

Psychiatric Disorders & ASD: Diagnosis and Treatment

Cassie Karlsson M.D.

Director, KSKidsMAP Autism/Neurodevelopmental Disorders/Intellectual Disabilities Program (KANDID)

Director, KU-Wichita Neuropsychiatry/Neurodevelopmental Disorders Lifespan Clinic

Director, Child & Adolescent Psychiatry Fellowship

Department of Psychiatry and Behavioral Sciences



1

Disclosures

I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial services discussed in this CME activity



2

Overview

- The Business of Phenotypes
- Impact of Genetics on Diagnosis and Prescribing
- Treatment of Behavioral Phenotypes
- Diagnosis and Treatment of Co-occurring Psychiatric Disorders
- Recognizing Side Effects/Drug Monitoring
- The Art of Titrating and Tapering
- Practice Questions and Case Example

3

Describe this
animal...



4




5

phe·no·type

- 'fēnə, tīp/
- *Noun* Biology
- noun: phenotype; plural noun: phenotypes
- the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment

6

	Flower color	Flower position	Seed color	Seed shape	Pod shape	Pod color	Stem length
P	Purple	Axial	Yellow	Round	Inflated	Green	Tall
p	White	Terminal	Green	Wrinkled	Constricted	Yellow	Dwarf
F ₁	Purple	Axial	Yellow	Round			



Phenotype Red Pink White

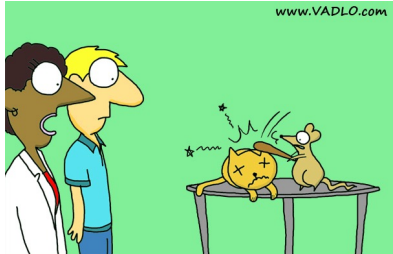
Genotype RR Rr rr

7



8

www.VADLO.com



"Mouse had no discernible phenotype.. till the cat jumped on him!"

9

Behavioral Phenotype

- A behavioral phenotype is the characteristic cognitive, personality, behavioral, and psychiatric pattern that typifies a disorder

Cassidy SB, et al. Behavioral phenotypes in genetic syndromes: genetic clues to human behavior. *Adv Pediatr* 2002;49:59-86.

10

The Autism "phenotype"

- Persistent deficits in social communication and social interaction across multiple contexts
- Restricted, repetitive patterns of behavior, interests, or activities

Diagnostic and Statistical Manual of Mental Disorders, DSM-5

11

Heterogeneity in ASD: Distinct Genetic Underpinnings

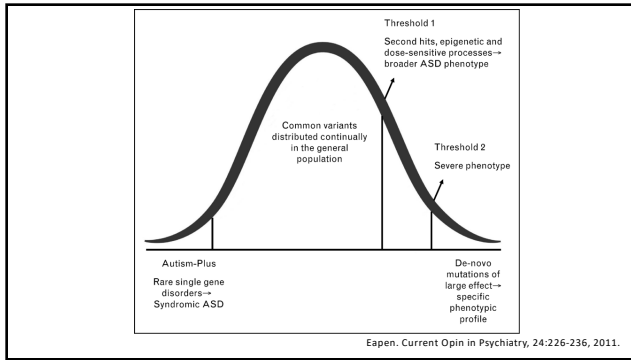
Autism plus
phenotype

Broad autism
phenotype

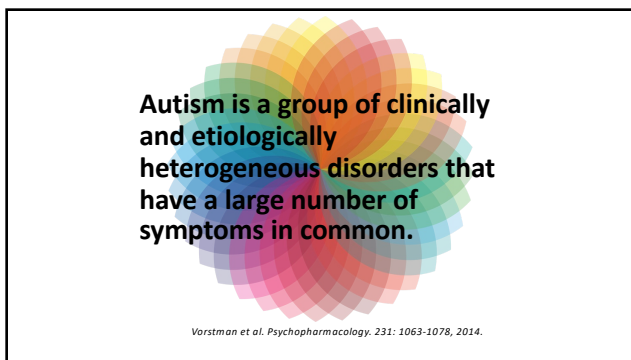
Severe and
specific autism
phenotype

Eapen. *Current Opin in Psychiatry*, 24:226-236, 2011.

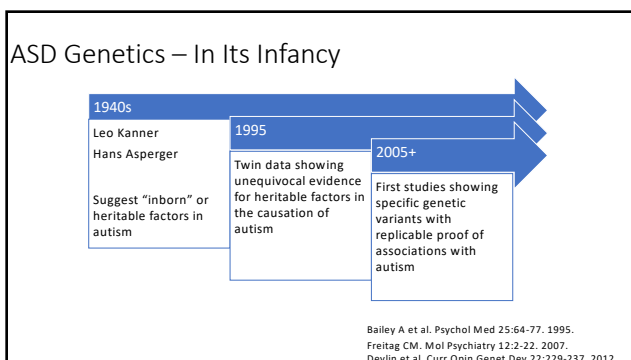
12



13



14



15

Linking Genetics to Pharmacotherapy



16

When to consider medication?

1. Evidence that the target symptoms are ***interfering substantially*** with learning/academic progress, socialization, health, safety, or quality of life.
2. ***Suboptimal response*** to available behavioral interventions and environmental modifications.
3. Evidence that the target behavioral symptoms or psychiatric diagnoses are ***amenable to pharmacologic intervention***.

Myers SM. Pediatric Annals. 38(1):42-9, 2009 Jan.

17

Psychotropic Use in ASDs

- Recent data suggest that about half of children with ASD in the U.S. are prescribed psychotropic medications, and medication use tends to increase with age
- Medications are primarily used to target behaviors associated with autism, rather than "core symptoms" of impaired social relatedness, impaired communications, and restricted patterns of behaviors/interests.



18

Target Behavioral Symptoms (Phenotype)

- Irritability
 - Impulsive aggression, severe temper tantrums, self-injurious behavior
- Interfering stereotyped and/or repetitive thoughts & behaviors
 - Hand-flapping, rocking, spinning
 - Hoarding, telling or asking, touching/tapping/rubbing, self-damaging or self-mutilating behaviors
- Hyperactivity/inattention
 - Common in individuals with ASD (estimated 40-59% of children with ASD meet criteria for ADHD)

19

Irritability

- Best data available is for treatment of irritability associated with ASDs
- Antipsychotics
 - Typical – Haloperidol, Pimozide, Chlorpromazine
 - Atypical – Risperidone, Aripiprazole, Clozapine, Olanzapine, Quetiapine, Ziprasidone, Paliperidone

Only Risperidone (Risperdal) and Aripiprazole (Abilify) are FDA approved for the treatment of irritability in children with ASDs.

20

Interfering Repetitive Behaviors

- **Selective Serotonin Reuptake Inhibitors (SSRIs) & Tricyclic Antidepressants (TCAs)**
 - SSRIs include: Fluoxetine (Prozac), Sertraline (Zoloft), Citalopram (Celexa), Escitalopram (Lexapro), Fluvoxamine (Luvox)
 - TCAs: Clomipramine (Anafranil) – side effects often preclude use (sedation, cardiac)
 - Efficacious in treatment of interfering repetitive behaviors in OCD, which led to trials for patients with ASDs
 - Mixed results in ASDs with very limited data - some studies show efficacy over placebo in decreasing repetitive behaviors, but may be more poorly tolerated (increased energy, impulsivity, hyperactivity, irritability, GI symptoms)

21

Hyperactivity/Inattention

- Children with ASDs and symptoms of ADHD respond to ADHD medications at a reduced rate compared to typically developing peers.
- Stimulants (Methylphenidate most studied)
 - Response rates in studies often around 50%
 - Diagnosis of High Functioning ASD (previously Asperger vs. Autism) linked with a higher response rate, and sometimes fewer adverse effects
 - Adverse effects common (irritability, agitation, headaches, decreased appetite, weight loss, insomnia, depression, emotional lability)

22

Hyperactivity/Inattention

- Atomoxetine (Strattera)
 - Found superior to placebo in the only double-blind placebo controlled trial
 - One open-label study showed improvement in irritability, social withdrawal, stereotypy, and repetitive speech – although to a lesser extent
 - Side effects (usually mild to moderate, though in one open-label 42% discontinued due to side effects): irritability, mood swings, insomnia, sedation, mood swings/aggression

23

Hyperactivity/Inattention

- Alpha-2 Agonists –
- Clonidine & Guanfacine (Guanfacine XR [Intuniv] FDA approved for treatment of ADHD)
 - Hyperactivity/Inattention response rates in a few trials (Guanfacine) ranged from 24-49%
 - Responders more likely to have High Functioning ASD (previously a diagnosis of Asperger's or PDD-NOS vs. Autism)
 - Side effects: drowsiness, insomnia, irritability, constipation, nocturnal enuresis
 - In addition to hyperactivity/inattention, clinically often used to help with sleep (clonidine) and sometimes impulsivity/irritability/aggression

24

Future Directions

- Currently no medications are available or FDA approved for treating the core symptoms of Autism Spectrum Disorders
 - Oxytocin – neuropeptide associated with development of emotional and social affiliative behaviors – some decreases in repetitive behaviors
 - Cholinergic Agents – (donepezil) – some increases in receptive/expressive language, REM sleep, improved CARS scale
 - Glutamatergic Agents – (D-Cycloserine, memantine) – some improvements in CGI scales and ABC subscale for lethargy/social withdrawal

Either major problems, lower power studies, or failure to find positive results (overall limited evidence) to support use of any of the above for treatment of core symptoms at this point

25

Pharmacotherapy Conclusions


- **Interfering repetitive behaviors** – SSRIs demonstrate less efficacy and are more poorly tolerated in children with ASDs when compared to typically developing children and adults with ASDs
- **Irritability** - *Antipsychotics are the most efficacious*, and may show concurrent improvements in hyperactivity and stereotypy
- **Hyperactivity/Inattention** – Stimulants show some benefit, but are less efficacious and cause more side effects than in typically developing children with ADHD
- More research is needed for medications for both the associated behavioral symptoms and core symptoms of autism

26

Common Comorbid Conditions in ASD

- Intellectual Disability
- Seizure disorders
- **Mood Disorders**
- **Anxiety disorders**
- **ADHD**

27



ASD & Psychiatric Comorbidity

- Comorbid psychiatric illness is common
 - One study showed 72% of children with ASDs across intellectual abilities were found to have 2 or more comorbid psychiatric diagnoses (Leyfer et al, 2006)
- Psychiatric comorbidity increases the level of impairment
 - Increased behavioral problems
 - Social relationship impairment
 - Decline in general functioning

28

Treating Comorbid Psychiatric Disorders

- Careful history required to diagnose comorbid psychiatric disorders in children with Autism, but still require the same diagnostic criteria in children/adults who are typically developing
- Treatment is often similar (ie Depakote/Lithium for Bipolar Disorder, SSRIs for depression) – however, remember increased side effects and paradoxical reactions in this population.
- Start low and go slow!

29

Mood Disorders (Depression & Bipolar Disorder)

- Prevalence in ASDs unclear, may be increased risk
 - Higher rates of mood disorders in parents of children with ASDs (Mazefsky et al, 2008)
 - Significant psychosocial stressors (especially in higher functioning individuals aware of their social deficits)
- Avoiding Overdiagnosis:
 - Emotion regulation is highly variable in this population: mood swings does not necessarily equal mood disorder or bipolar disorder
 - Consider baseline functioning – does this represent a qualitative/quantitative change vs. temperamental in nature?
 - Rule out underlying medical issues

30

Anxiety Disorders

- Often considered the most common comorbid diagnosis - 40% comorbidity rate, has been cited up to 80% (Simonoff et. al, 2008)
- Important to gather history from multiple sources, as anxiety can manifest differently in different environments, particularly in younger children
- Children often do not indicate internal distress and anxiety building up until reaching the "peak"

31

Anxiety Disorders

- Increases in these symptoms in ASDs may be evidence of anxiety:
 - Repetitive questions or statements
 - Activity, hyperactivity, or restlessness
 - Temper tantrums
 - Crying
 - Withdrawal from or avoidance of situations
 - Aggression
 - Self-injurious behaviors
 - Stereotypies, repetitive movements or behaviors
- (Autism Comorbidity Interview, ACI, Lainhart)

32

Attention-Deficit/Hyperactivity Disorder

- Considered common in ASDs (often diagnosed prior to ASD diagnosis)
- Important to consider the individual's mental age – how developmentally inappropriate are the ADHD symptoms?
- Differentiate from other potential etiologies that might affect attention – intellectual disability, learning disorder, hearing impairment, anxiety, mood disorder, etc.

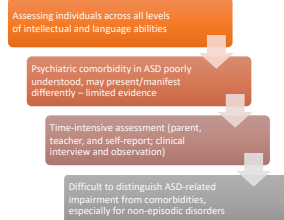
33

Oppositional Defiant Disorder

- Should be diagnosed conservatively in ASDs
- Misdiagnosis of ODD leads to a misunderstanding of what is causing behaviors (ie purposeful, manipulative), and potentially ineffective treatment interventions
- Difficulty with change and insistence on routine are not generally considered "defiant" behaviors in ASD
- Annoying others is "purposeful" in ODD, and those with ASDs may not be aware their habits/behaviors annoy or impact others

34

Factors Complicating Psychiatric Diagnosis in ASDs



35

Targeting Treatment

-  Etiology of ASDs thought to involve complex interactions between multiple genetic and environmental factors
-  Few medications and limited evidence base for treating symptoms associated or comorbid with autism, and none that effectively treat core symptoms
-  Behavioral interventions are the most successful approaches for treating core symptoms and improving outcomes in people with ASDs

36

Pharmacotherapy in ASD: Review Articles

Pharmacotherapy to Control Behavioral Symptoms in Children With Autism

[Carolyn A. Royle](#) & [Christopher J. McDougle](#)

2012 Aug;13(11):1615-29. doi: 10.1517/14656566.2012.674110. Epub 2012 May 3.

Psychopharmacological Interventions in Autism Spectrum Disorder

[Robert F. Accornero](#), [Christen Kidd](#), [Laura C. Polite](#), [Charles A. Henry](#), & [Christopher J. McDougle](#)

2016;17(7):937-52. doi: 10.1517/14656566.2016.1154536. Epub 2016 Mar 7.

Pharmacological Management of Behavioral Disturbances in Children and Adolescents With Autism Spectrum Disorders

[Martine Lamy](#) & [Craig A. Erickson](#)

2018 Oct;48(10):250-264. doi: 10.1016/j.cppeds.2018.08.015. Epub 2018 Sep 24.

37

Recognizing Medication Side Effects

• Antipsychotics

- Akathisia
- Extrapyramidal symptoms (cogwheel rigidity, tardive dyskinesia)
- Metabolic syndrome (weight gain, elevated lipids, elevated glucose/A1C)
- Decrease in White Blood Cells
- Sedation
- QTc prolongation
- Constipation

• SSRIs

- Agitation/Aggression
- Insomnia or sedation
- GI upset
- Headaches
- Can see EPS/akathisia with SSRIs

Stimulants

- Agitation/Aggression (may see a spike when the medication is wearing off)
- Insomnia
- Decreased appetite
- Emotional Lability
- High blood pressure/cardiac arrhythmia
- Hallucinations

Benzodiazepines

- Paradoxical reaction – agitation/aggression/insomnia
- Sedation

Alpha-2 Agonists

- Sedation
- Low blood pressure and heart rate
- Irritability
- Enuresis/constipation
- Dizziness/headaches

38



Titration and Tapering – Tips for Success

39

TITRATION

- Think about starting at LOW doses, and waiting for longer periods of time before increasing the dose
- Medications are often discontinued due to side effects before ever having a chance to be effective, forever to be listed as a "failed trial" or "adverse reaction"
- There is often a sense of urgency to have a medication work quickly, but no time is saved if the patient has side effects, the med must be stopped, and a new med started
 - Examples: When I hear about increased aggression on antipsychotics, I am always suspicious about side effects, and always ask what dose was started, and how quickly titrated
 - What dose ranges would you start in a child/adolescent with a neurodevelopmental disorder?

Risperidone (0.25 to 0.5mg once daily before increasing to BID)
 Aripiprazole (1-2 mg daily before increasing to BID)
 Sertraline (12.5 mg)
 Fluoxetine (2.5 to 5 mg)
 Methylphenidate (2.5 to 5 mg)

40

Tapering Antipsychotics

- Cholinergic rebound
 - Symptoms may be severe but relatively brief and predictable- nausea, vomiting, restlessness, anxiety, insomnia, fatigue, malaise, myalgia, diaphoresis, rhinitis, paraesthesia, GI distress, headaches and nightmares.
- Withdrawal dyskinesia (within 4-6 wks of discontinuation)
 - Constant general chorea (can involve face/limbs/vocalizations)
 - Will usually resolve on it's own over time
 - More severe cases may require treatment (usually restarting low dose of antipsychotic and tapering more slowly)
- How to avoid withdrawal symptoms?
 - Reduce dose by 25% every 1-2 weeks.** May need to be smaller reductions at the end of the taper. If worsening symptoms, consider holding off for longer before further reduction.

41

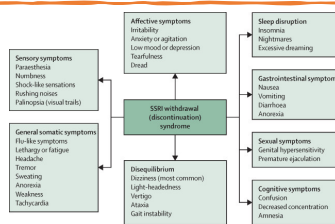
Tapering SSRIs

Withdrawal symptoms can LOOK LIKE recurrence of depression and anxiety.

Studies have shown that brief tapers over 2-4 wks minimally better than abruptly stopping SSRIs in terms of withdrawal symptoms.

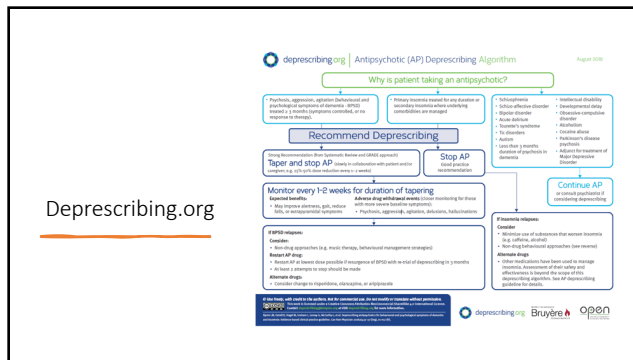
How to Avoid Withdrawal Symptoms?

Reduction by 25% every 2+ wks, likely need to reduce by smaller amounts toward the end of the taper.



Horowitz & Taylor. The Lancet. March 2009.

42



43

AACAP Statement on Pharmacogenomic Testing

AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY

- In October 2018, the Food and Drug Administration (FDA) issued a safety communication warning against the use of genetic tests with unapproved claims to predict medication response.
- Only a small fraction of the available commercial products have undergone randomized controlled trials in adults only.

Current studies are limited by:

- Potential conflicts of interest
- Small sample sizes
- Short duration of follow-up
- Lack of blinding
- Lack of appropriate control groups

Additionally, numerous factors affect medication response unaccounted for by genetic variation. Genetic variations are managed clinically with slow and thoughtful medication management.

Furthermore, pharmacogenomic testing provides little meaningful information when two or more medications are used concurrently.

44

AACAP Statement on Pharmacogenomic Testing

AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY

- The American Academy of Child and Adolescent Psychiatry recommends:**
- Clinicians avoid using pharmacogenetic testing to select psychotropic medications in children and adolescents.**
- Future high-quality prospective studies to assess the clinical significance of pharmacodynamic and combinatorial pharmacogenomic testing in children and adolescents.**

Approved by Council March 2020

45



46

Quiz

No specific medications are available or FDA approved for treating the core symptoms of Autism Spectrum Disorders

A. True
B. False

47

Answer: TRUE

- No medications approved or with evidence-based effectiveness in treating "core symptoms" of ASDs.
- Only 2 medications are FDA-approved for behavior related problems associated with Autism in children:
- **Risperidone & Aripiprazole** – atypical antipsychotics used for the symptomatic treatment of irritability in autism, which includes aggression, deliberate self-injury and temper tantrums.
- Most medications used for symptomatic treatment of ASDs are prescribed "off-label".

48

Quiz

Children with Autism Spectrum Disorders often require higher doses of medications to achieve similar results seen in typically developing children

- A. True
- B. False

49

Answer: False

- Children with ASDs are more likely to respond to lower doses of medications, and have a higher risk of side effects to common medications used in pediatric psychiatric populations.
- **Medications to use cautiously in children with ASDs:**
- **Benzodiazepines** – increased risk of disinhibition, confusion
- **Stimulants** – increased risk of agitation/side effects, and less efficacious at treating ADHD symptoms than in typically developing children
- **SSRIs** – less efficacy in decreasing repetitive-type behaviors (ie OCD symptoms) than in the general population, and are more poorly tolerated in children with autism (ie activation)

50

CASE
VIGNETTE

- You are seeing a 7 yr-old child diagnosed with an ASD in your clinic. His parents are concerned that he has seemed more anxious and angry over the last few months and "cannot sit still". His teachers are beginning to wonder if he has ADHD in addition to Autism, and his parents think they might be right. He is even having trouble adhering to his visual schedules, which have been so helpful in the past. His parents feel distraught – things seemed to be so much better after Aripiprazole was added to treat his severe aggression several months ago, and now things are going downhill again.

51

Which of the following is the most important to recognize when treating or referring this child?

- A. He has developed ADHD and needs appropriate treatment immediately to preserve recent progress at home and school.
- B. He has become accustomed to his low dose of Aripiprazole, and needs an increase in dose in order to preserve his recent progress at home and school.
- C. He may be having a medication side effect.

52

Answer: C

- **Recognizing Akathisia:**
- Characterized by agitation, increased restlessness, driven behavior, insomnia, dysphoria, impulsivity – can include aggressive behaviors, self-injurious behaviors, even suicidality
- Prevalence ~30% in people prescribed antipsychotics in the general population, estimated much higher in children and in individuals with developmental delays
- Often misdiagnosed as ADHD, mania, psychotic agitation, or anxiety
- Children - especially those with developmental delays - have difficulty articulating this feeling of internal distress

53

Answer: C

- **What to do?**
- Consider akathisia anytime your patient is experiencing these symptoms on an antipsychotic
- Be cautious when increasing antipsychotic dose - worsening "target" symptoms may be evidence of akathisia
- Consider lowering antipsychotic dose – stopping abruptly increases risk of emergent withdrawal syndrome/abnormal movements
- Even if you are not the person prescribing these medications, recognizing these symptoms can have a significant impact on your patient's quality of life, functioning and outcome.

54



55
