

Psychopharmacology in Autism Spectrum Disorders

CHILD & ADOLESCENT MENTAL HEALTH

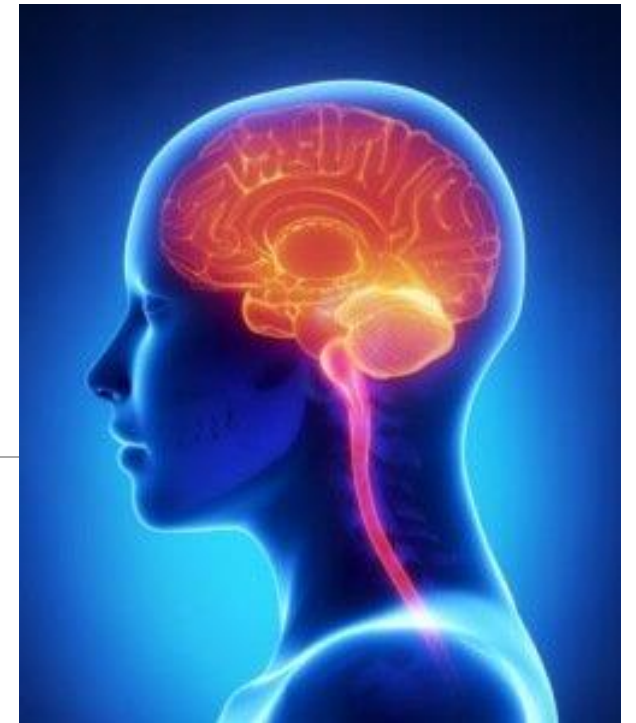
ECHO PROGRAM

JUNE 4, 2020

CASSIE KARLSSON MD

ASSISTANT PROFESSOR OF CLINICAL PSYCHIATRY

INDIANA UNIVERSITY SCHOOL OF MEDICINE





Square Pegs & Round Holes

Describe this animal...












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

	Flower color	Flower position	Seed color	Seed shape	Pod shape	Pod color	Stem length
P	Purple 	Axial 	Yellow	Round	Inflated 	Green 	Tall 
	White 						
F ₁	Purple 						



Phenotype

Red

Pink

White

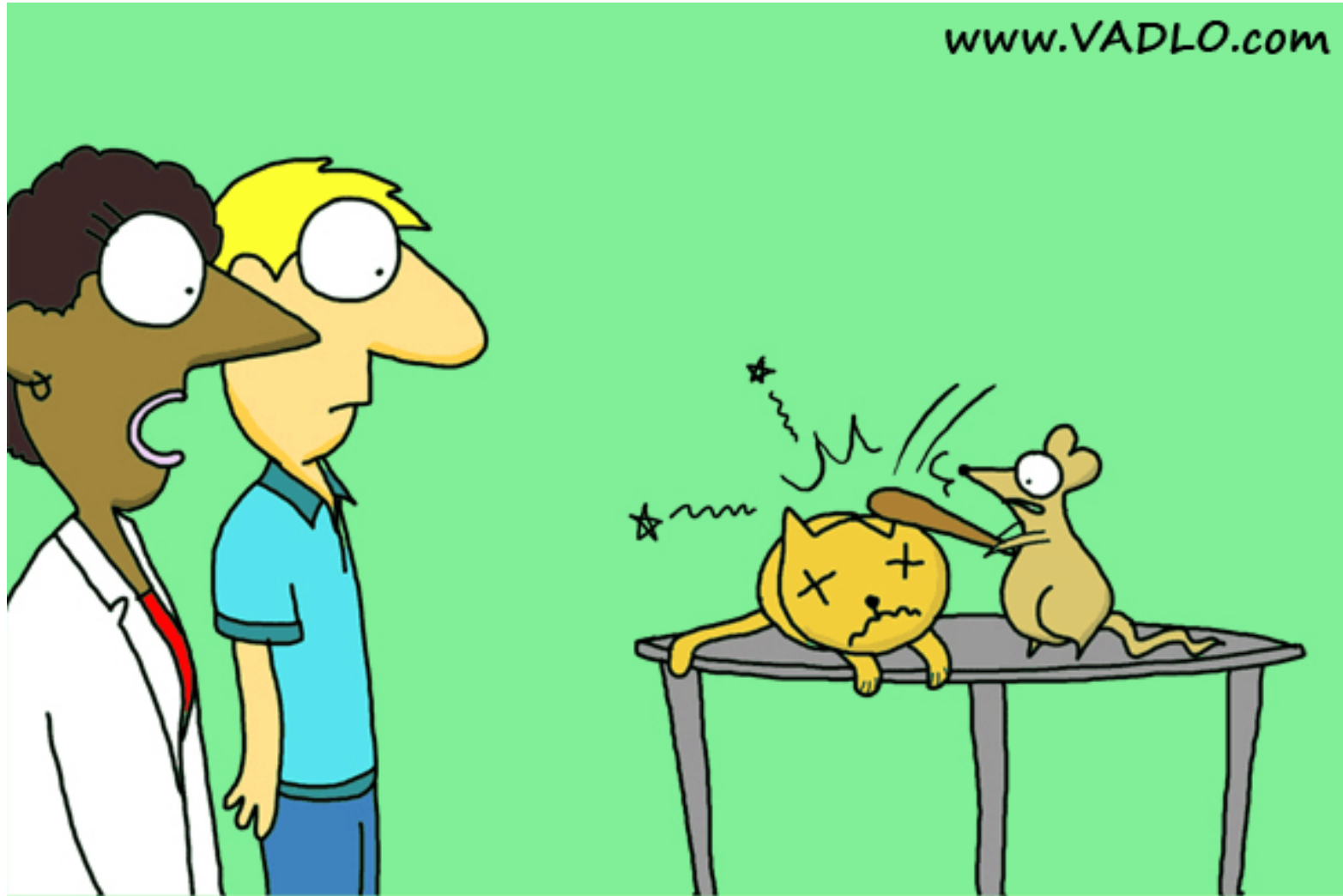
Genotype

RR

Rr

rr





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

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.



The Autism “phenotype”

Persistent deficits in social communication and social interaction across multiple contexts

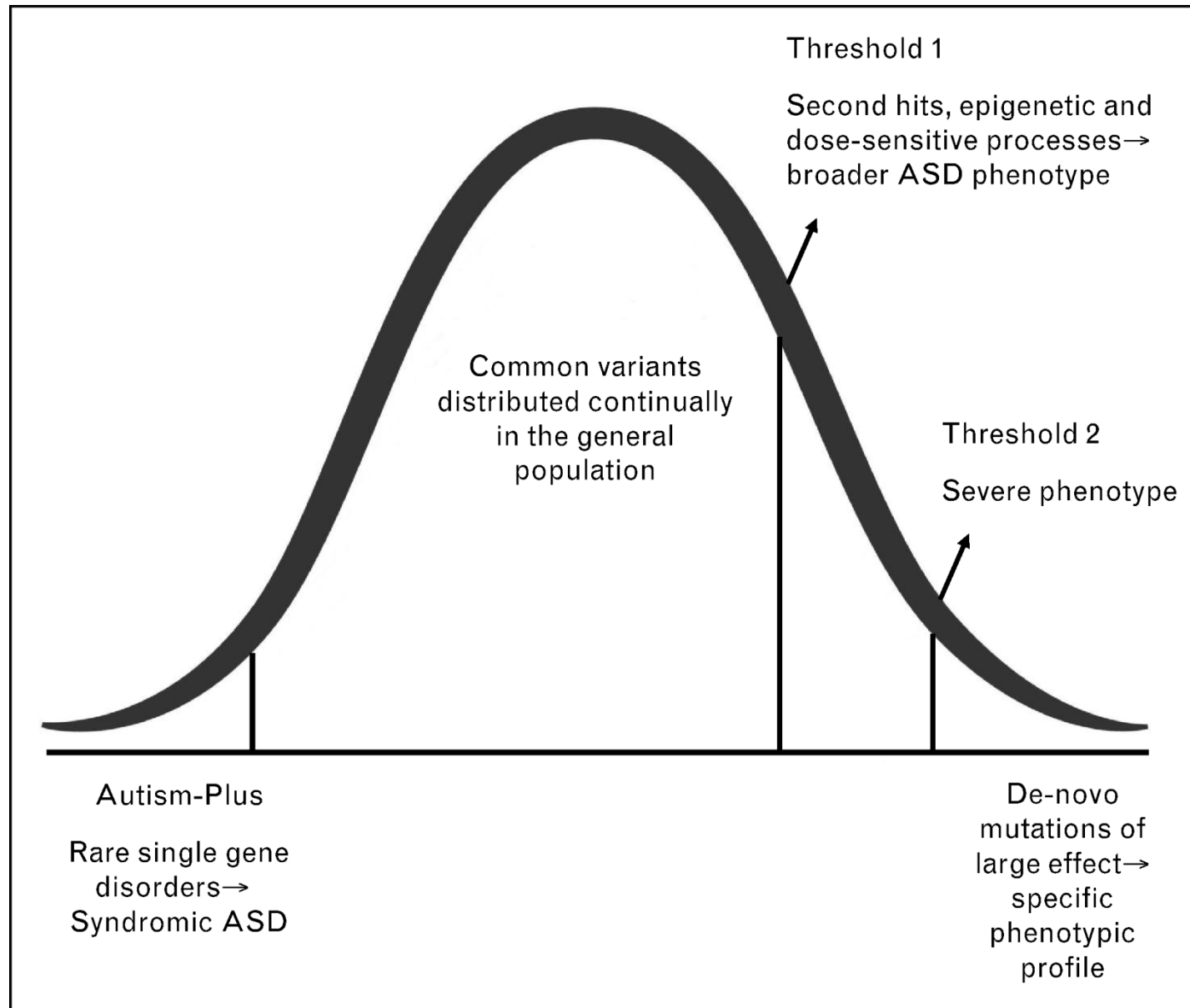
Restricted, repetitive patterns of behavior, interests, or activities

Heterogeneity in ASD: Distinct Genetic Underpinnings

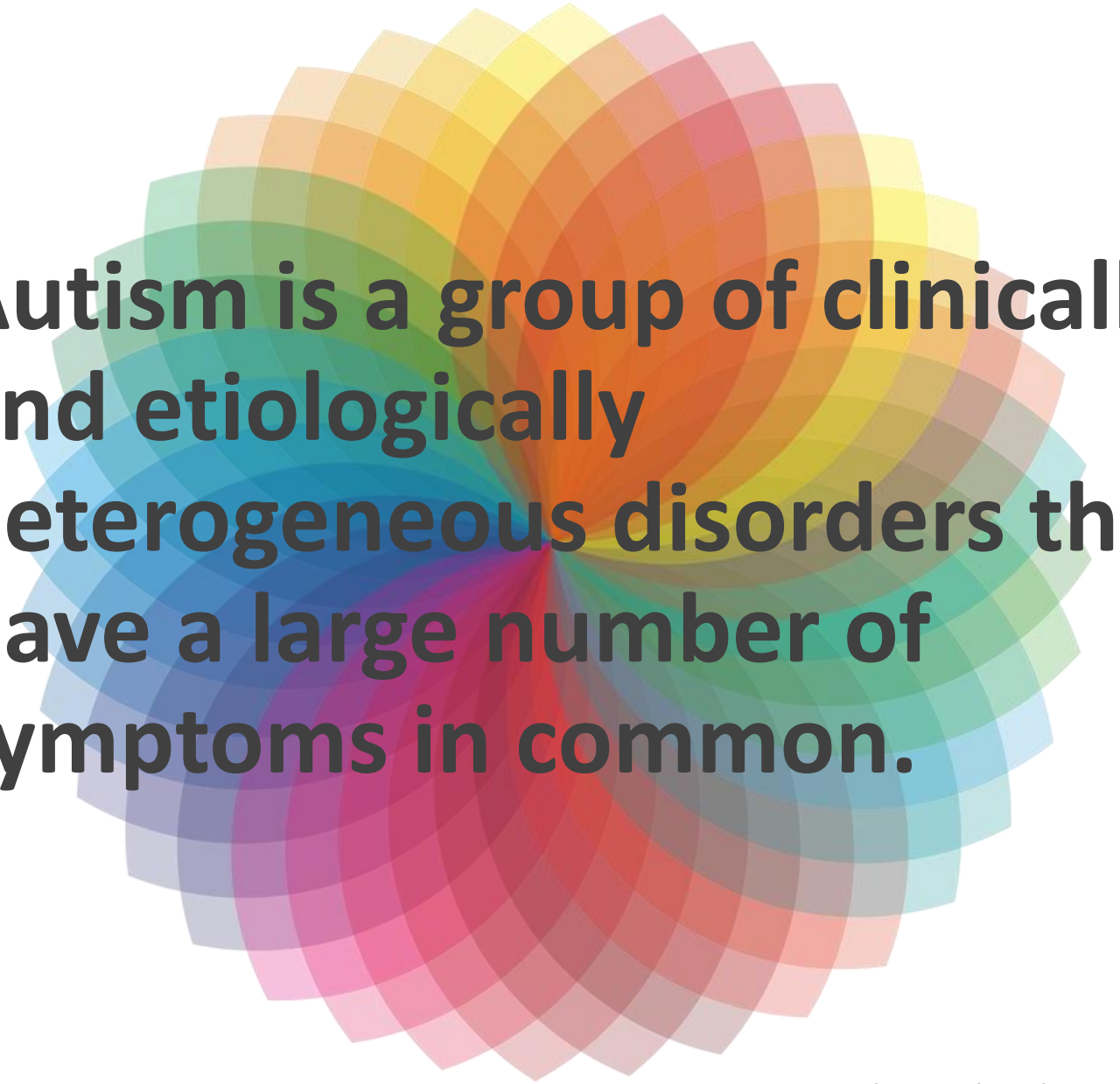
Autism plus phenotype

Broad autism phenotype

Severe and specific autism phenotype



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



Autism is a group of clinically and etiologically heterogeneous disorders that have a large number of symptoms in common.

Vorstman et al. Psychopharmacology. 231: 1063-1078, 2014.

ASD Genetics – In Its Infancy

1940s

Leo Kanner

Hans Asperger

Suggest “inborn” or heritable factors in autism

1995

Twin data showing unequivocal evidence for heritable factors in the causation of autism

2005+

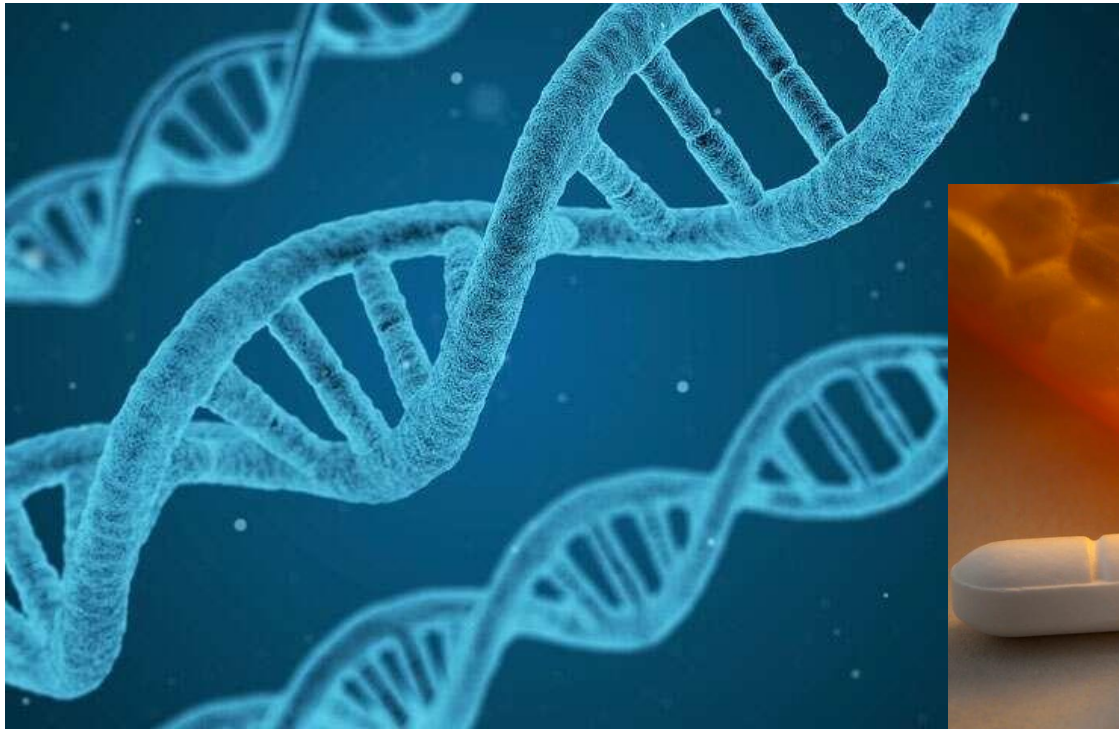
First studies showing specific genetic variants with replicable proof of associations with autism

Bailey A et al. Psychol Med 25:64-77. 1995.

Freitag CM. Mol Psychiatry 12:2-22. 2007.

Devlin et al. Curr Opin Genet Dev 22:229-237. 2012.

Linking Genetics to Pharmacotherapy



AACAP Statement on Pharmacogenomic Testing

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.

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

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.



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)

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.

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.

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)

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)

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

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

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

Common Comorbid Conditions in ASD

Intellectual Disability

Seizure disorders

Mood Disorders

Anxiety disorders

ADHD

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

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!

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

Next Time...

Diagnosis and treatment of Comorbid Psychiatric Disorders

Recognizing Side Effects/Drug Monitoring

The art of titrating and tapering

Practice Questions and Case Examples

QUESTIONS?

