# Anxiety and Depression in Children and Adolescents with Autism Spectrum Disorders

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# Case Study

## Case Study: Thomas

- 11-year-old student with history of ASD, OCD, anxiety, and maladaptive behaviors
- He has had a long history of special education services since entering school
- He is in a self-contained classroom for ASD students and is doing reasonably well
  - Enjoys school and attends regularly
  - Doing well academically
  - Has trouble with verbal expression
  - Occasionally becomes very anxious and obsessed about germs and cleanliness, including excessive hand washing

**ASD = autism spectrum disorder; OCD = obsessive-compulsive disorder.**

## Case Study: Thomas (continued)

- Cognitive abilities (WISC-III)
  - FS IQ: 87, V IQ: 91, P IQ: 84
  - Mild verbal dysfluency
- Behavior has been generally fine recently, but has a history of impulse control problems and difficulties managing his anxiety
- Favorite activities include computer games and watching TV movies and sports
- Has been involved in special needs sports activities

**WISC-III = Wechsler Intelligence Scale for Children, Third Edition; IQ = intelligence quotient; FS = full scale; P = performance; V = verbal.**

## Case Study: Thomas (continued)

- Presenting problems
  - Escalating anxiety-related symptoms
    - Excessive worrying about the future
    - Ruminates about death
    - Fears something terrible will happen to family members
    - Needs constant reassurance from others
  - Associated impairments
    - Trouble concentrating and completing tasks
    - Increased social avoidance
    - Difficulty falling asleep
    - Refusing to go to school

# Autism Spectrum Disorder: Brief Review

## Autism Spectrum Disorders

- Includes Autism, Asperger syndrome, PDD-NOS, and CDD
- Required features
  - Social/communication deficits
  - Restricted, repetitive patterns of behavior, interests, activities
    - Addition of sensory criteria
- Symptoms must be present in early childhood
- Symptoms together limit and impair everyday functioning

CDD = childhood disintegrative disorder; PDD-NOS = pervasive developmental disorder not otherwise specified.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. Arlington, VA: American Psychiatric Publishing, Inc.; 2013.

## *DSM-5* Criteria: Social Communication

- Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, manifested by all of the following
  - Deficits in social-emotional reciprocity
  - Deficits in nonverbal communicative behaviors
  - Deficits in developing and maintaining relationships appropriate to the developmental level

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. Arlington, VA: American Psychiatric Publishing, Inc.; 2013.

## *DSM-5* Criteria: Restricted/Repetitive Behaviors

- Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least 2 of the following
  - Stereotyped or repetitive speech, motor movements, or use of objects
  - Excessive adherence to routines
  - Highly restricted, fixated interests that are abnormal in intensity or focus
  - Hyper- or hypo-reactivity to sensory input or unusual sensory interests

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. Arlington, VA: American Psychiatric Publishing, Inc.; 2013.

## *DSM-5* Criteria: Other Aspects

- Symptoms must be present in early childhood
- Symptoms together limit and impair everyday functioning

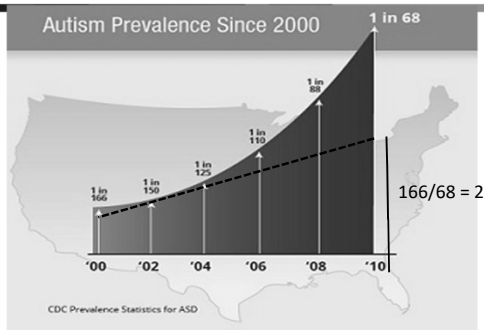
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. Arlington, VA: American Psychiatric Publishing, Inc.; 2013.

## What Else Can Look Like ASD?

- Social (pragmatic) communication disorder
- Nonverbal learning disability
- OCD
- Anxiety + language delay (with/without sensory issues)
- Cognitive delay + anxiety
- ADHD + severe anxiety and poor social skills

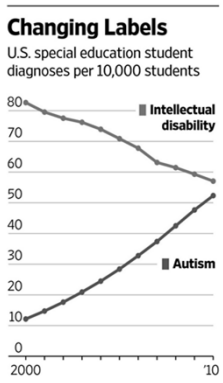
ADHD = attention-deficit/hyperactivity disorder.

## Prevalence of Diagnosis Steadily Increasing




Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators; Centers for Disease Control and Prevention. *MMWR Surveill Summ*. 2014;63(2):1-21.

## Is the prevalence of the diagnosis really increasing?




McGinty JC. 'Diagnostic Substitution' Drives Autism Spike. *The Wall Street Journal*. September 16, 2015.

## Autism Spectrum Disorders: Prognosis

- 15 outcome studies post-2000 (N = 1077) summarized
  - 12% to 30% with good outcomes
  - 20% to 47% with fair outcomes
  - 17% to 74% with poor/very poor outcomes
  - Large variations due to differences in study samples
- Predictors of good outcomes
  - Language / cognitive ability and adaptive skills
  - Family support / resources
  - Absence of comorbid psychopathology

**"Good"** = moderate to high levels of independence in job (or student) and/or living (may be at home with minimal supervision); some friends/acquaintances. **"Fair"** = some degree of independence or job, may require moderate levels of support and supervision but does not need specialist residential accommodation; no close friends but may have some acquaintances. **"Poor"** = requires specialist residential accommodation or hospital provision (or parental home with close supervision majority of the time); no friends or acquaintances.

Howlin P. Outcomes in Adults with ASD. In: Volkmar FR, et al (Eds). *Handbook of Autism and Pervasive Developmental Disorders*. Fourth Edition. Hoboken, NJ: John Wiley & Sons; 2014.

## Prevalence of Anxiety and Mood Disorders in ASD Youth

## Previous Diagnoses in Series of 234 Adolescents or Adults with ASD

| | |
|---|---|
| • Anxiety and anxiety-related disorders | 22.2% |
| • Depression | 19.7% |
| • Obsessive-compulsive disorder | 17.17% |
| • Schizophrenia diagnosed previously | 10.3% |
| • Schizophrenia definite | 0% |
| • Mania | 2.1% |
| • Substance abuse | 1.3% |

Tantam D. *Child Adolesc Psychiatr Clin North Am*. 2003;12(1):143-163, vii-viii.

## Anxiety in the Lives of People with ASD

- "… people with [ASD] live in a world that is more unpredictable and uncertain than it is for others whose intact nonverbal communication enables them to pick up patterns in social behavior."
- Uncertainty produces anxiety but anxiety does not cause ASD symptoms, merely worsens them
- Anxiety *increases* the social impairment by
  - Decreasing social skill performance
  - Increasing the frequency of any dysfunctional means that person with ASD might use in the face of anxiety
- "… slowness, ritualizing, making social blunders, aggression or irritability are all likely to worsen when a person with ASD becomes anxious."

Tantam D. *Child Adolesc Psychiatr Clin North Am*. 2003;12(1):143-163, vii-viii.

## Comorbidity in ASD Adults with Normal Intelligence

| Disorder | Asperger (n = 67) | PDD-NOS (n = 50) |
|---|---|---|
| ADHD | 36% | 52% |
| Mood | 52% | 54% |
| Anxiety | 51% | 50% |
| OCD | 21% | 30% |
| Substance-related | 6% | 28% |
| Psychotic | 15% | 10% |
| Cluster A | 56% | 54% |

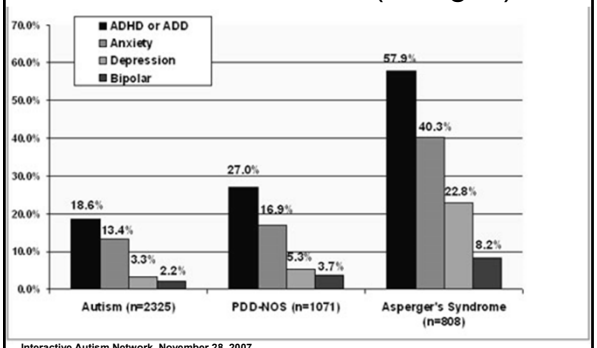
Hofvander B, et al. *BMC Psychiatry*. 2009;9:35.

## Comorbidity in ASD: Review of Literature

| Authors | Year | Age | N | Findings |
|---|---|---|---|---|
| Leyfer, et al | 2006 | 5–17 y | 109 | 37% had OCD |
| Joshi, et al | 2010 | 3–17 y | 217 ASD<br>217 cont | Much higher rates of anxiety disorders; 74% of ASD had ≥ 5 comorbid disorders |
| Davis, et al | 2011 | 2–14 y | 99 | Increased levels of anxiety noted, especially in those with better language |
| Strang, et al | 2012 | 6–18 y | 95 | 56% in clinical range for anxiety; 24% in borderline range for depression |
| Mannion, et al | 2013 | 3–16 y | 89 | > 15% had anxiety disorder; 46% had ≥ 1 comorbid disorder |

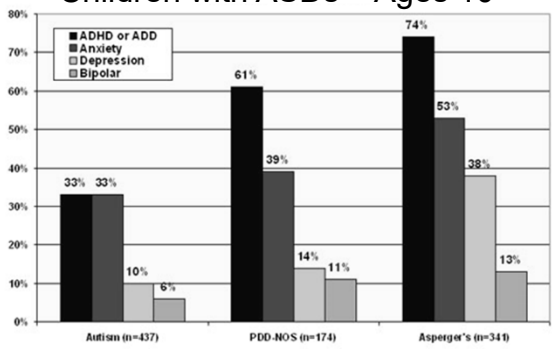
Mannion A, et al. *Research in Autism Spectrum Disorders*. 2013;7(12):1595-1616.

## Issues of Mood and Attention: Children with ASDs (All Ages)



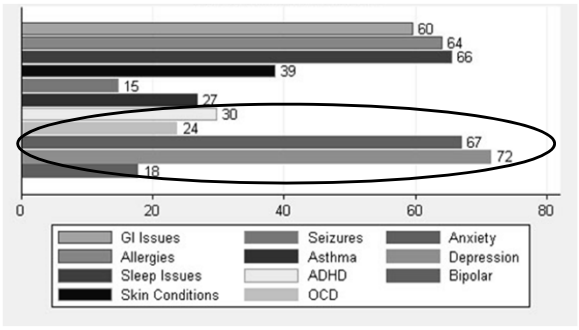

Interactive Autism Network. November 28, 2007. https://iancommunity.org/cs/ian_research_questions/attention_and_mood_issues. Accessed September 13, 2016.

## Disorders of Attention and Mood: Children with ASDs – Ages 10+




Based on Interactive Autism Network data as of August 17, 2007.

## Independent Adults with ASD Percentage with Co-occurring Conditions




Interactive Autism Network data updated September 8, 2009. N = 67.

## Assessment of Anxiety and Mood Disorders in ASD Youth

## Evaluation: Autism Spectrum Disorders

- Comprehensive, multidisciplinary evaluation
- Autism Treatment Network Protocol
  - Medical evaluation
  - Psychological / Psychiatric evaluation
  - Autism Diagnostic Observation Schedule (ADOS), other autism specific diagnostic tools
  - Screening for common, related medical issues
    - Sleep problems, GI problems
- *DSM-5* criteria insufficient – need to assess functioning

GI = gastrointestinal.

## Evaluation: Screening for Comorbidity

- Broad-band measures
  - Achenbach System of Empirically Based Assessment (ASEBA)
    - Child Behavior Checklist (CBCL) (eg, anxiety, depression subscales)
    - Teacher Report Form
  - Behavioral Assessment System for Children (BASC)
- Anxiety / Depression
  - Screen for Child Anxiety Related Emotional Disorders (SCARED)
  - Revised Children's Anxiety and Depression Scale (RCADS)
  - Child Depression Inventory (CDI)
  - In development: Anxiety Scale for Children – ASD (ASC-ASD)

**Volkmar FR, et al (Eds). *Handbook of Autism and Pervasive Developmental Disorders*. Fourth Edition. Hoboken, NJ: John Wiley & Sons; 2014.**

## Evaluation: Family/Parent Interview

- Problem description
  - Anxiety signs / symptoms
    - Need to distinguish between avoidance due to fear vs disinterest
  - Depressive signs/symptoms
    - Need to distinguish between irritability and low frustration tolerance
- Time course
- Stressors / triggers
- Family responses to worsening signs / symptoms
  - Ameliorating strategies
  - Ineffective strategies

**Volkmar FR, et al (Eds). *Handbook of Autism and Pervasive Developmental Disorders*. Fourth Edition. Hoboken, NJ: John Wiley & Sons; 2014.**

## Evaluation Questions

- What symptoms of anxiety are present? With what impact?
- Is the anxiety stimulus specific, spontaneous, or anticipatory?
- What is the degree of avoidance in daily life?
- What is the social / family context?
  - Reinforcers of symptoms
  - Family accommodation
- What is the child/adolescent's temperament, quality of attachment, stranger/separation response, childhood fears?

**Volkmar FR, et al (Eds). *Handbook of Autism and Pervasive Developmental Disorders*. Fourth Edition. Hoboken, NJ: John Wiley & Sons; 2014.**

## Evaluation Questions

- What signs/symptoms of mood disorder are present? With what intensity, frequency, and duration?
  - Inquire about irritability, mood shifts, crying episodes, and tantrums
  - Investigate vegetative signs of mood disorder (sleep, appetite, energy)
- What is the impact of mood signs/symptoms on daily life?
- What factors seem to improve or worsen the child's mood?
- Are there any associated medical disorders and medications?
- Is there a family history of anxiety and/or mood disorders?

**Volkmar FR, et al (Eds). *Handbook of Autism and Pervasive Developmental Disorders*. Fourth Edition. Hoboken, NJ: John Wiley & Sons; 2014.**

## Treatment Planning

- Review findings and diagnostic impression
- Educate about ASD and comorbid disorders
- Consider both protective and risk factors
- Elicit patient / family preferences and priorities
- Emphasize need for multimodal approach
- Help patient / family to get ready to take next steps

**Volkmar FR, et al (Eds). *Handbook of Autism and Pervasive Developmental Disorders*. Fourth Edition. Hoboken, NJ: John Wiley & Sons; 2014.**

## Evidence for Treatment of Anxiety and Mood Disorders in ASD Youth

- Treatment research is relatively sparse for anxiety and mood disorders in ASD children and adolescents
- Varied opinions about whether psychotherapy or pharmacotherapy, or a combination should be the first-line treatment
- Initial acute treatment depends on
  - Severity of presenting symptoms
  - Number of prior episodes
  - Chronicity
  - Age
  - Overall level of functioning
  - Contextual issues in family
  - School
  - Social
  - Negative life events
  - Adherence
  - Prior treatment response
  - Motivation for treatment

# Medical Treatment of Anxiety and Depression in Children and Adolescents with ASD

## Why Use Medications in ASD?

**Appropriate Reasons**

- To treat co-existing disorders (eg, anxiety depression, bipolar, ADHD)
- To improve psychiatric symptoms that are seriously interfering with functioning (eg, aggressive outbursts)
- To improve adaptation, functional level, learning, and overall quality of life

**Inappropriate Reasons**

- To sedate, silence, or keep patients still ("strait jacket")
- To appease family members, caregivers, etc.
- To treat ourselves (ie, our need to "do something")
- To experiment

## Most Commonly Used Medications

**Percentage of patients on medications**

- Antidepressants: 20% to 25%
- Antipsychotics: 10% to 15%
- Stimulants: 10% to 15%
- α-agonists: 10%
- Anticonvulsants: 5% to 10%

## Major Classes of Medications Used in the Treatment of Comorbid ASD

- Antidepressants
  - SSRIs
  - TCAs
- Novel Antipsychotics
  - Risperidone
  - Aripiprazole
- Anticonvulsants
  - Valproate

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

*"I couldn't help myself. My lack of serotonin made me do it."*

## Lack of Efficacy of Citalopram in Children with Autism Spectrum Disorders and High Levels of Repetitive Behavior: Citalopram Ineffective in Children with Autism

King BH, et al. *Arch Gen Psychiatry*. 2009;66(6):583-590.

## ASD Citalopram Study: 2009

- 12-week randomized, double-blind, placebo controlled trial
- 149 participants ages 5 to 17 years had ASD, Asperger disorder, or PDD-NOS; had illness severity ratings of at least moderate on the CGI-S and scored at least moderate on compulsive behaviors measured with the CYBOCS-PDD
- Doses titrated to 10 to 20 mg daily – mean (SD) maximum dosage of citalopram hydrobromide was 16.5 (6.5) mg/day by mouth (maximum, 20 mg/day)
- Participants stayed on either citalopram or placebo for 12 weeks
- Primary outcome measures included "very much improved" or "much improved on the CGI-I
- Secondary outcome measures was the score on the CYBOCS

**CGI = Clinical Global Impressions; CGI-I = CGI Improvement Scale; CGI-S = CGI Severity of Illness Scale; CYBOCS = Children's Yale-Brown Obsessive Compulsive Scales; CYBOCS-PDD = CYBOCS modified for PDD.**

## ASD Citalopram Study: 2009

- **Results**

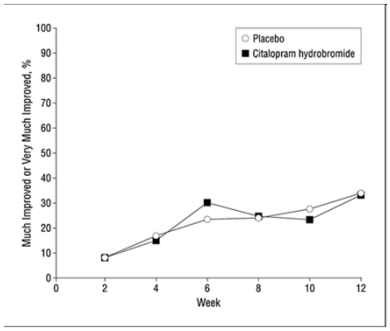
There was no significant difference in the rate of positive response on the CGI-I between the citalopram-treated group (32.9%) and the placebo group (34.2%) (relative risk, 0.96; 95% CI, 0.61–1.51; *P* > .99). There was no difference in score reduction on the CYBOCS-PDD from baseline (mean [SD], –2.0 [3.4] points for the citalopram-treated group and –1.9 [2.5] points for the placebo group; *P* = .81). Citalopram use was significantly more likely to be associated with adverse events, particularly increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia, and dry skin or pruritus

- **Conclusion**

Results of this trial do not support the use of citalopram for the treatment of repetitive behavior in children and adolescents with ASDs

**CI = confidence interval.**

## Percentage of Children with a Rating of "Much Improved" or "Very Much Improved" on the CGI-I during the 12-week Trial




## Summary of Studies: SSRIs

**Target symptoms in ASD patients that appear to improve only SLIGHTLY with SSRIs**

- Depression
- Aggression, temper outbursts
- Interfering repetitive phenomena
- Difficulty with transitions
- Language usage
- No evidence for improvements in social interaction

## Major Side Effects: SSRIs

- GI
  - Nausea
  - Vomiting
- Arousal
  - Sedation
  - Drowsiness
- Sexual
  - Reduced libido
- Behavioral
  - Activation
  - Agitation
  - Manic-like excitement
- Mood
  - Anxiety
  - Mood swings
  - Mania

## TCAs for ASD in Children and Adolescents: Meta-Analysis

- **Objectives:**

To determine if treatment with TCAs: 1) improves the core features of autism, including restricted social interaction, restricted communication, and stereotypical and repetitive behaviors; 2) improves non-core features such as challenging behaviors; 3) improves comorbid states, such as depression and anxiety; 4) causes adverse effects

- **Main Results:**

3 studies met the inclusion criteria for this review. 2 studies used clomipramine and 1 used tianeptine. All 3 trials were small, with between 12 and 32 participants. One of the clomipramine trials involved children and young adults, while the other 2 trials enrolled only children.

**Hurwitz R, et al. *Cochrane Database Syst Rev.* 2012;(3):CD008372.**

## TCAs for ASD in Children and Adolescents: Meta-Analysis (continued)

- **Main Results (continued):**

Adverse effects – increased drowsiness and reduced activity. The evidence of the impact of medications is contradictory. There was evidence of improvement in autistic symptoms, irritability, and OCD type symptoms, but conflicting evidence in relation to hyperactivity across the studies, and no significant changes found with inappropriate speech.

- **Conclusions:**

There is only limited evidence to support the use of clomipramine or tianeptine in the treatment of individuals with ASD, and some evidence of side effects that would limit their usefulness. Clinicians considering the use of TCAs in ASD need to be aware of the limited and conflicting evidence of effect and the side-effect profile of TCAs when discussing this treatment option with patients with ASD and their caregivers.

**Hurwitz R, et al. *Cochrane Database Syst Rev*. 2012;(3):CD008372.**

## Novel Antipsychotic Treatment for ASD: Early Studies

- Risperidone – most studied novel neuroleptic; reduction in maladaptive behaviors seen; FDA approved 2008
- Studies:
  - **McCracken JT, et al (RUPP Autism Network). *N Engl J Med*. 2002;347(5):314-421.**
  - **Shea S, et al. *Pediatrics*. 2004;114(5):e634-e641.**
  - **RUPP Autism Network. *Am J Psychiatry*. 2005;162(7):1361-1369.**
  - **McDougle CJ, et al. *Am J Psychiatry*. 2005;162(6):1142-1148.**
  - **Troost PW, et al. *J Am Acad Child Adolesc Psychiatry*. 2005;44(11):1137-1144.**
  - **Luby J, et al. *J Child Adolesc Psychopharmacol*. 2006;16(5):575-587.**
  - **Nagaraj R, et al. *J Child Neurol*. 2006;21(6):450-455.**
  - **Pandina GJ, et al. *J Autsim Dev Disord*. 2007;37(2):367-373.**
  - **Gencer O, et al. *Eur Child Adolesc Psychiatry*. 2008;17(4):217-225.**
- N = 249; Effect size: 0.89 – 1.37

**RUPP = Research Units on Pediatric Psychopharmacology.**

## Novel Antipsychotic Treatment for ASD: Early Studies

***Randomized Controlled Trials***

- Aripiprazole (**Marcus RN, et al. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1110-1119. Owen R, et al. *Pediatrics*. 2009;124(6):1533-1540.**) FDA approved 2009
- Olanzapine (**Hollander E, et al. *J Child Adolesc Psychopharmacol*. 2006;16(5):541-548.**)

***Open-Label Trials***

- Quetiapine (**Martin A, et al. *J Child Adolesc Psychopharmacol*. 1999; Findling RL, et al. *J Child Adolesc Psychopharmacol*. 2004;14(2):287-294. Corson AH, et al. *J Clin Psychiatry*. 2004;65(11):1531-1536.**)
- Ziprasidone (**McDougle CJ, et al. *J Am Acad Child Adolesc Psychiatry*. 2002;41(8):921-927.**)

***Case Reports***

- Clozapine (**Zuddas A, et al. *Am J Psychiatry*. 1996;153(5):738. Chen NC, et al. *J Clin Psychiatry*. 2001;62(6):479-480.**)

## Tolerability, Safety, and Benefits of Risperidone in Children and Adolescents with Autism: 21-Month Follow-up after 8-Week Placebo-Controlled Trial

- In a naturalistic study, 84 children and adolescents 5 to 17 years of age (from an original sample of 101) were assessed an average of 21.4 months after initial entry into a placebo-controlled 8-week trial of risperidone for children and adolescents with autism and severe irritability
- They were assessed at baseline and at follow-up on safety and tolerability measures (blood, urinalysis, ECG, medical history, vital signs, neurological symptoms, other adverse events), developmental measures (adaptive behavior, IQ), and standardized rating instruments.

**ECG = electrocardiogram.**
**Aman M, et al. *J Child Adolesc Psychopharmacol*. 2015;25(6):482-493.**

## Tolerability, Safety, and Benefits of Risperidone in Children and Adolescents with Autism: 21-Month Follow-up after 8-Week Placebo-Controlled Trial (continued)

- Of the 17 variables related to benefit, there were 4 (24%) that suggested significant benefits associated with recent risperidone use, 2 (VABS Social Skills and ABC Social Withdrawal) reflected possible increases in social relatedness, 1 (M-RLRS, Sensory Responses) reflected improvements in how participants interacted with others and the environment, and another (ABC-I) reflected fewer aggression/self-injury problems
- 5 variables could reflect adverse drug effects (AIMS [2 variables], Simpson–Angus, weight, BMI), and, of these, only weight gain (20%) was associated with recent risperidone use. We treated height as neutral (neither an index of tolerability nor of therapeutic change)

**ABC = Aberrant Behavior Checklist; ABC-I = ABC Irritability; AIMS = Abnormal Involuntary Movement Scale; BMI = body mass index; M-RLRS = Modified Real Life Rating Scale for Autism; VABS = Vineland Adaptive Behavior Scale.**
**Aman M, et al. *J Child Adolesc Psychopharmacol*. 2015;25(6):482-493.**

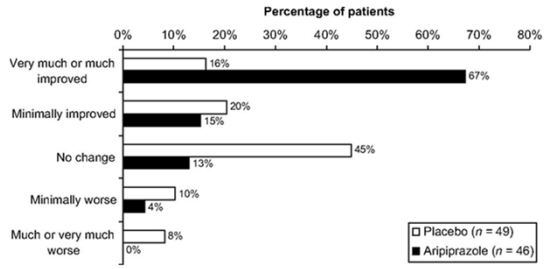
## Aripiprazole in the Treatment of Irritability in Children and Adolescents with ASD

- 8-week randomized, double-blind, placebo controlled trial
- 98 participants with ASD and irritability/aggression on the ABC-I
- Doses titrated to 5, 10, or 15 mg of aripiprazole or placebo daily
- 51 participants received placebo; 47 received aripiprazole
- Primary outcome measures included the CGI-I and the ABC-I

**Owen R, et al. *Pediatrics*. 2009;124(6):1533-1540.**

## Aripiprazole in the Treatment of Irritability in Children and Adolescents with ASD (continued)

**Distribution of CGI-I score at week 8 (LOCF; efficacy sample)**




Owen R, et al. *Pediatrics*. 2009;124(6):1533-1540.

## Aripiprazole for ASD: Meta-Analysis

- 2 RCTs with similar methods evaluated use of aripiprazole for a duration of 8 weeks in 316 children/adolescents with ASD
- Meta-analysis of study results revealed a mean improvement of -6.17 points on the ABC-I (95% CIs -9.07 to -3.26, -7.93 points on the ABC Hyperactivity subscale (95% CI -10.98 to -4.88) and -2.66 points on the ABC Stereotypy subscale (95% CI -3.55 to -1.77) in children/adolescents taking aripiprazole relative to those on placebo
- In terms of side effects, children/adolescents taking aripiprazole had a greater increase in weight, with a mean increase of 1.13 kg relative to placebo (95% CI 0.71 to 1.54), and had a higher RR for sedation (RR 4.28, 95% CI 1.58 to 11.60) and tremor (RR 10.26, 95% CI 1.37 to 76.63)

RCT = randomized controlled trial; RR = risk ratio.
Hirsch LE, et al. *Cochrane Database Syst Rev*. 2016;(6):CD009043.

## Aripiprazole for ASD: Meta-Analysis

- **Authors' Conclusions:**

Evidence from 2 RCTs suggests that aripiprazole can be effective as a short-term medication intervention for some behavioral aspects of ASD in children/adolescents. After a short-term medication intervention with aripiprazole, children/adolescents showed less irritability and hyperactivity and fewer stereotypies (repetitive, purposeless actions). However, notable side effects, such as weight gain, sedation, drooling and tremor, must be considered. One long-term, placebo discontinuation study found that relapse rates did not differ between children/adolescents randomized to continue aripiprazole vs children/adolescents randomized to receive placebo, suggesting that re-evaluation of aripiprazole use after a period of stabilization in irritability symptoms is warranted.

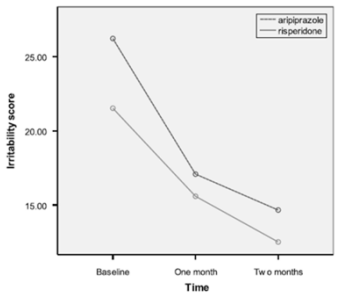
Hirsch LE, et al. *Cochrane Database Syst Rev*. 2016;(6):CD009043.

## A Head-to-Head Comparison of Aripiprazole and Risperidone for Safety and Treating ASD: Randomized Double-Blind Clinical Trial

- 59 children and adolescents with ASD were randomized to receive either aripiprazole or risperidone for 2 months
- The primary outcome measure was change in ABC scores. Adverse events were assessed
- Aripiprazole and risperidone lowered ABC scores over 2 months
- The rates of adverse effects were not significantly different between the 2 groups
- The safety and efficacy of aripiprazole (mean dose 5.5 mg/day) and risperidone (mean dose 1.12 mg/day) were comparable

Ghanizadeh A, et al. *Child Psychiatry Hum Dev*. 2014;45(2):185-192.

## A Head-to-Head Comparison of Aripiprazole and Risperidone for Safety and Treating ASD: Randomized Double-Blind Clinical Trial (continued)




Comparison of ABC-I scores between the 2 groups during the trial

Ghanizadeh A, et al. *Child Psychiatry Hum Dev*. 2014;45(2):185-192.

## Summary of Studies: Novel Antipsychotics

**Target symptoms in ASD patients that appear to improve with atypical antipsychotics**

- Enhanced social interaction
- Aggression, temper outbursts
- Interfering repetitive phenomena
- Difficulty with transitions

**Weight gain** is a major concern – new adjunctive agents (eg, metformin and topiramate) are being investigated

*FDA approval for risperidone and aripiprazole only

## Major Side Effects: Novel Antipsychotics

- Sedation
- Disrupted sleep
- Increased appetite
- Weight gain – "metabolic syndrome"
- Prolactin elevation (with risperidone)
- Extrapyramidal symptoms
- Heart rhythm disturbances* (ie, QTc)

*Ziprasidone and clozapine.

## Divalproex Sodium vs Placebo for the Treatment of Irritability in Children and Adolescents with ASD

- 12-week randomized, double-blind, placebo controlled trial
- 27 participants with ASD and irritability/aggression on the ABC-I
- Doses titrated to 250 mg bid (< 40 kg) or 500 mg bid (> 40 kg) in first week – monitored by blood level to therapeutic dose
- Participants stayed on either divalproex or placebo for 12 weeks
- Primary outcome measures included the CGI-I and the ABC-I
- Secondary outcome measures included the OAS-M and the CYBOCS

OAS-M = Overt Aggression Scale-Modified.
Hollander E, et al. *Neuropsychopharmacology*. 2010;35(4):990-998.

## Divalproex Sodium vs Placebo for the Treatment of Irritability in Children and Adolescents with ASD (continued)

- **Results:**

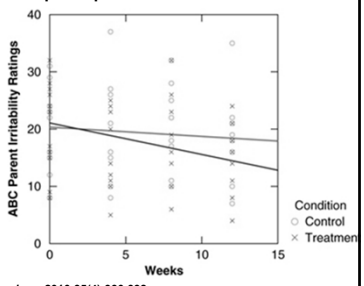
CGI-I. On the basis of intent-to-treat analyses, 10 of the 16 active treatment participants (62.5%) showed a response to irritability, whereas only 1 of the placebo participants (9.09%) showed a response (OR = 16.66). This effect is significant by Fisher's exact test ($P$ = .008). The odds ratio indicates that participants receiving treatment with divalproex sodium are over 16 × more likely to respond to treatment than participants receiving placebo

Hollander E, et al. *Neuropsychopharmacology*. 2010;35(4):990-998.

## Divalproex Sodium vs Placebo for the Treatment of Irritability in Children and Adolescents with ASD (continued)

**Improvements in ABC-I subscale in divalproex *vs* placebo-randomized participants over 12 weeks**

There is a significant weeks *x* condition interaction ($t$ = −2.09, df = 22.71, $P$ = .048), suggesting that the active group showed a drop of more than 0.53 points per week compared with the placebo group on the ABC parent irritability ratings




Hollander E, et al. *Neuropsychopharmacology*. 2010;35(4):990-998.

## Summary of Studies: Anticonvulsants

**Target symptoms in ASD patients that appear to improve with anticonvulsant mood stabilizers**

- Excessive mood swings and emotional instability
- Aggression, temper outbursts, explosiveness
- Manic and mixed manic-depressive episodes

**Weight gain** is a major concern – new adjunctive agents (eg, metformin and topiramate) are being investigated

## Major Side Effects: Anticonvulsants

### Valproate

- GI upset
- Tremor
- Sedation
- Increased appetite AND weight gain
- Alopecia
- Ataxia
- Rashes (rare)
- Abnormal liver enzymes

### Carbamazepine

- Drowsiness
- Dizziness, Ataxia
- Diplopia, blurred vision
- Nausea
- Fatigue
- GI upset
- Hyponatremia
- Aplastic anemia (very rare)

## Summary of Drug Treatment Strategies

- Prioritize Treatment Goals
- Specify Target Symptoms
- Employ rational choices to medication usage
  - *Antipsychotics*: social withdrawal aggression, SIB, bizarre behavior
  - *SSRIs*: anxiety, OCD, mood swings, depression
  - *Stimulants*, etc.: hyperactivity, impulsivity, inattention
  - *Mood stabilizers*: affective instability, impulsivity and aggression

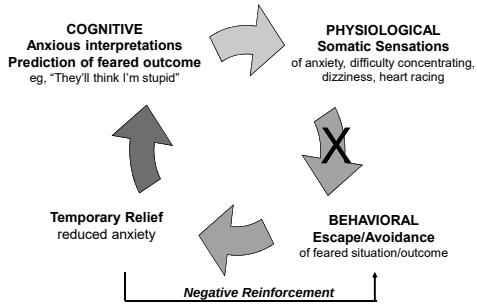
SIB = self-injurious behavior.

## Summary of Drug Treatment Strategies (continued)

- Monitor side effects
  - *SSRIs*: hypomania, serotonin syndrome, withdrawal
  - *Stimulants*: weight loss, insomnia, agitation, tics, compulsivity
  - *Antipsychotics*: sedation, weight gain, dyskinesia, cardiac, diabetes
  - *Anticonvulsant mood stabilizers*: weight gain, GI problems, sedation, hair loss (also watch for signs of hepatic failure, pancreatitis, agranulocytosis)
- Vary doses and use alternative medications in a given class
- Combine carefully and cautiously with synergy

## Psychosocial Treatment of Anxiety and Depression in Children and Adolescents with ASD

## The Cycle of Anxiety




## Treatment Components

- Build a therapeutic relationship
- Affect recognition
- Identify somatic reactions
- Relaxation
- Identify and change anxious thoughts
- Problem solving
- Self-evaluation and reward
- Graded exposure

## Therapies for Children with ASD: Behavioral Interventions Update

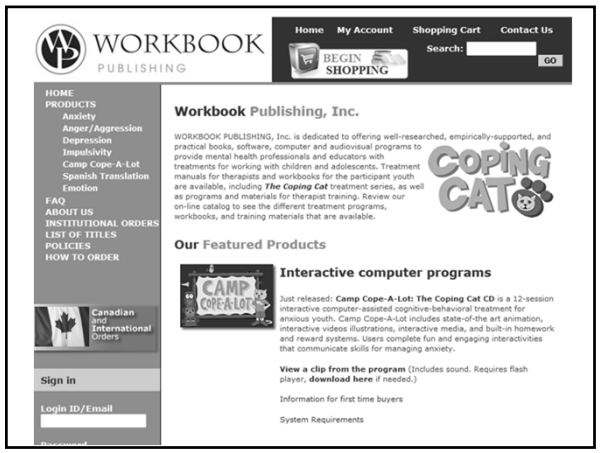
- "Six RCTs (five good and one fair quality) of interventions addressing conditions commonly associated with ASD identified for the current update measured anxiety symptoms as a primary outcome. Five of these studies reported significantly greater improvements in anxiety symptoms in the intervention group compared with controls. Two found positive effects of cognitive behavioral therapy (CBT) on the core ASD symptom of socialization, and one reported improvements in executive function in the treatment group."
- Note: there are no well documented evidence-based behavioral treatments for mood disorders in the ASD population

Weitlauf AS, et al. Therapies for Children wIth Autism Spectrum Disorder: Behavioral Interventions Update. Comparative Effectiveness Review No. 137.(Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2012-00009-I.) AHRQ Publication No. 14-EHC036-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

## The “Coping Cat” Program for Children with Anxiety and ASD: A Pilot RCT

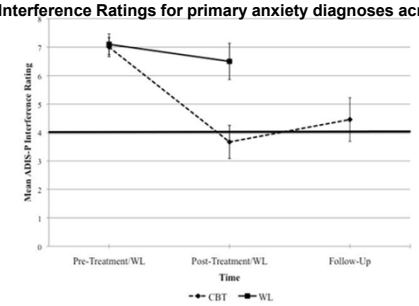
- 22 children (ages 8–14; IQ ≥ 70) with ASD and clinically significant anxiety were randomly assigned to 16 sessions of the Coping Cat program (CBT) or a 16-week waitlist
- Children in the CBT condition evidenced significantly larger reductions in anxiety than those in the waitlist. Treatment gains were largely maintained at 2-month follow-up
- Results provide preliminary evidence that a modified version of the Coping Cat program may be a feasible and effective program for reducing clinically significant levels of anxiety in children with high-functioning ASD

**CBT = cognitive-behavioral therapy.**
**McNally Keehn RH, et al. *J Autism Dev Disord*. 2013;43(1):57-67.**




## The “Coping Cat” Program for Children with Anxiety and ASD: A Pilot RCT

**ADIS-P Interference Ratings for primary anxiety diagnoses across time.**




**ADIS-P = Anxiety Disorders Interview Schedule-Parent Version; WL = waitlist.**
**McNally Keehn RH, et al. *J Autism Dev Disord*. 2013;43(1):57-67.**

## Case Study: Thomas

- Follow-up
  - Medical Treatment
    - Risperidone trial – controlled anxiety, but eventually led to excessive weight gain and hyperglycemia
    - Aripiprazole trial – continued reduction in anxiety without sedation and reduction in weight gain
    - Metformin added for control of hyperglycemia
  - Psychosocial Treatment
    - Family systems therapy helped parents reduce their overreactions to patient’s anxiety symptoms (eg, school avoidance, social withdrawal)
    - Coping Cat program improved patient’s ability to handle his anxiety
    - Social Skills therapy helped patient to engage with peers with greater level of competence

## Key Points

- Anxiety and mood disorders are highly prevalent in children and youth with ASD. Up to 50% have anxiety disorders and up to 35% have mood disorders that are impairing of function
- Assessing anxiety and mood disorders in children and youth with ASD should include use of screening tools, structured interviews, and careful delineation of key symptoms and their impact on functioning
- Medication management of anxiety and mood disorders includes use of antidepressants, novel antipsychotics, and anticonvulsant mood stabilizers
- Modified CBT for anxiety disorders has proven to be effective for this population; however, there are as yet no evidence-based psychosocial treatments for mood disorders