Pharmacotherapy of Autism Spectrum disorder

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- 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.

Core features of this disorder

impairments in:

- Social communication and social interaction
- Restricted and Repetitive patterns of behavior, interests, and activities

Associated behavioral features include:

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

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.

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

- **Dosage range for Risperidone : 0.5-1.5 mg/day**

- **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.

- ✓ In double-blind, placebo-controlled studies, haloperidol has been shown to be significantly superior to placebo in:
  - o reducing maladaptive behaviors
  - o decreasing occurrence of stereotypies
  - o 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 was compared with haloperidol and placebo in a controlled crossover trial that included 34 children with autistic disorder.

- 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**.

- **Additional study** could support the use of valproate as a more tolerable treatment option.

- 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.

INATTENTION
AND
ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Stimulants: Methylphenidate

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

- A RCT of methylphenidate in children with ASD and ADHD symptoms found a response rate of ***49% :***

✓ lower than rates reported for ADHD without ASD

✓ side effects were more frequent

- ***Given these findings, stimulant treatment remains appropriate in some cases.***

Atomoxetine: ***Stramox / Strattera***

- Non-stimulant
- Hyperactivity, Impulsivity, Inattention

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

- Side effects: Sedation, irritability

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.

Social Deficits

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

- **Oxytocin:** **Meta-Analysis:** current data are potentially promising, but additional, rigorous research is required.

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

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

REPETITIVE BEHAVIOR

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

Selective Serotonin Reuptake Inhibitors (SSRIs)

Atypical Antipsychotics

Other Drugs

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 = 9.9 mg/day) was superior to placebo in reducing repetitive behaviors.

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

Atypical Antipsychotics

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

- However, these effects were quantified using the **Aberrant Behavior Checklist stereotypy subscale**, whereas most of the SSRIs made use of the Children's **Yale-Brown Obsessive Compulsive Scale.**

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 = 30.3 mg/day), 34.6% were judged much or very much improved in symptoms of aggression, self-injury, irritability,hyperactivity, anxiety, depression, and insomnia.

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

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 symptoms.

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, social and stereotypic behavior.

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

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.

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.

- **Antipsychotics** may decrease withdrawal, stereotypies, and aggression and may facilitate learning.

- To date, the most data available support the use of **Risperidone and Aripiprazole** for treating irritability, aggression, self-injurious behavior, temper tantrums, and mood lability.

- **Serotonin reuptake inhibitors** and other antidepressants have been shown to reduce compulsions, anxiety, and depression in children with autism.

- In some cases, **naltrexone** may reduce hyperactivity, irritability, and self-injurious behavior.

- **Stimulants** may increase attention span and reduce hyperactivity.

THANK YOU

FOR YOUR ATTENTION