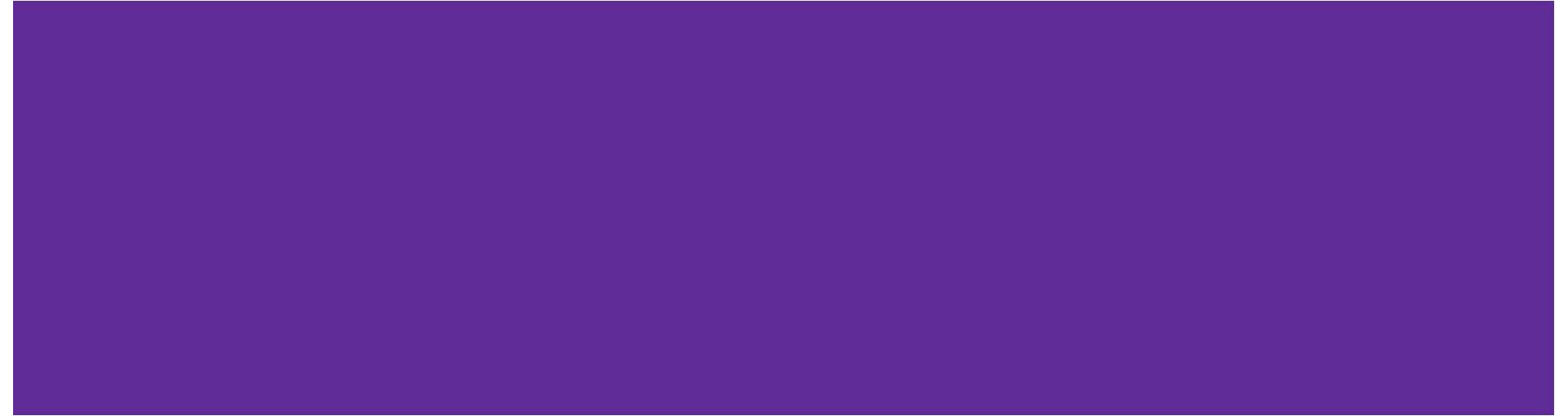


# Autism Spectrum Disorder



# Autism Spectrum Disorder (ASD)

- Behavioral disorder marked by deficits in social communication and restrictive repetitive behaviors



# The Three Functional Levels of Autism

## ASD Level 1 Requiring Support



difficulty initiating social interactions

organization and planning problems can hamper independence

## ASD Level 2 Requiring Substantial Support



social interactions limited to narrow special interests

frequent restricted/repetitive behaviors

## ASD Level 3 Requiring Very Substantial Support



severe deficits in verbal and nonverbal social communication skills

great distress/difficulty changing actions or focus

# Historical Overview of Medications

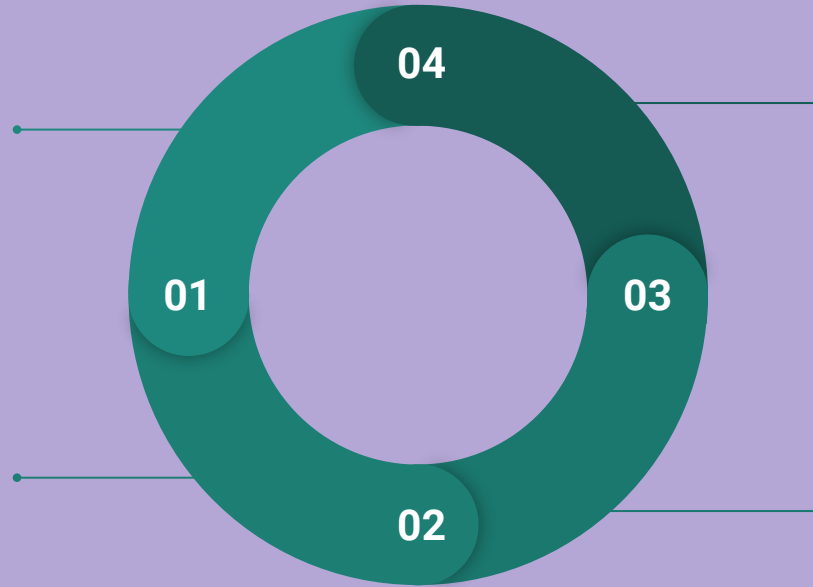


- **1943**
  - Leo Kramer named Autistic Disorder
  - Treatment was psychodynamic psychotherapy and the chief focus of intervention was the supposedly flawed parent–child relationship (Mohiuddin & Ghaziuddin, 2013)
- **1971**
  - Tricyclic antidepressants (Imipramine) (Campbell, Fish, Shapiro, & Floyd, 1971)
    - Mixed results
- **1978**
  - Antipsychotics- Haloperidol with behavior therapy (Campbell et al., 1978)
    - Acquisition of imitative speech
- **2006**
  - FDA approved Risperidone for autism related irritability (LeClerc, & Easley, 2015)
- **2009**
  - FDA approved Aripiprazole for the treatment of irritability associated with autistic disorder (Blankenship, Erickson, Stigler, Posey, & McDougle, 2010)
- **Other:**
  - Antidepressants, Stimulants, Norepinephrine Reuptake Inhibitors, Alpha-2 Adrenergic Agonists, Anticonvulsants (Mohiuddin & Ghaziuddin, 2013)

# Pharmacologic Treatment of ASD

1 in 59 children have an ASD diagnosis (CDC, 2014)

Around half of these children are taking at least one psychotropic medication (Madden, et al., 2017)

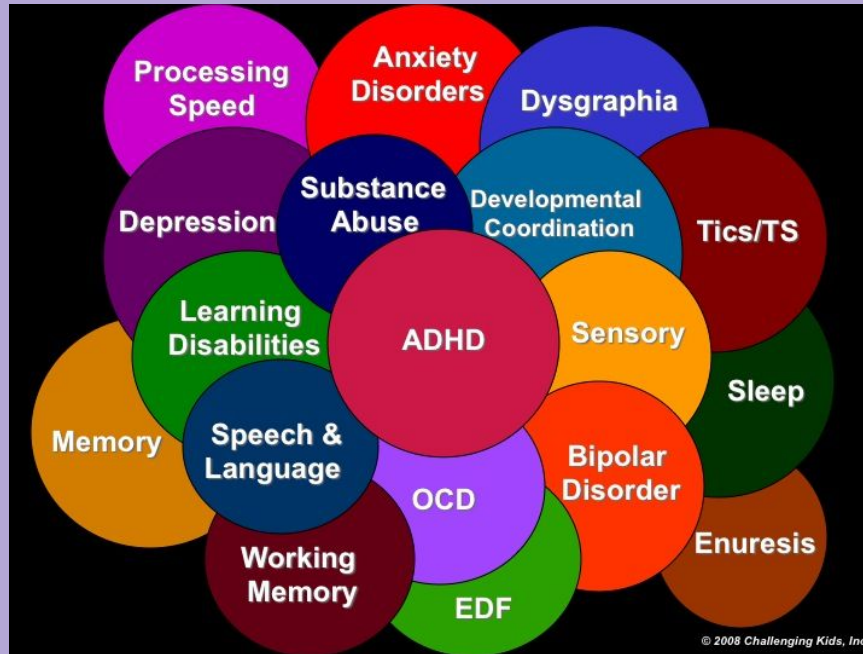


There are 2 medications that are FDA approved for use with children with ASD (FDA, 2005; 2014)

There are no approved medications to treat the core symptoms of ASD (Volkmar et al., 2014)

# Drug category considered best to treat ASD?

- Most prescribers using medication with patients with ASD are treating comorbidities or specific symptoms (Madden, 2017; Volkmar et al., 2014)



# Common pharmacological treatments: Stimulants

Brand Name	Generic Name	Targeted Symptoms	Side Effects	Additional Information
Adderall	Dextroamphetamine	Reducing hyperactivity	Serotonin Syndrome, growth suppression, seizures, dry mouth, diarrhea, insomnia, aggression	Includes short and long acting versions
Vyvanse	Lisdexamphetamine	Reducing hyperactivity	Serotonin Syndrome, seizures, growth suppression, dry mouth, nausea, aggression	Includes short and long acting versions
Focalin	Dexmethylphenidate	Reducing hyperactivity	Growth suppression, seizures, headache, blood pressure increase, aggression	Has a black box warning regarding dependence

# Common pharmacological treatments: SSRIs

Brand Name	Generic Name	Targeted Symptoms	Side Effects	Additional Information
Prozac	Fluoxetine	Improve repetitive behaviors, reduces feelings of sadness	Abnormal dreams, anorexia, dry mouth, insomnia, nausea	Longer washout period (4-6 days) than other SSRIs; boxed warning for increased suicidality
Zoloft	Sertraline	Reduces depressive symptoms	Nausea, diarrhea, tremors, dyspepsia (indigestion), decreased appetite, hyperhidrosis	Boxed warning for increased suicidality
Celexa	Citalopram	Reduces depressive symptoms	Insomnia, somnolence, agitation	Boxed warning for increased suicidality



# Common pharmacological treatments: Alpha 2 Agonists

<b>Brand Name</b>	<b>Generic Name</b>	<b>Targeted Symptoms</b>	<b>Side Effects</b>	<b>Additional Information</b>
Intuniv	Guanfacine	Calming hyperactivity, reducing aggression	Somnolence, fatigue, nausea, lethargy, hypotension	Includes short and long acting versions
Catapres	Clonidine	Calming hyperactivity, reducing aggression and tantrums	Drowsiness, headache, irritability, insomnia	Includes short and long acting versions

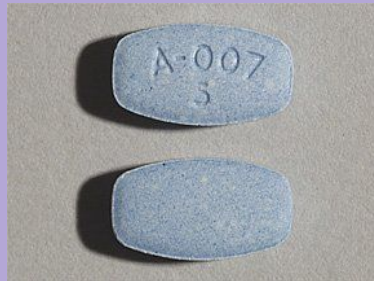
# Pediatric Indications: Antipsychotics

- Risperidone (Risperdal) and aripiprazole (Abilify) are FDA approved to treat irritability in children with ASD

<b>Brand Name</b>	<b>Generic Name</b>	<b>Targeted Symptoms</b>	<b>Side Effects</b>	<b>Additional Information</b>
Abilify	Aripiprazole	Approved for treatment of irritability; greater life satisfaction	Weight gain, sedation, fatigue, vomiting, tremors, drooling	Approved for children 6 and older
Risperdal	Risperidone	Approved for treatment of irritability; reduces tantrums, aggression, and self-injurious behavior	Weight gain, somnolence, increased appetite, fatigue, nausea	Approved for children 5 and older

# Dosing

- Aripiprazole (FDA, 2014)
  - Starting dose of 2mg daily → 5mg daily (recommended dose) → 10 to 15mg daily
- Risperidone (FDA, 2005)
  - Starting dose of 0.25mg daily → 0.5mg daily (recommended dose) → up to 3mg
  - 90% of patients saw improvement on doses between 0.5mg and 2.5mg daily



# FDA DSCs and side effects

## Risperidone

- 2011: Confusion with ropinirole (drug for Parkinson's and restless leg syndrome in adults; no pediatric indication)
- 223 reports

## Aripiprazole

- 2016: New compulsive behaviors (i.e., gambling, shopping, eating, sexual behavior)
- 169 reports

## All SGAs

- 2004: Metabolic issues (i.e., weight gain, glucose intolerance, hyperglycemia, diabetes mellitus, hyperlipidemia [high cholesterol], hypertension, stroke, premature mortality)

# Polypharmacy

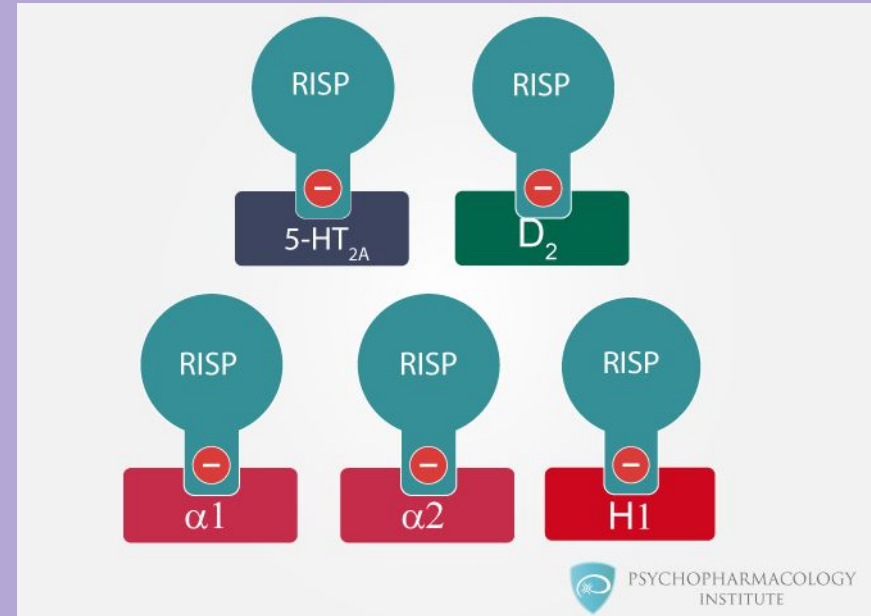
Anywhere from 10-20% of children with ASD are taking more than one psychotropic medication (Spencer et al., 2014)

- Antidepressants and ADHD medications (38% of subjects)
- Antipsychotics and ADHD medications (28%)
- Antipsychotics and antidepressants (20%)
- Antipsychotics, antidepressants, and ADHD medications (18%)



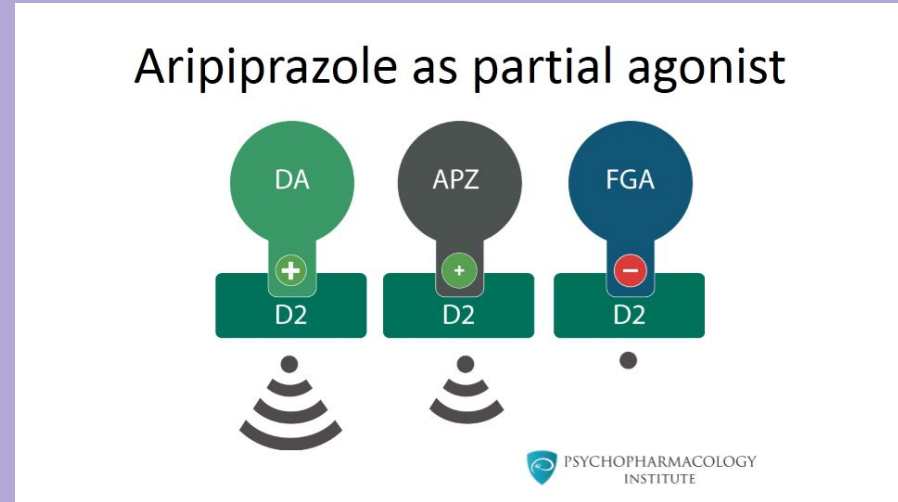
# Mechanism of Action of the Drug-Risperidone

- Risperidone (Risperdal)
- Agonist
- Blocks D2 (dopamine) and 5-HT<sub>2A</sub> (serotonin) receptors
- Competes with noradrenergic  $\alpha$ 1 and  $\alpha$ 2 receptors
- Lower doses:
  - Competes with dopamine
  - Low risk of side effects
- High doses:
  - Can cause Parkinsonian motor symptoms



# Mechanism of Action of the Drug-Aripiprazole

- Aripiprazole (Abilify)
- Partial agonist
- D2 (dopamine), D3 and 5-HT1A (serotonin) receptors
- Mean elimination half-life of Aripiprazole is about 75 h after oral administration
  - Reaches 94 h for dehydroaripiprazole, its active metabolite
- Steady-state concentrations are attained within 14 days of dosing



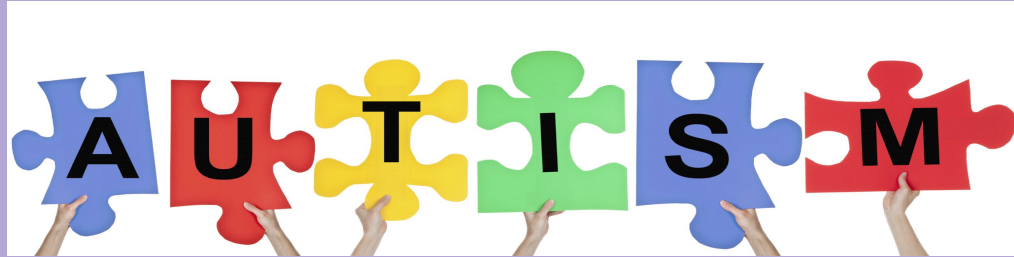
# Alternative Treatments

- Treatment can be divided into the following categories:
  - **Behavioral and Communication Approaches**
    - Applied Behavior Analysis
    - Occupational Therapy
    - Speech Therapy
    - Developmental, Individual Differences, Relationship-Based Approach (DIR; also called “Floortime”)
  - **Dietary Approaches** (*NOT evidence based*)
    - Removing certain types of foods from a child’s diet and using vitamin or mineral supplements
  - **Complementary and Alternative Medicine** (*NOT evidence based-potentially dangerous*)
    - Chelation (a treatment to remove heavy metals like lead from the body)
    - Biologicals (e.g., secretin)
    - Body-based systems (like deep pressure)





# Research on Combined Treatment



- **ABA and Medication** (Frazier et al., 2010)
  - Medication- (1) antipsychotics, (2) mood stabilizers, and (3) nonstimulant medications used to treat ADHD and/or sleep symptoms.
  - Results:
    - Behavioral treatment combined with antipsychotic medication was the most effective approach to reducing aggressive behaviors in youths with
- **Multiple Therapies** (Bowker, D'Angelo, Hicks, & Wells, 2011)
  - Most families adopt multiple treatment approaches
    - ABA (37%); physiological treatments (35%); standard therapies (34.9%); medications (14.6%)

# Best Practices for Treatment

- Behavioral
- Educational
- Communicative
- Pharmacologic

INCREASING **POSITIVE**  
**BEHAVIOR**



DECREASING **NEGATIVE**  
**BEHAVIOR**



My Daily Schedule

get off bus	backpack in cubby	gym	bathroom	table work	circle time
snack time	chores	bathroom	recess	physical therapy	centers
speech	bathroom	lunchtime	occupational therapy	goodbye circle	get on bus



# How future studies can improve research

- More studies are needed to examine:
  - Outcomes of combined treatments
  - Factors influencing psychotropic medication use in ASD
  - Effectiveness and safety of psychotropic medication for ASD



# Empirical Article Review

## Madden et al., (2017)- Psychotropic medication use among insured children with autism spectrum disorder

- **Aims:** This study examined psychotropic medication use among 7901 children aged 1–17 with autism spectrum disorder (ASD) in five health systems, comparing to matched cohorts with no ASD.
  - **Hypothesis:** That psychotropic treatment would be more common among children with ASD regardless of the presence of other psychiatric diagnoses, which could suggest that psychotropics were targeted at ASD symptoms.
- **Methods:** Part of the Autism Registry project of the Mental Health Research Network (MHRN)
  - Subjects were aged <18 years in 2010 and enrolled in one of the 5 health plans for at least 10 months in 2010 and at least 1 month in 2009
  - Age, sex, ASD diagnosis, other diagnoses
  - Age and sex were distributed identically in the two cohorts because of the matched 10:1 design
    - ASD N = 7901
    - No ASD N = 79,010

# Empirical Article Review

- **Results:**
  - Nearly half (48.5 %) of all children with ASD took psychotropic medications
    - Children without ASD at (7.7%)
  - Among children diagnosed with ASD, the most prevalent psychotropic treatments were medications that typically target ADHD (30.2 %), antipsychotics (20.5 %), antidepressants, (17.8 %), and mood stabilizers (9.1 %, combining anticonvulsants and lithium)
  - Among children diagnosed with ASD, older age, a diagnosis of Autistic Disorder and comorbid diagnosis of either depression or anxiety, or an attention disorder, were all significant positive independent predictors of any psychotropic medication use
- **Conclusions:** The widespread use of psychotropics we observed, particularly given weak evidence supporting the effectiveness of these medications for most children with ASD, highlights challenges in ASD treatment and the need for greater investment in its evaluation

# Empirical Article Review

- **Potential weaknesses:**
  - No explanation of subjects race/ethnicity
  - Did not obtain symptoms noted or targeted by prescribers, only diagnosis
  - Examined dispensing of medication, not actual use
  - Generalizability concerns:
    - Subjects obtained from 5 clinical sites on East and West coasts
    - Majority of subjects privately insured
    - Outdated ASD codes

# Tool for Progress Monitoring

## Pediatric Symptom Checklist-17 (PSC-17)

Caregiver Completing this Form: \_\_\_\_\_ Date: \_\_\_\_\_

Name of Child: \_\_\_\_\_

		Please mark under the heading that best fits your child			For Office Use		
		NEVER	SOME-TIMES	OFTEN	I	A	E
1.	Fidgety, unable to sit still						
2.	Feels sad, unhappy						
3.	Daydreams too much						
4.	Refuses to share						
5.	Does not understand other people's feelings						
6.	Feels hopeless						
7.	Has trouble concentrating						
8.	Fights with other children						
9.	Is down on him or herself						
10.	Blames others for his or her troubles						
11.	Seems to be having less fun						
12.	Does not listen to rules						
13.	Acts as if driven by a motor						
14.	Teases others						
15.	Worries a lot						
16.	Takes things that do not belong to him or her						
17.	Distracted easily						
		(scoring totals)					




# Risk-Benefit Analysis



## RISK-BENEFIT ANALYSIS: A WORKSHEET GUIDE TO WEIGHING PEDIATRIC PSYCHOTROPIC USE

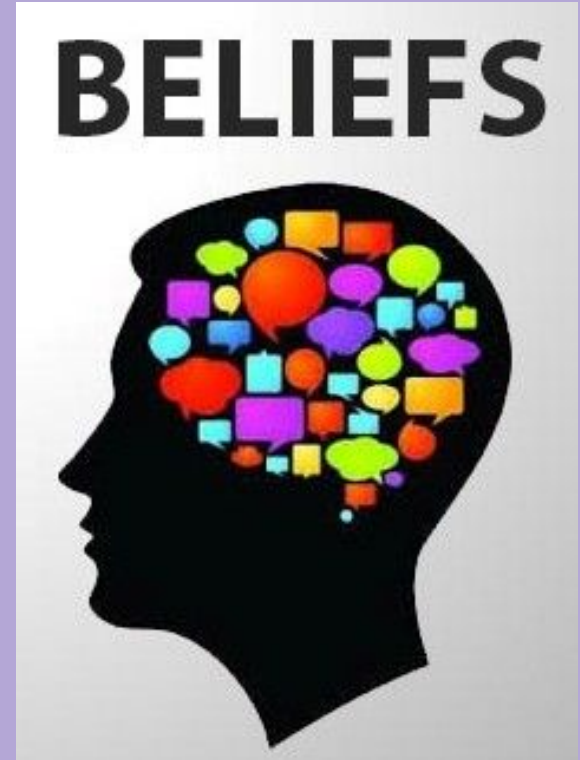
*Note for user: This risk-benefit worksheet is intended to guide thinking processes for decision-making when medication use is being considered. It is intended to help ensure that various risks, benefits and medication alternatives are systematically considered before decisions are finalized.*

Medication name:			
What is the <b>problem</b> this medication is intended to address?			
What are the <b>specific symptoms</b> targeted by this medication?			
RISKS		BENEFITS	
What are the <b>contraindications listed in the PI</b> for this medication?	<input type="checkbox"/> None	What are the <b>positive aspects</b> of using this medication for school and social functioning? Family and other functioning?	
	<input type="checkbox"/> not sure		
<input type="checkbox"/> yes, including:			
What <b>DSCs, Boxed Warnings, other AEs, and SEs</b> are listed in the PI with this medication and how will these be monitored?			
ALTERNATIVES			
Are there <b>other treatment options</b> available to address this problem and these symptoms?	<input type="checkbox"/> No		
	<input type="checkbox"/> not sure		
	<input type="checkbox"/> yes, including:	<i>Pros</i>	<i>Cons</i>
<b>Based on my risk-benefit analysis, at this time, I believe it is in the best interest of my patient to :</b>			
	<input type="checkbox"/>	try this medication	
	<input type="checkbox"/>	decline this medication	
	<input type="checkbox"/>	unsure, I will seek additional information	



# How our beliefs have changed

- Thinking about pharmacological treatments for ASD more broadly
- Remembering families perceptions and understand of pharmacological treatments
- Clinicians understanding of safety and explanation of pharmacological treatments



# Other Helpful Resources

Link for DSCs:

<https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111085.htm>

Medication Guides issued by the FDA for consumers are updated regularly at:

<https://www.fda.gov/Drugs/DrugSafety/ucm085729.htm>

The FDA recently made available a free brochure on its website entitled “Think it Through: A Guide to Managing the Risks and Benefits of Medicines” :

<https://www.fda.gov/Drugs/ResourcesForYou/ucm079492.htm>.

AACAP Practice Parameter for Treating Children with ASD (Volkmar, 2014)

AACAP Practice Parameter on the Use of Psychotropic Medication in Children and Adolescents (Walkup, 2009):

[https://www.aacap.org/AACAP/Resources\\_for\\_Primary\\_Care/Practice\\_Parameters\\_and\\_Resource\\_Centers/Practice\\_Parameters.aspx](https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx)



# Questions?



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