Chapter 26

Clinical Approach in Autism: Management and Treatment

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Additional information is available at the end of the chapter

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1. Introduction

The terms Autism and ASD (Autism Spectrum Disorders) can be interchangeable in the clinical setting, and have been used to describe one of the most intriguing neurobehavioral syndromes, that include the so-called "triad of Wing": problems in communication, social skills, and restrict repertoire of interests. However, it is somewhat difficult to precisely define autism, because of the imprecise boundaries between different kinds of ASD as well as the fact that there is no biological marker to date (Gottfried and Riesgo 2011).

By definition, in autism the social deficits are characterized by lack of interest in spontaneously sharing feelings, different levels of communication deficits, difficulties in imaginative plays, restrictive repertoire of interests, non-functional routine fixations, as well as stereotypies and other motor alterations, such as flapping with hands, circular movements and others (Nikolov, Jonker, and Scahill 2006; Gadia, Tuchman, and Rotta 2004).

While the criteria of the DSM-V (Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition) are not yet published, we still have to use the "older version". According with the DSM–IV 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 (Association 2002).

Although it will change in the near future, the five current clinical ASD diagnosis admitted by DSM-IV-TR (Gadia et al., 2004) are: a) Autistic Disorder; b) Asperger Disorder (AD); c) Rett Disorder; d) Childhood Disintegrative Disorder; e) PDD-NOS (Pervasive Developmental Disorder – Not Otherwise Specified).

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According with DSM-IV-TR, and in agreement with previous epidemiological data, our group found that the most prevalent ASD is the PDD-NOS, followed by Autistic Disorder, and then by Asperger Disorder. Accordingly, the Rett Disorder and the Childhood Disintegrative Disorder for sure are less frequently seen in the clinical practice (Longo et al. 2009).

The increasing levels of prevalence in ASD probably is due to several reasons, such as the changes in diagnostic criteria, the high level of awareness, the underestimation of former data, the massive information exchange regarding ASD, the public strategies, etc. The first description of autism was made by Hans Asperger, in 1938. In 1943, when Leo Kanner described a sample with 11 children, autism was a rare condition affecting not more than 4 in 10.000 children (Kanner 1943).

However, childhood autism is much more frequent and is identified in at least one in each 100 children nowadays. For instance, a recent paper describes prevalence of 2.6% of ASD in children aging from seven to twelve years of age (Kim et al. 2011).

Autism and ASD certainly have different kinds of approaches. These neurobehavioral syndromes can be addressed, for example, both from the clinical and from the experimental field. To our knowledge, at least in the academic environment, the best approach could be the translational type because it made us able to rapidly build a bridge between the experimental and the clinical field (Gottfried and Riesgo 2011).

Obviously, the earlier results usually came from the experimental research for several reasons. In general, the time spent in each one experiment can be shorter compared to clinical research; the environmental variables can be in part controlled, etc. By the other side, clinical research can be more time consuming and potentially more complicated to be performed. There is no doubt that both approaches are not mutually exclusive. Actually they are complementary.

Strictly speaking from the clinical perspective in autism, we can divide the clinical approach into two basic and complementary issues. The first one is the general management, including the confirmation of the correct diagnosis, the determination of the intensity of the compromise, and the evaluation of intensity level of eventual core behavioral symptoms. The last one encompasses several treatment options, which includes psychopharmacotherapy and different types of non-medical treatments.

As the first cases of autism were described in the early 40's, now we have adults with ASD. That is the reason to keep in mind how ASD symptoms usually change during lifetime. As time pass, different symptoms change differently and it is crucial to clinicians to know these differences.

In this context, the present chapter aimed to review (i) the general management of ASD from the clinical perspective; (ii) the lifetime changes in ASD symptoms; and (iii) the evidence-based treatment options.

2. General management of ASD from the clinical perspective

The general management of ASD from the clinical perspective encompasses both interventions in the family/environment as well as interventions addressed to the patient. Ideally, after

http://dx.doi.org/10.5772/54784

diagnosis confirmation, the best initial approach could be done by an interdisciplinary team including professionals coming from medicine, psychology and social sciences.

Obviously, before initiating any kind of intervention, several steps must be done as follows. First of all, the final diagnosis must be confirmed by a careful anamnesis as well double-checked using the DSM-IV criteria as well as a reliable clinical instrument such as Autism Diagnosis Interview-Revised (ADI-R) (Becker et al. 2012). The ADI-R is frequently used as a gold standard instrument for publication purposes, but it is problematic in the clinical practice for several reasons, such as it can miss same ASD cases as well as it need at least two hours to be completed. Then, the intensity of the ASD could be defined both from the clinical perspective and by one instrument such as CARS (Pereira, Riesgo, and Wagner 2008). Another critical issue is to delimitate if there is any associated mental disability and its degree of intensity. As clinicians, we know the prognostic importance of an unaffected intelligence in ASD patients.

The second step includes the definition of the parent's doubts, fears, and degree of awareness. Usually, after diagnosis confirmation, parents became stressed. Not infrequently they go to internet in order to search every kind of available information regarding autism. Because some information coming from internet can be inaccurate, at this point, it is very important to clarify which are the evidence-based types of therapies to date.

The third step could be the delimitation of environmental variables that needs to be addressed, starting from the home and family. Neighborhood and school needs to be evaluated both in terms of potential stressors and also because they can facilitates choosing a given type of therapy on an individual basis.

The next step is done by the identification of the target behaviors needing treatment. After core symptoms definition in each case, the different professional specialties that need to be involved are selected. In general, the team includes a physician specialized in ASD patients as well as one speech therapist and others professionals arising from health care and/or education with experience in children with ASD.

3. How ASD symptoms change during lifetime

All professionals who treat children and adolescents, both coming from health care as well as from education must know how behaviors can normally change during the normal neuropsychological development. In other words: there is an ontogenetic evolution on each one of the behavioral manifestations in the normally developed children.

For example: in terms of gender versus behavior, usually hyperactivity is more prevalent in normal boys when compared with normal girls. The humor control, the language skills and the social competence usually improves in normally developed children as long as time passes. Usually, normal girls tend to improve faster their language skills and their social competence when compared with normal boys. This knowledge is crucial to identify how different behavioral symptoms change during lifetime in ASD patients.

When the issue is childhood autism symptoms, there are no major problems in terms of information, because of most of the available publications are directed to pediatric patients. As a consequence, adult ASD symptoms are less frequently accessed in the available literature.

Researchers had noted that the prevalence of adult ASD may be underestimating and most of these patients reach adulthood without any diagnosis or treatment. This is especially true to patients with Asperger. (Szatmari et al. 1995; Arora et al. 2011).

More recently, an increasing interest is observed in prevalence and clinical presentation of ASD in adults. The few available prospective studies indicate a diagnostic stability through life (Billstedt, Gillberg, and Gillberg 2005), and near of 80% of individuals with ASD diagnosed in childhood continues to present scores within this spectrum during adolescence and adulthood (Rutter, Greenfeld, and Lockyer 1967).

It is important to mention the difficulties in making diagnosis of ASD in adult patients, because many of them have no information regarding their first years of life. If the diagnosis of ASD is hard to be made in adults, then the prognosis is equally affected. The prognostic studies in adults with ASD had includes patients with very different levels of cognitive, linguistic, social, and behavioral functioning (Howlin et al. 2004). Additionally, most of available the prognostic studies in adult ASD use small samples, which make impossible to obtain definitive conclusions.

Where searching literature regarding how ASD symptoms change during lifetime, a paucity of published information is promptly identified. Although the lack of publications, at least two different timelines could be identified in ASD patients: a) how ASD core symptoms change as time pass; b) how ASD-associated symptoms change with time.

3.1. How ASD core symptoms change during lifetime

The three core symptoms of ASD, the so-called "triad of Wing" are the following: social deficits, communication deficits, and restrict and repetitive behavior.

The social deficits persist as an important problem in adolescence and adult age and usually are accessed by the Autism Diagnostic Interview (ADI) and also by the Vineland Adaptive Behavior Scale (VABS). Our group translated into Brazilian Portuguese the ADI-R, considered the "gold-standard" in autism diagnosis and is extremely useful identifying social deficits (Becker et al. 2012). One study found that only 16.7% of adults with autism presented high scores in social domain of VABS. Additionally, more than half of patients had no social contact at all and one third showed strange social contact (Howlin, Mawhood, and Rutter 2000). In general, social deficits do not improve significantly as time pass.

The communication skills tend to improve. As a group, ASD patients tend to keep almost unchanged the idiosyncratic use of language as well as the inappropriate patterns of communication in adulthood. More recent research had shown that more than half of ASD patients present language below the level of ten years of age, when adults. When comparing ASD versus AD patients with similar age and cognition, it is identified a

http://dx.doi.org/10.5772/54784

slight superiority in language skills in the AD patient group (Mawhood, Howlin, and Rutter 2000; Howlin et al. 2004).

The restrictive repertoire of activities and interests do not change in intensity as long as time passes, but certainly the type of interest do change during lifetime. Only few studies address the restrictive repertoire of interests. According with Rutter and colleagues (1967), in a cohort study, although some improvement was identified, all of patients with repetitive behaviors during infancy continued presenting it 10 years later, with a trend to increasing frequency and intensity of such symptoms (Rutter, Greenfeld, and Lockyer 1967). Subsequent research showed that near of 90% of adolescents and adults with autism persisted with restrictive repertoire of activities and interests (Seltzer et al. 2003; Howlin et al. 2004).

Another recurrent preoccupation in ASD follow up is regarding the Intellectual Quotient (IQ). Although some studies revealed lifelong IQ stability, it seem to have a performance IQ decline and a verbal IQ increase as time pass. In reality, there is a paucity of studies regarding IQ changes lifelong in ASD patients. In patients with verbal and performance IQ above 70, these changes seem to be less intense (Howlin et al. 2004).

Core symptom	In adolescence	In adulthood
Social deficits	Persistence of social deficits. A discrete improvement can occur	Persistence of social deficits. A discrete improvement can occur
Communication deficits	Can improve, but some deficits persists	Can improve, but some deficits persists
Restrict repetitive behavior	Increase in frequency and complexity	Persists in 90%. Uncommon concerns and complex stereotypies can decrease. The focus of interests can vary

Table 1. How ASD core symptoms change during lifetime.

3.2. How ASD-associated symptoms change with time

There are few epidemiologic studies of the ASD-associated comorbidities changes as time pass. Consequently, to date any estimate need to be taken with caution.

In general, the comorbidities found in classic autism are different from the identified in Asperger patients, which is probably associated with cognition. As a result, classic autism is more associated to violent behavior, and psychosis. By the other side, Asperger disorder can be more linked to anxiety and/or depression.

The more prevalent psychiatric diagnosis in ASD patients is depression that seems to become more intense with age and frequently associated with anxiety (Howlin, Mawhood, and Rutter 2000). In our experience, the dyad depression/anxiety is more frequent in intelligence-preserved ASD patients, such as those with Asperger disorder. Additionally, anxiety seems to increase in stress situations and also during lifetime (Gottfried and Riesgo 2011). Because of their ability to identify their own difficulties (Cederlund, Hagberg, and Gillberg 2010), patients with Asperger are more prone to became depressed.

The second more frequent psychiatric disorder in ASD patients is probably bipolar disorder (Howlin, Mawhood, and Rutter 2000). Young ASD children experience more difficulties in mood stabilization. In addition, mood's changes occur more rapidly in children when compared with adults. As a result, in very young ASD children the humor can change almost instantaneously.

The prevalence of bipolar disorders as a whole can reach up to 33% in ASD patients (Abramson et al. 1992). Obsessive and compulsive symptoms are frequently identified in ASD, although is difficult to distinguish the pure obsessive-compulsive disorder from bizarre concerns common in patients with autism (Howlin, Mawhood, and Rutter 2000).

Adults with Asperger disorder can experience occasional episodes of psychosis, such as persecutory ideas, auditory hallucinations, paranoid idea or delusional thoughts. But schizophrenia is not common and must remain as a differential diagnosis (Howlin, Mawhood, and Rutter 2000). The abovementioned episodes of psychosis can be identified in up to 15% of Asperger patients after adolescence (Hofvander et al. 2009).

Hyperactivity is a frequent symptom in children with ASD, is more prevalent in boys than in girls, and can decrease as time passes. Although the concomitant aggressiveness itself usually decrease with aging, the consequences of aggressiveness can be worse with age increasing in patients with autism because of their increase of muscle strength. An overlap between ADHD and ASD is relatively common in childhood, but this association is rarely described in manuscripts with ASD adults (Stahlberg et al. 2004).

3.3. Prognosis for ASD patients in adulthood

Although there are no doubts regarding a substantial improvement in the management of autism in the last three decades, unfortunately even nowadays a minority of adults with autism is able to work, to live independently, as well to develop appropriate social skills. Most of these patients still live with their parents or other caregivers (Howlin et al. 2004).

It is known by far that the most important prognostic value is defined by the cognitive functioning in childhood. In this sense, the clinical problem eventually is to access intelligence in non-verbal ASD children. According with literature, children with autism and IQ above 70 had better global prognosis in adulthood (Howlin et al. 2004).

The ability to acquire functional language until the age of six years is also another prognostic landmark (Howlin et al. 2004). Better language and more preserved cognition are the two probably reasons to explain the best prognosis in Asperger disorder when compared with classical forms of autism.

4. Psychopharmacological treatment of ASD patients

Since to date there is no specific medication developed to autism itself, the psychopharmacologic approach is addressed to some core symptoms, such as hyperactivity, anxiety, depres-

http://dx.doi.org/10.5772/54784

sion, etc. Actually, medication is frequently required to decrease the "noise" surrounding autism, including a wide range of maladaptive behaviors and/or associated problems (Benvenuto et al. 2012). To our knowledge, psychopharmacotherapy can eventually improve adhesion to non-medical treatment of ASD patients (Gottfried and Riesgo 2011).

In our experience, we usually identify 2-5 ASD associated symptoms and/or diagnosis, including epilepsy. We have found disruptive behavior more frequently in ASD patients with cognitive impairment, as well as symptoms related with depression and/or anxiety in preserved intelligence ASD children (Gottfried and Riesgo 2011). Other related symptoms are: aggression, self-injury, impulsivity, decreased attention, anxiety, depression, and sleep disruption, among others.

Because ASD are chronic and markedly impairing situations in many cases, there is justifiably a high desire for effective treatments. By the other side, it is important to mention that there is a paucity of well conducted evidence-based studies of medications used in ASD patients. Not infrequently, this desire leads to premature enthusiasm for agents and interventions that appear promising in early reports but later do not withstand the rigor of randomized controlled trial (RTC).

Another critical issue is the co-occurrence of epilepsy in ASD patients which is almost twenty times more frequent when ASD patients are compared with children with typical development. The management of combined epilepsy can represent a challenge for clinicians. Several anti-epileptic drugs can determine an exacerbation of behavioral symptoms, and some psychotropic medications used in ASD patients may lower the seizure threshold (Benvenuto et al. 2012). In our experience, risperidone can be safely used up to 3mg/Kg/day, and higher doses can lead to seizures in susceptible patients. That is the reason why we prefer to perform an electroencephalogram before using psychoactive drugs in ASD children (Gottfried and Riesgo 2011). Therefore, it's mandatory to search a treatment strategy with the minor negative impact on this subgroup of patients

It should be noted that most psychotropic use in ASD is actually off-label, as currently there are only two medications approved for use in ASD children by the FDA (Food and Drug Administration). These drugs are risperidone and aripiprazole, which are effective to associated behaviors, but not to autism itself. The general principles for the pharmacotherapy in ASD are similar to the used in other neuropsychiatric conditions (Weinssman and Bridgemohan 2012).

In summary, the use of psychotropic medications, alone or in combination, should follow some guidelines, such as: be focused on specific targets, be used at the minimum effective dosage, as well as be used for short period of time (Benvenuto et al. 2012). Ideally, medications should be initiated only after behavioral and educational interventions are in place.

4.1. Disruptive behaviors

Disruptive behaviors in ASD children may include irritability, aggression, explosive outbursts (tantrums), and/or self-injury. These symptoms can be identified in almost two thirds of ASD patients and certainly have the biggest impact on the care of affected individuals, as well as

marked distress for their families (Benvenuto et al. 2012; Kanne and Mazurek 2011). Although behavioral and environmental approaches are recommended as the initial treatment, more severe or even dangerous behaviors usually result in requests for urgent pharmacologic intervention (Kaplan and McCracken 2012; Weinssman and Bridgemohan 2012). In our experience, this type of symptoms is more frequently found in intelligence disabled ASD patients (Gottfried and Riesgo 2011).

In the past, conventional neuroleptic agents such as haloperidol have been used in disruptive behaviors of autistic patients (Benvenuto et al. 2012; Miral et al. 2008; Kaplan and McCracken 2012). Our group showed that risperidone is superior when compared with haloperidol in one experimental research using hippocampal cells (Quincozes-Santos et al. 2010). Additionally, in the clinical research, at least one study proved that risperidone is more effective than haloperidol in ASD patients (Miral et al. 2008). There are two RTC suggesting that haloperidol is effective in disruptive behaviors of ASD children (Campbell et al. 1982; Miral et al. 2008), but sedation and other side effects including dyskinesia and extrapyramidal symptoms limits its use (Weinssman and Bridgemohan 2012).

As a result, to date atypical antipsychotic seem to be more helpful in treatment of disruptive behaviors. Currently, risperidone and aripiprazole are the only second-generation antipsychotic drugs that have shown to decrease disruptive behaviors in large-scale, controlled, double-blind studies (Benvenuto et al. 2012; Kaplan and McCracken 2012; Weinssman and Bridgemohan 2012).

Before the approval by FDA in 2006, risperidone was carefully studied by the NIMH Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. A multiphasic trial comparing risperidone with placebo was performed by RUPP for the treatment of aggressive behaviors in patients aged 5 to 17 years with ASD. There was an initial double-blind, 8-week RCT study (McCracken et al. 2002).

The studies found that risperidone, in mean doses of 2,08mg/d, was effective for reducing moderate to severe tantrums, aggression, and self-injurious behavior in children with autism. There wasn't evidence of side effects such as dyskinesia or dystonia. However, the observed weight gain of 5,6kg for the risperidone group was more than twice the expected weight gain over a 6-month period (McCracken et al. 2002; Kaplan and McCracken 2012).

Risperidone was approved by the FDA in 2006 for the treatment of disruptive symptoms in children and adolescents aged from 5 to 16 years with autism, with a maximum recommended dose of 3 mg/d. In our experience, risperidone was initially used in dose up to 6 mg/d. As time pass, we noted that if no response was obtained with 3mg/d, no more increments were useful. Coincidentally, this daily regimen seems to be the seizure threshold in susceptible patients (Gottfried and Riesgo 2011).

Aripiprazole was approved by the FDA for the treatment of disruptive behavior in ASD patients aged 6 to 17 years in 2009. Two large controlled studies documented the short-term efficacy of aripiprazole at 5, 10 or 15 mg/d for severe aggression and irritability in young subjects with autistic disorder. The most commonly reported adverse events were drowsiness and weight gain, with extrapyramidal symptoms mostly in the fixed-dose study, but these

http://dx.doi.org/10.5772/54784

events rarely led to treatment discontinuation (Marcus et al. 2009; Owen et al. 2009). Aripiprazole dosing and response can vary considerably; the usual recommended clinical dose for maintenance is between 5 and 15 mg/d (Kaplan and McCracken 2012).

Other atypical antipsychotics lack large-scale controlled studies. Small open-label reports suggest variable benefits of olanzapine (Potenza et al. 1999), clozapine (Beherec et al. 2011), and ziprasidone (Malone et al. 2007), which have possible support, versus quetiapine, which has not appeared to be beneficial. Other medications of different classes have been used, such as alpha-2 agonists, mood stabilizers, beta blockers, SSRI (selective serotonin reuptake inhibitors), all of them without evidence-based studies of efficacy in disruptive behavior to date (Weinssman and Bridgemohan 2012).

Probably due the co-occurrence of epilepsy in ASD, the use of some antiepileptic drugs has been used in the management of maladaptive behaviors (Gottfried and Riesgo 2011). Divalproex sodium has been demonstrated to be efficient not only in decreasing irritability/aggression, but also in improving of repetitive behaviors, social relatedness and mood instability (Hollander et al. 2006; Hollander et al. 2010).

Adjunctive topiramate therapies can decrease irritability, hyperactivity and inattention (Hardan, Jou, and Handen 2004; Mazzone and Ruta 2006). Moreover, the combination of topiramate with risperidone has been proved superior to risperidone monotherapy in reducing irritability and severe disruptive symptoms (Rezaei et al. 2010). In our experience, this specific combination would be helpful in preventing or at least decreasing the weight gain due to risperidone usage in ASD patients.

Although preliminary data of open-label studies showed that levetiracetam may reduce hyperactivity, impulsivity, mood instability and aggression in autistic children, a RCT suggest that levetiracetam does not improve behavioral disturbances of ASD (Weinssman and Bridgemohan 2012), as well lamotrigine (Belsito et al. 2001).

4.2. Hyperactivity and inattention symptoms

These symptoms are frequently identified in ASD patients. Inattention, hyperactivity and impulsivity may be related to comorbid ADHD (attention deficit hyperactivity disorder) and/or to baseline anxiety of these children (Murray 2010; Rommelse et al. 2010; Benvenuto et al. 2012) Weinssman & Bridgemohan, 2012). It is known that children with ASD and ADHD have more clinical impairments than children with ASD alone (Gadow, DeVincent, and Pomeroy 2006; Kaplan and McCracken 2012).

The potentially useful drugs for inattention and hyperactivity in ASD could be stimulants, alpha-2 adrenergic agonists, atypical antipsychotics as well as anticonvulsant mood stabilizers. To date, there is strong evidence that both stimulants and risperidone are effective for hyperactivity. If the inattention and/or hyperactivity behaviors are due to anxiety, SSRI may be a useful choice (Weinssman and Bridgemohan 2012).

Psychoestimulants and other medications used in typically developing children with ADHD have been evaluated as a therapeutic option for treatment of ADHD symptoms

in patients with ASD. The largest trial undertaken by RUPP Autism Network has demonstrated that methylphenidate (MPH) was reasonably efficacious in patient with both ASD and ADHD (RUPP 2005). Convergent evidence from different studies confirms a positive effect on social behaviors (joint attention, response to bids for joint attention, self-regulation, and regulated affective sate), hyperactivity, inattention and impulsiveness (Di Martino et al. 2004; Jahromi et al. 2009). However, response rate to MPH is lower in ASD children compared with children with ADHD without ASD (Weinssman and Bridgemohan 2012). In ASD children, MPH should be started at the lowest dosage ant titrated slowly because of these patients are more prone to experience side effects.

As the same observed with MPH, atomoxetine has initially demonstrated a lower efficacy in ASD patients with ADHD than in ADHD children without autism (Posey et al. 2007; Charnsil 2011). Nevertheless, more recent studies showed significant reductions in ADHD symptoms in high-functioning ASD boys (Zeiner, Gjevik, and Weidle 2011).

Regarding the use of antipsychotic drugs in inattentive/hyperactive ASD patients, secondary analyses from large RTCs demonstrated that risperidone and aripiprazole are associated with large reduction of hyperactivity in children with ASD (McCracken et al. 2002; Owen et al. 2009; Weinssman and Bridgemohan 2012).

Despite the small number of RCT, another option is the use of alpha-2 agonists drugs in ASD children with inattention, hyperactivity, and impulsivity. The use of guanfacine in autistic children has showed modest improvement in the domains of hyperactivity, inattention, insomnia, and tics (Scahill et al. 2006; Handen, Sahl, and Hardan 2008; Weinssman and Bridgemohan 2012). Clonidine is effective in reducing sleep disorders of children with ASD, with a consequent daily improvement of attention deficits, hyperactivity, mood instability and aggressiveness (Jaselskis et al. 1992; Ming et al. 2008). However, only two RCT have been conducted for this class of agent (Weinssman and Bridgemohan 2012).

4.3. Stereotypy and repetitive behaviors

One of the core symptoms in ASD children is perseverative or repetitive behaviors usually associated with difficulties in change interests, which can interfere in the quality of life of patients and parents. Stereotypies and repetitive behaviors are not unique to ASD and can be found in other developmental disorders, although clinicians and researchers agree that these tend to be more frequent in ASD (Kaplan & McCracken, 2012; Leekam et al., 2011). By the other hand, difficulties in changing interests, in the context of a developmental disorder, is one of the hallmarks of autism.

Before use of medication, behavioral therapies should be performed. In our experience, poor cognitive performance can be one of the limitations to behavioral therapy. If the child is mentally disabled, the non-medical approach can be unsuccessful. In this situation, when these symptoms are intense enough to cause impairments to academic performance and/or interpersonal relationships, pharmacologic treatment is often considered.

http://dx.doi.org/10.5772/54784

Because of the similarity of this cluster of autistic symptoms to anxiety as well as other serotonin-related disorders such as obsessive compulsive disorder has led clinicians to use and researchers to investigate the efficacy of SSRI in the treatment of repetitive behaviors and rigidity. Other possibilities in terms of medication include clomipramine, atypical antipsychotics and valproate (Weinssman & Bridgemohan, 2012).

To date, although the lack of high quality evidence that SSRI are effective to stereotypy and repetitive behaviors, we still use this class of medication in clinical practice. In a meta-analysis of published trials with different classes of antidepressants, including SSRI and tricyclic antidepressants, the small benefit of these drugs on repetitive behavior disappeared after statistical adjustment (Carrasco et al., 2012).

Other types of SSRI were tested in ASD children with stereotypy and repetitive behaviors, for example: fluvoxamine, sertraline, paroxetine, citalopram and escitalopram. There is one unpublished trial of fluvoxamine, which was poorly tolerated by children (McDougle et al., 1996). There are no RCT of sertraline and paroxetine in ASD children (Weinssman & Bridgemohan, 2012). The largest published trial of citalopram (mean dose 16mg/d) found no effect at all on repetitive or compulsive behavior but found a possible effect on challenging behaviors (King et al., 2009). Others RCT didn't show strengths of evidence for effect of citalopram or escitalopram to reduce repetitive or challenging behavior (McPheeters et al., 2011).

Concerning antipsychotic drugs, in the RUPP studies, stereotypies and repetitive behaviors were examined as secondary outcomes and then risperidone achieved levels of statistical significance in reduction of repetitive behavior (McDougle et al., 2005). Similarly, aripiprazole studies showed that the agent significantly improved repetitive behaviors over placebo (Marcus et al., 2009; Owen et al., 2009).

There is only one small RCT which shows the efficacy of valproate in repetitive behaviors of ASD children (Hollander et al., 2006). Our group avoids the usage of valproate in such symptoms. In summary, from the clinical point of view, it is hard to improve stereotypy and repetitive behaviors with pharmacotherapy. As a matter of fact, sometimes these symptoms can be more uncomfortable to parents than patients.

4.4. Mood instability

In clinical practice, mood instability is more difficult to control in ASD patients compared with typically developed children (Gottfried & Riesgo, 2011). Different drugs have been used, including antipsychotics, SSRI, and lithium. The problem is that none of these medications have been studied with RCT specifically for mood regulation in ASD pediatric patients (Weinssman & Bridgemohan, 2012).

If mood lability is associated with disruptive behavior, the best choice could be atypical antipsychotics. If this symptom is associated with depression and or anxiety, the use of SSRI could be considered. It is important to remember the higher possibilities of behavioral activation in ASD patients after SSRI use, leading to hypomaniac states in susceptible children.

4.5. Sleep disorders

Sleep disorders can be identified years before an unequivocal diagnosis of autism. Not infrequently, we face with sleep complaints in very young babies who lately will develop the whole clinical picture compatible with ASD. By the other hand, sleep disorders occur more frequently in ASD patients compared with developing children (Benvenuto et al., 2012; Miano & Ferri, 2010).

Sleep disorders tend to be under-recognized valued in the ASD patient group, probably because they can be considered less disabling than aggression and repetitive behaviors; however, ongoing abnormal sleep patterns are very disruptive to the overall quality of family life and interfere with patient daytime functioning. Parents frequently ask for medication and then physicians are confronted with the lack of FAD-approved treatments for this problem (Kaplan & McCracken, 2012; Weinssman & Bridgemohan, 2012).

Before use of medication, is important to ensure appropriate sleep hygiene as well as to use behavioral intervention. Pharmacology is recommended only when psychosocial treatments fail. Melatonin administration in ASDs is reported to be safe, well tolerated and efficient in improving sleep parameters and daytime behavior, and in decreasing of parental stress (Malow et al., 2011; Rossignol & Frye, 2011).

Core symptoms	Medications	Level of evidence
Aggressiveness	Risperidone*	Large scale double blind RCT
Irritability	Aripiprazole*	Large scale double blind RCT
elf-injury	Olanzapine	Double blind RCT
Other disruptive behaviors	Clozapine	Small open label reports
	Ziprazidone	Small open label reports
	Valproic acid	RCT
	Topiramate	RCT
Hyperactivity	Metilfenidate	Crossover RCT
Inattention	Atomoxetine	Crossover RCT
	Risperidone*	Large scale double blind RCT**
	Aripiprazole*	Large scale double blind RCT**
	Guanfacine	RCT
	Clonidine	Small open label reports
Repetitive behavior	Risperidone*	Large scale double blind RCT**
Stereotypies	Aripiprazole*	Large scale double blind RCT**
	Fluoxetine	RCT
	Valproic acid	RCT
Sleep disorders	Melatonin	RCT

*FDA-approved medications for ASD children; **Secondary analysis; RCT = randomized controlled trials

Table 2. Psychopharmacological treatment in ASD patients

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5. Non-medical treatment of ASD patients

The treatment of ASD evolves professionals coming from different area and usually is characterized by comprehensive and intense programs encompassing both patients and families. Early identification is critically important to ensure that families have the opportunity to reap the many unique benefits that may arise from early intervention efforts. For example, intervention efforts that occur early during a child's development may have the advantage of increasing brain plasticity, which may enhance outcomes (LeBlanc & Gillis, 2012).

In our experience, children with low intensity ASD treats, when early-treated can eventually get out from de ASD diagnosis when accessed by CARS, a rating scale of autism symptoms (Gottfried & Riesgo, 2011).

The non-medical intervention programs are directed to the core social, communication and cognitive issues in autism. The objectives of each one program are selected according with the specific abilities and difficulties as well as the actual neurodevelopmental phase of the ASD patient. As a result, this kind of intervention needs to be customized (Dawson & Burner, 2011; LeBlanc & Gillis, 2012).

In general, the following types of therapy can be used both isolate or in different combinations: behavioral, occupational, speech therapy as well as psychopedagogic therapy. Although the non-medical treatments for ASD patients can be different from each other, they usually had the same goals, such as to give the child the best degree of independent functioning as well as to improve quality of life from the patient and family (Myers & Johnson, 2007).

There is a consensus that facing a suspicious case of ASD in children the treatment must be promptly initiated, independently of the type of non-medical treatment, because of the brain plasticity in the developing child (LeBlanc & Gillis, 2012; Lord & McGee, 2001).

Besides the large number of non-medical type of treatment, there are some of them with good level of evidence. According with the National Autism Center's Standard Report, after a systematic review of literature available from 1957 to 2007, at least 11 treatment methods for ASD were considered with good level of evidence.

Additionally, there are some problems in evaluating the efficacy of non-medical treatments in ASD patients. For example, the small sample sizes, the different methodologies, the difficulty in the outcome measures, etc.

5.1. Behavioral treatment

The therapies involving behavioral and educational strategies are the main components of the non-medical treatments of ASD children. The only psychoeducational treatment that meets the criteria as well-established and efficacious intervention for ASD to date is the behavior treatment (Dawson & Burner, 2011; LeBlanc & Gillis, 2012).

There is consensual that behavioral therapy must be intensive with at least 25 hours per week, all year long. There are two main types of behavioral treatments: interventionists and non-interventionists. Among the first group of available therapies, there are three principal methods: a) Applied Behavior Analysis (ABA); b) Treatment and Educational of Autistic and related Communication-handicapped Children (TEACCH); c) developmental/relationship-based therapy (Floortime). Some of these strategies use combinations of different models and are denominated integrative models. To date, there is no evidence that integrative models are better than the original models (Weinssman & Bridgemohan, 2012). By the other side, one example of non-interventionist behavioral therapy is the Picture Exchange Charts System (PECS).

5.1.1. ABA (Applied Behavior Analysis)

Aims to teach the absent child skills through the introduction of these skills in stages. Usually, each one of the skills is individually showed, presenting it coupled with an indication or instruction. When necessary, any support that is offered should be removed as soon as possible. (Ospina et al., 2008; Warren et al., 2011). In the clinical setting, we have identified problems in terms of improvement from the classroom as well as a trend to overestimate the efficacy of ABA.

5.1.2. Treatment and Educational of Autistic and related Communication-handicapped Children (TEACCH)

Use structured activities and environment to help ASD patients to improve compromised area. The model is adapted to each one child and addresses environment organization as well as predicable routines in order to adapt the environment to make it easier for the child to understand it, and understand what is expected of her. TEACCH programs are usually given in a classroom, but can also be made at home. Parents work with professionals as co-therapists for techniques that can be continued at home. It is used by psychologists, special education teachers, speech therapists and trained professionals (Myers & Johnson, 2007).

5.1.3. Floortime

The main objective is to teach fundamental skills expected to the level of development which were not acquired in a given ASD patient age, but to date the efficacy evidences are still inconclusive (Ospina et al., 2008). Our group is conducting an evidence-based research to find out if this treatment is reliable.

5.1.4. Picture Exchange Communication System (PECS)

This non-interventionist behavioral therapy enables non-verbal children to communicate by using figures. PECS can be used at home, in the classroom or in several others environments (Bondy & Frost, 2001). A meta-analysis showed that PECS is a promising intervention (Ganz et al., 2012).

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Psychoeducational treatments	Example	Effectiveness
Interventional Models	ABA* TEACCH Denver model Floortime	Well established Insufficient evidence to recommend one over another
Specific behaviors	Focal behavior intervention	Well established
Communication	PECS	Promising results
Social skills instruction		Promising results
Integrative Models	Focal behavior intervention	Insufficient evidence to recommend one over another
Parental role	Parent-mediated intervention programs	Inconsistent results Small size studies
Sensory integration therapy		Inconsistent results
Occupational therapy		Little research
*Suggested by Autism Center Guidelines		

Table 3. psychoeducational treatment of ASD patients

5.2. Complementary and alternative therapies

Complementary and alternative medicine (CAM) encompasses different kinds of medical and healthcare systems, practices, and products usually not considered to be a part of the conventional medicine. There are several proposed CAM systems to treat ASD children, but to date still without recognized efficacy by FDA. As a result, they are considered "off label". Interestingly, more than 70% of ASD patients are treated by CAM (Rossignol, 2009).

It is important to note that the definition of CAM is slightly different when used in ASD when compared with other medical disorders. That difference is due the fact of many of the psychoeducational therapies used in ASD children, although not considered conventional medical therapies; they are well accepted methods treating this group of patients.

In terms of scientific support, there are three main groups of CAM: a) promising treatments; b) treatments with some degree of scientific evidence; c) treatments with no scientific proved efficacy to date (Rossignol, 2009).

5.2.1. Promising CAM

These types of treatment showed the highest level of evidence and include music therapy, naltrexone, and acetyl-cholinesterase inhibitors (Rossignol, 2009). Concerning music therapy, there is evidence that it is able to improve social interaction as well as communication skills (Gold et al., 2006; Kim et al., 2008). Our group conducted a RCT using music therapy in ASD patients and we identified the promising effect of this treatment (Gattino et al., 2011). There is

a comprehensive RCT been done testing the efficacy of music therapy in ASD patients (Geretsegger et al., 2012).

5.2.2. CAM with little evidence

This group of therapies may include the use of carnitine, ocytocin, vitamin C, tetrahydrobiopterin, adrenergic alfa-2 agonists, hyperbaric oxygen therapy, immune-modulatory treatment, and anti-inflammatory treatment (Rossignol 2009). Caution is needed with the hyperbaric oxygen therapy because of the potential adverse effects, such as barotrauma, reversible myopia, oxygen toxicity, and seizures (Weinssman & Bridgemohan, 2012).

5.2.3. CAM with no proved efficacy to date

Several of the proposed CAM for ASD had no proved efficacy to date, for example: use of carnosine, multi-vitamin and mineral complexes, piracetam, omega-3 fatty acids, selective diets, vitamin B6, magnesium, chelation, cyproheptadine, glutamate antagonists, acupuncture, auditory integration training, massage, neuro-feedback, and others (Rossignol, 2009).

6. Clinical recommendations in ASD

The following clinical recommendations can be done as a result of more than twenty years of personal clinical practice in Child Neurology dealing with ASD children, among other neuropediatric situations. For instance, our Child Neurology Unit (http://www.ufrgs.br/neuropediatria) usually makes more than 16,000 neuropediatric evaluations per year.

From the clinical point of view, it is important to remember the ongoing changes in DSM criteria for ASD diagnosis. To date, we still deal with five different diagnosis of autism, according with DSM-IV criteria. Even after modifications due the new DSM-V classification, ASD children will remain as a heterogeneous group, making difficult the exact clinical diagnosis.

It is important to remember that ASD diagnosis can be catastrophic to parents. As a result, an incorrect diagnosis would be even worse. That is the reason to be careful in terms of making ASD diagnosis as well as to make a double check if diagnosis is really correct.

After finishing a list of the prominent symptoms, the next step is to decide if they are intense enough to deserve treatment, which is not easy. Some symptoms seem to be more unpleasant to parents than the ASD child. At this point, there is no guideline to follow, and the previous clinical experience is extremely helpful.

Usually the non-medical treatment is started earlier than the use of medications. It is important to remember the relevance of evidence-based CAM, since there are a great number of proposed non-medical treatments.

In general, medications are used in addition to non-medical treatments. The best medication approach would be monotherapy, but it is not always possible in the real clinical

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world. Another critical problem in terms of psychopharmacotherapy is the paucity of well-conducted RCT, as pointed before in this chapter, especially in the table 2. To date, there are only two FDA-approved antipsychotic medications for ASD in children: risperidone and aripiprazole.

Risperidone was approved by FDA in 2006. The usual dose varies from 1 to 3mg/day. In our practice, 3mg/day of risperidone seems to be the cutoff dose in terms of seizure susceptibility. We have identified patients who experienced seizures with doses higher than 3mg/day. Aripiprazole was FDA-approved in 2009 and the daily dose is up to 15mg.

Because of ASD patients are almost twenty times more prone to have epilepsy when compared with normally developing children, and because of many of the drugs used in autism can decrease the seizure threshold in susceptible children, it is important to assure that there is a previous normal EEG before prescribing psychopharmacotherapy.

7. Conclusions and future remarks

The clinical approach includes a general management as well as two types of not excluding treatment strategies: one with medication and another without medication. From the clinical point of view, these two types of treatment are, in fact, complementary.

In the clinical practice, numerous types of treatment have been proposed and there is urgent need to choose any one of them in short period of time. Searching literature, a lack of well conducted RCT was identified. As a result, caution is the best form to approach ASD cases.

Future perspectives in the treatment of ASD probably will include immunomodulation, quantic biochemistry, stem cell therapy and other forms of approach after careful RCT attesting its efficiency.

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