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Antipsychotics in the Treatment of Autism

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1. Introduction

The neurobehavioral syndromes are more frequent than we usually think. They are clinical challenges, because they demand knowledge from the physician as well as time for the correct approach. Such complaints are very frequent in hospital and addition to the private practice. For example, according to a survey carried out in our Hospital, the Child Neurology Unit made 10,622 evaluations in 2010, most of which were neurobehavioral syndromes including autism and other Pervasive Development Disorders.

Because of the subtlety of the boundaries between Neurology and Psychiatry, the term neurobehavioral could also be called neuropsychiatric. These boundaries have been explored both in the clinical (Nunes and Mercadante, 2004) and in the experimental area (Quincozes-Santos et al., 2010). It is important to build a bridge between the clinical and the experimental research, especially when the issue is neuropsychiatric disorders. This linkage indubitably enhances the common knowledge of neurobehavioral alterations as well as it promotes the reciprocal enthusiasm.

One of the most intriguing neurobehavioral syndromes is autism. The challenge starts with the difficulty of defining the disorder, continues with the limitations imposed by the lack of a clinical marker, and ends with the difficulties in the experimental research field.

The word autism was used for the first time by the Swiss psychiatrist Eugen Bleuler in 1911. "Autism" came from the Greek word "autos," meaning self. However, the landmark paper describing autism came from the Austrian psychiatrist Leo Kanner, who described eleven children that shared common behavior, with a peculiar inability to establish affective and interpersonal contact. He published the paper "Autistic disturbances of affective contact" in the *Journal Nervous Child* (Kanner, 1943).

In 1944, the Austrian pediatrician Hans Asperger described cases of children with some behavioral characteristics that resembled those of children with autism, but with a peculiar type of language as well as normal cognitive performance (Gadia et al., 2004). He published an article in German in 1944 entitled "Die 'Autistischen Psychopathen' im Kindesalter" in *Archiv fur Psychiatrie und Nervenkrankheiten* that was translated into English only in 1989.

To date, more than half a century since Kanner's study, the number of papers in PubMed containing the word *autism* has risen above 17,000. From this total, the percentage of

published papers comprising different keywords correlated to autism (see Figure 1), reveals that the most frequent words in a set of selected targets were *developmental*, *brain* and *psychiatry*. Curiously, the word *environment* occurs in only 5% of papers. It was a surprise, considering evidence indicating that environment plays a role in the development of autism (Landrigan, 2010). In fact, the prevalence of autism is higher than previously thought and if it is rising, the rise might be associated with a shift in the environment. Further, the appearance of keywords related to glial cells (*astrocyte*, *oligodendrocytes* and *microglia*) can be noted, and, as expected, in less than 2% of papers indicating an emerging and promising field of investigation on ASD.

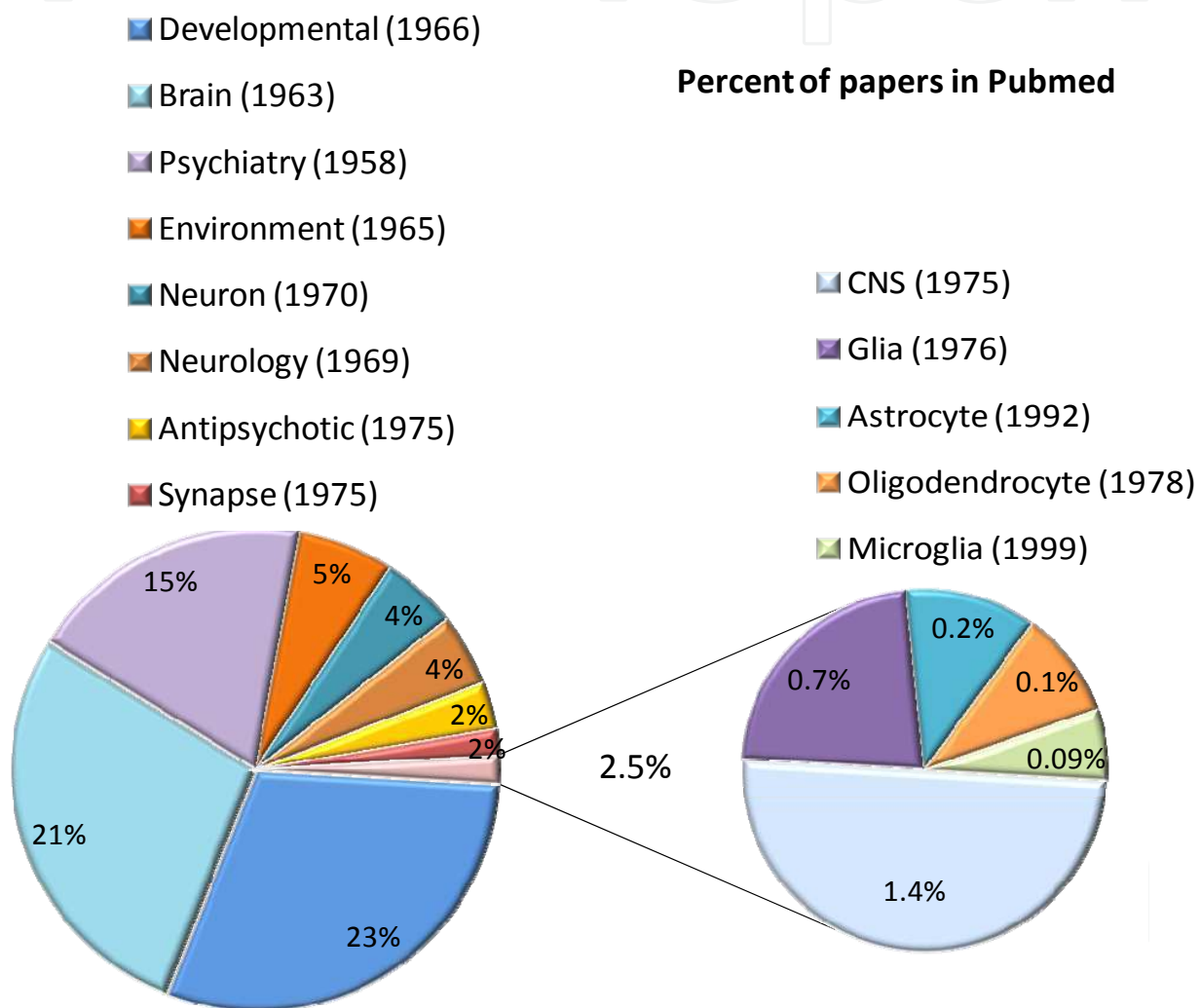


Fig. 1. **Number of papers published in PubMed.** Values were obtained combining the word “autism” with selected keywords related to ASD and neural studies. Number in parenthesis indicates the first year of publication in PubMed of each word combination. Keyword autism = 100% = 17,199 papers. E.g. autism + developmental = 23%, with the first paper with this combination having been published in 1966. Data was obtained in March 23, 2011.

According to the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition criteria, there are five clinical situations that could be encompassed by the term “PDD”

(Pervasive Developmental Disorders) or “ASD” (Autism Spectrum Disorders) with the same meaning of PDD or autism. The terms PDD or ASD are interchangeable and they are widely used in clinical practice to refer to children with autism or any other of the related disorders (Gadia *et al.*, 2004). Actually, the terms PDD and ASD are not a specific diagnosis, but a kind of umbrella with five different diagnostic categories based on clinical findings.

The five clinical ASD diagnoses admitted by DSM-IV-TR (APA, 2002) are: a) Autistic Disorder; b) Asperger Disorder; c) Rett Disorder; d) Childhood Disintegrative Disorder; e) PDD-NOS (Pervasive Developmental Disorder – Not Otherwise Specified).

In terms of frequency, our group found that the most prevalent ASD is the PDD-NOS, followed by Autistic Disorder, and then by Asperger Disorder. Rett’s Disorder and Childhood Disintegrative Disorder are seen less frequently in the clinical practice (Longo *et al.*, 2009).

One of the major challenges of cognitive neuroscience is to understand how changes in the structural properties of the brain affect the plasticity exhibited whenever a person develops, ages, learns a new skill, or adapts to a neuropathology (Keller and Just, 2009). There are many hypotheses in this field attempting to explain the genetics, neurotransmitter imbalances, early childhood immunizations, xenobiotic and teratogenic agents, and maternal infection (Buehler, 2011).

With the advent of electroencephalography, the aberrant patterns observed in patients with autism have contributed to the contemporary understanding of the syndrome as a brain-based disorder. There is a positive correlation between increasing radiate white matter volume and motor skill impairment in children with autism (Mostofsky *et al.*, 2007). Moreover, macrocephaly is observed in 15-35% of patients with autism (Bailey *et al.*, 2008).

The clinical onset of autism appears to be preceded by two phases of brain growth abnormalities: a reduced head size at birth, followed by sudden and excessive increase between 1–2 months and 6–14 months of age (Pardo and Eberhart, 2007), which may reflect a disruption of multiple fundamental processes during the patterning and organization of a cortical cytoarchitecture. The effects of these disrupted processes may be manifested widely, with atypical or adaptive behaviors associated with these changes.

Considering that the etiology of autism still unknown and that there are no effective medical treatments that address the core symptoms of ASD concerning communication, inappropriate social interactions and restricted interests or behaviors, the promise of future medical treatments for ASD is through the identification of the underlying pathophysiological mechanisms, and treatment of these molecular and cellular deficits (Coury, 2010).

The psychopharmacotherapy used in autism is generally addressed to behavioral symptoms, such as: anxiety, lack of attention, irritability, hyperactivity, humor oscillations, sleep disturbances, aggressiveness and self-injury. Another clinical problem in ASD is epilepsy, reaching up to twenty times more frequency in autism. Even though, many of the above mentioned behavioral symptoms could be reduced after treatment; the antipsychotic drugs can adversely facilitate epilepsy.

Nevertheless, the antipsychotic treatment in ASD has expanded, sometimes accompanied by several clinical and metabolic side-effects of primary concern (weight gain, hyperglycemia and dyslipidemia), especially by the greater risk within the pediatric population.

In this context, the present chapter aimed to review (i) the neurotransmitter dysfunctions in ASD and the most commonly prescribed antipsychotics; (ii) the vantages and advantages regarding to the antipsychotics side effects and (iii) the non-neuronal possible targets of atypical antipsychotics in brain.

2. Ligand-receptor dysfunctions in autism

The wide diversity of core characteristics of ASD and the variety of comorbidities makes the diagnostic procedure and clinical management of the patient more difficult. In the immature brain, the neuronal migration and emplacement are modulated paracrinally by neurotransmitters and their receptors (Manent and Represa, 2007). The complex functions being related to neurotransmitters during brain development indicates that these molecules can play central roles in a wide variety of neurobiological alterations associated with ASD.

Likewise, the multifactorial basis of ASD is engineered by complex developmental changes in the brain that occur during the first few years of life. These changes include alterations (a) at the anatomical level, in the limbic system (hippocampus and amygdala), cerebellum, cortex, basal ganglia and brainstem (Bauman and Kemper, 2005) and (b) at the neurochemical level, in a number of key ligand-receptor systems, including serotonergic, dopaminergic, noradrenergic, cholinergic, opioid, amino acids and hormone mechanisms (Lam *et al.*, 2006). Full understanding of these systems in the brain involves different areas of knowledge such as genomics, neurochemistry, electrophysiology, and behavior.

2.1 Most prevalent neurotransmitter/receptor dysfunctions in ASD

2.1.1 Serotonergic system

The neurotransmitter serotonin is synthesized from the essential aminoacid tryptophan. Firstly, tryptophan is hydroxylated (by tryptophan hydroxylase) into 5-hydroxytryptophan, which is then decarboxylated (by aromatic L-amino acid decarboxylase) resulting in serotonin or 5-hydroxytryptamine (5-HT).

Serotonin has been linked to a wide variety of behaviors including those having to do with feeding and body-weight regulation, social hierarchies, aggression and suicidal behavior, obsessive compulsive disorder, alcoholism, anxiety, and affective disorders. This neurotransmitter plays two important roles in the mammalian brain: it regulates serotonergic outgrowth and maturation of the target regions in the developing brain (Whitaker-Azmitia, 2005), and modulates the function and plasticity of the adult brain (Catalano, 2001).

The function of serotonin in ASD has been investigated by means of biomarker, neuroimaging and genetic approaches (Scott and Deneris, 2005). An important investigation by positron emission tomography (PET) shows that the normal brain developmental peak of 5-HT synthesis cannot be observed in children with autism (Chandana *et al.*, 2005; Chugani *et al.*, 1999).

5-HT has been shown to reside in platelets and is best measured in a whole blood assay. One of the most consistent biological findings related to autism is elevated whole blood 5-HT levels found in about 1/3 of cases, which may be connected to cellular immune abnormalities found in autism, as 5-HT display immunoregulatory effects primarily via 5-HT_{1A}, 5-HT₂ and 5-HT₃ receptors located on lymphocytes and monocytes/macrophages (Burgess *et al.*, 2006). Besides hyperserotonemia, the binding of 5-HT₂ receptors seems to be decreased in platelets or whole blood (Cook *et al.*, 1993) and in the cerebral cortex of individuals with autism (Murphy *et al.*, 2006).

Polymorphisms in the promoter region of the serotonin transporter gene SLC6A4 have also been reported to be associated with autism and cortical gray matter volume (Pardo and Eberhart, 2007). The gene ITGB3 has been suggested as a regulator of serotonin levels in autism based on genetic association studies (Weiss *et al.*, 2006).

2.1.2 Dopaminergic system

Dopamine (DA) is a catecholamine synthesized from the essential amino acid tyrosine. Once ingested, tyrosine is hydroxylated (by tyrosine hydroxylase) into L-dihydroxyphenylalanine (L-DOPA), which is then converted into dopamine via the enzyme DOPA decarboxylase.

Most DA-containing neurons lie in the midbrain. In particular, three important DA systems project from the *substantia nigra* and the ventral tegmental area. The dopaminergic system modulates a wide range of behaviors and functions, including cognition, motor function, brain-stimulation reward mechanisms, eating and drinking behaviors, sexual behavior, neuroendocrine regulation, and selective attention (Lam *et al.*, 2006).

The role of DA in autism begins with the observation that some DA blockers (i.e., antipsychotics), appear to be effective in treating some aspects of autism. Specifically, the antipsychotics supposedly to decrease hyperactivity, stereotypies, aggression, and self-injury (Young *et al.*, 1982). In addition, animal research has shown that stereotypies and hyperactivity can be induced by increasing dopaminergic functioning. These observations suggested that dopaminergic neurons could be overactive in autism, which led to studies of DA function. These studies have been performed using several methods, including blood and urine measurements of DA and its major metabolite, and measurements of this metabolite in CSF (Lam *et al.*, 2006).

The investigations of DA transporter binding have shown a significant and local increase of function in the medial region of the orbitofrontal cortex in patients with autism (Nakamura *et al.*, 2010). PET studies showed increased striatal dopamine D₂ receptor binding in children with autism confirming the over functioning in the dopaminergic system (Fernell *et al.*, 1997). Also, there are evidences pointing increased dopamine synthesis and storage in the striatum and frontal cortex of adults with Asperger syndrome (Nieminen-von Wendt *et al.*, 2004). The orbitofrontal cortex is a key structure in the network underlying emotional regulation. Dysfunction in the orbitofrontal-limbic circuit may be associated with behaviors in autism, such as impulsivity, difficulties in changing the focus of interest and aggressive behavior (Nakamura *et al.*, 2010).

2.1.3 Cholinergic system

Acetylcholine (ACh) is a simple molecule synthesized from choline and acetyl-CoA through the action of choline acetyltransferase and is the neurotransmitter found at the neuromuscular junction, in the autonomic nervous system ganglia and at multiple sites in the CNS (Fagerlund and Eriksson, 2009). There are two kinds of ACh receptors: nicotinic and muscarinic. Both are found in the brain, although muscarinic receptors are more prevalent.

The role of acetylcholine in ASD has been investigated due to neuropathological deficits found in cholinergic neurons located in the basal forebrain of individuals with autism (Bauman & Kemper, 1994), suggesting that a disruption in this system could be linked to the cognitive deficits that often accompany autism (e.g., problems with attention, learning) (Lam *et al.*, 2006).

2.1.4 Catecholaminergic system

Noradrenaline (NA) is a catecholamine that is synthesized from DA through the action of the enzyme DA beta-hydroxylase. Nearly every region of the brain receives input from noradrenergic neurons (Lam *et al.*, 2006). The neuronal projections from *locus coeruleus* are distributed widely throughout the brain, and play a critical role in attention, filtering of irrelevant stimuli, stress response, anxiety, and memory (Harris and Fitzgerald, 1991).

Since many of these functions are impaired in individuals with autism, researchers have investigated whether noradrenergic system shows alterations. Recent studies of people with autism have demonstrated variants at two polymorphic sites of the β_2 -adrenergic receptor (ADRB2) leading to increased activity which could result in increased risk of autism (Cheslack-Postava *et al.*, 2007).

Noradrenergic activity has been assessed in autism via the measurement of NA and its central and/or peripheral metabolites in the blood, urine, and CSF. Noradrenergic function can be measured in the blood as NA itself, and as its principal central metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG). Unlike some of the other neurotransmitter systems, central and peripheral noradrenergic systems are tightly coupled with blood and CSF concentrations being highly correlated (Lam *et al.*, 2006).

2.1.5 Opioid system

Opioid receptors are G protein-coupled receptors, characterized by 7 transmembrane domains, and are located in the periphery and in all areas of the CNS. These receptors are known to be involved in integrating information about pain in the following areas: the brainstem, the medial thalamus, the spinal cord, the hypothalamus, and the limbic system. They are termed μ (mu), κ (kappa), and δ (delta) receptors. Morphine is considered the prototypical μ -agonist.

There is an “opioid hypothesis” suggesting that childhood autism may result from excessive brain opioid activity during the neonatal period which may constitutionally inhibit social motivation, yielding autistic isolation and aloofness (Sahley and Panksepp, 1987). Interestingly, some children with autism seem to feel less pain when compared with typically developed children. The hypothesis of excessive brain opioid activity is based on a similarity between autistic symptomatology and abnormal behavior induced in young animals by injections of exogenous opioids and the therapeutic effects of the long lasting opioid receptor blocking agent naltrexone in autism. Naltrexone is a Food and Drug Administration (FDA)-approved drug used as an opiate antagonist for treating opiate drug and alcohol addiction since the 1970's. It is a competitive antagonist of opioid receptors OPRM1, OPRD1 and OPRK1 and was used in children with autism in cases of hyperactivity (Desjardins *et al.*, 2009).

2.1.6 Aminoacid-neurotransmitter system

The activation of specific GABA and glutamate receptors during cell migration is necessary to the regulation of radial and tangential migrations (Manent and Represa, 2007) and an imbalance in this system can be involved in several brain pathologies. There is increasing evidence to suggesting a role for the opioid system in the control of pathophysiology of neurological disorders (Alzheimer's, Parkinson's, and Huntington's diseases, spinal cord injury, epilepsy, hypoxia, and autism) (Nandhu *et al.*, 2010).

Recent studies have pointed to abnormalities in glutamate and GABA neurotransmission in ASD, e.g. mutations in glutamate receptor genes *GRIN2A* and *GRIK2* and multiple GABA receptor genes (Webb, 2010). Therefore, additional studies are necessary to better understand glutamate metabolism in ASD.

From the translational point of view, the fact that ASD patients are up to twenty times more prone to have epilepsy, added to the abovementioned information, can let us suppose that the possible relationship between autism and epilepsy can be explained, at least in part, as a consequence from the imbalance between GABA and glutamate functioning.

2.1.7 Hormone-melatonin system

The discovery of melatonin in 1958 (Alberti, 1958) heralded a new field of research in reproductive physiology. Melatonin is produced in the dark by the pineal gland and is a key regulator of circadian and seasonal rhythms. A low melatonin level has been reported in individuals with ASD caused by a primary deficit in N-acetylserotonin O-methyltransferase (ASMT) (Melke *et al.*, 2008), an enzyme that catalyzes the final reaction in melatonin biosynthesis.

Melatonin is metabolized to 6-hydroxy-melatonin in the liver and the main metabolite excreted is 6-sulphatoxy-melatonin. Isolated measurements of melatonin are difficult to interpret given its circadian secretion. However urinary excretion of 6-sulphatoxy-melatonin may be helpful in studying pineal function.

3. Behavioral symptoms and psychopharmacotherapy on ASD

The qualitative deficits in the social interaction of children with autism may manifest themselves as social isolation and/or inappropriate social behavior characterized by poor eye contact, a difficulty to participate in group activities, affective indifference or inappropriate manifestation of affection or a lack of social or emotional empathy (Gadia *et al.*, 2004). Children with Asperger disorder may also possibly not have any kind of problems in eye contact, but they may have some social inadequacy, particularly due to their difficulties with understanding the metaphors, the jokes and some social rules and behaviors. There is no available drug for improving the social abilities of ASD patients (Rotta and Riesgo, 2005).

The difficulties in communication occur in varying degrees in verbal as well as the non verbal ability to share information. Some children do not develop any kind of communication skills. Others speak an immature language characterized by abnormal prosody, inappropriate intonation, jargon, echolalia, the reversal of pronoun, etc. Those who maintain adequate capacity of expression may have the inability to initiate or continue a conversation appropriately. On the other hand, children with Asperger disorder may not have clear difficulties in communication. Their language may actually be characterized by a particularly correct speech. There is no available drug designed for improving the capacity of communication capacity in ASD patients. The best treatment for this problem is provided by speech therapy (Rotta and Riesgo, 2005).

The repetitive and stereotyped patterns of behavior, characteristic of autism include resistance to any sort of changes, the insistence on certain routines, the excessive attachment to objects and the fascination with the movement of parts, such as wheels or propellers.

Children with autism may be more interested in objects rather than people. Although some children seem to play, they may be more concerned in aligning, handle or throw away toys than use them into their symbolic purpose. The motor and verbal stereotyped pattern of behavior may also be observed in certain activities such as clapping hands repeatedly, circling, repeating certain words, phrases, jingles or even complete songs. If these stereotyped and repetitive patterns of behavior are part of an anxiety disorder, maybe they can ameliorate with anti-anxiety medications (Gadia *et al.*, 2004).

From the clinical point of view, some of these above mentioned behavioral symptoms may also occur in children with mental disability without autism, and this is a recurrent problem. Additionally, patient with autism may have varied degrees of mental disability ranging from no impact in the cognitive performance, that may occur in Asperger disorder, to the

opposite side of the spectrum, characterized by of moderate mental disability that usually occur in the classic form of autism. This overlay of diagnostics, autism versus mental disability, albeit sometimes partial, can create difficulties to clinicians.

Fortunately, there are some clinical instruments that could help in distinguishing between autism and mental disability without autism, such as the Autism Screening Questionnaire (ASQ). The ASQ is useful both in the clinical practice as well as from the research point of view and its translation and validation is already available for different languages and countries (Sato *et al.*, 2009).

During routine clinical practice, the ideal situation would be to add the DSM-IV-TR (APA, 2002) criteria with the so-called “handmade diagnosis”, which means the personal experience prudently combined with the officially adopted parameters. Once the diagnosis is confirmed, there is inaccuracy in measuring the autism behavior symptom’s intensity. For sure, it could be easier to establish, from the clinical point of view, when compared and interconnected with the research approach.

Frequency and intensity of behavioral and psychological symptoms could be easily accessed by the physician through his making use of previous experience. However,, the same symptoms rating could be somewhat more difficult from the research perspective. One of the most useful clinical instruments for this purpose is the CARS (Childhood Autism Rating Scale), that already was translated and validated in several languages and countries (Pereira *et al.*, 2008).

In addition to the DSM-IV-TR criteria, there are other clinical findings that are frequently observed. These findings are not listed in the commonly used guidelines for autism diagnosis. For example, children with autism may have hypersensitivity to certain sounds or noises, such as a kitchen mixer, a jackhammer or fireworks. These noises can be extremely uncomfortable, leading children to covering ears with their hands and sometimes to screaming (Gomes *et al.*, 2004). Other findings not listed in the official autism criteria of autism includes: a) children with autism may keep walking on his toes for more time when compared with children with typical development; b) children with autism may have a higher pain threshold in comparison with people with typical development; c) children with autism may feel uncomfortable with the usual pediatric clinical maneuvers, such as touching or auscultation procedures; d) patients with autism may demonstrate a fear for people approaching, etc.

Sleep disorders can be identified in young children with ASD, occasionally even before the diagnosis confirmation. This symptom can be devastating to parents due its intensity. The mean age of ASD patients with sleep disorders is usually between one and three years of age, but disorders may also be identified earlier. From the research perspective, sleep disorders in these patients could be one interesting field. Sleep disorders, if not improving response to a non-medical approach, may be treated with Melatonin or with benzodiazepines.

Usually, one of the first behavioral symptoms in patients with ASD is language delay. In this case, it is mandatory to rule out hearing impairment before autism is diagnosed. In this group of patients, a normal global development it is not uncommon until about 18 or 24 months of age, followed by loss of language and social interaction. This diminution in social and communications skills may begin with poor eye contact, followed by a clear disinterest in people as opposed to objects. In this sense, it is important to monitor the development of these skills in children that show autistic symptoms, especially throughout the period when a child is between one and three years of age (Rotta and Riesgo, 2005).

When it comes to cerebral hemispheres specialization during childhood, language seems to be one of the most powerful inducers. In addition, language can also be useful in differentiating between autism and Asperger disorder. By definition, language can be unremarkable in Asperger's patients, while language is usually absent in the severe forms of autism. Actually, patients with Asperger have preserved both language and cognition, especially the latter. Sometimes, patients with Asperger present a peculiar type of pedantic and extremely correct language, leading the parents of these children to be proud of their adult-like type of expressive language (Rotta and Riesgo, 2005).

In certain cases, clinicians may have difficulties with distinguishing between these two diagnostics as the following questions arise. Is this a case of "high functioning autism" or an Asperger disease? Actually, from the clinical perspective, it is sometimes impossible to differentiate between these situations. However, it is somewhat easier to differentiate the pure form of autism from Asperger disease. In the clinical practice a simple rule exists which states that children with autism usually "live in their own world". By the other side, patients with Asperger in general "live in our world in their own way".

In terms of clinical diagnosis, to date we have no biological marker. Consequently, previous clinical experience is needed in order to assure a safe approach. Furthermore, some patients may have so many associated behavioral alterations that the core diagnosis, as for example ASD, could be delayed or may not even be taken into consideration.

For instance, some children's behavior may show up to five alterations associated with ASD. The initial clinical diagnosis may be ADHD (Attention-Deficit/Hyperactive Disorder), and/or Bipolar Disorder, Anxiety Disorder, Depressive Disorder, Tics Disorder, etc. During the follow-up inevitably it will be clear that the principal diagnosis is actually ASD, and all the other diagnostics are just ASD associated features.

From the clinical perspective, one of the most prevalent behavioral symptoms is the pure form of hyperactivity, especially in the mentally disabled patients. It must be kept in mind that any type of environmental change can provoke this specific symptom and/or can deteriorate other associated behavioral manifestations. The approach of agitation can include both behavioral and/or psychopharmacological treatment. In these cases, when patient are extremely agitated and/or disorganized, the use of antipsychotics is one of the best choices. Unfortunately, there is a paucity of evidence-based studies of the efficacy of the antipsychotic drugs in treating autism.

The co-occurrence of ADHD and ASD is no rarity and, from the psychopharmacological perspective, it is crucial to define which one of the two is the principal cause of impairment, because the wrong choice of medication can deteriorate the patient's behavior. For example, stimulants drugs can provoke an increase in hyperactivity in ASD patients with concomitant ADHD. Long action stimulants in particular may have this effect.

In the clinical practice, at present, risperidone and aripiprazole are the better choice to ASD associated agitation. This, antipsychotic drugs are already approved by FDA for the treatment of childhood autism. Other medications related to the psychopharmacotherapy in ASD are described in Table 1. Initially, the main dosage of risperidone was considerably high, reaching up to 6mg/day. Today, clinicians are aware that, if there is no response to 3mg/day, probably no benefit will be obtained with higher doses of risperidone.

Further, in clinical practice, coincidentally this specific daily dose regimen of 3mg/day of risperidone seems to be the threshold dose for inducing seizure in susceptible children. In Child Neurology, we frequently have to deal with patients with epilepsy. The mean

prevalence of epilepsy in non-autistic children is about 1%. In comparison, the mean prevalence of epilepsy in children with ASD children reaches 20%, a rate that is clearly of both clinical and statistical significance. The possible relationship between ASD and epilepsy is one of the coming and intriguing challenges to be studied. This relationship is one of the “state of art” issues in autism, both from the clinical point of view as well as from the research perspective.

A further frequent symptom of behavior in clinical practice with ASD patients is the instability of the baseline mood. Children’s mood normally changes faster than with adults’ mood. Increasing our knowledge of mood regulation in childhood specifically, it is important to remember that mood changes in ASD patients occur more rapidly when compared with typically developed children. This kind of symptom may occur both in the mentally disabled and in the Asperger group of patients. If one ASD patient also has epilepsy, the addition of sodium divalproate can both protect against seizures and at the same time improve the mood control. Dealing with patients with a refractory humor deregulation is not unlikely. The use of lithium still is the best choice in some cases of severe mood oscillations.

Although not being an unchangeable rule, from the clinical point of view, the intensity of behavioral symptoms is clearly related to both with gender and cognition. The usual observation is that behavioral symptoms are more prominent in girls than in boys with autism. Additionally, we frequently see that the intensity of these symptoms is inversely related to cognition.

One of the principal prognostic factors in the clinical approach is cognition. In this sense, the main problem is how to evaluate the cognition in non-verbal ASD patients. Our group is now conducting a research in order to find the most useful clinical tool to evaluate cognition in non-verbal ASD patients. One of the possibilities is to attempt to use the same instruments used in another group of patients, such as those children without autism who are candidates to auditory prosthesis.

From the clinical perspective, feeding problems are frequently identified. Usually ASD patients have difficulties with changing their alimentation. For example, they are capable of repeating the same menu week after week without any complaint. Weight gain can also occur in autism, and sometimes it is difficult to identify its etiology. It can be a result of a stereotyped and exaggerated consumption and/or it can also be a consequence of the use of antipsychotic drugs. Further, children with autism may present several types of food allergy.

Additional useful clinical information could be how different behavioral symptoms change during the lifetime of ASD patients. First of all, obviously there is an ontogenetic evolution of each one of the behavioral manifestations in normally developed children. In other words, it is crucial to know how behavior can normally change during childhood neuropsychological development. For instance, hyperactivity would be a “normal” finding until children reach the age of five years because of the normal brain maturation that occurs from the occipital lobe towards to the frontal cerebral lobe.

In terms of gender versus behavior, usually hyperactivity is more prevalent in normal boys when compared with normal girls. Humor control, language skills and social competence usually improve in normally developed children as time passes. Normal girls tend to improve faster their language skills and their social competence when compared with normal boys.

	Selected primary publications	First publication in ASD	Clinical information
Psychostimulants			Used in child neurology and psychiatry to treat attention deficit disorder, narcolepsy, and some forms of refractory depression, when used combined with antidepressants
Methylphenidate	(Barison and Massignan, 1956)	(Hoshino <i>et al.</i> , 1977)	
Pemoline	(Lucas and Knowles, 1963)	(King <i>et al.</i> , 1993)	
Buspirone	(Goldberg, 1979)	(Realmuto <i>et al.</i> , 1989)	
Antidepressants-tricyclic			Indicated to treat depression and/or associated anxiety. Imipramine may be also useful to treat nocturnal enuresis and/or associated sleep disorder
Imipramine	(Lehmann <i>et al.</i> , 1958)	(Campbell <i>et al.</i> , 1971)	
Clomipramine	(Volmat <i>et al.</i> , 1968)	(Brodkin <i>et al.</i> , 1997)	
Desipramine	(Olesen, 1963)	(Gordon <i>et al.</i> , 1992)	
Antidepressants-SSRI			The selective serotonin reuptake inhibitors (SSRI), are the most commonly prescribed antidepressants, relatively safe and generally cause fewer side effects than other types of antidepressants. They may be also be useful in the whole associated spectrum of anxiety symptoms
Paroxetine	(Lassen, 1978)	(Posey <i>et al.</i> , 1999)	
Fluoxetine	(Fuller <i>et al.</i> , 1974)	(Mehlinger <i>et al.</i> , 1990)	
Fluvoxamine	(Saletu <i>et al.</i> , 1977)	(McDougale <i>et al.</i> , 1990)	
Escitalopram	(Hyttel, 1977)	(Anderson <i>et al.</i> , 2002)	Antidepressant drug.
Antipsychotics (t, typical; a, atypical)			Antipsychotic drugs are used to treat psychosis and other mental and emotional conditions. In ASD they are frequently used to treat aggressiveness and/or agitation. In patients with mental disability and ADHD (Attention Deficit/Hyperactivity Disorder) risperidone may be more efficient when compared with methylphenidate
Haloperidol ^t	(Divry <i>et al.</i> , 1959)	(Faretra <i>et al.</i> , 1970)	
Risperidone ^a	(Faretra <i>et al.</i> , 1970)	(Purdon <i>et al.</i> , 1994)	
Olanzapine ^a	(Fuller and Snoddy, 1992)	(Malek-Ahmadi and Simonds, 1998)	
Quetiapine ^a	(Pullen <i>et al.</i> , 1992)	(Martin <i>et al.</i> , 1999)	
Ziprasidone ^a	(Bench <i>et al.</i> , 1993)	(Alessi, 2003)	
Aripiprazole ^a	(Kikuchi <i>et al.</i> , 1995)	(Rugino and Janvier, 2005)	
Clozapine ^a	(Ueki <i>et al.</i> , 1970)	(Atlas and Gerbino-Rosen, 1995)	
Antiepileptic (anticonvulsant)			There are at least two clinical reasons for their use: the frequent co-occurrence of epilepsy in ASD patients and/or the also frequent co-occurrence of affective disorders, especially mood disorders.
Valproic acid	(Lance and Anthony, 1975)	(Sovner, 1989)	
Carbamazepine	(Donner and Frisk, 1965)	(Gadow, 1992)	
Topiramate	(Maryanoff <i>et al.</i> , 1987)	(Pellock, 2004)	
Antiopioid			Naltrexone is an opioid

Naltrexone	(Martin <i>et al.</i> , 1973)	(Sahley and Panksepp, 1987)	receptor antagonist with higher affinity for mu receptors than other opioid receptor subtypes. Nowadays, this drug is not used in ASD patients.
Mood stabilizer			
Lithium	(Andreani, 1957)	(Campbell, 1975)	Lithium, discovered in 1817, was noticed to have mood stabilizing properties in the late 1800s. It is an extremely useful drug in ASD
Hormones			
Melatonin	(Alberti, 1958)	(Jan and O'Donnell, 1996)	Melatonin is a hormone that plays a key role in regulating circadian rhythms. Their use in treating sleep disorders resulted in weaker clinical responses than expected.

Table 1. **Psychopharmacotherapy in ASD.** Pharmacotherapy options in ASD based upon the following target symptom clusters: inattention/hyperactivity, interfering repetitive and stereotypic behavior, aggression and self-injurious behavior, humor oscillations, anxiety and the core social impairment of autism.

Analyzing changes in ASD patient’s symptoms during lifetime, it is clear that hyperactivity is more prevalent in boys than in girls and it is know that hyperactivity can decrease as time passes (Guan *et al.*, 2010). Although aggressiveness itself usually decreases with childhood development, we know that the consequences of aggressiveness can worsen with increasing age of patients with autism owing to the increase of muscle strength.

Anxiety can increase in stress situations and also can worsen during their lifetime in patients with ASD, especially in children with a less affected cognitive function, like patients with Asperger disorder. In this specific group of patients, the most frequent behavioral symptoms are depression and/or anxiety.

As time passes, communication tends to improve in children that are and/or became able to communicate. This improve in communication skills is clearly more prominent in the patients with Asperger disorder when comparing with other ASD patients.

The restricted repertoire of activities and interests does not change in intensity as time passes, but certainly the types of interests change. Interestingly, the social deficits do not improve significantly throughout patient’s lives.

3.1 Historical landmarks of psychopharmacotherapy

In 1949, the Australian psychiatrist John Cade showed that lithium calmed maniac patients, and Mogens Schou in Denmark confirmed Cade's findings in a double-blind study in 1954. About 20 years later, in 1970, the FDA finally approved lithium to treat patients with manic-depressive illness. The first publications related to lithium treatment and ASD were in 1975.

The first antipsychotic drug, chlorpromazine, was discovered by the French pharmacologist Henri Laborit. In 1944, he noted the antihistamine activity of chlorpromazine, as well as other compounds and started to use these drugs in a pharmacological combination to prevent surgical shock. However, he curiously observed that chlorpromazine, besides

preventing surgical shock, also induced calmness in patients before the operation. Laborit had the bright idea of trying the antipsychotic on schizophrenics and found that it stopped their symptoms. In consequence, he had unintentionally discovered the first antipsychotic drug.

In the same year, methylphenidate was synthesized by Ciba chemist Leandro Panizzon, who named the compound Ritalin™ because his wife Margherite (nicknamed Rita) used to take this drug as a stimulant before playing tennis.

The first effective pharmacologic treatment for depression was discovered by the clinician Roland Kuhn in 1956. This drug was the tricyclic antidepressant imipramine. Kuhn published the results of his observations in the *Schweizerische Medizinische Wochenschrift* (Swiss Weekly Medical Journal) in 1957. Heinz Lehmann, Clinical Director at Douglas Hospital, Montreal, Canada, treated depressed with equally good results. Lehmann and two co-workers published their results in the *Canadian Medical Association Journal* in 1958 (Lehmann *et al.*, 1958).

The typical antipsychotic drug, haloperidol, was discovered by Paul Janssen and was developed in 1957 by the Belgian company Janssen Pharmaceutica. It was approved by the by the U.S. Food and Drug Administration (FDA) in April 12, 1967.

The work which eventually led to the discovery of fluoxetine began at Eli Lilly and Company in 1970 with collaboration of Bryan Molloy and Robert Rathbun. After 20 years, the first papers related to the fluoxetine treatment of ASD patients were published.

In 1988, the American psychiatrist John Kane demonstrated that clozapine achieved a good response in schizophrenic patients refractory to treatment with other antipsychotic drugs; the FDA approves the drug in 1989.

The atypical antipsychotic risperidone was developed by Janssen-Cilag, first released in 1994, approved by the FDA in the same year to use in adult psychiatric patients and approved for treating ASD only two years later. In the brain, risperidone binds multiple neurotransmitter receptors, having a strong affinity to the serotonin 2A (5-HT_{2A}) and dopamine D₂ receptors, and a good affinity for the α -1 and α -2C adrenergic receptors and for the serotonin receptors 6 and 7 (5-HT₆ and 5-HT₇).

4. Antipsychotic side effects in ASD

The first generation of antipsychotics, today called typical antipsychotics, functions by blocking the effects of dopamine, controlling hallucinations and delusions. Because of this primary function, this medication is also named neuroleptic which means “seizing the neuron”, with high efficiency to some symptoms of autism (lack in social behavior, stereotypical behavior) and in behavioral impairments that may be associated with autism (aggressive behavior, hyperactivity). However, the use of typical antipsychotics, like haloperidol, can induce extrapyramidal side effects, which often lead to persistent tardive dyskinesia, limiting the long term use of these drugs.

Atypical antipsychotics have been prescribed for ASD symptoms as they have lower frequency and intensity of side effects compared with the typical one. However, an important concern related to the use of atypical antipsychotics is the inducement of endocrine and metabolic side-effects (weight gain, obesity, and related metabolic abnormalities such as hyperglycemia and dyslipidemia). Obesity is a risk to the development of metabolic syndrome and may result in a high-risk state for future cardiovascular morbidity and mortality in adult age (Goeb *et al.*, 2010).

The atypical antipsychotics risperidone, olanzapine, quetiapine and ziprazidone are most commonly prescribed for ASD. However, only two atypical antipsychotics have been approved by the FDA for treating irritability in autistic children. Risperidone was approved in late 2006, followed by aripiprazole in 2009.

5. Non-neuronal targets of Risperidone

All complex nervous systems consist of two main cell types, neurons and glial cells. In the past 20 years evidence has accumulated that supports the existence of bidirectional communication between glial cells and neurons (Froes *et al.*, 1999; Gomes *et al.*, 2001). Based on this context, it is important to consider that if the functional unit of the brain is not only orchestrated by neurons but rather by the neuron-glial complex, consequently must assume that both neuronal and glial cells are involved in neural diseases.

There are three main types of glial cell populations in the CNS, termed *astrocytes* a diverse population of cells with numerous functions; *oligodendrocytes*, the myelinating cells of the CNS (McLaurin and Yong, 1995) and *microglia*, considered the immune cells of the CNS, responding to any kind of pathology with a reaction termed microglial activation (Hanisch and Kettenmann, 2007).

The idea that astrocytes, like neurons, might take up diverse roles in the development and function of the CNS has slowly been gaining recognition (Westergaard *et al.*, 1995). Nowadays, a considerable amount of evidence has revealed a more active role of astrocytes in the physiology of the CNS than previously believed (Araque *et al.*, 2001). It has been found that these cells play a crucial role in maintaining normal brain physiology during development, releasing molecules important for neuronal survival and dendrite formation. Also, astrocytes have been emerging as key modulators of neuronal excitability, synaptic transmission (Perea and Araque, 2009) and blood-brain barrier (Wang and Bordey, 2008). Common astrocytic reactions that occur in the pathological states are cellular swelling, hypertrophy-hyperplasia (astrogliosis) and proliferation (astrocytosis).

Morphology of astrocytes varies depending on regional localization and shape changes potentially may influence neuronal activity and injury via ion channels, neurotransmitter receptors and transporters on their processes (Theodosis *et al.*, 2008). In this context, we have investigated the effect of risperidone on astroglial cells, evaluating morphology, membrane integrity, viability, secretion of S100B, a neurotrophic astrocyte-derived protein and glutamate metabolism (glutamate uptake, glutamine synthetase activity and glutathione synthesis).

We demonstrate for the first time that risperidone was able to modulate cell morphology and glial adhesion (Quincozes-Santos *et al.*, 2008), contributing to the proposal that glial cells also are targets of antipsychotics. In addition, risperidone also increased S100B secretion by astroglial cells. S100B is a calcium-binding protein involved in the regulation of cytoskeleton and the proliferation of astrocytes. Beyond its intracellular role, S100B, depending on its concentration, works as a cytokine for neighboring cells (astrocytes, neurons, and microglia) and is able to protect hippocampal neurons against glutamate toxicity. Extending these findings to brain plasticity in ASD, it would be possible to conceive that risperidone stimulates S100B secretion which in turn can stimulate neuronal activity in patients.

Astrocytes respond to neuronal activity via ion channels, neurotransmitter receptors, and transporters on their processes, a plasticity that has important functional consequences since

it modifies neurotransmission. We described a significant increase in glutamate uptake and in glutamine synthetase (GS) activity by astroglial cells in the presence of risperidone (Quincozes-Santos *et al.*, 2010).

Astrocytes are the only cells in the brain that have the important ability to convert glutamate into glutamine via GS. Glutamine, in turn, is taken up by neurons and used for the synthesis of glutamate (and then GABA, in GABAergic neurons). However, glutamate has another important destination in astrocytes, particularly GSH (glutathione) synthesis (Dringen *et al.*, 1999). Glutamate serves as a substrate per se for GSH synthesis and as a moiety for exchange by cysteine, another substrate for GSH synthesis. Moreover, concomitantly with the increase in glutamate uptake and GS activity, an increase in the content of GSH was seen, reinforcing the antioxidant activity of astroglial cells mediated by risperidone. In this context, astrocyte clearance of glutamate from the synaptic cleft is an important aspect to be considered in autism, from both the physiopathologic and the pharmacologic point of view.

As evidence emerging indicates that signaling between perisynaptic astrocytes and neurons at the tripartite synapse display important roles when neural circuits are formed and refined (Araque *et al.*, 1999), we propose an integrative model of the tripartite synapse modulated by this antipsychotic during treatment *in vivo* (Figure 2).

Most studies about pathological abnormalities in brains of patients with autism report differences in neuronal plasticity and migration patterns rather than alterations in glial cells (Minshew and Williams, 2007; Minshew and Keller, 2010). Also, these cells have many functions that could be relevant to abnormalities described in psychiatric disorders such as schizophrenia (Rothermundt *et al.*, 2004). However, the majority of studies about cellular mechanisms of antipsychotic drug treatment focus on neuronal effects. Therefore, a possible role of astrocytes has been largely neglected in ASD research.

6. Clinical recommendations of antipsychotics in ASD

The following clinical recommendations can be made after twenty years of clinical practice in Child Neurology. During this time, more than one thousand of ASD patients were seen, if children seen in private practice are added to those treated in our Child Neurology Residence Program.

First of all, it is important to remember that until now ASD encompasses five different clinical diagnostic categories. These diagnostic categories will change with the new DSM-V classification. Even the widely used expression “ASD” may disappear. Even after the changes of the new classification, what is now called ASD will remain as a heterogeneous group both in terms of behavioral symptoms as well as in terms of medical diagnosis.

In other words, before planning a psychopharmacological treatment in ASD, it is important to be sure that the diagnosis is correct. We must remember that this type of diagnosis can be catastrophic to parents and consequently an incorrect diagnosis would be even worse. This is probably one of the most important clinical recommendations. Before medications usage, make a double check in every diagnosis of this group of children.

Another important remark is that each one of the five currently adopted clinical diagnostics, considered individually, also has its own behavioral heterogeneity, when taken individually. For instance, one particular case of autism may initially present as a confused mix of different behavioral complaints that could hide the main diagnosis.

There is no single medication that can be successfully used in ASD as a whole. The guidelines recommend that monotherapy would be the best choice, but often this is difficult

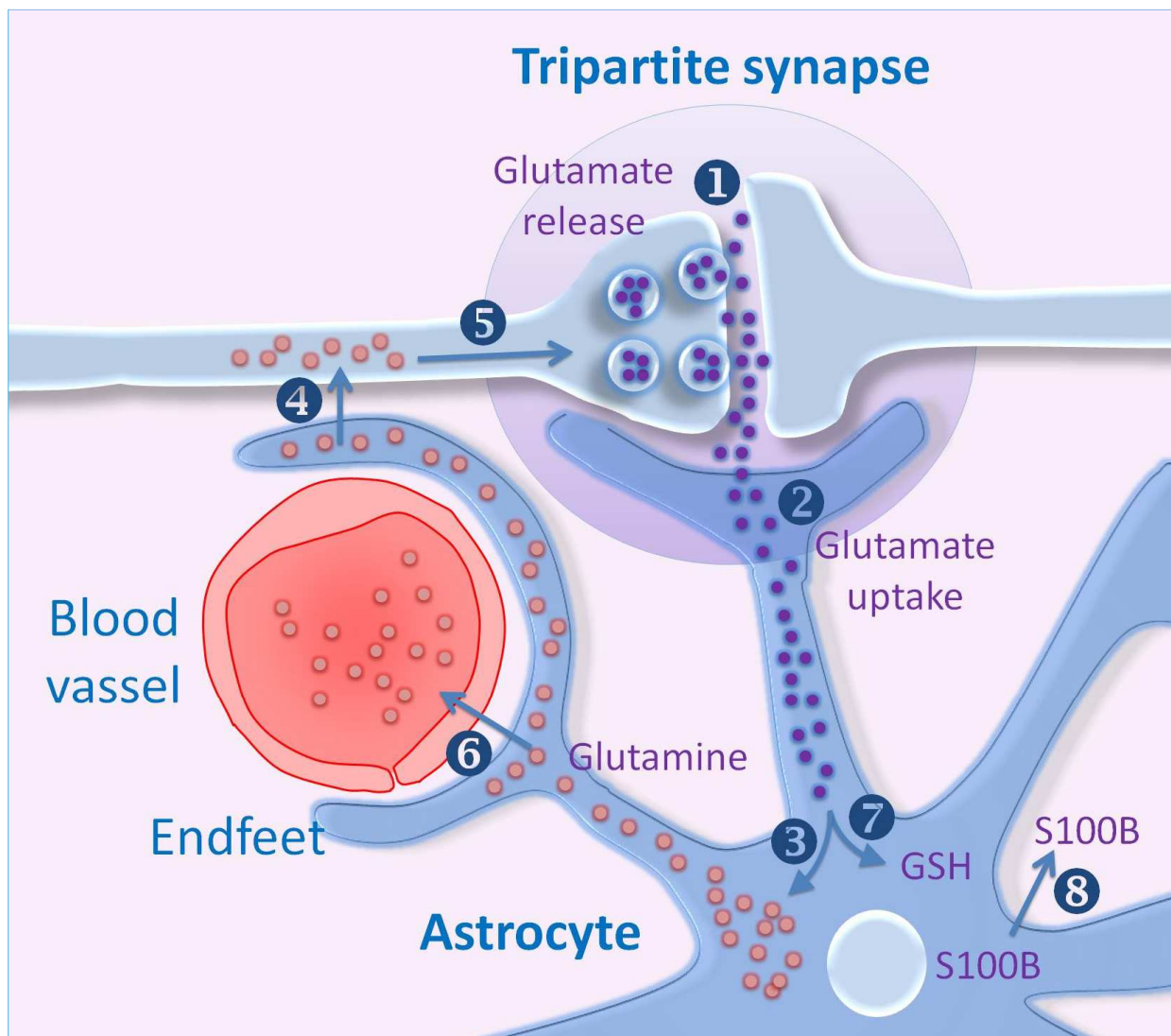


Fig. 2. Hypothesis for the influence of Risperidone on tripartite synapse supported by its influence on astroglial cell culture and on hippocampal slices. After the release of glutamate at the synaptic cleft (1), risperidone improves glutamate uptake by astrocytes (2); stimulates the enzyme GS to convert glutamate into glutamine (3), which in turn is taken up by neurons (4), followed by resynthesis of glutamate (5) and/or transported to the blood (6). Additionally, risperidone is able to stimulate the synthesis of another important fate of glutamate in astrocytes, the tripeptide L-glutamyl-L-cysteinyl-glycine or glutathione (GSH) (7), and to promote the secretion of the trophic factor S100B (8). This hypothesis was proposed considering the direct effect of risperidone on astroglial cells (numbers 2, 3, 7 and 8).

or even impossible to do in the real clinical world. Although there is no ASD-specific medication, the psychopharmacologic treatment can decrease the “noise” surrounding autism, as well as facilitate the non pharmacological treatments. It is important to remember that the psychopharmacological approach is only one of the available treatments for ASD patients.

The first clinical recommendation is to identify as clearly as possible each one of the behavioral symptoms. It would be extremely useful to make a list of these behavioral targets. After making the list, it is important try to put these targets into a ranking of clinical

relevance, in order to choose which one of the behavioral symptoms is more prominent and/or requires prompt relief.

The second clinical recommendation is to decide if each one of the selected behavioral targets really will require psychopharmacological treatment. Obviously, this decision is somewhat more complicated and is not available in any guideline. This is the art included in clinical practice. The only safe way to make this decision is to use the previous experience. It would be helpful to discover whether a given behavioral symptom is more uncomfortable for parents or to the patient. For example, stereotyped and repetitive movements are frequently more unpleasant to parents than to the child, which can obtain a sort of relief of anxiety with these repetitive movements. In this case, no medication would be used. Instead the best recommendation would be try to find a use for the stereotyped movements.

If the given symptom really requires psychopharmacological treatment, the third clinical recommendation is to choose which would be the better medication. This appears problematic because of the paucity of good evidence based studies with regard to the efficacy of medications in the treatment of autism.

Different categories of drugs have been used to treat autism for years, despite the lack of proved efficacy of the majority of them. The following list of drugs that have been used in autism is obviously incomplete; antiepileptic drugs, mood stabilizers, antidepressants, anti-anxiety drugs, sleep inducers, stimulants, antipsychotics, etc.

Since there is no medication for autism itself, we must choose which of the undesirable behaviors could be ameliorated by antipsychotic medication. Of all of the symptoms presented by ASD patients, disrupted behavior and irritability probably are the best responders to antipsychotic drugs. It is important to mention that many of the drugs used in the psychopharmacological treatment in autism, including antipsychotics, can decrease the seizure threshold (Tuchman, 2009). Because of ASD children are almost twenty times more prone to have epilepsy when compared with a child who had a normal neurodevelopment, probably it would be safer to consider the usefulness of an electroencephalogram examination before prescribing psychoactive drugs. Also, before prescribing antipsychotic drugs, it is useful to obtain a baseline laboratory profile, which includes a complete blood count, evaluation of blood lipids and glucose, liver function as well as prolactin levels. It is also important to measure the weight and height as well as the blood pressure. It is also prudent to make a complete physical and neurological examination.

After prescribing antipsychotic drugs, it is necessary to monitor both the above mentioned measures, such as laboratorial findings as well as the clinical examination findings. In clinical practice, different antipsychotic drugs have been used, but only few of them still continue in the medical arsenal. To date, atypical antipsychotic drugs are preferred when compared with the typical antipsychotic drugs because of their relative safety in terms of side effects, especially neurologic impregnation.

In the past, haloperidol was the typical antipsychotic more frequently used in the treatment of children. The daily dose usually ranges between 1 to 2 mg. The most problematic side effect of haloperidol seems to be neurological side effects manifested by Parkinson-like symptoms, extrapyramidal signs and/or tardive dyskinesia.

Many of the available atypical antipsychotic drugs used in adult patients have also been used in children. The most frequently prescribed antipsychotics for ASD patients are risperidone, olanzapine, quetiapine, clozapine, ziprasidone and aripiprazole, however only two of them have been approved by the FDA for use in childhood autism. Risperidone was

the first atypical antipsychotic drug to be approved by the FDA, in 2006. The second drug of this group of medications was aripiprazole, which was approved in 2009. The usual daily dose of risperidone varies from 1 to 3 mg, and the usual daily dose of aripiprazole is up to 15 mg in children and adolescents. Aripiprazole seems to be better when compared with risperidone in terms of side effects, because as there is a relatively lower risk of metabolic side effects and/or weight gain.

7. Conclusions and future remarks

The first generation of antipsychotics (now called typical) has been used since the 1950s, and is dopamine-2 (D2) receptor antagonist. Nevertheless, the second generation, or atypical, has many clinical applications in neuropsychiatric practice (Schwartz and Stahl, 2011). Since the mid-1990's, it is clear that atypical antipsychotics are safer in regard to inducing fewer extrapyramidal symptoms and tardive dyskinesia.

At first sight, the bulk of neurochemical research in autism has been inconclusive. In addition, the high levels of use of many different psychotropic agents, often in combination, is concerning and is necessary to study the results of interactions of different types of medical and educational treatment for children with ASD.

As a result of our translational research in autism, we became enthusiasts of changing the traditional "neuronal neuropsychiatry" approach into the modern "neuroglial neuropsychiatry" concept. In our opinion, the first one is somewhat simplistic because is totally based only on the neurons activity, and the last one is indubitably the more comprehensive, because there is no way to deny the importance of glial cells working together with neurons in the neurobiology of development and behavior, coincidentally two of the most altered areas in ASD patients.

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Autism Spectrum Disorders - From Genes to Environment

Edited by Prof. Tim Williams

ISBN 978-953-307-558-7

Hard cover, 400 pages

Publisher InTech

Published online 06, September, 2011

Published in print edition September, 2011

Autism spectrum disorders are a major topic for research. The causes are now thought to be largely genetic although the genes involved are only slowly being traced. The effects of ASD are often devastating and families and schools have to adapt to provide the best for people with ASD to attain their potential. This book describes some of the interventions and modifications that can benefit people with ASD.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Carmem Gottfried and Rudimar Riesgo (2011). Antipsychotics in the Treatment of Autism, Autism Spectrum Disorders - From Genes to Environment, Prof. Tim Williams (Ed.), ISBN: 978-953-307-558-7, InTech, Available from: <http://www.intechopen.com/books/autism-spectrum-disorders-from-genes-to-environment/antipsychotics-in-the-treatment-of-autism>

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