Pharmacotherapy of Autism Spectrum disorder

Malek, A., MD

Professor of Psychiatry

Child & Adolescent Psychiatrist

Tabriz University of Medical Sciences

maleka@tbzmed.ac.ir

- Pharmacotherapy is *one component of a treatment plan* for children with autism.

- Pharmacotherapy is aimed at target symptoms in order *to increase the ability of these children to participate in educational and other psychosocial interventions.*

- *No medication* has been identified that effectively treats the *core social disability* of autism.

ASD core symptoms

- Deficits in social interaction
- Restricted/repetitive behaviors or interests

Associated behavioral features include:

- Aggression,
- Irritability, Temper tantrums
- Self-injurious behavior,
- Hyperactivity, Impulsivity
- Attention problems,
- Mood lability,
- Anxiety, obsessions, and compulsions

- Individuals with ASD are likely to experience more severe adverse effects than typically developing individuals.
- Therefore, achieving an effective dose with minimum adverse effects can be a challenging task.
- **Treatment should be initiated in small doses**, and increased about every five half-lives of the drug,
- It may take 4–6 weeks of titration to determine the therapeutic dose for every individual case.

Abrupt behavioral deterioration associated with face slapping or head banging in a more cognitively impaired individual

A search for any associated ear infection, erupting wisdom teeth, etc.

- Pharmacological treatment of core ASD symptoms

Social Deficits

- **There are no medications which have consistently been shown to be effective for the social deficits of ASD.**

- **Glutamatergic drugs and oxytocin:**

  are currently the most promising.

- **Oxytocin:** **A recent meta-analy**sis of 12 RCTs suggested that oxytocin had no significant effect on social communication even though individual RCTs had reported improvements from oxytocin.

- Larger studies with better methodology are needed.

- **A subsequent clinical trial: Oxytocin enhanced orientation to social information in specific subgroups of individuals with ASD only.**

- Some researchers:

abnormalities of the **glutamatergic system** may contribute to the emergence of autism spectrum disorder.

- High glutamate levels occur in children with the formerly labeled Rett syndrome.

- A recent study of the glutamatergic agent ***memantine*** showed good tolerance but **no statistically significant improvement** in core ASD symptoms, including social domains.

Amantadine

- Thirty-nine children and adolescents (ages 5–19 years) in a double-blind, placebo-controlled trial (5 mg/kg/day):

- Parent ratings did not demonstrate a statistically significant change in irritability and hyperactivity.

- However, clinician ratings of improvement in behavioral changes of hyperactivity and inappropriate speech were significantly higher in the amantadine group than in the placebo group.

- **Sulforaphane**, insulin growth factor 1 (IGF-1) await further work to prove their efficacy in modifying ASD core symptoms, as do glutamatergic agents.

- Acetylcysteine is probably not effective.

- ***Tetrahydrobiopterin***, a coenzyme that enhances the action of enzymes: the results were not significant.

- Post hoc analysis of the core symptoms of autism revealed a **significant improvement in social interaction score after 6 months of active treatment.**

- These results suggest:

a possible effect of Tetrahydrobiopterin on the social functioning of children with autism.

- Targeting the gut microbiome, including **probiotic treatment and fecal microbiota transplants**:

as novel and potential therapeutics for ASD conditions

However there is little evidence to support:

- ✓ the use of nutritional supplements or dietary therapies for children with ASD

- ✓ or any relationship between maternal food intake and child's diet and the development of ASD/symptoms severity.

- Risperidone may have a secondary effect through improvement in irritability.

- Analysis of data from two multi-center trials: risperidone was effective for the treatment of social disability in children with ASD.

REPETITIVE BEHAVIOR

Repetitive behavior, including self-injury, is a treatment-refractory symptom.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Atypical Antipsychotics

Other Drugs

- A 2020 meta-analysis of studies on a wide range of currently available pharmacological agents showed **evidence supporting only antipsychotic medication.**

- Another recent meta-analysis of nine studies found **no evidence for any pharmacological agent in reducing RRBIs.**

SSRIs

An early trial was promising in using fluoxetine in reducing repetitive behaviors in ASD.

Subsequent studies using citalopram/fluvoxamine were negative.

A recent Cochrane review found no evidence supporting the use of SSRIs in children with ASD.

Fluoxetine……

- Low-dose liquid fluoxetine (mean dosage = 10 mg/day) was superior to placebo in reducing repetitive behaviors.

- Case reports of fluoxetine treatment for ASD: improvements in irritability, stereotypies, and inappropriate speech.

When using fluoxetine to treat repetitive behaviours in ASD patients, doses much lower than those used to treat depression are normally required. It is advisable to use a liquid preparation and begin at the lowest possible dose, monitoring for adverse effects. A suitable regime is outlined in Box 5.4.

Box 5.4 Use of fluoxetine in children and adolescents

Liquid fluoxetine: (as hydrochloride) 20mg/5mL
2.5mg/day a day for 1 week; note that 2.5mg = 0.625mL which is difficult to measure accurately.

Follow with flexible titration schedule based on weight, tolerability and adverse-effects up to a maximum dose of 0.8mg/kg/day (0.3mg/kg for week 2, 0.5mg/kg/day for week 3, and 0.8mg/kg/day subsequently). Reduction may be indicated if adverse effects are problematic.

Atypical Antipsychotics

- Studies of risperidone and aripiprazole, in addition to detecting improvements in irritability and aggression, also found improvement in repetitive behavior.

- Risperidone is effective in reducing RRBIs in **children who have high levels of irritability or aggression,**

  (thus making doubtful any specific efficacy for repetitive behaviors)

Other Drugs:

A number of studies have examined the utility of **tricyclic antidepressants;**

clomipramine in particular has demonstrated efficacy in a randomized controlled trial.

In practice, its use is limited by concerns regarding side effects, including severe urinary retention and worsening aggression.

- Clomipramine was compared with desipramine for the treatment of autistic disorder in a double-blind crossover study:

  - Clomipramine was significantly superior to both desipramine and placebo on ratings of autistic symptoms, including stereotypies, anger, and compulsive ritualized behaviors.

- One patient had a grand mal seizure during the second week of clomipramine therapy.

- Clomipramine dosage reduction was necessary in two patients because of QT interval prolongation in one case and severe tachycardia in the other.

Venlafaxine

- The effectiveness of venlafaxine was assessed in an open study of 10 patients (ages 3–21 years).
- Six of 10 patients (mean dosage = 24.4 mg/day) were much or very much improved.
- Improvements were shown in repetitive behaviors, restricted interests, social deficits, communication and language function, inattention, and hyperactivity.
- Side effects of venlafaxine included behavioral activation, nausea, inattention, and polyuria.

Mirtazapine

- In an open-label study of mirtazapine (dosage mean = 30 mg/day),

35% improved in symptoms of aggression, self-injury, irritability,hyperactivity, anxiety, depression, and insomnia.

- Mirtazapine did not improve symptoms of social or communication impairment.

Naltrexone

- Double-blind, placebo-controlled trials have reported modest improvement of symptoms, including:

- Decreased self-injurious behavior, improved socialization,
- Increased attentiveness and communication; improved socialization,
- Decreased withdrawal, increased proximity seeking, increased eye contact, increased attentiveness, and
- Decreased restlessness and affective lability; decreased irritability; decreased hyperactivity and irritability;
- Decreased restlessness and hyperactivity;

- Dosage ranges of naltrexone were 0.5–1.5 mg/kg in these studies.

- There were no significant changes in cardiovascular parameters of heart rate or systolic blood pressure for children with autism treated with naltrexone.

- In other controlled trials, naltrexone demonstrated no superiority over placebo in producing beneficial changes in social behavior and stereotypic behavior.

- *These researchers therefore did not advocate the routine use of naltrexone for children with autism.*

AGGRESSION AND IRRITABILITY

Atypical Antipsychotics

Risperidone & Aripiprazole

- *FDA approval* for the treatment of irritability associated with Autism Spectrum disorder including symptoms of:

  aggression, deliberate self-injuriousness, temper tantrums, and mood lability

Box 5.3 FDA Guidance for risperidone dosing in children and adolescents[68]

Doses of Risperidone in Paediatric Patients with Autism Spectrum Disorders (by total mg/day)

Weight categories	Days 1–3	Days 4–18	Increments if dose increases are needed	Dose range
<20kg*	0.25mg	0.5mg	+0.25mg at ≥2 week intervals	0.5mg–3mg**
≥20kg	0.5mg	1.0mg	+0.5mg at ≥2 week intervals	1.0mg–3mg***

*Caution should be exercised for children <15kg – no dosing data available
**Therapeutic effect plateaus at 1mg/day
***Those weighing >45kg may require higher doses – therapeutic effect plateaus at 3mg

- **Adverse events of Risperidone:**

  increased appetite, fatigue, drowsiness, dizziness, and drooling

- **Risperidone** is *superior to placebo in preventing relapse*, with relapse rates of 25% and 75%, respectively.

- **Aripiprazole:**
- Dosage range: 5-15 mg/day

- Side effects:

sedation, dizziness, insomnia, akathisia, nausea, and vomiting.

Olanzapine

Open studies:

- Significant improvements in hyperactivity, social relatedness, self-injurious behavior, aggression, irritability.

- One small randomized controlled trial of olanzapine ***did not*** demonstrate improvement on measures of irritability.

Clozapine

- A case series of three children with autistic disorder treated with clozapine (up to 100 mg/day) for 3 months reported a %40 improvement in measures of abnormal object relationships, negativism, fidgetiness, and hyperactivity.

- After 8 months of clozapine treatment (mean daily dose = 200 mg), two of the children showed a substantial improvement in language and communication skills.

Quetiapine

Open studies:

- No significant behavioral improvements were found from baseline to endpoint.

Typical Antipsychotics

Haloperidol

- ✓ the most widely studied typical antipsychotic for the treatment of autism.

- ✓ European Medicines Agency (EMEA) has approved Haloperidol for persistent, severe aggression.

- ✓ In double-blind, placebo-controlled studies, haloperidol has been shown to be significantly superior to placebo in:
  - reducing maladaptive behaviors
  - decreasing occurrence of stereotypies
  - decreasing hyperactivity, temper tantrums, withdrawal.

- Optimal dosages of haloperidol in these studies ranged from 0.25 to 4 mg/day.

- The most common side effects:

  sedation, and acute dystonic reactions (25 %)

- **Reversible haloperidol-related dyskinesias** have been reported in ***29%*** of autistic children.

- Factors related to the development of haloperidol-induced acute dyskinesias in studies of autistic children include:

  female gender and perinatal complications

Pimozide

- Pimozide compared with haloperidol and placebo in a controlled crossover trial:

- Pimozide and haloperidol were significantly more effective than placebo in reducing maladaptive behavior and aggressiveness.

Antiepileptic Drugs/Mood Stabilizers

- **Sodium valproate** has been found to be an effective treatment for aggression in ASD in **one randomized controlled trial**.

- Of the other antiepileptics,

levetiracetam and ***lamotrigine***

(studied in a randomized fashion)

found to be ***ineffective.***

Lamotrigine……

- Twenty-eight children (ages 3–11 years) with autistic disorder participated in a double-blind, placebo-controlled study of lamotrigine (mean dosage = 5 mg/kg/day).

- There were no significant differences between the lamotrigine and placebo groups on severity of behavioral symptoms.

- No children in the study were withdrawn because of rash.

Lithium

- Case studies have reported the effectiveness of lithium in improving manic-like symptoms in children with autism.

- Whilst controlled studies support **the use of mood stabilizers in the treatment of persistent aggression** in children they are not as effective as SGAs for the treatment of irritability in ASD.

- Limited data support **the combination of risperidone and topiramate** being better than risperidone alone.

- Using **Benzodiazepines** to manage irritability and aggression in ASD is not recommended.

- However, it may be necessary to manage acute aggression with a BZ.

- The possibility of behavioral disinhibition which may worsen aggression must be born in mind.

Buspirone

- In a open trial, 22 children and adolescents were treated with buspirone (dosage range = 15–45 mg/day).

- 73% showed moderate to marked improvement in anxiety and irritability.

INATTENTION
AND
ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Stimulants: Methylphenidate

- ***Evidence supports the use of stimulants in individuals with ASD who have significant ADHD symptom.***

✓ with a response rate of ***49%***

✓ lower than rates reported for ADHD without ASD

✓ side effects were more frequent

Atomoxetine: ***Stramox / Strattera***

- Non-stimulant

❑***moderate improvement*** in ADHD in children with ASD compared to placebo, with ***adverse effects*** comparable to studies in non-ASD populations.

Clonidine and Guanfacine

- ***In clinical practice***, the alpha-2 agonists are frequently used for ***both ADHD symptoms and irritability in children with ASD.***

- Their efficacy is well established in larger trials of **children without ASD**, and ***there is a small body of evidence specific to ADHD symptoms in ASD.***

Clonidine….

- A RCT crossover study with transdermal clonidine or placebo in **nine patients**:

  Significant improvement with clonidine in social relationship, affectual responses, and sensory responses.

- In a RCT of clonidine in **eight children:** modestly effective in reducing irritability and hyperactivity.

Insomnia

- ***Children with ASD have significant sleep problems with:***

sleep-onset insomnia,

sleep-maintenance insomnia

irregularities of the sleep–wake cycle

- Melatonin, has been shown in **17 studies to be beneficial in children with ASD.**
- A meta-analysis of five studies showed good **efficacy with doses ranging from 1mg to 10mg**
- Melatonin is usually **very well tolerated.**
- One RCT showed that, whilst melatonin improved sleep onset, **child's behavior during the day did not improve**

- A **prolonged-release Melatonin** product has been recently approved in Europe for the treatment of insomnia in autism.

- Risperidone may benefit sleep difficulties in those with extreme irritability.

- Anxious or depressed child:

  antidepressants may be beneficial.

- Insomnia due to hyperarousal may benefit from clonidine or clonazepam.

Summery

- There is no evidence that pharmacotherapy is effective in treating the core social and communication deficits in autistic disorder.

- However, medications have been shown to be useful in treating associated symptoms, such as hyperactivity, inattention, stereotypies, self-injurious behavior, tantrums, aggression, mood lability, and anxiety.

- **The evidence to date shows reasonable efficacy of:**

✓

✓risperidone, aripiprazole for irritability and aggression,

✓use of methylphenidate, atomoxetine and guanfacine for ADHD,

✓melatonin for sleep problems

- But limited efficacy of:
  - ✓ SSIRs for anxiety, depression and repetitive behaviors.
  - ✓ In some cases, **naltrexone** may reduce hyperactivity, irritability, and self-injurious behavior.
  - ✓ The evidence for antiepileptics remains inconsistent.
  - ✓ There is a potential role for α2 agonists, glutamatergic, (GABA)ergic agents and oxytocin but these require further investigation.

THANK YOU

FOR YOUR ATTENTION