Relevant issues in the pharmacological treatment of autism spectrum disorders: a critical review

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Abstract
Introduction
Autism spectrum disorder (ASD) is a neurodevelopmental disorder with a multifactorial aetiology and characterized by severe abnormalities in communications, social awareness and skills, and the presence of restrictive and stereotyped patterns of behaviours. There is no specific treatment for ASD, and pharmacological treatment aims to control behavioural symptoms such as aggressiveness, self-harm, fits of anger, hyperactivity and stereotyped behaviours. The aim of this review is to describe the state-of-the-art pharmacological treatment provided for ASD in the past five years, including clinical implications such as effectiveness and side effects of drugs generally prescribed.

Materials and methods
We carried out a literature research and study selection, by searching for published biomedical literature in PubMed.

Results
In keeping with the search criteria selected for our review, we selected only the reviews published in the past five years, excluding the articles that focused only on a single drug. Our search yielded a total of 188 reviews that matched our search criteria.

Conclusion
There is no consensus on the use of psychopharmacological treatments in autism. Although there are many clinical observations, only few controlled studies have validated the efficacy and safety of these treatments.

Introduction
According to the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorder (fourth edition, text revision; DSM-IV/TR), the autism spectrum disorder (ASD) is defined as a group of pathological conditions characterized by impairment in social interaction, impairment in verbal and nonverbal communication and restricted, repetitive and stereotyped patterns of behaviour, interest and activities. The aetiology and pathogenesis of ASD are still poorly understood and, besides behavioural-development-educational strategies, no biomedically effective therapies are currently available.

The ASD includes:
- autism
- Asperger syndrome
- pervasive developmental disorder not otherwise specified
- childhood disintegrative disorder
- Rett syndrome

Autism is certainly the most prevalent disorder among ASDs, as it has been estimated that globally 62 out of 10,000 people are affected. ASD averages a 4.3:1 male-to-female ratio. The delay or abnormality in language, social interaction and imaginative play must be present before age 3, in order to diagnose an ASD.

One of the most important changes in the fifth edition of the DSM (DSM-V, released at the American Psychiatric Association’s annual meeting in May 2013) is the introduction of ASD. Rett syndrome is no longer included among ASDs.

Other than separate diagnostic categories, in the new manual the symptoms of people with ASD are shown on a continuum, with some individuals showing mild symptoms and others showing symptoms much more severe. The concept used is ‘autistic spectrum’. This spectrum allows clinicians to account for the variations in symptoms and behaviours from person to person.

Prognosis of ASD varies. Treatments and educational interventions are designed to decrease morbidity, maximizing the adaptive functioning and competence of the subject. The recent increase in ASD prevalence in general population and lack of specific and effective treatments make it necessary that research and sanitary institutions try out new treatment modalities that can be added and enhance the efficacy of those previously used.

There is no specific treatment for ASD or any known methods of primary prevention. Treatment programs must be tailored specifically to meet the needs of each child. Non-pharmacological therapies most commonly used are as follows: occupational therapy, alternative-communicative therapy and speech and psychomotor therapy. Pharmacological treatment aims to control the behavioural symptoms of ASD, such as repetitive and stereotyped activities, irritability and aggression, hyperactivity and inattention, and obviously, social impairment. This review aims to describe the state-of-the-art pharmacological treatment for ASD as provided in the past five years, including clinical implications such as treatment efficacy and side effects of drugs generally prescribed.
Materials and Methods

We made a literature research and study selection, by searching for published biomedical literature in PubMed. The search criteria used were as follows:

- article types: review
- publication dates: 5 years
- species: humans
- languages: English
- key words: autism, pharmacological treatment.

We also used the guidelines provided by the Italian ISS (October 2011) for treatment of ASDs in children and adolescents.

In addition, we used references of selected reviews in order to more precisely examine the state-of-the-art pharmacological treatment of ASD.

Results

Through a first research on PubMed, we have found 610 results that included articles focusing on the characteristics, effectiveness and the actual use of a single drug as well as several reviews that dealt with different pharmacological treatments for ASD.

On the basis of search criteria developed for this review, we selected only those reviews published during the past five years, excluding all articles focusing on a single drug. Finally, we selected a total of 188 reviews that focused on multiple treatment modalities. During the analysis, we picked 39 reviews that we found more suitable for our study. The remaining 149 reviews were excluded, since some of them described too specific clinical cases that hardly met our study requirements; some others described autism only as secondary to other pathologies, such as tuberous sclerosis complex and the fragile X syndrome; and still others discussed new therapeutic targets undergoing clinical trials. As a result, we decided to exclude those reviews that we found not consistent with our study’s purpose.

Discussion

The series of articles that we chose to review for our study highlight the lack of a specific pharmacological treatment for autism and the use of a mainly symptomatic drug therapy.

Psychotropic medications may be effective in treating various behavioural symptoms of autism, such as hyperactivity, lack of attention, agitation, insomnia, aggression, self-injury, irritability, repetitive and compulsive behaviours, and anxiety.

There are varieties of different pharmacological agents that are effective in improving behavioural symptoms of ASD. Generally, medications prescribed include the following: Haloperidol (dopamine antagonist), Risperidone (dopamine and serotonin antagonist), Clomipramine (a tricyclic antidepressant), Fluvoxamine, Fluoxetin, Sertraline (SSRIs), Naltrexone (opioid receptor antagonist), Buspirone (serotonin agonist), Methylphenidate (noradrenergic drug), Propanolol and Clonidine (sympatholytic medications). Also, a wide range of drugs, vitamins or methods are used in clinical practice, selected after periodic observations of their positive effects: secretin, vitamin b6 and b12, magnesium, lithium, carbamazepine and valproate.

Therefore, the choice of drug treatment is also based on the complexity of clinical condition, with particular attention to the specific cluster of symptoms presented by the subject.

We will now analyse in detail the most important symptoms and the main drugs used in treatment. Possible target symptoms for treatment are as follows: self- and hetero-aggressiveness, irritability, hyperactivity and impulsivity, psychomotor agitation, stereotyped and repetitive behaviours, and insomnia.

Self- and hetero-aggressiveness

Most common causes of aggression in autistic patients concern the following: unrecognized pain, constipation, seizures, hypoglycaemia; reduced ability to understand the actions and their consequences; reduced ability to communicate and express wants and needs; reduced ability to mimic; conflicts with peers and care givers; social and psychological dysfunction; and psychiatric factors (psychosis, depression, mania, suicidal and homicidal ideation). The circuits neurotransmitter involved in aggressive behaviour are as follows: dopaminergic, noradrenergic and serotoninergic systems and endogenous opiates. The most effective drugs for aggressive symptoms include the following: antipsychotics (typical and atypical), psychostimulants (methylphenidate) and opioid receptor antagonists (naltrexone). Haloperidol improves tantrums and hyperactivity and also social withdrawal and stereotypes and learning and language skills. Risperidone is better than placebo in treating irritability, repetitive behaviour, aggression, anxiety, depression and nervousness. In 2009, the FDA has approved aripiprazole for treating irritability related to autism. Methylphenidate is useful for treating aggression associated with impulsivity and hyperactivity. Naltrexone is an opiate antagonist that has been evaluated for treating ASDs, thanks to the demonstrated efficacy of endogenous opioids such as β-endorphin and encephalins in regulating social behaviour. Use of Naltrexone has also been reported to have achieved significant improvements in the treatment of self-injurious behaviour, hyperactivity, social withdrawal, agitation and irritability in ASDs.

Hyperactivity and impulsivity

Scientific evidences show the use of psychostimulant drugs, non-stimulants, and alpha agonists has vastly improved the clinical efficacy of treatment of hyperactivity and impulsivity. Another drug, Methylphenidate, has also been found to be effective in improving the behavioural symptoms such as hyperactivity, impulsivity and attention.

Atomoxetine has a superior ability to understand the actions and their consequences; reduced ability to communicate and express wants and needs; reduced ability to mimic; conflicts with peers and care givers; social and psychological dysfunction; and psychiatric factors (psychosis, depression, mania, suicidal and homicidal ideation). The circuits neurotransmitter involved in aggressive behaviour are as follows: dopaminergic, noradrenergic and serotoninergic systems and endogenous opiates. The most effective drugs for aggressive symptoms include the following: antipsychotics (typical and atypical), psychostimulants (methylphenidate) and opioid receptor antagonists (naltrexone). Haloperidol improves tantrums and hyperactivity and also social withdrawal and stereotypes and learning and language skills. Risperidone is better than placebo in treating irritability, repetitive behaviour, aggression, anxiety, depression and nervousness. In 2009, the FDA has approved aripiprazole for treating irritability related to autism. Methylphenidate is useful for treating aggression associated with impulsivity and hyperactivity. Naltrexone is an opiate antagonist that has been evaluated for treating ASDs, thanks to the demonstrated efficacy of endogenous opioids such as β-endorphin and encephalins in regulating social behaviour. Use of Naltrexone has also been reported to have achieved significant improvements in the treatment of self-injurious behaviour, hyperactivity, social withdrawal, agitation and irritability in ASDs.

short-term efficacy over placebo in treating the symptoms of hyperactivity/impulsivity in children and adolescents with ASDs and coexisting attention deficit and hyperactivity disorder (ADHD)-like symptoms\textsuperscript{16}. Guanfacine is the most effective drug among alpha agonists\textsuperscript{17}.

**Repetitive behaviours**

Fluoxetine is the first-line treatment choice for repetitive behaviours. It (selective serotonin reuptake inhibitor; SSRI) has shown several benefits, including reductions in rituals and stereotyped and repetitive behaviours in children and adolescents with ASDs\textsuperscript{18}. One major aspect of its clinical efficacy is that it has been shown to be effective even when used in combination with risperidone\textsuperscript{19} and other mood stabilizers such as sodium valproate\textsuperscript{20}.

**Insomnia**

Melatonin may be an effective treatment for sleep disorders that persist even after behavioural interventions. Abnormalities in the circadian rhythm and low levels of melatonin and/or derivatives of melatonin have been demonstrated in autism. There is also a clear correlation between melatonin levels and autistic behaviours. Genetic abnormalities may contribute to deficiency in production of melatonin or can alter the functionality of receptors in a small percentage of patients with ASD. Therefore, intake of melatonin leads to an improvement in behaviour during the day as well as improvements in sleep duration, sleep latency and latency in night-time awakenings\textsuperscript{21–22}.

The pharmacological characteristics of these drugs, such as dosage and side effects, cannot be fully described in this review since a dedicated investigation and an accurate analysis are required.

We consider it more appropriate to point out the percentage of non-responders among autistic patients. All medications aim to treat symptoms of both ASD and other co-morbidities. As clinical practice demonstrates, it is hard diagnose co-morbidity due to the complexity of clinical cases. Therefore, a missing or a wrong diagnosis of co-morbidity could lead to an inappropriate pharmacological treatment. This factor could partially explain the percentage of the non-responders. This critical analysis underlines three important considerations. Only a few randomized controlled clinical trials with a reliable sample size (representative samples with 30 or more subjects) have been conducted so far, and our search did not draw out any long-term study that focused on patients diagnosed with ASD and was conducted on the basis of approved standardized criteria and instruments (e.g. Autism Diagnostic Observation Schedule [ADOS] and/or Autism Diagnostic Interview-Revised [ADI-R]). As a matter of fact, use of psychotropic medications in developmental age, especially for those suffering from psychopathological disorders such as autism, is more frequently associated with a lack of reliable clinical trials. Second, several clinical evidences are based on open-label trials. Even if their results do not always indicate certainty, they can be considered a good starting point for further randomized controlled clinical trials in future. However, they cannot be used for validating the prescription of a psychotropic medication. Third point concerns the possibility of prescribing particular drugs during the developmental age. In fact, there is a clear lack of scientific data in literature. As a result, with few available scientific evidences, many psychotropic drugs (especially second-generation antipsychotics) cannot be prescribed during developmental age, as they do not have demonstrated effectiveness and tolerability to support their prescription to certain age groups. Use of these molecules is therefore considered off-label. This poses an important limit to the possibility of treatment in children and adolescents. Finally, we considered it appropriate to give a nod to non-conventional treatments, such as biomedical and nutritional treatments and also the ‘ineffective’ ones. There are no scientific evidences to support the recommendation of casein/gluten-free diets, nutritional supplement of vitamin B6, magnesium and omega-3 for DSA patients, except for cases individually assessed and meeting certain criteria and/or need for treatment. However, in recent times, we see more frequently an increase in the use of these and other ‘unconventional’ methods, at the expense of treatments considered scientifically valid, and with the risk of somatic progression in the subject. In this sense, we want to underline that randomized controlled clinical trials about ineffective therapies are present in literature, for example, those focusing on the use of digestive enzymes\textsuperscript{23} and those on the use of human immunoglobulins\textsuperscript{24}.

**Conclusion**

When we talk about pharmacological treatment for autistic patients, we have to remember that these patients belong to a subgroup of children, adolescents and adults with autistic disorder characterized by the presence of particular target symptoms, such as aggressiveness, self-harm, fits of anger, hyperactivity, stereotyped behaviours and so on. Furthermore, before using psychopharmacological drugs, especially during developmental age, we have to consider the verified effectiveness of a drug that acts on behavioural symptoms and the possible side effects related to its treatment, avoiding those drugs that have serious side effects, whenever possible. Atypical antipsychotics are currently first-line pharmacological agents used in treating irritability and associated behaviours in children with ASD. However, there is no consensus on the use of psychopharmacological treatments for autism. Although there are many clinical observations, only few controlled

studies have validated the efficiency and safety of these treatments. At present, studies are not conclusive enough, drugs are generally limited to treating only severe disorders, in which case the usual psycho-educational approaches are not sufficient.

**Abbreviations**


**References**