# Pharmacotherapy in Autism Spectrum Disorders

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# Treatment Overview

# Pharmacologic Interventions

- Research on psychopharmacological treatments for ID/ASD is limited, with few large-scale, unbiased studies.
- Existing studies mainly involve children with ASD, due to challenges in consenting adults with ID/ASD for research.
- Medications often target behavioral symptoms like anxiety, aggression, self-injurious behavior, hyperactivity, and sleep disturbances.
- Despite evidence limitations, medications can be crucial in comprehensive treatment plans for ID/ASD.

# Pharmacologic Interventions

- Many individuals in ASD studies also have comorbid ID, and they tend to be more sensitive to medication side effects.
- No medications are FDA-approved specifically for the core symptoms of ID/ASD.
- The most evidence-supported targets for medication are hyperactivity, irritability, repetitive behaviors, self-injurious behavior, and anxiety/depression.
- Sleep disturbances, common in those with developmental disorders, are frequently addressed with medication.

# Pharmacologic Interventions

Summary of Target Symptoms and Pharmacologic Treatment

| Target Symptom | Treatment Medications/Classes to Consider |
|---|---|
| Hyperactivity | Stimulants, atomoxetine, $\alpha_2$-agonists |
| Irritability/aggression | Risperidone, aripiprazole |
| Repetitive behaviors | Risperidone, aripiprazole, fluoxetine, clomipramine, fluvoxamine |
| Self-injurious behavior | Risperidone, clomipramine, naltrexone |
| Anxiety/depression | SSRIs |
| Sleep | Melatonin, ramelteon, clonidine, trazodone, mirtazapine, zolpidem, donepezil, benzodiazepines |

# Hyperactivity

- High comorbidity of ADHD in individuals with ID/ASD, with rates around 30% in nonclinical populations and 41% to 78% in clinical settings.
- Treatment for ADHD symptoms in those with ID/ASD is similar to the general population, using **stimulants**, **α2-agonists**, and **atomoxetine**.
- Children with ASD might have **increased side effects** and a **lower response** to ADHD medications compared to those without ASD.

# Stimulants

- Increase dopamine & norepinephrine in the brain: aiding ADHD symptom management.
- Meta-analysis found **methylphenidate** effective for ADHD in children with Pervasive Developmental Disorders (PDD), particularly for **hyperactivity**.
- Children with PDD respond to methylphenidate but have lower effect sizes and more adverse effects than typically developing children with ADHD.
- Methylphenidate dosages range from 0.29 to 0.45 mg/kg/dose, with optimal doses showing improvement in symptoms within the first week.
- While methylphenidate is proven beneficial, children with PDD experience more side effects like **decreased appetite**, **insomnia**, and **irritability**.
- Amphetamine treatment for ADHD in children with ASD is not well-studied, but is considered when methylphenidate is not effective or causes significant side effects.

# α2-Agonists

- α2-Agonists, such as clonidine and guanfacine, may help ADHD by modulating norepinephrine in the brain, increasing attention.

- Initially used for hypertension, these medications have also shown benefits for ADHD symptoms.

- A small study on clonidine in children with PDD indicated medium effect sizes for ADHD symptoms and irritability, but smaller for hyperactivity and stereotypic behavior.

# α2-Agonists

- Adverse events for clonidine : **hypotension** ; **drowsiness**

- Guanfacine treatment showed improvement in ADHD symptoms in children with PDD, with side effects like: drowsiness; irritability; enuresis.
- A study on guanfacine extended release found significant improvements in hyperactivity and ADHD symptoms in children with ASD-related disorders.
- While clonidine and guanfacine appear beneficial for treating ADHD in children with ASD/ID, **more research is needed** to fully understand their efficacy and safety in this population.

# Atomoxetine

- Atomoxetine, used for ADHD, increases norepinephrine by inhibiting its reuptake.
- Dosing starts once daily, with adjustments after at least 3 days aiming for an optimal dose.
- Clinical improvements are usually seen within 1 to 2 weeks.
- A meta-analysis by Reichow et al found
- significant benefits of atomoxetine on global ADHD symptoms and hyperactivity in children with PDD, in one major study.
- However, the same study noted no significant change in inattention and oppositional behavior with atomoxetine.

# Atomoxetine

- Children with PDD experienced more nausea, decreased appetite, and early morning awakening on atomoxetine.
- The effective dose range for atomoxetine in children with PDD is comparable to that in neurotypical children with ADHD.
- Atomoxetine appears to be effective for hyperactivity in children with PDD, with dosing and side effects similar to those without developmental disorders.

# Other Medications

- TCAs, acting as SNRIs, were once used for ADHD treatment and have been studied in children with ASD.
- A study found clomipramine and desipramine superior to placebo in reducing hyperactivity in children with ASD.
- TCAs can cause antimuscarinic effects like dry mouth, vision issues, and urinary retention, plus serious cardiac risks.
- They are metabolized by cytochrome P450 enzymes; inhibitors can increase their levels and side effects.

# Other Medications

- Atypical antipsychotics like risperidone and aripiprazole have shown benefits for hyperactivity in ASD, used when other treatments fail.
- The Autism Speaks network includes atypical antipsychotics in their treatment algorithm for ADHD symptoms in ASD after other options.
- Emerging treatments showing promise for hyperactivity in ASD include ω-3 fatty acids and tianeptine, with pentoxifylline and topiramate as adjuncts to risperidone.
- Stimulants are highly effective for treating ADHD in children.
- The American Academy of Child and Adolescent Psychiatry and the American Academy of Pediatrics favor methylphenidate for preschool-aged children, after trying behavioral therapy.
- Methylphenidate metabolizes slower in preschool children, necessitating a lower starting and optimal dose.

# Irritability/Aggression

- Irritability/aggression in children with ASD is best supported by research for pharmacological treatment.
- Consensus guidelines nationally and internationally recommend **risperidone** and **aripiprazole** for autism-related irritability.
- Evidence comes from four large randomized controlled trials (RCTs) focusing on these medications.
- Risperidone and aripiprazole are the only medications FDA-approved for treating irritability in children and adolescents with autistic disorders, specifically aged 5–17 for risperidone and 6–17 for aripiprazole.

# Risperidone

- Studies by McCracken et al and Shea et al, each lasting 8 weeks, investigated risperidone in children and adolescents with autistic and other pervasive developmental disorders, showing significant improvements in irritability and other behaviors.
- Most participants had comorbid intellectual disability, with 64% to 81% affected.
- Risperidone was effective in reducing irritability, hyperactivity, and stereotypy, with some evidence for improving social withdrawal and inappropriate speech.
- Definition of treatment response varied between studies, with high response rates observed in the risperidone groups compared to placebo.
- Common side effects of risperidone included: **increased appetite, fatigue, drowsiness, extrapyramidal symptoms, notable weight gain**.
- Risperidone doses in these studies were lower than those used in early-onset schizophrenia treatment in children without ID.-
- Risperidone treatment is associated with **increased serum prolactin levels**.
- A study on adults with ASD also found risperidone effective in reducing aggression, with **sedation** and **weight gain** as common adverse effects.

# Aripiprazole

- Studies by Marcus et al and Owen et al, each lasting 8 weeks, evaluated aripiprazole in children and adolescents with autistic disorder, showing significant improvement in irritability, hyperactivity, and stereotypy.
- Response rates to aripiprazole were higher compared to placebo, with notable improvement in inappropriate speech in one study.
- Common ADRs: **sedation**, **fatigue**, **vomiting**, **increased appetite,** and **extrapyramidal symptoms (EPS);** aripiprazole associated with **weight gain** but **reduced prolactin levels**.
- Final daily dosing of aripiprazole varied across studies, with lower doses effective for ASD symptoms compared to doses for schizophrenia or bipolar disorder in children.

# Antipsychotics

- Risperidone and aripiprazole are FDA-approved for ASD-related irritability, with risperidone increasing and aripiprazole decreasing prolactin levels.
- Other antipsychotics like **haloperidol**, **pimozide**, **olanzapine**, and others have shown benefits for ASD irritability, with **risperidone outperforming haloperidol in efficacy**.
- In adults with ID, risperidone, haloperidol, and placebo all reduced aggression, with no significant difference in effectiveness.

# Other Medications

- Two RCTs on **valproate** for ASD-related irritability/aggression showed **mixed results**: one found no significant difference, while the other showed valproate as superior to placebo.
- Valproate's effectiveness varied in these studies, with one reporting significant improvements and the other not.
- Adverse effects in valproate treatment included increased appetite and elevated ammonia levels in some cases.
- Both studies aimed for specific blood valproate levels, indicating monitored dosage.
- Other medications like **buspirone**, **clomipramine**, **clonidine**, and several others have limited evidence for treating irritability in ASD.
- Reichow et al's meta-analysis found methylphenidate had moderate benefits for irritability in children with PDD, though not statistically significant.

# Repetitive Behaviors

- Medications like SSRIs and TCAs have been explored for treating repetitive behaviors in ASD due to their success in obsessive-compulsive disorder and the link between repetitive behaviors and anxiety in ASD.
- However, the evidence supporting the effectiveness of SSRIs and TCAs for repetitive behaviors in ASD is inconsistent.

# SSRIs

- Research on SSRIs for repetitive behaviors in ASD has produced **mixed outcomes**.
- A study by Hollander et al showed that low-dose fluoxetine was effective in reducing repetitive behaviors in children with ASD, with a medium to large effect size.
- Another RCT comparing citalopram to placebo found no significant difference in reducing repetitive behaviors in children with ASD.
- However, an RCT with adults showed that **fluvoxamine** significantly improved repetitive thoughts and behaviors.
- These varying results highlight the inconsistent evidence for SSRIs' effectiveness in treating repetitive behaviors in individuals with ASD.

# TCAs

- **Clomipramine** was found to be effective in treating repetitive behavior in children with ASD, outperforming both placebo and desipramine in a study by Gordon et al.
- The effective clomipramine **dose** and blood levels were relatively **high** in this study, with some serious adverse events like seizures and cardiac issues noted.
- Another study by Remington et al compared clomipramine with haloperidol, finding a **high discontinuation rate** for clomipramine due to adverse effects.
- SSRIs (fluoxetine) and TCAs (clomipramine) may reduce repetitive behaviors in children with ASD, but clomipramine's side effects can be a significant concern.
- In adults with ASD, SSRIs like fluvoxamine have shown efficacy in reducing repetitive behaviors.

# Antipsychotics

- Antipsychotics, specifically **aripiprazole** and **risperidone**, have strong evidence for reducing repetitive behaviors in children with ASD.
- The efficacy of these antipsychotics was primarily noted in studies focusing on irritability, where they also impacted stereotypy positively.

- Risperidone showed significant reductions in compulsive behaviors and sensory motor behaviors in both children and adults with ASD.
- An RCT by McDougle et al also highlighted risperidone's effectiveness in reducing repetitive behaviors in adults with ASD.

- Olanzapine, tested against placebo, did not show significant improvement in obsessive-compulsive symptoms, aggression, or irritability in ASD, but was associated with greater adverse effects like weight gain.

# Stimulants

- In Reichow et al's meta-analysis, methylphenidate showed moderate benefits in reducing stereotypies in children with Pervasive Developmental Disorders (PDD), though these findings were not statistically significant.

# Other Medications

- Valproate was effective in reducing irritability in children with ASD in Hollander et al's study but did not significantly improve repetitive behaviors.
- A small RCT on ω-3 fatty acids (fish oil) showed no significant difference compared to placebo in reducing stereotypies, despite a moderate effect size.
- Chugani et al's study on buspirone did not find significant overall treatment differences but suggested potential as an adjunct therapy for restrictive and repetitive behaviors in ASD.

# Self-Injurious Behaviors

- Self-injurious behavior (SIB) is viewed either as self-directed aggression or as a repetitive, stereotyped behavior, influencing its pharmacological treatment approach.
- Treatment strategies for SIB often overlap with those for aggression and repetitive behaviors in ASD.
- The research on SIB includes findings that both align with and differ from studies on aggression and repetitive behaviors, indicating a distinct yet related area of study within the context of developmental disorders.

# Typical and Atypical Antipsychotics

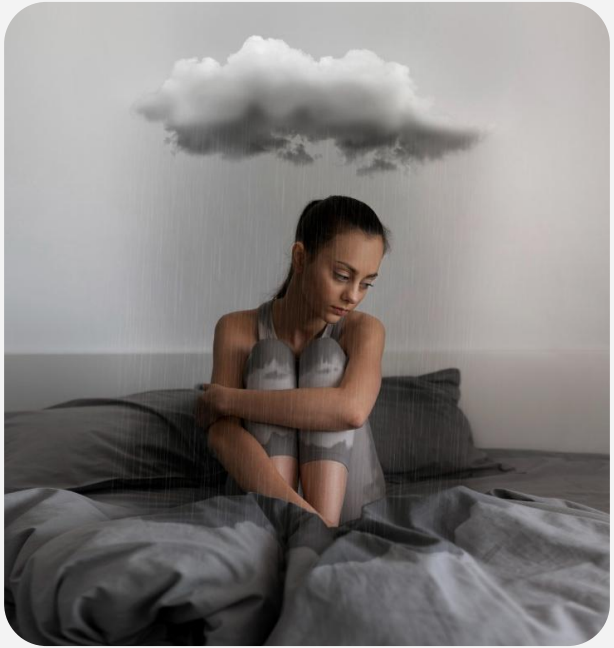
- RCTs on typical antipsychotics like haloperidol, fluphenazine, chlorpromazine, and thioridazine have shown inconclusive benefits for reducing self-injurious behavior (SIB) in developmental disorders.
- Risperidone, an atypical antipsychotic, has more substantial evidence from RCTs indicating its effectiveness in improving SIB, particularly in children with ID and adults with ASD.
- Improvements in SIB with risperidone were significant in some studies and associated with side effects such as weight gain and somnolence.

# Antidepressants

- Clomipramine effectively reduces self-injurious behavior but has notable adverse effects.
- Fluoxetine has demonstrated efficacy in decreasing compulsive skin picking in two RCTs.
- Fluvoxamine reduced repetitive behavior and aggression in adults with ASD in an RCT.
- Case reports and open-label studies suggest potential benefits of buspirone and paroxetine for self-injurious and repetitive behaviors.

# Naltrexone

- A systematic review of naltrexone in adults with ID found it effective in reducing self-injurious behavior (SIB) in 50% of participants, especially in those with severe and profound ID.
- Minor adverse effects reported with naltrexone include **weight loss**, **loss of appetite**, **thirst, yawning, mild liver function abnormalities**, **nausea**, and **tiredness**, with dosages ranging from **0.5 to 2 mg/kg**.
- The literature suggests risperidone, naltrexone, and clomipramine as effective for reducing SIB in individuals with developmental disabilities, with risperidone having the most robust data.
- Fluoxetine and fluvoxamine also show potential benefits in reducing SIB but have less evidence supporting their use.



# Anxiety/Depression

# SSRIs

- Individuals with Pervasive Developmental Disorders (PDDs) have a high prevalence of comorbid anxiety and mood disorders.
- **SSRIs** are frequently used to treat anxiety and depression in children with developmental disorders due to their efficacy and safety in typically developing children.
- There is a **lack** of large double-blind, placebo-controlled trials on SSRI use for depression or anxiety in children with developmental disorders, but case reports and open-label studies show benefits for anxiety in ASD.
- Children with developmental disorders might react differently to SSRIs in terms of adverse event risks, dosing needs, and symptom targets.
- In cases of poor SSRI response, **risperidone** might be considered, with careful monitoring for potential anxiety increase.

# Adverse Events

- Children with developmental disorders may experience more adverse events from SSRIs, particularly **emotional/behavioral side effects**, compared to typically developing children.
- Studies on fluoxetine and citalopram in children with developmental disorders found higher rates of **agitation**, **insomnia**, and **anxiety/nervousness**, with some needing dose reductions.
- In contrast, RCTs on fluoxetine and citalopram in typically developing children with OCD or depression reported fewer behavioral side effects, with more physical complaints like **headaches**, **GI** issues, and **insomnia**.
- Specifically, a high percentage of children with ASD treated with citalopram reported **increased energy, impulsiveness, hyperactivity, stereotypy, and sleep disturbances**, markedly higher than in typically developing children treated for depression.
- These findings indicate that children with developmental disorders have a distinct profile of SSRI side effects compared to their typically developing peers.

# Dosing

- Children with Pervasive Developmental Disorders (PDD) often need **smaller SSRI doses** compared to typically developing children and may face more adverse effects at higher doses.
- In Hollander et al's study, children with PDD had a mean final daily fluoxetine dose of 9.9 mg, significantly lower than the doses used for typically developing children with OCD, which were 24.6 mg and 64.8 mg in different studies.
- Similarly, children with ASD in the King et al study received a mean daily citalopram dose of 16.5 mg, while typically developing children with depression tolerated higher doses, around 24 to 26 mg.
- However, in adults with ASD, SSRI dosages tend to align more closely with those used for typically developing adults, indicating that the lower dosage requirement in children with PDD might change with age.

# Target Symptoms

- Studies on anxiety and depression in children with ASD often use rating scales designed for typically developing children.
- Higher parent-reported anxiety in children with ASD correlates with IQ above 70, more significant social impairment, and older age, with those having better adaptive social behaviors potentially feeling more anxious.
- For depression, higher IQ and age are linked to greater depression symptoms, and lower self-perceived social competence is associated with higher depression levels.
- Adults with ASD who have higher social functioning are more likely to be categorized as depressed, suggesting an awareness of social impairments may increase anxiety or depression symptoms.
- Anxiety and depression in individuals with ASD might manifest differently, like in behaviors of rigidity, tantrums, and social avoidance, challenging the identification and treatment based on conventional scales.
- SSRIs may benefit children with PDD in treating classic anxiety and depression symptoms, but the effective dosing often needs to be lower to minimize adverse emotional and behavioral effects.

# Sleep

1. Melatonin
2. Ramelteon
3. Clonidine
4. Trazodone
5. Mirtazapine
6. Diphenhydramine
7. Zolpidem
8. Donepezil and Memantine
9. BZDs

# Thanks For Your Attention