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Diagnosis and Treatment of Anxiety & Mood Disorders in Autism Spectrum Disorder

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Disclosures



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“Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.”



Psychiatric Comorbidities are Common in ASD, yet Data is Sparse

Lifetime prevalence by age 30 years and hazard ratio (HR) compared to age- and sex-matched controls¹

- Anxiety: 50%, HR 3.45
- Bipolar disorder: 7.3%, HR 9.34
- Depression: 54.1%, HR 2.81

Psychiatric comorbidity	Number of published controlled trials (n≥30)
Anxiety	1
Depression	0
Bipolar disorder	0

¹Kirsch, A. C., Huebner, A., Mehta, S. Q., et al. (2020). Association of Comorbid Mood and Anxiety Disorders With Autism Spectrum Disorder. *JAMA pediatrics*, 174(1), 63–70.



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ANXIETY DISORDERS



Anxiety in ASD

- ASD increases the risk of having an anxiety disorder by 3.5x
- Cumulative incidence of anxiety disorder by age 30 years is 50%
- Diagnosis may be more challenging
- More severe symptoms of ASD, aggression, and poorer social functioning

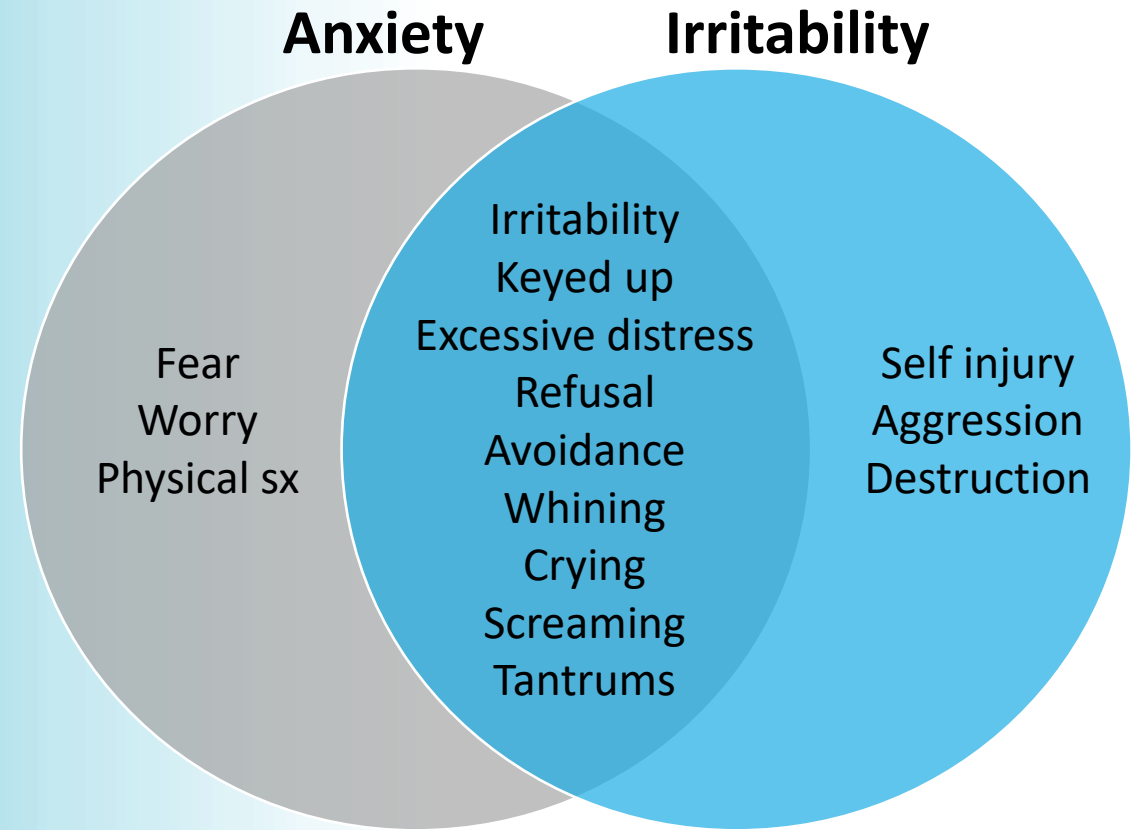
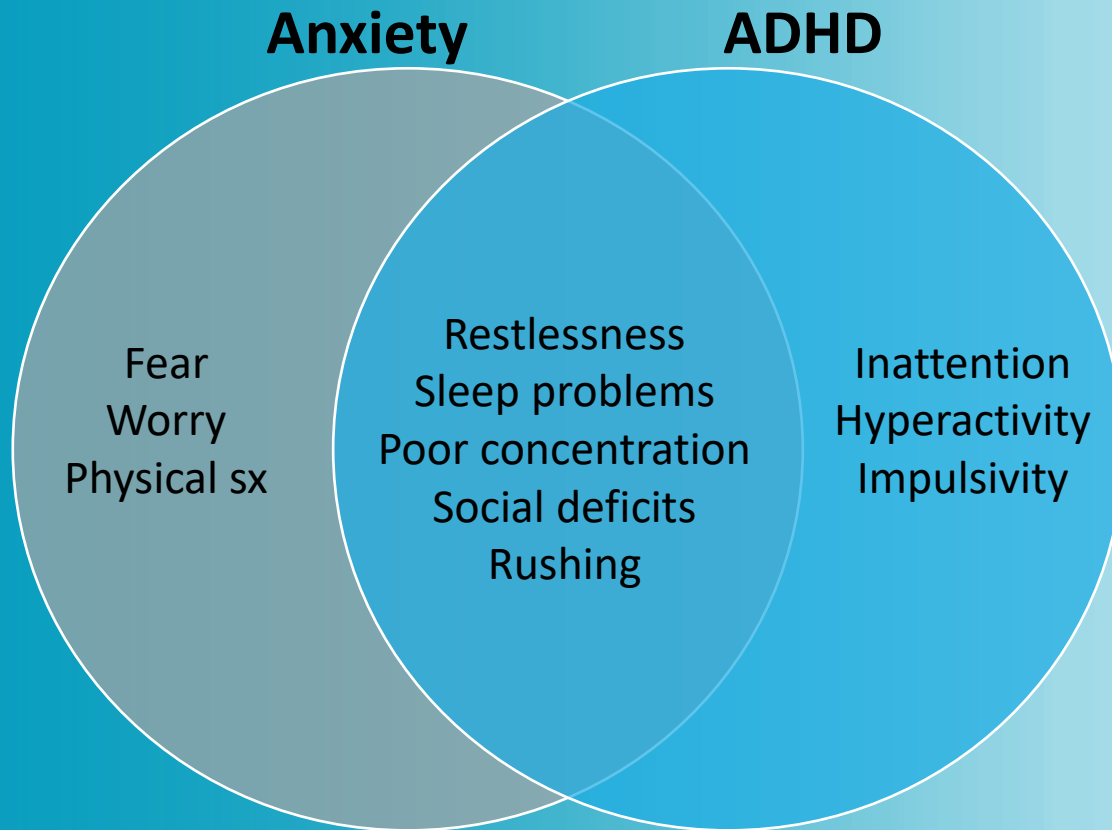
Content of fears/worry

- Sensory related fears or phobias (e.g., toilet flushing)
- Anxiety about transitions/change
- Anxiety about social interactions related to confusion rather than negative evaluation

Behaviors

- Skin/nail picking
- Pacing
- Bolting
- Crying
- Checking
- Questioning
- Rocking
- Rubbing

Anxiety, the Great Imitator





Anxiety can have a wide variety of presentations in ASD

”

“She was really scared at her cardiology appointment because she thought the doctor was going to take her heart out and kill her.” – *Mother of child with ASD*

”

“His favorite thing to do is go to the grocery store but the possibility of deviating from his grocery store routine is very anxiety provoking. He needs constant reassurance that it will happen the way it always does.” – *Mother of young adult with ASD*

”

“When he’s anxious he can’t stop moving. And when things get really bad, he dumps liquids out of containers and shreds clothes and furniture.” – *Mother of adult with ASD*



Clinical Examination for Anxiety

Heart rate

Look at hands/fingers (nail biting/picking)

Look at face and arms (skin picking/scratches)

Pacing

Bouncing legs

Rocking

Need to leave exam room frequently

Development of Parent-Rated Anxiety Scale for ASD



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- Focus groups involving 48 parents of children with ASD + anxiety (3-17 years)
- Interview guides to elicit observations about:
 - Manifestations of anxiety
 - Events and situations associated with anxiety
 - How the child manages anxiety
 - Impact of anxiety on the family
 - Relevance of the 25 Child Anxiety Symptom Inventory items

Qualitative coding + expert consultation -> 52 new candidate items

Development of Parent-Rated Anxiety Scale for ASD



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- 990 parents completed an online survey of the 52 new items + 20 CASI items on a 0-3 scale
 - (0 = not present; 1 = present sometimes, not a real problem; 2 = often present and a problem; 3 = very frequent and a major problem)
- Factor analysis + item response theory analyses -> single factor with 25 items
- 116 youth with ASD + mild anxiety participated in clinical assessment to evaluate the validity and reliability of the 25 items
 - Convergent validity with the SCARED (0.83)
 - Divergent validity with ABC and RBS subscales (0.33-0.66)
 - Good test-retest reliability (0.88, 0.86)
 - No difference in mean PRAS-ASD scores between boys/girls or ID/no ID

Parent-Rated Anxiety Scale for ASD



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Sample Items (0-3)

Uneasy in new situations

Overly fearful of weather events

Paces or does other repetitive behaviors when tense or worried

Complains about physical problems

Over-reacts when things do not go as planned

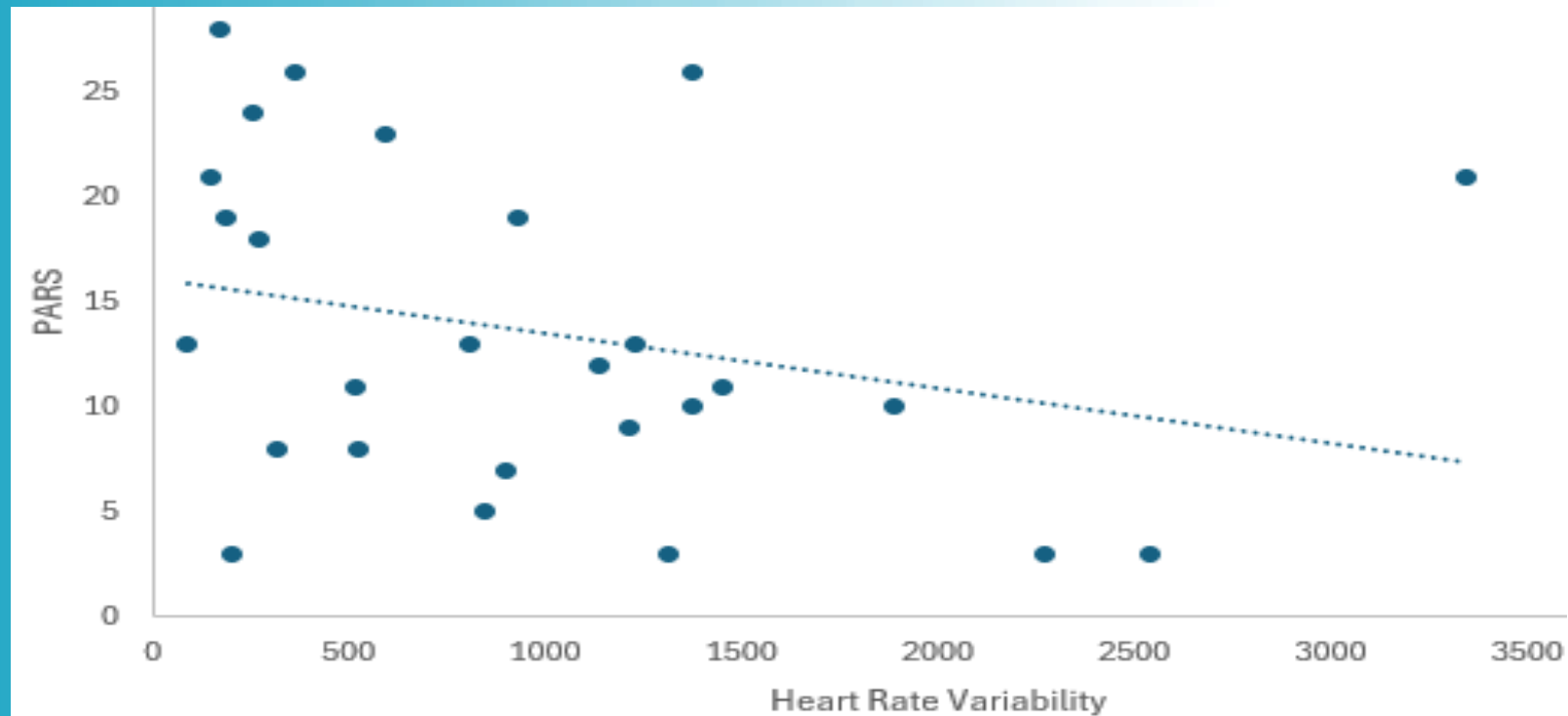
Gets stuck on what might go wrong

Consistently avoids certain situations due to anxiety

Needs a lot of reassurance that things will work out

Scahill et al. J Am Acad Child Adolesc Psychiatry 58(9):887-896, 2019

Heart Rate Variability at Rest is Associated with Anxiety in ASD



Anxiety severity versus low frequency heart rate variability (ms²) in youth with ASD at rest. PARS: Pediatric Anxiety Rating Scale. Spearman's rho: -0.34. p=0.04.

FDA Approved Treatments for Anxiety Disorders in Youth



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Medication	Disorder	Age (years)
Escitalopram	Generalized anxiety disorder	7-17
Fluoxetine	OCD	7-17
Fluvoxamine	OCD	8-17
Sertraline	OCD	6-17
Duloxetine	Generalized anxiety disorder	7-17

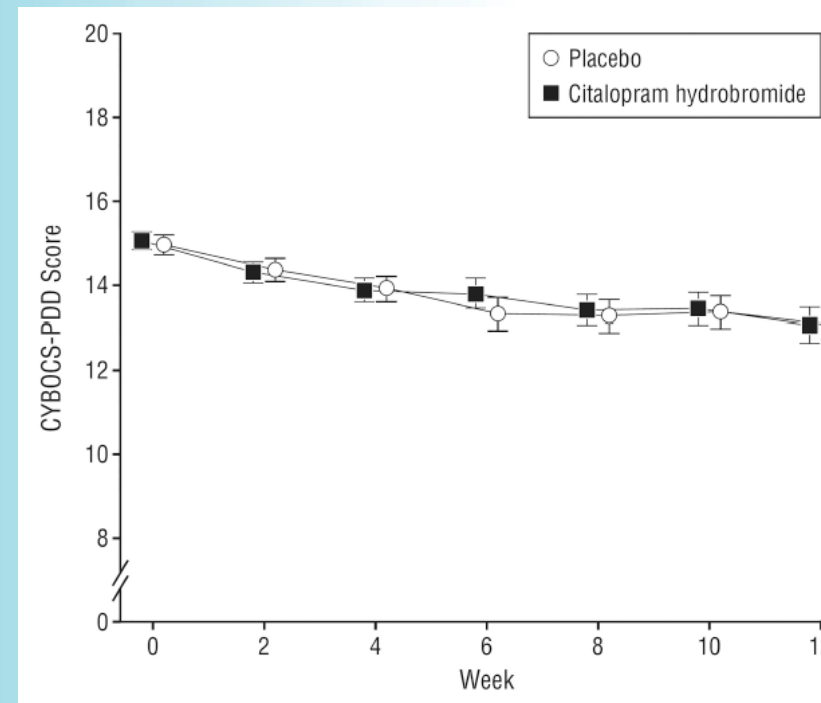


Citalopram for Repetitive Behaviors in Children with ASD

159 children (5-17 years) with ASD randomized to citalopram (mean dose: 16.5 mg per day) or placebo for 12 weeks

Adverse events: high rates of increased energy (38%), anger/irritability (25%), aggression (23%) on citalopram

SSRIs/SNRIs have not been studied for anxiety in ASD





Buspirone (1/2)

5-HT_{1A} receptor partial agonist.

FDA approval for the treatment of generalized anxiety disorder in adults.

Negative trials in neurotypical youth

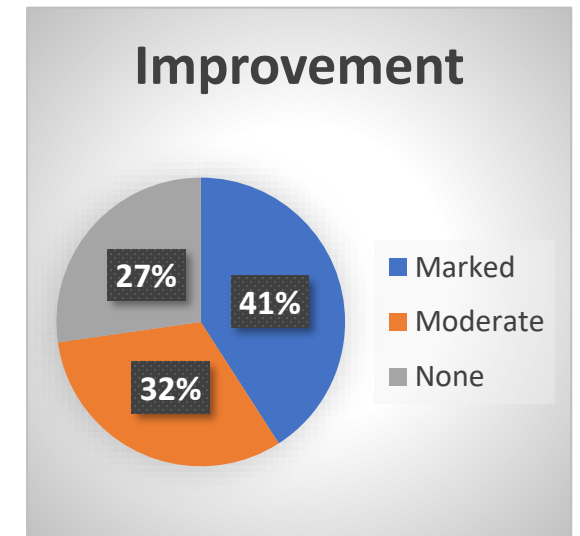
8-week open-label trial of buspirone for anxiety in PDD

N = 22, (ages 6-16 years) with PDD-NOS or autistic disorder, majority inpatients

Starting dose = 5 mg tid, maximum dose = 45 mg/day, mean dose = 29.3 mg/day

Adverse effects:

- Initial sedation = 2
- Slight agitation = 2
- Initial nausea = 1



Buitelaar, J. K., et al. (1998). *The Journal of clinical psychiatry*, 59(2), 56-59.



Bupirone (2/2)

- Retrospective chart review of 30 youth with ASD treated with bupirone
- 67% responded to 16-week course of bupirone
- Planning a RCT incorporating psychophysiologic measures

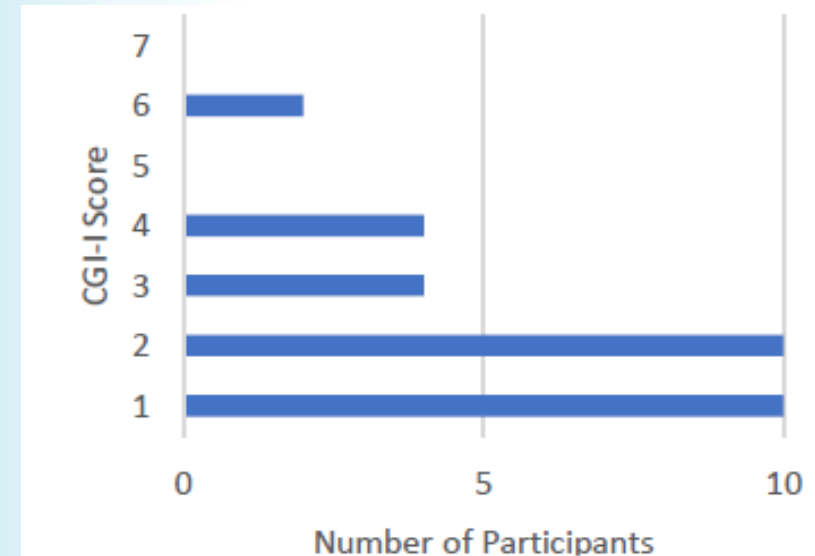


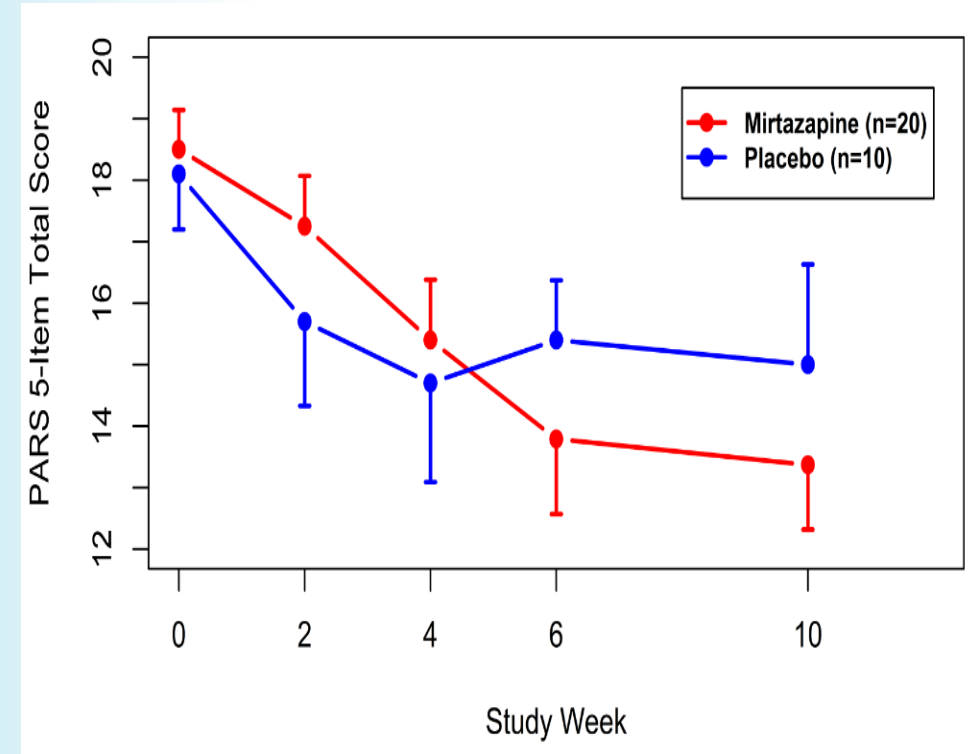
Figure 2. Bupirone Pilot Study in ASD, N=30. Treatment response was defined as a CGI-I rating of “very much improved” (CGI-I =1) or “much improved” (CGI-I=2).

Thom et al. Unpublished data



Mirtazapine

- 10-week randomized, double-blind, placebo-controlled trial
- 30 children with ASD (5-17 years) treated with mirtazapine or placebo
- Primary outcome measures: Pediatric Anxiety Rating Scale (PARS) and CGI-I
- Mirtazapine resulted in significant within-group decrease in anxiety (ES 1.76, $p < 0.001$)
- No statistically significant differences in mean 10-week change between mirtazapine and placebo
- Adverse events: no severe adverse events or suicidality. Most common adverse events included sedation, appetite increase, and irritability. No significant differences in adverse event frequency between mirtazapine and placebo.



McDougle CJ, et al. *Neuropsychopharmacology*. 2022;47(6):1263-1270.

Anxiety Treatment Pathway

