Management of Autism Spectrum Disorders

Dr. Anita Narayanan, MD

Objectives

1. Participants will be able to outline the steps to develop a management plan for a child with autism spectrum disorder.
2. Participants will be able to name and describe use of 1-3 psychotropic medications in autism spectrum disorder.
3. Participants will be able to describe current evidence to support use of medications.

Autism Treatment

- Complex disorder that impacts each child differently
- Treatment for autism spectrum disorder is an intensive, comprehensive undertaking that involves the child's **family** and a **team** of professionals.
- Individualized & dependent on child's specific strengths and needs

Behavior Intervention

- Early intervention improves outcomes for cognitive/adaptive skills and educational attainment.

- The National Research Council recommends **25 hours** of structured intervention per week.
  - •ABA or other developmental program (one-on-one or small group)
  - •Parent delivered intervention
  - •Speech-language therapy
  - •Occupational therapy

Applied Behavioral Analysis (ABA)

- Started early 1960s
- Teach communication, play, social, academic, self-care, work/community living skills
- Reduce problem behaviors
- Customized
- Skills broken into small step
- Use of ABC's of behavior (Discrete Trial Teaching)
- Data collection and analysis plays critical part

Early Start Denver Model

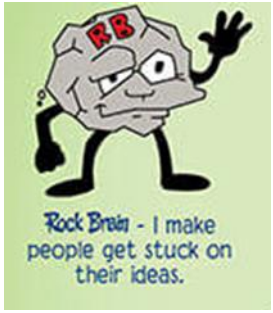
- Relationship focused developmental model based on ABA core features
  - •Focuses on children 12-48 months
  - •Sensitive to normal developmental sequence
  - •Deep parental involvement
  - •Focus on interpersonal exchange and positive affect
  - •Shared engagement with joint activities

Social Issues in ASD

- Fewer friends
- Less satisfying relationships
- More feelings of loneliness
- Lower self-esteem
- Higher rates of bullying and teasing
- Social skill impairments → academic and work underachievement

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

Social Skills Interventions



- Teacher/therapist facilitated
- Can involve trained peers/siblings/parents
- Individual or group based
- Often includes visuals (pictures, videos)

Social Skills Interventions

Table 2
Examples of lesson topics for social skills groups

Elementary School Age Group[22]	Adolescent Social Skills Group[21]
Getting to know someone	Meeting new people/asking questions
Body talk (nonverbals)	Using body talk
Dealing with emotions	Using body signals to express and understand emotions
Conversation	Being positive
Making impressions	Keeping the conversation going/active listening
Teasing vs humor	Teen obstacles
Friendship tips	Sharing opinions

Social Stories

- Social learning tool that supports exchange of meaningful information between person with autism and others

- Identifies important cues in given situation; rules, routines, preparing for upcoming event

Social Skills – Physical Activity

- It's hard!
    - Working on a team
    - Learning specific movements/form
- Local examples:
    - NCH Play Strong Program
    - Recreation Unlimited

Comorbid Medical Conditions

- 95% of 4-8 year olds with ASD have <u>at least one</u> comorbid condition

  - •ADHD
  - •Anxiety
  - •Seizures
  - •Genetic disorders
  - •GI disorders
  - •Sleep dysfunction
  - •Pica

Comorbid Psychiatric Conditions

Psychiatric Comorbidity	Percentage
ADHD	60%
Anxiety	40-66%
Depression (higher SI)	12-33%
ODD or Conduct Disorder	16-28%
OCD	*difficult to distinguish from core ASD symptoms
Psychotic Disorder	12-17%
Any Psychiatric Disorder	70-90%

Other Comorbid Conditions

Condition	Percentage
Intellectual disability or GDD	40-50%
Language disorder	30% minimally verbal or nonverbal
Seizure disorder	20-30%*
Tics/Tourette's disorder	14-38%
Gastrointestinal	9-70%
Sleep disorder	50-80%
Feeding problems	75%

Toolkits from Autism Speaks™

- 100 Day Kit
- A Friend/Grandparent/Parent and Sibling Guide to ASD
- Toilet Training
- High-Functioning ASD
- Blood Draw
- Challenging Behaviors
- Dental
- Feeding
- Constipation
- Medication Decision Aid
- Pica
- Sleep
- Successful Haircut
- IEP
- Financial Planning
- Employment
- Advocacy
- Puberty

Psychopharmacology

- Principles of psychopharmacologic management of individuals with ASD are same as those without.
- Few behavior rating scales are standardized for children with ASD.
- Target specific symptoms that are clearly defined.
- Periodically re-evaluate.
- Children with ASD are more sensitive to psychopharmacotherapy and more likely to have adverse effects (start low, titrate slow)
- Also less likely to be able to report side effects

Psychopharmacology for ASD

- Medications DO NOT treat core symptoms.
- Only Risperidone and Aripiprazole have FDA approval to treat irritability in ASD.
- Off-label use of medication is common.
- Response rates tend to be lower than in non-ASD children.
- Medication use data from ATN and IAN
    - 3-5 year olds: 10-11%
    - 6-11 year olds: 38-46%
    - 12-17 year olds: 65%
    - Polypharmacy: 40%

Target Symptom – Irritability and Aggression

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

Zero Hero℠
Create a safe day. Every day.

Atypical Antipsychotics

- Abilify (Aripiprazole)
  - •Meta-analysis showed significant reduction in irritability, hyperactivity, stereotypic behavior on *Aberrant Behavior Checklist* (ABC)
  - •Response rate ~ 55%
- Risperidone (Risperdal)
  - •Meta-analysis showed significant reduction in irritability on ABC
  - •Associated with significant weight gain
  - •Response rate ~ 65%

Atypical Antipsychotic Side Effects

Weight gain

Metabolic effects

Sedation (temporary)

Drooling

Extrapyramidal symptoms

Hyperprolactinemia

Rare but serious

- Tardive dyskinesia
- Neuroleptic malignant syndrome
- Heart rhythm irregularities

Selected adverse effects of antipsychotic medications for schizophrenia

	Weight gain/diabetes mellitus	Hyper-cholesterolemia	EPS/TD	Prolactin elevation	Sedation	Anticholinergic side effects	Orthostatic hypotension	QTc prolongation
First generation agents								
Chlorpromazine	+++	+++	+	++	+++	+++	+++	+++
Fluphenazine	+	+	+++	+++	+	–/+	–	–/+*
Haloperidol	+	+	+++	+++	++	–/+	–	Oral: ++ IV: +++
Loxapine	++	ND	++	++	++	+	+	–/+*
Perphenazine	++	ND	++	++	++	+	–	–/+*
Pimozide	+	ND	+++	++	+	+	+	++¶
Thioridazine△	++	ND	+	+++	+++	++++	++++	++
Thiothixene	++	ND	+++	++	+	+	+	ND
Trifluoperazine	++	ND	+++	++	+	+	+	ND
Second generation agents								
Aripiprazole	+	–	+	–	+	–	–	–/+*
Asenapine	++	–	++	++	++	–	+	+
Brexpiprazole◇	+	+	+	–/+	+	–/+	–/+	–/+*
Cariprazine◇	+	–/+	++	–/+	+	–/+	–/+	–/+*
Clozapine§	++++	++++	–/+	–/+	+++	+++	+++	++
Iloperidone	++	++	–/+	–/+	+	+	+++	+
Lurasidone	–/+	–/+	++	–/+	++	–	+	–/+*
Olanzapine	++++	++++	+	+	++	++	+	++
Paliperidone	+++	+	+++	+++	+	–	++	+
Pimavanserin	+	–	–/+	–	+	+	++	+
Quetiapine	+++	+++	–/+	–/+	++	++	++	++
Risperidone	+++	+	+++	+++	+	+	+	++
Ziprasidone	–/+	–/+	+	+	+	–	+	+++

Monitoring Guidelines

	Every Visit	Baseline	3 months	6 months	Annually
Fasting blood glucose		X	X	X	X
Fasting lipid panel		X	X	X	X
BMI	X	X	X	X	X

Target Symptom – Inattention and Hyperactivity

Stimulants

- Meta-analysis (n=94) showed methylphenidate > placebo for ADHD
- Trend toward improving irritability and stereotypy
- However, irritability is most common reason for discontinuation

Methylphenidate (MPH)

MTA Study effect size of .80 for typically developing children (MTA Cooperative Group, 1999)

Response rate was around 75%

RUPP MPH study in ASD effect size was 0.2-0.54 (depending on dose)

RUPP MPH response rate was 49%

Non-stimulants

- Alpha-agonists
  - •Guanfacine – RCT (n=11) with 45% response rate in hyperactivity
  - •Clonidine – RCT (n=8) improvement in irritability, stereotypy, hyperactivity, and inappropriate speech
- Atomoxetine
  - •1st RCT (n=16) improvement in hyperactivity on ABC
  - •2nd RCT (n=97) reduced ADHD rating scale hyperactivity/impulsivity and inattention, but response less than non-ASD children (57% vs 63%)

Target Symptom – Anxiety/Depression, OCD

SSRIs

- 6 RCTs
- Mixed results, but largest trial with citalopram (Celexa) showed no effectiveness
    - increased risk adverse side effects, ex: elevated energy level
- Fluoxetine – 44 children with ASD; beneficial in reducing repetitive behaviors measured on CY-BOCS
- Sertraline – open-label trials in adults with ASD show improvement in repetitive behaviors
- Cochrane Review of SSRIs for repetitive behavior showed no benefit

Target Symptom - Sleep

Meta-analysis of Melatonin

- Some evidence that children with ASD have abnormal circadian cycle
- 6 studies: improved daytime behavior
- 18 studies: improved sleep duration, onset latency, & nocturnal awakening.
- Improvement compared to placebo:
  - Duration (by 44 minutes), g=1.07
  - Onset Latency (by 39 min.), g=2.46

Other sleep agents

- Iron supplementation – for low ferritin levels in restless sleepers
- Clonidine – alpha-agonist with sedative effects; effective in reducing sleep latency and nighttime awakening in children with ASD.
    - •Monitor BP
    - •Counsel overdose risks
- Trazodone – antidepressant and sedative properties; open label studies show improvement in maintenance and onset
    - •Priapism risk

Other sleep agents

- Mirtazapine (Remeron) – 31% improvement in sleep quality in an open-label study
    - Not enough info to determine risk:benefit

- Gabepentin (Neurontin) – decrease sleep latency, decrease restless leg syndrome symptoms

Complementary and Alternative Treatments

Alternative Treatments

- Elimination diets
- Probiotics
- Medical marijuana
- Dietary supplements
- Hyperbaric oxygen
- Chelation
- Acupuncture
- Yoga
- Pet therapy
- Chiropractic care

Alternative Treatments

- Recent review by Brondino, et al.
- Encouraging evidence for:
  - •Music therapy
  - •Sensory integration therapy
  - •Acupuncture
  - •Massage
- Little evidence for other CAM treatments
- BUT – 28% of families use CAM at any given time
- Remember to ask, and work *with* families

References

1. Quintana H, Birmaher B, Stedge D, et al. Use of methylphenidate in the treatment of children with autistic disorder. J Autism Dev Disord 1995; 25:283.
2. Handen BL, Johnson CR, Lubetsky M. Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. J Autism Dev Disord 2000; 30:245.
3. Research Units on Pediatric Psychopharmacology Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Arch Gen Psychiatry 2005; 62:1266.
4. Pearson DA, Santos CW, Aman MG, et al. Effects of extended release methylphenidate treatment on ratings of attention-deficit/hyperactivity disorder (ADHD) and associated behavior in children with autism spectrum disorders and ADHD symptoms. J Child Adolesc Psychopharmacol 2013; 23:337.
5. Towbin KE. Strategies for pharmacologic treatment of high functioning autism and Asperger syndrome. Child Adolesc Psychiatr Clin N Am 2003; 12:23.
6. Aman MG, Farmer CA, Hollway J, Arnold LE. Treatment of inattention, overactivity, and impulsiveness in autism spectrum disorders. Child Adolesc Psychiatr Clin N Am 2008; 17:713.
7. Leskovec TJ, Rowles BM, Findling RL. Pharmacological treatment options for autism spectrum disorders in children and adolescents. Harv Rev Psychiatry 2008; 16:97.
8. Sturman N, Deckx L, van Driel ML. Methylphenidate for children and adolescents with autism spectrum disorder. Cochrane Database Syst Rev 2017; 11:CD011144.
9. Scahill L, McCracken JT, King BH, et al. Extended-Release Guanfacine for Hyperactivity in Children With Autism Spectrum Disorder. Am J Psychiatry 2015; 172:1197.
10. Fankhauser MP, Karumanchi VC, German ML, et al. A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. J Clin Psychiatry 1992; 53:77.

References

11. Jaselskis CA, Cook EH Jr, Fletcher KE, Leventhal BL. Clonidine treatment of hyperactive and impulsive children with autistic disorder. J Clin Psychopharmacol 1992; 12:322.
12. Ghanizadeh A. Atomoxetine for treating ADHD symptoms in autism: a systematic review. J Atten Disord 2013; 17:635.
13. Harfterkamp M, van de Loo-Neus G, Minderaa RB, et al. A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry 2012; 51:733.
14. Arnold LE, Aman MG, Cook AM, et al. Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. J Am Acad Child Adolesc Psychiatry 2006; 45:1196.
15. Hazell P. Drug therapy for attention-deficit/hyperactivity disorder-like symptoms in autistic disorder. J Paediatr Child Health 2007; 43:19.
16. McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med 2002; 347:314.
17. Barnard L, Young AH, Pearson J, et al. A systematic review of the use of atypical antipsychotics in autism. J Psychopharmacol 2002; 16:93.
18. Soomro GM, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). Cochrane Database Syst Rev 2008; :CD001765.
19. Williams K, Brignell A, Randall M, et al. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). Cochrane Database Syst Rev 2013; :CD004677.
20. Hollander E, Phillips A, Chaplin W, et al. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. Neuropsychopharmacology 2005; 30:582.
21. McDougle CJ, Kresch LE, Posey DJ. Repetitive thoughts and behavior in pervasive developmental disorders: treatment with serotonin reuptake inhibitors. J Autism Dev Disord 2000; 30:427.

References

22. McDougle CJ, Naylor ST, Cohen DJ, et al. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. Arch Gen Psychiatry 1996; 53:1001.
23. McDougle CJ, Brodkin ES, Naylor ST, et al. Sertraline in adults with pervasive developmental disorders: a prospective open-label investigation. J Clin Psychopharmacol 1998; 18:62.
24. Hellings JA, Kelley LA, Gabrielli WF, et al. Sertraline response in adults with mental retardation and autistic disorder. J Clin Psychiatry 1996; 57:333.
25. King BH, Hollander E, Sikich L, et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism. Arch Gen Psychiatry 2009; 66:583.
26. Brondino N, Fusar-Poli L, et al. Complementary and alternative therapies for autism spectrum disorder. Evid Based Complement Alternat Med 2015; Article ID 258589

Supplementary Slides

Baseline & endpoint ABC scores by group

	----Risperidone---		----Placebo---		
ABC Scale	Baseline Mean	Endpoint Mean	Baseline Mean	Endpoint Mean	*p*
Irritability	**26.2**	**11.3**	**25.5**	**21.9**	< .0001
Lethargy	16.4	8.9	16.1	12.0	< .05*
Stereotypy	10.6	5.8	9.0	7.3	< .0001
Hyperactivity	**31.8**	**17.0**	**32.3**	**27.6**	**< .0001**

** after adjusting for multiple comparisons not significant*