Autistic disorder

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Autistic disorder: current psychopharmacological treatments and areas of interest for future developments

Autismo: tratamentos psicofarmacológicos e áreas de interesse para desenvolvimentos futuros

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Abstract

Autistic disorder and the group of related conditions defined as pervasive developmental disorders are chronic neurodevelopmental disorders starting in early childhood and affecting a significant number of children and families. Although the causes and much of the pathophysiology of the disorder remain unknown, in recent years a number of available medication treatments have been identified as holding promise in alleviating some of the most disabling maladaptive behaviors, associated with pervasive developmental disorders. However these treatments do not address the core symptoms of the disease and oftentimes their side effects outweigh their benefits. Therefore there is substantial need for new medications that are safer and more effective in addressing the behavior symptoms of autism. The aim of this review is to highlight the available current pharmacotherapies and those emerging treatments with potential to enhance the treatment options of patients with pervasive developmental disorders.

Keywords: Autistic disorder; Antipsychotic agents; Anticonvulsants; Antidepressant agents; Disease management

Resumo

O transtorno autista e o grupo de condições relacionadas definidas como transtornos invasivos do desenvolvimento são transtornos de neurodesenvolvimento crônicos que começam na infância precoce e afetam um número significativo de crianças e suas famílias. Ainda que as causas e muito da fisiopatologia do transtorno sejam desconhecidas, em anos recentes, vários tratamentos medicamentosos disponíveis têm sido identificados como contendo a promessa de aliviar alguns dos comportamentos mal-adaptativos mais comprometedores associados aos transtornos invasivos do desenvolvimento. No entanto, esses tratamentos não enfocam os sintomas nucleares da enfermidade e, geralmente, seus efeitos colaterais excedem os benefícios. Portanto, há uma necessidade substancial de novas medicações que sejam mais seguras e mais eficazes em tratar os sintomas comportamentais do autismo. O objetivo desta revisão é o de destacar as farmacoterapias correntes disponíveis e aquelas emergentes e que tenham potencial de melhorar as opções de tratamento de pacientes com transtornos invasivos do desenvolvimento.

Descritores: Transtorno autístico; Agentes antipsicóticos; Anticonvulsivantes; Agentes antidepressivos; Manejo clínico

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Introduction

Autism is a neuropsychiatric disorder developing in early childhood. It is part of a group of conditions, defined as PDDs, often referred to also as "autistic spectrum" disorders. Common feature of the PDDs is pervasive impairment in several areas of functioning, namely social interaction, communication and the presence of repetitive behaviours and restricted interests. These deficits develop relative to the individual's mental age and usually become evident by the 3rd year of life. Often they are accompanied by some degree of mental retardation. There are several types of PDD defined in the Diagnostic and Statistical Manual Fourth Edition of the American Psychiatric Association.[1] They include autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's disorder and PDD - Not Otherwise Specified (PDD-NOS). In the International Classification of Diseases-10,[2] these are given similar, though not identical labels. ICD-10 includes also two other categories, Atypical Autism and Overactive Disorder Associated with Mental Retardation and Stereotyped Movements.

Autistic disorder by definition begins prior to the age of 3 years.[1] The diagnosis requires presence of disturbance in three domains: 1) social interaction; 2) communication; 3) restricted interests and stereotyped patterns of behavior. The social deficits manifest themselves as lack of spontaneous interest in sharing enjoyment, failure to use non-verbal means of communication (body language, gestures, facial expression, eye contact) to regulate social interactions, and failure to develop peer relationships appropriate for age and developmental level. The communication disturbance is evidenced by lack of spoken language, or delayed and deviant language. There may be stereotyped, repetitive, or idiosyncratic use of language, which does not have communicative intent. If there is adequate language ability, there is lack of interest in initiating or sustaining conversation. Play is impaired. Spontaneous imaginative play and social imitative play appropriate for developmental level is absent or substantially delayed. Restricted interests and activities involve usually an encompassing preoccupation with one or several topics, which may be abnormal in focus, intensity or both (e.g. train schedules; prime numbers; laundry detergents etc). Disabling adherence to non-functional routines is also common. Stereotyped movements and mannerisms such as hand flapping, body rocking, staring, is present.

Autism and the related PDDs are one of the leading causes for developmental disability. Over 300,000 individuals in the US have been diagnosed with autism spectrum disorder.[3] The condition has serious socio-economic consequences, because it begins in childhood, it is chronic, and the disability can be substantial. The costs to society are significant in terms of special educational programs, support services, residential institutions and loss of productivity for the affected individuals, but also family members. The financial, and more importantly, emotional burden to the parents and families of affected children, can also be substantial. There are no established definitive treatments, but there is a plethora of treatments with limited at best empirical support or "alternative treatments" with no scientific evidence at all. The disabling nature of the disorder and the lack of sufficiently effective treatments continue to stir keen public interest, sometimes propelling novel unproven treatments to instant fame and publicity. Unfortunately the initial enthusiasm often leads to the disappointment of many hopeful and dedicated patients.

Typically, first line treatment for children with autism include psychosocial treatments and educational interventions with the goal of maximizing language acquisition, improving social and communication skills and extinguishing of maladaptive behaviors. Currently there are no available standard medication treatments, addressing the core symptoms of autism. There are no pharmacological treatments currently approved by the US Food and Drug Administration for autism. Despite the limited empirical support psychopharmacological treatment of children and adults with autism appears to be common in clinical practice. When used, pharmacologic interventions usually target specific symptoms, accompanying the core symptoms, and severely impairing the individual's functioning, often not allowing for "first line" educational and behavioral interventions to take pace (e.g. aggression, self-injurious behavior; compulsive rituals, low frustration tolerance with explosive outbursts, hyperactivity etc.). The agents used commonly in clinical practice belong to diverse medication groups, are non-specific to the symptoms targeted, and affect a wide range of neurological and brain functions, not affected necessarily by autism. Although medications may improve the quality of life for some patients, medication benefits maybe narrow in scope. Moreover, available data make it difficult to predict which patients will respond positively to which medication. Finally long term benefits for any of the agents used in autism are largely unknown and a significant portion of patients discontinue once perceived beneficial medication use due to loss of efficacy or side effects. Studies are under way now to determine the utility of longer term use of some of the more popular agents.

The current research in the area of pharmacological treatments for autism borrows treatments from psychiatric conditions for symptoms that might be relevant for autism. The newer psychotropics, particularly the atypical antipsychotics and the selective serotonin reuptake inhibitors (SSRIs) have more benign side effect profiles than older counterparts. There is urgent need, however, for the development of new agents, specific to autism, and possibly attacking core symptoms of the disease. The hope is that the advances in knowledge of the biological substrates for autism will lead to the development of new such compounds.

Existing treatments

This section will provide an overview of the major drug categories commonly used in the treatment of children and adults with autism and related conditions.

Atypical antipsychotics (AAPs), are a group of drugs originally developed to treat psychosis. The group includes compounds brought to the market over the past 10 years as safer and better tolerated alternatives to the existing "typical" antipsychotics. Medications in this group include clozapine, risperidone, olanzapine, quetiapine, ziprazidone and aripiprazole. These compounds are widely used in autism and other PDDs to treat severe maladaptive behaviors and have largely replaced the traditional (typical) antipsychotics such as haloperidol and chlorpromazine. The target symptoms for pharmacotherapy with AAP typically include aggression, self-injury, property destruction or severe tantrums. The impetus for studying these agents in PDDs was derived largely by research on haloperidol, done by Magda Campbell's group in New York.[4] The AAPs, however offer distinct advantages over the typical antipsychotics represented by haloperidol. The AAPs have lower risk of inducing neurological side effects such as

Parkinsonism in the short term and perhaps tardive dyskinesia (TD) in the long term. In addition, because these newer compounds have been also reported to improve the "negative" symptoms of schizophrenia (abulia, avolia, flat affect), there is interest in the notion that this may be relevant to the social withdrawal and lack of spontaneous interaction in autism. The fact that AAPs are also effective for treatment of tics[5] with a similar magnitude of effect as the high potency typical antipsychotics, also suggests that the AAPs may be of benefit in the treatment of stereotypies associated with PDDs as well.

The reduced occurrence of dyskinesias and the purported improvement in negative symptoms of schizophrenia may be related to the dual action of five-hydroxytryptamine (5-HT) to dopamine (DA) receptor blockade.[6] Alternatively, it has been suggested that the AAPs do not bind as tightly to post-synaptic dopamine receptors, permitting them to be displaced by endogenous dopamine in the striatum.[7] To date clozapine, risperidone, olanzapine, quetiapine, ziprazidone and aripiprazole, have each been examined in the treatment of autism and other PDDs albeit with varying levels of empirical support. Recent data suggest that risperidone is emerging as the standard treatment for aggression, tantrums, and self-injury in children, adolescents and adults with PDDs.

1. Clozapine

Clozapine was the first atypical antipsychotic to be introduced in the US. The drug's ability to block 5-HT2A, 5-HT2C, 5-HT3 and DA D1-D4 receptors has been proposed as its mechanism of action. Two reports have described the use of clozapine in autism in four subjects. In the first study, three children who displayed marked hyperactivity, fidgetiness, or aggression were treated for up to 8 months with doses ranging from 200 to 450 mg per day. Two of the three children showed sustained improvement, though the third had a return of symptoms to baseline levels after an initial response. Chen et al. 2001 reported the case of a 17-year-old male with autism and severe mental retardation who showed significant reduction in signs of "overt tension", hyperactivity, and repetitive motions in response to clozapine 275 mg per day, during a 15-day hospitalization.[8] These case studies provided limited support for the use of clozapine.

The low use of clozapine in autism probably reflects concerns about the risk of blood dyskrasia and seizures that are associated with the drug. Additionally frequent blood draws (weekly) are required to monitor for agranulocytosis, which can be challenging in children with autism.

2. Risperidone

Risperidone has high affinities for DA D2-D4, 5HT2A, 5-HT2C receptors.[9] Multiple open label studies and case series,

as well as double blind placebo controlled trials in children, adolescents and adults have described beneficial effects of risperidone in individuals with autism and other PDDs. The Research Units in Pediatric Psychopharmacology (RUPP) Autism Network recently completed a multi-site trial evaluating the short- and long-term efficacy of risperidone in children and adolescents with autism accompanied by severe tantrums, aggression and/or self-injurious behavior.[10] The first phase of the study was an eight week randomized double blind trial of risperidone versus placebo. The second phase was a 4-month-open-label extension for all subjects who showed a positive response. The benefits of risperidone were remarkably stable without the need for dose increase. In a third phase subjects were randomly assigned to continue active medication or to a gradual withdrawal to placebo over a 3-week period. The third phase was terminated after it became clear through interim analysis that the relapse rate is significantly greater in the placebo group. The primary outcome measures were the Irritability subscale of the Aberrant Behavior Checklist (ABC) (Table 1) and the Improvement item of the Clinical Global Impression scale (CGI-I) (Figure 1).
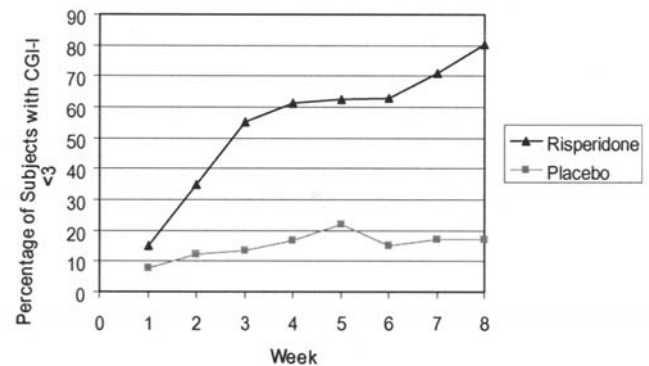

Figure 1 – Much improved or very much improved on CGI-I

The large magnitude of treatment effect found (43% difference in the mean change for the main outcome measure between risperidone and placebo) contrasts to treatment effects for haloperidol (differences of 15%-20% in similar studies).[4] In addition, the side effects associated with risperidone were less than those with haloperidol in previous studies. Although there was significant improvement in hyperactivity and stereotypies, there was little evidence of benefit for core features of autism in the short term. Secondary analyses on long-term effects on adaptive function are ongoing.

Table 1 - Baseline and endpoint scores on Aberrant Behavior Checklist by treatment group[1]

ABC subscale	Risperidone		Placebo		Effect		
	Baseline	Endpoint	Baseline	Endpoint			
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F^2	p^3	Size[4]
Irritability	26.2 (7.9)	11.3 (7.4)	25.5 (6.6)	21.9 (9.5)	27.57	< .0001	1.2
Social withdrawal	16.4 (8.2)	8.9 (6.4)	16.1 (8.7)	12.0 (8.3)	4.89	< .03	0.4
Stereotypy	10.6 (4.9)	5.8 (4.6)	9.0 (4.4)	7.3 (4.8)	11.32	< .0001	0.8
Hyperactivity	31.8 (9.6)	17.0 (9.7)	32.3 (8.5)	27.6 (10.6)	25.56	< .0001	1.0
Inappropriate speech	4.8 (4.1)	3.0 (3.1)	6.5 (3.6)	5.9 (3.8)	6.68	< .03	0.3

[1] RUPP Autism Network, 2002. Used with permission.
[2] Degrees of freedom = 1, 262.
[3] Derived from random regression analysis using data from baseline, weeks 2, 4, 6 and 8.
[4] Calculated with baseline and endpoint scores only: difference in active minus difference in placebo, divided by pooled standard deviation.

3. Olanzapine

Olanzapine has high affinity for DA D1, D2 and D4 receptors, for 5-HT2A, 5-HT2C and 5-HT3 receptors.[11] It has not been studied in a placebo-controlled randomized fashion in children or adults with PDD. Several case studies have reported positive results;[12-13] one open label trial[14] and one randomized parallel group design trial with haloperidol[15] reported generally positive results, though significant weight gain did occur. Recent reports of drug-induced diabetes in adults treated with olanzapine[16] may make clinicians reluctant to continue using it in autism.

4. Quetiapine

Quetiapine has a relatively low to moderate affinity for D1 and D2 receptors, moderate affinity for 5HT2A receptors, and higher affinity for alpha1-adrenergic, H1-histaminic receptors.[17] One open label trial with a small number of subjects, concluded that quetiapine was poorly tolerated and ineffective in their sample.[18]

5. Ziprazidone

Ziprazidone is a potent antagonist of 5-HT2A and D2 receptors, though it has relatively greater affinity for 5-HT2A receptors. Unlike quetiapine, it has low affinity for adrenergic and histaminergic receptors.[19] One open label study and one retrospective chart review study have shown some promise for its usefulness in PDD.[20-21] Double blind placebo controlled studies are needed to substantiate these findings.

6. Aripiprazole

Aripiprazole is the most recent addition to the list of available AAPs. It is classified as a partial dopamine agonist due to a novel mechanism of action.[22] It has the capacity to bind with presynaptic dopamine receptors (D2 and D3) and serotonin 5HT1A, acting as partial agonist, and to 5HT2A acting as antagonist. It also binds to alpha1A, muscarinic and histaminergic receptors with minimal antagonism. Studies in adults with schizophrenia have shown it to be an effective antipsychotic with a low risk of side effects and causing no weight gain.[23] One open-label trial with 5 patients 5-18 years-old diagnosed with PDD reported improvement in maladaptive behavior associated with PDD in all 5 subjects.[24] The subjects received aripiprazole for a minimum of 8 weeks and response was determined by a Clinical Global Impressions-Improvement (CGI-I) scale rating of "much improved" or "very much improved".

More pilot studies of aripiprazole are under way at several sites.

Serotonin reuptake inhibitors (SRIs)

Serotonin reuptake inhibitors (SRIs) such as clomipramine, fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram and escitalopram are a group of chemically unrelated compounds that potently inhibit the reuptake of serotonin (5-hydroxytryptamine or 5-HT) at the presynaptic transporter site. Clomipramine is a tricyclic antidepressant (TCA) that inhibits the reuptake of both norepinephrine and serotonin. The other compounds are more selective for serotonin reuptake and are collectively termed selective serotonin reuptake inhibitors (SSRI). Although commonly used in clinical practice, the SRIs have not been systematically studied in the PDDs.

SSRIs in PDD

1. Clomipramine

Two studies with crossover design (with desipramine) provided some evidence that clomipramine may be superior to desipramine in reducing repetitive behaviors and stereotypies.[25] One subject treated with clomipramine had a seizure; other adverse effects of clomiptamine included prolonged QTc interval (ECG change) in one subject and tachycardia in another. Open label studies of clomipramine, including both children and adults, reported beneficial effects in mixed populations of PDD patients.[26-28] One study showed generally poor response to clomipramine.[29] Adverse effects including urinary retention, drowsiness, aggressive behavior and mood instability were common. Concerns about lowered seizure threshold in this seizure-prone population, the need for electrocardiographic and blood level monitoring, and the inconsistent evidence of benefit, have made many clinicians reluctant to use clomipramine in children with PDD.

2. Fluoxetine

One recent placebo controlled crossover trial examined the effects of liquid fluoxetine on repetitive behaviors in 45 children and adolescents diagnosed with PDDs.[30] The outcome measures included measures of repetitive behavior and global improvement. Liquid fluoxetine in small doses was found more effective than placebo in treating repetitive behaviors with effects size in the moderate to large range. Fluoxetine effect did not separate significantly from placebo on the global improvement measure. Liquid fluoxetine did not significantly differ from placebo on treatment emergent side effects. One open label study has also shown indications of potential benefit from fluoxetine in the treatment of repetitive behaviors in autism.[31] Of note responders tended to be in the lower age group (less than 15). The study noted a high frequency of activation characterized by hyperactivity, insomnia and irritability.

3. Fluvoxamine

Fluvoxamine was helpful for compulsive behavior and aggression as well as increased prosocial behavior, in adults with autism, who participated in a double-blind placebo controlled study.[32] A similar study in children however showed negative results with side effects of behavior activation (hyperactivity, disinhibition, insomnia and aggression) in 12 out of 16 subjects.* Another open label study in children with PDD and anxiety or OCD, in which lower daily doses were used, showed no statistically significant benefit for the study group as a whole, but 8 out of 14 subjects showed "a positive response" (33). Activation leading to discontinuation occurred in only 3 subjects, suggesting that activation is dose related.

4. Sertraline

No controlled studies on sertraline in subjects with autism have been published. Several open label studies have demonstrated benefits for aggression, repetitive and self-injurious behavior in adults with PDD.[34-35] In a case series[36] eight out of nine children with autism, sertraline showed significant improvement in anxiety, irritability and ability to manage transitions. Two exhibited agitation when the dose was raised to 75 mg/d.

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* McDougle, unpublished 2002

5. Paroxetine

No controlled studies have been published with paroxetine in the treatment of individuals with autism. Two single case reports described decreased self-injurious behavior in one case, and reduction in irritability, temper tantrums and preoccupations in another.[37-38] An open label study of adults with mental retardation, some of them with PDD, described effectiveness of paroxetine for treatment of aggression at one month, but not at 4 month follow up.[39]

6. Citalopram and escitalopram

One retrospective review of the medical charts of 15 children and adolescents diagnosed with PDDs assessed the effectiveness and tolerability of treatment with citalopram.[40] Anxiety and mood symptoms, as well as PDD symptoms, were found significantly improved on a clinician rated global improvement measure. Five of the patients (33%) reported "mild side effects". No studies on the use of escitalopram for treatment of PDDs have been published yet in the US. A federally funded multisite study of citalopram in children with PDD targeting repetitive behavior is currently under way in the US.

7. Mirtazepine

Mirtazepine is an atypical antidepressant in that it possesses both serotoninergic and adrenergic activity. An open label trial treating 26 children with autism reported modest efficacy for symptoms including aggression, self-injury, irritability, hyperactivity, anxiety, depression and insomnia. Adverse effects were minimal and included increased appetite, irritability and transient sedation.[41]

In summary, the available evidence provides only limited support for the use of SRIs in children with PDD. The studies conducted have been small in sample sizes and with poorly described target symptoms. Support for the use of these compounds for treatment of repetitive behaviors in children, adolescents and adults with PDD is stronger. Generally safe in short-term trials, these agents seem more likely to cause behavior activation in children, and more commonly in younger children.

Stimulants

The stimulant medications (methylphenidate, d-amphetamine, and d,l-amphetamine) are a well established treatment for Attention Deficit Hyperactivity Disorder (ADHD) in typically developing children. Strong evidence for the long term benefits of well managed stimulant medication was provided by a recent large multicenter trial sponsored by the National Institute for Mental Health (NIMH).[42] Motor restlessness, hyperactivity, distractibility and disruptive behavior are common symptoms in children with PDDs. The use of stimulants in the population of children with PDD and hyperactivity has been the focus of recent interest (Table 2).

Community and clinic-based surveys indicate that the stimulants are commonly used in children with PDD. Published data suggest that stimulant medication can be effective in children with developmental disabilities and ADHD symptoms. However children with developmental disabilities and ADHD are at higher risk of adverse effects from stimulant treatment than typically developing children with ADHD. Also the rate of responders and the mean percentage of improvement are somewhat lower. Preliminary results from the RUPP Autism Network are consistent with these general conclusions. In the RUPP study, 66 children participated in a crossover study involving three dose levels of methylphenidate and placebo.

Miscellaneous compounds
1. Mood stabilizers

Anticonvulsants are commonly used in clinical practice in the treatment of autistic children and adults. This has to do partly with the high incidence of seizure disorder in autistic individuals. However this class of compounds has been also evaluated in several case studies and small open-label studies in the treatment of aggression and behavior dyscontrol associated with autism. Single cases have been reported on the use of lithium carbonate in the treatment of refractory aggression in adults with autism.[43-44] A retrospective case series of divalproex sodium use in the treatment of children and adults with autism reported favorable changes in instability, repetitive behaviors and aggression.[45] A study of lamotrigine in 28 children with autism showed no separation between active drug and placebo on measures of stereotypies, lethargy, irritability, hyperactivity, emotional reciprocity, sharing pleasures and in language and communication, socialization, and daily living skills noted after 12 weeks.[46] Concern about adverse skin reactions in children – skin rash and Steven-Johnson Syndrome – cause many clinicians to be reluctant about the use of this drug in children.[47]

Table 2 - Placebo-controlled studies of methylphenidate in developmentally disabled populations

Author, year	n	Age	Population	Design	Dose	Teacher measure	Parent measure
Varley et al., 1982	10	4-15	ADHD+ MR	X-Over	5-60 mg/day	13%[2]	14%[3]
					15-120 mg/day	19%[2]	20%[3]
Hagerman et al., 1988	15	4-12	ADHD+ Fra-X	X-over (d-amphetamine)	0.3 mg/kg/dose	21%[2]	11%[2]
Handen et al., 1990	12	6-9	ADHD+ MR	X-Over	0.3 mg/kg/dose	44%[2]	-
					0.6 mg/kg/dose	58%[2]	-
Aman et al., 1991	30	4-16	ADHD+ MR	X-Over (thioridazine)	0.4 mg/kg/dose	18%[2]	-
Aman et al., 1993	28	5-13	ADHD+ MR	X-Over (fenfluramine)	0.4 mg/kg/dose	35%[1]	20%[1]
Aman et al., 1997	30	5-14	ADHD+ MR	X-Over (fenfluramine)	0.4 mg/kg/dose	23%[1]	21%[1]
Quintana et al., 1995	10	7-11	Autism	X-Over	10-20 mg bid	11%[2]	31%[1]
Handen et al., 1999	10	4-6	ADHD+ MR	X-Over	0.3 mg/kg/dose	32%[2]	-
					0.6 mg/kg/dose	47%[2]	-
Handen et al., 2000	13	5-11	ADHD+ PDD	X-Over	0.3 mg/kg/dose	43%[2]	-
					0.6 mg/kg/dose	56%[2]	-
Pearson et al., 2003	24	10.9 (mean)	ADHD+ MR	X-Over	0.15 mg/kg/dose	13%[2]	7%[3]
					0.3 mg/kg/dose	27%[2]	12%[3]
					0.6 mg/kg/dose	58%[2]	16%[3]

[1] ABC Hyperactivity; [2] Conners Teacher Hyperactivity Index; [3] Conners Parent Hyperactivity Index
Note: Percent change = (change in active treatment - change in placebo) / baseline, or   (placebo endpoint – active endpoint) / placebo.

2. Naltrexone

Naloxone and naltrexone are opiate antagonists that have been evaluated in autism. Naloxone is short-acting and has to be administered parenterally. This limits its clinical applications. The plasma half-life of orally administered naltrexone is between 4 and 10 hours. The use of these compounds in autism is based on the putative role of endogenous opioids such as beta-endorphin and encephalins in the regulation of social behavior. Results from animal studies suggest that opioids may play a role in maternal-infant attachment by influencing feelings of social comfort and reducing separation distress reactions. Initial reports of open-label studies with naltrexone in autism seemed promising,[48-49] but results of subsequent placebo-controlled studies were disappointing. Modest benefits were observed in hyperactivity,[50-51] but no positive effects for language function or communication.[52] Common side effects were sedation and decreased appetite.

3. Secretin

There was much initial excitement concerning the use of the gastrointestinal peptide secretin in the treatment of autism.[53] A series of randomized, double-blind, placebo-controlled trials of intravenous infusion of the agent followed. Indeed, secretin is the best-studied drug for treatment of autism, involving nearly 600 children. The results of these studies are remarkably consistent showing no evidence of efficacy for secretin in autism.

Altogether nearly 500 children with autism or PDD have been studied during randomized clinical trials of secretin. Thus although it is perhaps the best-studied treatment for autism, secretin is not effective (Table 3).

Table 3 - Studies investigating treatment with secretin

Author	n	Design	Result
Sandler et al. 1999	60	Single dose vs placebo	No difference
Dunn-Geier et al. 2000	95	Randomized placebo controlled	No difference
Coniglio et al. 2001	60	Single dose vs placebo	No better than placebo on parent rated symptoms of autism or language skills 6 weeks after injection
Carey et al. 2002	12	Single site	No benefit for language
Corbett et al. 2001	8	Single site	No benefit
Owley et al. 2001	56	Multi site	No benefit

Several promising new directions have originated in the research of drugs for autism. Neuroimmune therapies are based on proposed viral and autoimmune mechanisms in the aetiology of autism. An extensive body of literature regarding immune abnormalities in autistic disorder has been published.[54] Only limited number of treatment studies have been conducted in this area. DelGuidice-Asch reported that open label, intravenous immunoglobulin was of only limited benefit in a minority of subjects, if at all.[55] Sandler et al. reported a 8-week open label trial of the antibiotic vancomycin in 10 children with "regressive" onset autistic disorder, following antecedent broad-spectrum antimicrobial exposure.[56] Eight of the ten children were noted to show improvement in communication and behavior during the study, with return to baseline upon drug discontinuation. The authors concluded that there is possible gut flora – brain connection, which warrants further investigation. Controlled studies of drugs having direct effect on immune function have not been conducted in autistic disorder.

Glutaminergic function has been recently researched vigorously and is considered to be affected in a number of neuropsychiatric disorders.[57] Parallels are drawn between schizophrenia, which is considered a hypoglutamatergic disorder and autism, which also has been suggested to represent a hypoglutamatergic disorder.[58] Negative symptoms of schizophrenia, including social withdrawal, resemble behaviors characteristic of autistic disorder, and are thought to be related to glutaminergic receptor function. 5-HT2A antagonist and Glutamate agonist have been proposed as potential therapy for autism.[58] One compound of interest is D-cycloserine (DCS) a partial agonist of the strychnine-insensitive glycine recognition site or glycineB-site on the NMDA receptor complex. Originally DCS was used to treat tuberculosis with a mild side effect profile. Largely because full glycineB agonists (e.g. glycine, d-serine) often produce serious side-effects like neurotoxicity, DCS and other partial agonists are receiving more and more attention for their modulatory effects at the NMDA receptor complex. At low doses (50 mg/d or < 20 mg/kg) DCS has an agonistic profile, but at higher doses it can displace agonists with higher intrinsic activity and show an antagonistic profile, such as anticonvulsive activity.

Based on the glutamatergic receptor hypofunction hypothesis and the fact that DCS has, at least at lower doses, a facilitatory effect at the NMDA receptor, there might be a role for DCS in autism. DCS has been shown to facilitate learning and memory recovery. This was experimented through fear extinction measured with potentiated startle in rats.[59] Recently the findings of potential benefit for DCS as an addition to antipsychotics in the treatment of schizophrenia were substantiated in an fMRI study, which found that the beneficial effect of DCS on negative symptoms of schizophrenia was associated with enhanced temporal lobe function.[60] An open label pilot-study with DCS in humans with Autistic Disorder found an association with reduced social withdrawal and increased social responsiveness as measured on the social withdrawal subscale of the ABC.[61] Only at the highest dose some adverse effects were reported.

In combination the above mentioned effects in schizophrenia and the positive preliminary findings of Posey et al. suggest DCS as a possible treatment option for autism, as mono- or adjunct therapy. Larger double-blind placebo-controlled randomized clinical trials seem warranted.

Amantadine hydrochloride is another glutaminergic compound acting as a noncompetitive antagonist at the NMDA receptor. King et al 2001 examined the effects of amantadine in a double-blind placebo-controlled trial involving 39 individuals with autistic disorder.[62] There was no statistically significant difference in parent rated measures of irritability and hyperactivity between amantadine and placebo. Clinician-rated measures of hyperactivity and inappropriate speech showed statistically significant improvement in the amantadine group. The drug was well tolerated.

Conclusion

Advances in the pharmacological treatment of autistic disorder have followed biological research in that area since it began in the 1950s and have been modest. Only a limited number of randomized, placebo-controlled studies have been published. Recent action of the US NIMH to fund the RUPP autism network has resulted in completion of the largest controlled therapeutic trial in autistic disorder to date. Although with disappointing results, the recent series of secretin studies demonstrate improved capacity in the field to carry out rigorous

clinical trials examining efficacy and safety. Future research is likely to include additional trials of antipsychotics in individuals with autistic disorder and PDD. Assessment of long-term safety and efficacy is needed with all therapeutic agents. Larger controlled studies of stimulants and SRIs have been already undertaken and are likely to inform further clinical practice. New compounds, based on advances in understanding the pathophysiological underpinnings of the disorder, are also likely to emerge. Trials looking at the combination and sequencing of pharmacological and behavioral treatments are needed and have been launched by the RUPP Autism Network.

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