The Role of Pharmacologic Treatment in Autism Spectrum Disorder

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Abstract

Behavioral, educational, and family therapies combined with early recognition and intervention is the current standard for management of children with autism spectrum disorder (ASD). Despite these interventions, many children still retain behavioral disturbances that negatively impact their quality of life. Researchers have estimated more than 50% of adolescents with ASD are prescribed medications to help them manage behaviors or comorbid conditions, over half of whom experience psychotropic polypharmacy. Only risperidone and aripiprazole are FDA-approved for ASD patients, although numerous medications are used "off-label" and in combination to treat behavioral disturbances. There is limited research supporting greater therapeutic benefits than side effects of other atypical antipsychotics, SSRIs, SNRIs, stimulants, and TCAs for ASD management. The studies currently available have shown possible efficacy for "off-label" drugs, but the evidence is far from comprehensive or conclusive. Further clinical investigation is needed in order to develop standards of care for the use of psychotropic pharmaceuticals to treat maladaptive behaviors associated with ASD.

Introduction

Autism spectrum disorder (ASD) is a neurological condition marked by qualitative difficulties in social interaction, difficulties in communication, repetitive behavior, and a narrow range of interests. ASD is regarded as one of the most prevalent developmental disorders, affecting approximately 1 in 44 children in the United States. The current treatment recommendations involve early intervention with educational therapies such as speech therapy, sensory integration therapy, and auditory therapy. This has proven to be effective, but some individuals with ASD have particular challenges with overactivity, impulsiveness, tantrums, aggression, and self-injury. These behaviors strain caregivers and limit the child's ability to participate in educational therapies to the fullest. Due to this, some clinicians have turned to adjuvant pharmacotherapy. Currently, the FDA has only approved risperidone and aripiprazole, both antipsychotic drugs, for the treatment of irritability in patients with ASD. The effectiveness of these medications is controversial among practitioners, and thus, other pharmacological management strategies have been adopted. This study discusses the research and proposals about the potential effectiveness of pharmacological adjuvant therapies and their associated risks for children with ASD.

Methods

Literature Search

- Performed in December 2021 using Science Direct, Google Scholar, and PubMed
  - Search Terms: " autism spectrum disorder OR ASD OR pervasive developmental disorder OR autism AND drug therapy OR pharmacologic therapy OR pharmacological treatment OR pharmacologic management OR medication"
- Inclusion Criteria:
  - Relevance to the special interest topic
  - Published in peer-reviewed journal
  - Published 1993 or later
  - Clinical trials involving pediatric patients (mean age < 21 years old)
  - Emphasis on studies with a randomized & controlled design
- Exclusion Criteria:
  - Studies without documented clinical trial
  - Clinical trials involving animals
  - Clinical trials involving adults (mean age > 21 years old)

Results

1. **McCraken J, Shah B, McGough J, et al. Risperidone in children with autism and serious behavioral problems.** ***New England Journal of Medicine*****. 2002;347(23):1890-1891. doi:10.1056/nejm200212053472316**
   - Multisite, randomized, double-blind trial of 101 children ages 5 to 17 years old testing risperidone compared with placebo. After eight weeks of treatment, 56.9% decrease in irritability observed.
2. **Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders.** ***American Academy of Pediatrics*****. 2004;114(5). doi:10.1542/peds.2003-0264-f**
   - Randomized, double-blind trial of 79 children ages 5 to 12 years old testing risperidone as compared with placebo. Extrapyramidal symptom incident rate was as high as 27.5% of children.
3. **Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of Aripiprazole in children and adolescents with irritability associated with autistic disorder.** ***Journal of the American Academy of Child & Adolescent Psychiatry.*** **2009;48(11):1110-1119. doi:10.1097/chi.0b013e3181b76658**
   - Randomized, placebo-controlled, parallel-group study of 218 children and adolescents ages 6 to 17 years testing aripiprazole as compared with placebo resulted in statistically significant improvement in Aberrant Behavior Checklist Irritability subscale scores.
4. **Malone R, Cater J, Sheikh R, et al. Olanzapine versus haloperidol in children with autistic disorder: An open pilot study.** ***Journal of the American Academy of Child & Adolescent Psychiatry*****. 2001;40(8):887-894. doi:10.1097/00004583-200108000-00009**
   - Randomized, open-label study of 12 children mean ages 7.8 ± 2.1 years testing olanzapine versus haloperidol
5. **Loebel A, Brams M, Goldman RS, et al. Lurasidone for the Treatment of Irritability Associated with Autistic Disorder.** ***J Autism Dev Disord*****. 2016;46(4):1153-1163. doi:10.1007/s10803-015-2628-x**
   - Randomized, double-blind, fixed-dose, placebo-controlled study of 150 children ages 6 to 17 years old testing lurasidone as compared with placebo
6. **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(3):582-589. doi:10.1038/sj.npp.1300627**
   - Multicenter, randomized, placebo-controlled study of 146 children ages 7.5 to 18 years old testing fluoxetine as compared with placebo
7. **Carminati GG, Gerber F, Darbellay B, et al. Using venlafaxine to treat behavioral disorders in patients with autism spectrum disorder.** ***Prog Neuropsychopharmacol Biol Psychiatry*****. 2016;65:85-95. doi:10.1016/j.pnpbp.2015.09.002**
   - Randomized, double-blind study of 13 participants median age 20.5 years old testing venlafaxine as compared with placebo
8. **Gordon CT, State RC, Nelson JE, Hamburger SD, Rapoport JL. A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder.** ***Arch Gen Psychiatry*****. 1993;50(6):441-447. doi:10.1001/archpsyc.1993.01820180039004**
   - Randomized, double-blind crossover study of 24 participants ages 6 to 18 years old testing clomipramine as compared with placebo
9. **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(3):245-255. doi:10.1023/a:1005548619694**
   - Randomized, double-blind, placebo-controlled crossover study of 13 children ages 5.6 to 11.2 years old testing methylphenidate as compared with placebo

Discussion

Due to the wide variety of treatment options, the inherent complexity of psychotropic medications, and a lack of clear guidance, choosing a treatment plan can be a daunting task for patients and their families. While individual decisions on treatment plans must be made by the clinicians in conjunction with the patients, more research should be performed to build a repository of knowledge for clinicians to draw from. Many of the discussed studies show statistically significant improvements in aberrant behaviors, but broader studies need to be performed with **larger sample sizes** to accurately assess the risks of negative side effects. Without this complete risk profile, it can be difficult to predict how a certain medication will impact a child without relying on trial and error. Additionally, more research needs to be done on the mechanisms of action of many psychotropic drugs, particularly in regard to its impact on the pathology of ASD, which also requires more research to understand. Despite these challenges, patients and their families can be hopeful that these "off-label" medications can provide some relief of symptoms.

Conclusion

The best practice for medical practitioners managing ASD-related behavioral issues is to remain as educated as possible about different possible treatments, especially if the only two FDA approved antipsychotics are not well tolerated. It is extremely important to work closely with families and keep them educated with reasonable expectations for different drug treatments. Of the potential risks, it is particularly crucial to discuss which drugs have an inherent risk of causing drowsiness and sedation for school-aged children. Likewise, it is crucial for practitioners and families to express their experiences with different ASD treatments in hopes more research is conducted in the future. The role of pharmacological management in ASD has an incredible amount of potential, but is far from comprehensive and needs further clinical investigation in order to have a maximized impact on the lives of patients and caregivers.

Figure 1. Approach to prescribing medication to manage ASD in children

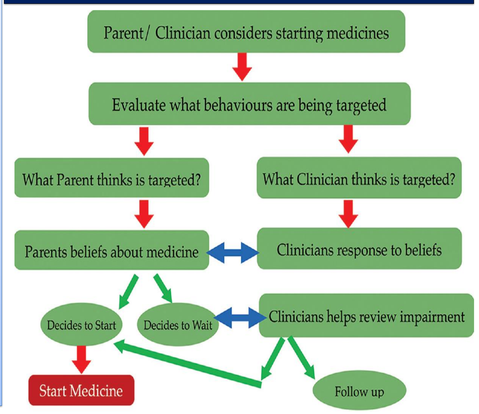

Table 1. Comparison of Results

Study	Medication	Therapeutic Effects	Side Effects
1 and 2	**Risperidone (Risperdal)**	▪ Aberrant Behavior Checklist Irritability Subscale Scores: 56.9% reduction in the Irritability score for treatment group, as compared with a 14.1 percent decrease in the placebo group (P<0.001) ▪ Aberrant Behavior Checklist Irritability Subscale Scores: 64% improvement over in the irritability score for treatment group, almost double that of placebo-treated subjects (31%)	• Risperidone therapy was associated with an average weight gain of 2.7+/-2.9 kg, as compared with 0.8+/-2.2 kg with placebo (P<0.001). • Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group than in the placebo group (P<0.05 for each comparison) • Extrapyramidal symptoms incidence: 27.5%
3	**Aripiprazole (Abilify)**	▪ Aberrant Behavior Checklist Irritability Subscale Scores: 14.4-point reduction in the irritability score for treatment group, as compared with an 8.4-point decrease in the placebo (P<0.05)	• Fatigue, vomiting, somnolence, tremor, presyncope, and aggression • Impulse-control problems such as gambling behavior and binge eating
4	**Olanzapine (Zyprexa)**	• Clinical Global Impressions (CGI) Improvement Item: 5 out of 6 patients rated as responders • Children's Psychiatric Rating Scale (CPRS): Subjects showed improvement on the CPRS Autism Factor (F 1,9 = 24.4, P=0.0008)	• Weight gain and sedation
5	**Lurasidone (Latuda)**	• Aberrant Behavior Checklist Irritability Subscale Scores: Lurasidone did not significantly differentiate from placebo on the primary endpoint	• Weight gain, sedation, somnolence, vomiting
4	**Haloperidol (Haldol)**	• Clinical Global Impressions (CGI) Improvement Item: 3 out of 6 patients rated as responders • Children's Psychiatric Rating Scale (CPRS): Subjects showed improvement on the CPRS Autism Factor (P= 0.0008)	• Weight gain and sedation • Dyskinesias incidence: 33.9%, majority reversible • Risk of tardive dyskinesia
6	**Fluoxetine (Prozac)**	• Children's Yale-Brown Obsessive Compulsive Scale, modified for pervasive developmental disorder (CYBOCS-PDD): 3.72-point reduction in mean score for treatment group, as compared with a 2.53-point decrease in placebo group	• Irritability, mood disturbance, nausea, vomiting, and sleep disorders
7	**Venlafaxine (Effexor)**	• Aberrant Behavior Checklist (ABC), Behavior Problems Inventory (BPI): multivariate analyses showed the venlafaxine population to have lower values with respect to the placebo	• Sedation and drowsiness
8	**Clomipramine (Anafranil)**	• Autism Relevant Subscale of the Children's Psychiatric Rating Scale: Clomipramine was superior to both placebo and desipramine on ratings of autistic symptoms (including stereotypies), anger, and compulsive, ritualized behaviors (P < .05)	• Sedation, hostility, impatience, hyperactivity
9	**Methylphenidate (Ritalin)**	• Conners Hyperactivity Index: minimum 50% decrease, ratings of stereotypy and inappropriate speech also decreased	• Social withdrawal and irritability

Atypical antipsychotic | Typical antipsychotic | SSRI | SNRI | TCA | Stimulant