, Q 6-12 mo	Baseline Q 2 wk x 2 mo Q 3-6 mo
Pregnancy	Baseline	Baseline	Baseline
Electrolytes	Baseline With drug levels	n/a	Baseline, 2 wk, Q 12 mo
Renal function	Baseline, Q 3 mo, annually	Baseline	Baseline, annually
TSH	Baseline, Q 3 mo, Q 3-6 mo	Baseline	Baseline

AACAP Treatment Guidelines for Bipolar Disorder

Without Psychosis

- Monotherapy with mood stabilizer or SGA
  - (Li, VPA, CBZ, OLZ, QUE, RISP)
  - Partial response, try augmentation
    - Li + (VPA, OLZ, QUE, RISP)
    - VPA + (OLZ, QUE, RISP)
    - CBZ + (OLZ, QUE, RISP)
- No response, try switching to different monotherapy agent above

With Psychosis

- Mood stabilizer + SGA
  - (Li, VPA, CBZ) + SGA
  - Partial response, try augmentation
    - Li + VPA + SGA
    - Li + CBZ + SGA
- No response, try different combination from above

Li = lithium; VPA = valproate; CBZ = carbamazepine; OLZ = olanzapine; QUE = Quetiapine; RISP = risperidone

Other mood stabilizers used (minimal evidence in children and adolescents)

- No FDA Approval
- Often used in combination with other mood stabilizers
  - Gabapentin
  - Topiramate

How a prescriber determines what medication to use

- History of response
- Family history to medication response
- Receptor profile of medication
- Drug interactions
- Dosing and dosage forms
- Monitoring/adherence issues
- Concurrent medical history
- Cost
- Treatment refractory
- Pregnancy and Lactation
- Patient preference
- Side Effects
- Efficacy

Non-medication treatments

- Lifestyle activities that can help with mood stabilization
  - Exercise
  - Increased activity in areas of interest
  - Social interactions
  - Stable/consistent sleeping and appetite

Therapy

- Applied Behavioral Analysis (ABA)
- Parent-Child Interactive Therapy (PCIT)
- Parent Management Training (PMT)
- Interpersonal and social rhythm therapy (IPSRT)
- Cognitive behavioral therapy (CBT)
- Trauma focused therapy (based on trauma history or diagnosis)
- Dialectical Behavior Therapy (DBT)
- Family-focused therapy

Therapy

- Applied Behavioral Analysis (ABA)
  - "gold standard" for autism treatment
  - system of autism treatment based on behaviorist theories
  - bring about meaningful and positive change in behavior.
  - "correct" behaviors can be taught through a system of rewards and consequences (or, more recently, rewards and withholding of rewards)

Therapy

- Parent-Child Interactive Therapy (PCIT)
  - behavior-based, family-oriented therapy designed to help improve the parent-child relationship through interaction
  - parent and child interact with therapist in separate room and directing the interaction through use of bug in the ear device
- Parent Management Training (PMT)
  - educating and coaching parents to change their child's problem behaviors using principles of learning theory and behavior modification

Therapy

- Interpersonal and social rhythm therapy (IPSRT)
  - focuses on the stabilization of daily rhythms, such as sleeping, waking and mealtimes.
  - consistent routine for better mood management
  - bipolar disorder

Therapy

- Cognitive behavioral therapy (CBT)
  - identifying unhealthy, negative beliefs and behaviors and replacing them with healthy, positive ones
- Trauma focused therapy (based on trauma history or diagnosis)
  - addressed in prior webinar
    - TF-CBT, EMDR, CPP, therapy for complex trauma

Therapy

- Dialectical Behavior Therapy (DBT)
  - focus on emotional regulation
- Family-focused therapy
  - family support and communication

How to engage your provider/physician

- In the past the relationship between physicians and patients was paternalistic
- **Currently** the expectation is that the provider works with the patient
  - We expect questions, dialogue, and your input into the process of evaluation and decision making
- It may not be a physician--you may have a nurse practitioner, physician assistant, or resident in training that you are working with

How to engage your provider/physician (Providing information on past treatment)

- It is tremendously helpful for the provider/physician to be informed of prior treatments
- Providing documentation of past hospitalizations, outpatient treatment, medications, any medical history is critical
- This is sometimes challenging for children in custody but anything you can do to facilitate quick access to treatment history is critical

How to engage your provider/physician (be empowered to question)

- **A key component of informed consent includes**: the information needed about treatment that needs to be communicated to the guardian in order to get consent to treat
- If you are not receiving the information needed to give consent **ask for it**
- If you don't understand what is being told to you **ask questions until you do understand**

How to engage your provider/physician (ongoing feedback to them is important)

- It is **critical for ongoing treatment to have the input of those who spend time with the child.**
  - This can be the caseworker, foster parent, teacher, etc.

How to engage your provider/physician (obtain the information you need)

- Educate yourself on the treatment provided
- Be familiar with possible side effects (especially serious ones)
  - If you don't know them then ask about them
  - Be aware of possible side effects the child is experiencing so you can communicate them
    - Antipsychotics—NMS (life threatening)
    - Mood Stabilizers (Stevens-Johnson Syndrome with Carbamazepine)
- Be aware of monitoring necessary for medications used
  - Metabolic monitoring with antipsychotics
  - Drug levels and other labs with mood stabilizers

How to engage your provider/physician

- **Questions you have re: how to engage your provider/physician**

Medication Information Resources

- American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameters
  - https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx
- National Alliance on Mental Illness (NAMI) Treatment Resources, Mental Health Medications
  - http://www.nami.org/Learn-More/Treatment/Mental-Health-Medications
- Psychotropic Medication Utilization Parameters for Children and Youth in Foster Care (5th Version)
  - https://www.dfps.state.tx.us/Child_Protection/Medical_Services/documents/reports/2016-03_Psychotropic_Medication_Utilization_Parameters_for_Foster_Children.pdf
  - Tables begin on page 8

Questions