Evidence-Based Treatment Approach to Autism Spectrum Disorders

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CME | EDUCATIONAL OBJECTIVES

1. Identify effective treatment modalities for ASD.
2. Prioritize treatment strategies based on manifesting comorbid symptoms in ASD.
3. Gain knowledge of ineffective/debunked treatments for autism.

Currently, the best supported treatments of the core features of autism spectrum disorders are behavioral therapies aimed at remediating social and language impairments. However, when comorbid irritability, anxiety, or attentional deficits hinder remediation efforts, psychopharmacologic and psychotherapeutic treatments can be considered to improve...
outcomes. This review summarizes the evidence supporting current treatments for the core features and comorbid problems of autism spectrum disorders.

PHARMACOLOGICAL TREATMENT OF CORE AUTISM FEATURES

Social impairment/withdrawal, communication/language impairment, and restricted repetitive patterns of behavior, interests, and stereotyped movements are the primary features of autism spectrum disorders (ASD). Social and language impairments can be understood as arising out of defects in the normal encoding of these skills gained through interaction with the environment. None of the psychotropic medication classes evaluated thus far can repair or improve these impairments (Table, see page 571).

On the other hand, stereotypical movements, such as hand flapping, can be increased by anxiety; thus, they theoretically can be targeted by available psychotropic medications. However, when anxiety treatments such as SSRIs have been studied in children with ASD and repetitive behaviors, the results have been disappointing or contradictory. To date, no psychotropic treatment can be said to have solid empirical support for the treatment of stereotypies in children with ASD. Several psychological interventions currently in use for ASD core symptoms are also unsupported or have limited scientific basis. One noteworthy exception is applied behavior analysis (ABA). Primarily a set of intensive one-on-one behavioral interventions for ASD, key features of ABA include:

1. Intensive treatment for at least 20 to 40 hours per week;
2. Initiating treatment as young as 2 to 4 years of age;
3. Individualized interventions for each client targeting a specific range of symptoms and skills;
4. Active parental participation;
5. Reshaping behaviors or teaching new skills by employing multiple, repeated, and consistent positive reinforcements for positive change while not rewarding maladaptive behaviors; and
6. A format that typically begins as one-to-one intervention with progression to a group format. Specific intervention techniques such as intensive discrete-trial training (DTT), Picture Exchange Communication System (PECS), and pivotal response training (PRT), draw upon core concepts of ABA regarding the reshaping and reduction of aberrant behaviors across several core symptoms of autism. Using meta-analytic methods, Ospina and colleagues reviewed the effectiveness of different ABA models. More than 1,000 peer-reviewed scientific articles have reported on the effectiveness of intensive ABA intervention; patients enjoyed significant improvements in daily living skills, such as toileting and feeding, academic performance, communications skills, and social skills. Despite these positive results, several limitations and feasibility issues are important to consider when recommending ABA treatment, such as cost, amount of time required by the family, and practitioner availability.

TREATING COMORBIDITIES

Our review identified three major comorbid symptoms of ASD that are reasonable targets for interventions: irritability, hyperactivity, and anxiety. Treatments include psychosocial interventions, medications, and combinations of both. For irritability and anxiety, combination treatments are superior in that they take advantage of the decrease in emotional distress resulting from medications to then teach regulation skills more successfully to the child and his or her caregivers (see Table, page 571).

Irritability/Aggression

Two atypical antipsychotics, risperidone and aripiprazole, have FDA approval for the treatment of irritability/aggression in patients with ASD. Since 2000, five randomized controlled trials have studied risperidone’s effect in irritable patients with ASD (see Table, page 571). Some studies included open-label extensions of the original protocol, sometimes followed by randomized discontinuations. Of the five studies, four showed unequivocal improvements in irritability, while the fifth was equivocal. Overall, they support a robust improvement in irritability/agression with risperidone treatment.

To date, there have been only two randomized controlled trials on the efficacy of aripiprazole in children and adolescents with ASD, both of which found clinically and statistically significant reductions in irritability. It is important to note that aripiprazole may have a better side effect profile than risperidone (ie, lower incidence of extrapyramidal reactions, weight gain, and metabolic syndrome).

There have been several studies with haloperidol, most before 2000, demonstrating efficacy in treatment of irritability and aggression in ASD patients. Notably, two comparison studies with risperidone showed efficacy, although risperidone was superior to haloperidol. Because of its unfavorable side effect profile (notably, dyskinesias), haloperidol is used primarily in treatment-refractory patients. Although the single study of olanzapine used a small sample, it showed a decrease in irritability but at the cost of significant weight gain. As a result of the large incidence of weight gain and metabolic syndrome, olanzapine should be used only after exploring other alternatives such as aripiprazole and risperidone.

To our knowledge, no randomized controlled trials have investigated the
effects of the other atypical antipsychotics in patients with ASDs. Studies of the efficacy of methylphenidate, atomoxetine, selective serotonin reuptake inhibitors (SSRIs), and valproate for irritability associated with autism all yielded negative results (see Table). Two randomized controlled trials for naltrexone were identified: one was negative,21 and one along with an extension study had equivocal results for treating aggression22,23 (these studies were published before 2000 and, thus, are not included in the Table).

Ghaziuddin has underscored the benefits of parent behavioral management strategies for use with the parents of ASD youth.24 Initial investigations suggest that parent treatments and combined parent/child treatments may prove to be of incremental benefit for treatment of irritability.25

Hyperactivity/Inattention

Three of four randomized controlled trials since 2000 that examined the effect of risperidone on hyperactivity/impulsivity showed significant improvements compared with placebo,8,10,12 while one did not.11 Both randomized controlled trials of aripiprazole found statistically significant reductions in scores of hyperactivity.15,16

All three studies (one in preschoolers) of the effect of methylphenidate on attention-deficit/hyperactivity disorder (ADHD) symptoms in ASD patients showed positive results for reducing hyperactivity and inattention.7,26,27 However, in two of these studies, MPH was found to be less efficacious and associated with more frequent adverse effects in children with ASDs as compared with typically developing children with ADHD.7,27

To our knowledge, there is only one randomized controlled trial of the effect of atomoxetine in individuals with ASDs; it showed a reduction in hyperactivity comparable to that seen in the methylphenidate trials, but with fewer intolerable side effects.28

One randomized controlled trial of the effect of clonidine on hyperactivity was identified.29 It also was done before 2000 and, thus, is not in the Table. It showed equivocal results in a very small sample size of only eight patients.

Given the risks of metabolic adverse effects with atypical antipsychotics, the ratio of risk to benefit favors using methylphenidate, atomoxetine, or clonidine for the treatment of hyperactivity/impulsivity in ASD patients before moving on to risperidone or aripiprazole. Metabolic risks are sufficiently worrisome that in addition to methylphenidate, atomoxetine, or clonidine, even a trial of guanfacine (despite the lack of randomized controlled trials documenting its efficacy) may be considered before exposing patients to the risks of atypical antipsychotics when hyperactivity or inattention are the target symptoms.

Anxiety

Lainhart and Folstein underscored the importance of the early treatment of anxiety among children with ASD.30 They noted that without appropriate interventions, the presence of anxiety could potentially generalize to other forms of affective disturbance and result in more significant functional impairment. There are few medication studies in ASD patients that measured anxiety as an outcome. Risperidone is the only agent for which randomized controlled trials have shown improvement in anxiety in this population, though not consistently.8-10,31

Most researched psychologically based interventions for anxiety and

### TABLE.

**Results of Randomized Controlled Trials of Select Agents in the Treatment of Autistic Spectrum Disorders**

<table>
<thead>
<tr>
<th>Intervention (and number of studies)</th>
<th>Core Symptoms</th>
<th>Comorbid Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Social impairment/withdrawal</td>
<td>Language/communication impairment</td>
</tr>
<tr>
<td>Risperidone (6)</td>
<td>Ineffective</td>
<td>Ineffective</td>
</tr>
<tr>
<td>Aripiprazole (2)</td>
<td>Ineffective</td>
<td>Effective*</td>
</tr>
<tr>
<td>Methylphenidate (3)</td>
<td>Ineffective</td>
<td>Ineffective</td>
</tr>
<tr>
<td>Atomoxetine (1)</td>
<td>Effective*</td>
<td>Ineffective</td>
</tr>
<tr>
<td>Valproate (3)</td>
<td>Ineffective</td>
<td>Ineffective</td>
</tr>
<tr>
<td>SSRIs (4)</td>
<td>Ineffective</td>
<td>Ineffective</td>
</tr>
</tbody>
</table>

*Decreases in symptom ratings in one or more randomized controlled trials, likely due to decreases in comorbid symptoms that interfere with social or language functioning. Source: Munshi K, et al.
comorbid disorders associated with ASD are cognitive-behavioral therapies (CBT). These may be effective for the obsessiveness and resulting oppositionality often seen in these children.

Sofronoff and colleagues developed CBT designed for anxiety among ASD children and modified it into a six-session protocol. Children were randomly assigned to three arms: combined intervention plus parent training; intervention only; and waitlist control (no intervention). The combined treatment proved to be superior in its positive effect.

Ooi and colleagues used a full 16-session intervention that incorporated multisensory intervention cues and self-monitoring of emotional reactivity. Chalfant and colleagues adapted these interventions into a group-based format that supplemented the anxiety-based interventions with group dynamic activities. Wood and colleagues used a flexible CBT approach that included psychoeducation, cognitive restructuring, home-based interventions, coping strategies, increased self-awareness and monitoring of feelings, social skills practice, and parent interventions. Beaumont and Sofronoff relied on a computer game to teach emotional recognition, regulation, and social interactions.

All of these cognitive-behavioral and social skills treatments tend to focus on enhanced social functioning and generalization of skills; to improve self-monitoring and regulation of anticipatory fears of inadequacy that exacerbate symptoms such as anxiety; and to try to reduce the public expression of circumscribed interests that impede social engagement.

**Depression, Sleep Disturbances, and Other Comorbidities**

Malow underscored the benefits of behavioral treatments that target sleep hygiene, sleep restriction, and reduction of interfering behaviors in ASD children. Although there have been descriptions of the symptoms and impairments in functioning associated with the presence of depression, and also ADHD among ASD youth, no formal treatment studies, including open trials, have been reported. It is anticipated that such interventions can be undertaken and will provide some benefit for patients.

There are few studies on combined pharmacotherapy and psychosocial interventions, but those available demonstrate superior efficacy.

**COMBINED INTERVENTIONS**

There are few studies on combined pharmacotherapy and psychosocial interventions, but those available demonstrate superior efficacy. The results of a randomized controlled trial by Aman and colleagues concluded that compared with medication (risperidone or aripiprazole) alone, medication with a lower antipsychotic dose, plus parent training, resulted in greater reduction of serious maladaptive behavior in children with Pervasive Developmental Disorders (PDD). Similarly, a recent retrospective review by Frazier and colleagues demonstrated the superior effectiveness of medication plus intensive behavioral intervention in youth with ASD and aggressive behavior compared with medication alone.

**Experimental Agents**

There are some data to support the benefit of drugs that act on the glutamate receptors (such as the NMDA receptor) in the treatment of autism. King and colleagues studied the effects of amantadine (an NMDA receptor antagonist) in autistic children and found some evidence of improvement, and it was well-tolerated. Niederhofer and colleagues used tianeptine (also thought to be a glutaminergic modulator) for autistic children who had not tolerated or responded to other medication trials. They reported modest effectiveness in the short-term treatment of irritability of some autistic children, based on significant improvements in the several subscales of the Aberrant Behavior Checklist (ABC), including irritability, hyperactivity, inadequate eye contact and inappropriate speech. Tianeptine is an antidepressant mostly used in some European countries that is neither FDA approved in the US nor recommended for children younger than 15 years of age.

There has been increasing interest in the effect of other drugs acting on the glutamate system (D-cycloserine, memantine) and oxytocin in improving social impairment in ASDs. These agents have been studied in patients with PDD, including a study (unpublished, but presented at academic meetings as a poster) on D-cycloserine, a retrospective review on memantine, and an open-label trial on oxytocin. There is some evidence of efficacy, but until there are more studies done that show positive results, these agents cannot be recommended for use in ASDs.

**CONCLUSION**

Effective pharmacotherapy for core autism features may be available in
the not-too-distant future. For single gene defects causing ASDs, basic knowledge of the functions of the affected gene is already being translated into novel treatments that may correct the defects in synaptic functioning that lead to the mental retardation and autistic symptoms in these disorders (eg, metabotropic glutamate receptor antagonists to correct defects in Fragile X disorder).

These therapies may prove effective in some children with idiopathic ASDs. Ultimately, future randomized controlled trials developed to test these molecules will need to incorporate social and language remediation protocols to see if the agent studied will accelerate social and language skill acquisition in patients with ASDs.

REFERENCES


