

Advances in Drug Treatments for Children and Adolescents with Autism and Other Pervasive Developmental Disorders

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Abstract

Autism is a disorder characterised by abnormalities in language and social development, and repetitive behaviours. Antipsychotics, including haloperidol and risperidone, are the most widely studied drugs for reducing symptoms in children and adolescents with autism. When administered at relatively low dosages, antipsychotics have been shown to reduce repetitive behaviours (stereotypies) and social withdrawal, as well as a number of related symptoms, such as hyperactivity, aggression, self-abusive behaviour, temper tantrums, lability of mood and irritability. Adverse effects of antipsychotics include sedation, dizzi-

ness, increased appetite, weight gain, changes in the electrocardiogram parameters, drooling, hyperprolactinemia and a risk of drug-related dyskinesias.

Other agents have been less well studied for the treatment of autism, but there are suggestive data regarding their safety and efficacy. Of these agents, a number have been investigated, based on theories about the aetiology of autism, including SSRIs and naltrexone, although the efficacy of these agents has been limited. Stimulant drugs have been shown to reduce hyperactivity and improve focus, but they may cause behavioural worsening, weight loss and stereotypies *de novo*. Secretin is a treatment that has received much media attention after reports of efficacy from small open studies, but all controlled studies have failed to show any benefit. In autism, alternative treatments have also been used, but none have shown benefit in well-designed studies.

Autism is a serious childhood disorder that is characterised by abnormalities in reciprocal communication and socialisation, and other symptoms, such as repetitive behaviours, insistence on sameness and restricted interests.^[1] It is the prototypical disorder included in the pervasive developmental disorders in DSM-IV.^[1] The other pervasive developmental disorders have presentations similar to autism, but there are quantitative or qualitative differences in their symptomatology.

Many mainstay non-pharmacological treatments for affected children are directed at improving language and socialisation, including educational programmes, speech and occupational therapies, and behavioural and psychosocial approaches. Drug treatment has a place in reducing symptoms and can enhance the quality of life of children and adolescents and their families. When used judiciously, drug treatment can also make the child or adolescent more amenable to the non-pharmacological treatment modalities.

This article reviews drug treatments for children and adolescents with autism with an emphasis on data from controlled studies. Alternative treatments are briefly discussed as well. The drug treatment studies published to date have been short-term (table I), with the exception of some of the studies of antipsychotics, making it necessary for clinicians to extrapolate from short-term data when administering drug treatment long term. The studies of alternative treatments that we review are limited by meth-

odological flaws including small sample size and study designs with limited controls.

1. Drug Treatments

1.1 Antipsychotics

Antipsychotics, including both the conventional and atypical agents, are the class of drugs that have been the most studied in autism. As is the case for all drug treatments in autism, antipsychotics are not curative but can be used to reduce symptoms, thereby enhancing the effects of other ongoing psychosocial and educational treatments.

1.1.1 Haloperidol

The conventional agent, haloperidol, is among the most studied agents in autism. Its use has been investigated in both short-term^[3-7] and long-term studies.^[25] Administered at low dosages, it was found to be effective in reducing hyperactivity, aggression, self-injurious behaviour, temper tantrums, lability of mood, irritability, social withdrawal and stereotypical behaviours.^[2,4,26] However, haloperidol administration was associated with the development of drug-related dyskinesias.^[27] The concern about drug-related dyskinesias, in part, led to the study of atypical antipsychotics in autism, drugs that purportedly cause fewer dyskinesias.^[28]

1.1.2 Risperidone

Of the atypical agents, risperidone is the most extensively studied for use in children with autism.

Not only are there a number of favourable open reports,^[29-38] but a large double-blind placebo-controlled multi-site study of risperidone in children with autism, conducted by the Research Units on Pediatric Psychopharmacology Autism Network, reported efficacy in this population.^[2] The subjects, 101 children with autism, aged 5–17 years (mean, 8.8 ± 2.7), were treated for 8 weeks with either risperidone 0.5–3.5 mg/day (mean, 1.8 ± 0.7 mg/day) or placebo. The inclusion criteria for the study required the presence of tantrums, aggression and self-injurious behaviour, which were measured using the irritability subscale of the Aberrant Behavior Checklist (ABC). Risperidone was significantly superior to placebo on both of the study's primary efficacy measures, the irritability subscale of the ABC and the Clinical Global Impressions-Improvement (CGI-I) item. Adverse effects included weight gain, increased appetite, fatigue, drowsiness, dizziness and drooling. Thus, a body of evidence indicates that risperidone may be a relatively well tolerated and effective treatment in children with autism.

Extrapyramidal symptoms and dyskinesias have been reported with risperidone usage in this population,^[35] albeit at a lower rate than with conventional agents such as haloperidol.^[39,40] Notably, risperidone is the only atypical antipsychotic that has been associated with sustained hyperprolactinemia in adults.^[41] In fact, it may cause greater increases in prolactin than some of the conventional antipsychotics such as haloperidol.^[41] Dunbar and colleagues^[42] assessed the impact of risperidone on growth and sexual maturation. The report pooled data from five studies that included 700 children with disruptive behaviour disorders who were aged 5–15 years, 350 of whom received risperidone for 11 or 12 months. They found that the children treated with risperidone had a mean increase in height (1.2cm greater than the reference population) and experienced no delay in progression through Tanner staging. Thus, the increases in prolactin level were not correlated with any interference in growth or sexual maturation.

1.1.3 Olanzapine

Apart from those on risperidone,^[4] most studies of atypical agents have been of open treatment design.

Olanzapine was studied in an open trial that included an established comparator treatment of haloperidol.^[43] The subjects were 12 children, aged 4.9–11.8 years (mean, 7.8 ± 2.1), diagnosed with autism. Of these, six were randomised to olanzapine 5–10 mg/day (mean, 7.9 ± 2.5 mg/day) and six to haloperidol 0.5–2.5 mg/day (mean, 1.4 ± 0.7 mg/day). Olanzapine was found to be as effective as haloperidol on the study efficacy measures (the CGI-I and the Children's Psychiatric Rating Scale). The most common adverse events with olanzapine were sedation and weight gain. As is true for risperidone, weight gain should be monitored and findings discussed with families. Also, laboratory studies for lipid, glucose and haemoglobin A1c levels should be considered, especially in patients with significant weight gain.

1.1.4 Ziprasidone

Ziprasidone, an atypical antipsychotic that is purportedly weight neutral,^[44] has been investigated in two open-label studies.^[45,46] The main safety concern for this drug is that administration has been associated with prolongation of the corrected QT interval (QTc) [mean = 20 msec]. The relevance of such a 20 msec increase in the QTc is unclear, particularly in children. It is a signal, however, that this agent has an effect on ventricular repolarisation.^[47]

In a case series of 12 patients (mean age, 11.62 years), diagnosed with autism or pervasive developmental disorders that were not otherwise specified, McDougle and colleagues^[46] reported that ziprasidone was effective in half of the patients. Overall, they did not gain weight and, in fact, over the course of the study, patients had a mean weight loss of 5.8 ± 12.5 lb. It should be noted that five of the 12 patients were receiving other antipsychotic agents during the initial phase of ziprasidone treatment, a confounding factor in the assessment of whether weight changes were a result of terminating treatment with the other agent. No post-treatment electrocardiograms were performed to assess the effect of ziprasidone on QTc.

Malone and colleagues^[45] reported on a 6-week open trial of ziprasidone. The subjects were eight

Table I. Selected double-blind, placebo-controlled studies of pharmacological treatments in children and adolescents with pervasive developmental disorder

Drug	Dose (daily)	No. of patients analysed	Age (y)	Sex	Outcome	Adverse events	Design	Reference
Antipsychotics								
Risperidone	0.5–3.5mg Mean = 1.8	101	5–17 Mean = 8.8	82 males 19 females	Positive	Weight gain, increased appetite, fatigue, drowsiness, dizziness, drooling	Parallel	2
Haloperidol	0.25–4.0mg Mean = 0.8	45	2–7.6 Mean = 4.5	35 males 10 females	Positive	Sedation, acute dystonic reaction	Crossover	3
Haloperidol	0.5–3.0mg	40	2.3–6.9 Mean = 4.6	29 males 11 females	Positive	Sedation, acute dystonic reaction	Crossover	4
Haloperidol	0.75–6.75mg	87	3–16	69 males 18 females	Positive	Sleepiness	Crossover	5
Pimozide	1.0–9.0mg							
Haloperidol	1.0–4.0mg	10	2.1–7 Mean = 4.7	6 males 4 females	Positive	Sedation, acute dystonic reaction	Crossover	6
Haloperidol	0.5–4.0mg Mean = 1.65	40	2.6–7.2 Mean = 4.5	32 males 8 females	Positive	Sedation	Factorial	7
SSRIs								
Fluoxetine	4.8–20mg Mean = 9.9	39	5–16 Mean = 8.2	30 males 9 females	Positive	None compared with placebo	Crossover	8
Fluvoxamine	25–250mg Mean = 106.9	34	5–18 Mean = 9.5	29 males 5 females	Negative	Insomnia, hyperactivity, agitation	Parallel	9
Stimulants								
Methylphenidate	0.3 mg/kg bid or tid 0.6 mg/kg bid or tid.	13	5.6–11.2 Mean = 7.4	10 males 3 females	Positive	Irritability, social withdrawal	Crossover	10
Methylphenidate	10mg bid 20mg bid	10	7–11 Mean = 8.5	6 males 4 females	Positive	None compared with placebo	Crossover	11
Levoamphetamine	3.5–42mg Mean = 13.4	12	3–6 Mean = 5.4	10 males 2 females	Negative	Weight loss, decreased appetite, irritability, increased stereotypies	Crossover	12
Levodopa	900–2250mg Mean = 1487							
Dexamfetamine (dextroamphetamine)	1.25–10mg	16	3–6 Mean = 4.3	13 males 3 females	Negative	Irritability, hyperactivity, withdrawal, increased stereotypies, decreased appetite	Crossover	13
Liothyronine (triiodothyronine)	12.5–75µg Mean = 47							

Continued next page

Table I. Contd

Drug	Dose (daily)	No. of patients analysed	Age (y)	Sex	Outcome	Adverse events	Design	Reference
α-Adrenoceptor agonists								
Transdermal clonidine	0.005 mg/kg	9	5–33 Mean = 12.9	All males	Positive	Redness/itching at patch site, sedation, fatigue, irritability	Crossover	14
Clonidine	4–10 μ g/kg	8	5–13.4 Mean = 8.1	All males	Positive	Drowsiness, decreased activity, hypotension, irritability	Crossover	15
Opiate antagonists								
Naltrexone	0.74–1.2 mg/kg	23	3–7	NR	Positive	Sedation, slowed down	Crossover	16
Naltrexone	1.0 mg/kg	13	3.4–8.5 Mean = 5.4	12 males 1 female	Positive	Drowsiness, crying, aggression	Crossover	17
Naltrexone	0.5 mg/kg	10	5–14 Mean = 9.5	5 males 5 females	Negative	None	Crossover	18
Naltrexone	0.5–1.0 mg/kg	41	2.9–7.8 Mean = 4.9	34 males 7 females	Positive	Sedation, vomiting, decreased appetite	Parallel	19
Peptide hormones								
Porcine and synthetic secretin	1 dose	85	3–12	NR	Negative	NR	Parallel	20
Porcine secretin	2 doses	64	2–7	55 males 9 females	Negative	NR	Parallel	21
Porcine secretin	1 dose	56	3–12 Mean = 6.7	48 males 8 females	Negative	Rash, vomiting, screaming	Crossover	22
Porcine secretin	1 dose	60	3–10	NR	Negative	Irritability, hyperactivity, nausea/vomiting	Parallel	23
Synthetic secretin	1 dose	60	3–14	NR	Negative	NR	Parallel	24

bid = twice daily; **NR** = not reported; **tid** = three times daily.

males diagnosed with autism (DSM-IV) who ranged in age from 12.1 to 16.8 years (mean age, 14.4 years). Ziprasidone was individually titrated between dosages of 40 and 160 mg/day (mean, 91.4 ± 47). Four subjects were classified as treatment responders using the CGI-I. Adverse effects associated with ziprasidone administration included drowsiness and decreased appetite. One child had a dystonic reaction. The change in QTc, from baseline to the end of the study, ranged from -13 to 52 msec (mean, 17.3 ± 27.8), similar to that reported in adults.^[48] The change in body mass index ranged from -1.61 to 1.85 (mean, 0.064 ± 1.0), indicating that ziprasidone was weight neutral. Overall, the data suggest that ziprasidone may have a place in treating this population, particularly in those for whom weight gain is an issue.

1.1.5 Quetiapine

Reports concerning the use of quetiapine in the treatment of children with autism have been less promising than the previously mentioned drugs. Both Martin et al.^[49] and Findling et al.^[50] reported that quetiapine was not effective in open treatment studies. However, more data are needed, as few studies with quetiapine have been conducted.

1.1.6 Clozapine

There are reports from open-label studies of efficacy for clozapine in this population.^[51,52] However, clozapine is associated with an increased risk of agranulocytosis, a risk not shared by the other atypical antipsychotics. Because agranulocytosis can be fatal, clozapine can be prescribed only in the presence of frequent and ongoing blood testing, which is problematic in children. Additionally, clozapine decreases the seizure threshold, which is a particular problem in autism because children with autism have a substantial risk of developing seizure disorders.^[53,54]

1.2 SSRIs

Children with autism have repetitive behaviours and often a restricted range of interests. This has led to speculation that the symptoms in autism parallel the obsessions and compulsions found in patients

with obsessive-compulsive disorder (OCD), and that children with autism may respond to treatments used in the treatment of OCD.

In a study conducted at the National Institute of Mental Health,^[55] the tricyclic antidepressant clomipramine, which has serotonin reuptake inhibiting properties, was compared with desipramine, another tricyclic antidepressant, which is a less specific serotonin reuptake inhibitor, under double-blind placebo-controlled conditions. The subjects were 30 patients, aged 6–23 years, diagnosed with autism. Clomipramine treatment was associated with a reduction of symptoms, including compulsive ritualised behaviours. Both drugs reduced hyperactivity. However, clopiramine administration was associated with a number of adverse events, including prolongation of the QTc, severe tachycardia and grand mal seizures.^[55] Subsequently, an open study of clomipramine in a younger population of children with autism (aged 3.5–8.7 years) reported that most subjects had behavioural worsening along with other adverse events, including urinary retention, severe constipation and insomnia.^[56] An additional study of clomipramine that included adolescents with autism reported that adverse events led to a high drop out rate (12 of 32; 37.5%).^[57] Regardless, interest in this agent has waned since the introduction of the SSRIs, drugs that have also been effective in treating OCD.

Chart reviews and open-labeled reports on the use of SSRIs in children with autism include studies of fluoxetine,^[58–60] citalopram^[61,62] and venlafaxine,^[63] with most reporting that the drugs appeared to reduce symptoms in this population. In a study that included 23 children with autism, Cook et al.^[58] reported that open-label fluoxetine was effective in reducing symptoms as rated by the CGI-Severity Score. The subjects ranged in age from 10 to 16 years and fluoxetine dosages ranged from 20mg every other day to 80 mg/day. Six of the 23 (26%) subjects with autism experienced adverse events such as restlessness, hyperactivity, agitation and insomnia. DeLong et al.^[60] described open-label usage of fluoxetine in children with autism, and

suggested that the drug may be safe and produce positive results.

Of the two double-blind and placebo-controlled studies of SSRIs in children and adolescents with autism^[8,9], one had some positive findings,^[8] while the other found no treatment effect.^[9] In the study by Hollander et al.,^[8] the primary focus was to investigate the effectiveness of liquid fluoxetine in reducing repetitive behaviours in children and adolescents with autism. Of the 45 subjects randomised to treatment, 39 were included in the analyses of safety and efficacy. The authors found that fluoxetine reduced repetitive behaviours, but that the drug was not effective in reducing global behaviours. In this study, there were no significant differences in adverse events between the drug treatment and placebo groups. McDougale and colleagues^[9] conducted a double-blind, placebo-controlled trial of fluvoxamine in children and adolescents and found that the drug was no more effective than placebo, although adverse effects were encountered. In the study, only one of 18 subjects in the fluvoxamine group responded, while none of the 16 in the placebo group responded. Of note, the same group conducted a double-blind, placebo-controlled study in adults with autism^[64] and found that fluvoxamine, at dosages ranging from 200 to 300 mg/day (mean, 276.7 ± 42 mg/day), was superior to placebo on measures of global improvement and measures of repetitive behaviour, maladaptive behaviour and aggression. Adverse events in adults included sedation and nausea.

When considering the use of SSRIs and other antidepressants in children with autism, it is important to note that there has been a concern that these drugs may cause agitation and suicidality in children, making it prudent to warn patients of this possibility.^[65,66] In this population, the risk of agitation may be a particular concern as behavioural worsening has been noted with other classes of drugs, including the stimulants and antipsychotic agents.^[10,12,13]

1.3 Stimulants

There are few controlled studies that have examined the use of stimulants in children with autism. The evidence, mainly from small studies,^[10-13] suggests that stimulants can reduce hyperactivity and increase attention in some children with autism. For example, in a double-blind, placebo-controlled, crossover design study, Quintana et al.^[11] investigated the use of two dosages of methylphenidate (10mg or 20mg twice a day) in 10 children diagnosed with autism and aged 7–11 years, and reported a reduction of hyperactivity. Similarly, in a double-blind placebo-controlled crossover study, Handen et al.^[10] reported that methylphenidate 0.3 mg/kg and 0.6 mg/kg, given twice- or three-times daily, reduced hyperactivity.

However, some children with autism demonstrate behavioural worsening with these agents.^[10,12,13] Adverse effects include increased social withdrawal and irritability,^[10,13] worsened hyperactivity, increased and *de novo* stereotypies, as well as decreased appetite and weight loss.^[12,13]

Thus, the studies to date have involved few subjects, but the findings suggest that stimulants may be helpful in reducing hyperactivity in some children with pervasive development disorders, but that these agents can also cause behavioural worsening.

1.4 Naltrexone

Naltrexone, an opiate antagonist, was studied as a treatment to reduce symptoms in autism based upon the hypothesis that symptoms are the result of an abnormality in the endogenous opioid system.^[67-69] However, the response to naltrexone in this population has been minimal, with some studies showing no effect.^[18,65] The largest double-blind placebo-controlled study was conducted by Campbell et al.^[19] In a parallel group design, children with autism, aged 2–7 years, were randomised to naltrexone (up to 1.0 mg/kg/day) or placebo. The only significant effect of naltrexone was a reduction of hyperactivity, a finding replicated by others.^[16,17] The data also suggested that naltrexone administration was associated with a reduction in self-injurious

behaviours, a finding replicated in some,^[70] but not all, studies, including those in adults.^[71,72]

1.5 α -Adrenoceptor Agonists

Studies suggest that α -adrenoceptor agonists, including clonidine and guanfacine, can be effective for the treatment of attention-deficit hyperactivity disorder and tics.^[73,74] Controlled data regarding the use of these agents in children with autism is limited. In a 12-week double-blind, placebo-crossover study, Fankhauser et al.^[14] investigated the use of transdermal clonidine 0.005 mg/kg/day in nine males diagnosed with autism and ranging in age from 5 to 33 years. The authors reported a significant reduction in self-stimulation, stereotyped body movements, hyperactivity and hypervigilance. Adverse effects included sedation and fatigue.

Employing a double-blind, placebo-controlled, crossover design, Jaselskis and colleagues^[15] investigated the use of clonidine in eight male children diagnosed with autism, ranging in age from 5 to 13.4 years. The drug was administered three times daily and the dosage was individually titrated (4–10 μ g/kg/day or 0.15–0.20 mg/day). The authors reported a modest reduction in irritability and hyperactivity. However, only two of the eight children could tolerate long-term treatment with clonidine, due to adverse effects that included irritability, drowsiness and hypotension.

No controlled studies of guanfacine in children with autism have been published.

2. Other Treatments

2.1 Secretin

Secretin, a peptide hormone produced in the duodenum, promotes pancreatic secretion of sodium bicarbonate and water^[75] and has been used to evaluate pancreatic function. There are two forms of secretin, a porcine-derived form (no longer available) and a human-derived synthetic form^[76]. Children with autism who have received secretin have reported adverse effects including diarrhoea, consti-

pation, vomiting, hyperactivity, flushing and irritability.^[77]

In 1998, Horvath et al.^[78] reported that three children with autistic spectrum disorders had reduced autism-related symptoms after they received secretin 2 IU/kg of as part of gastrointestinal testing. This report was widely disseminated by the media, leading many parents to seek secretin for their children with autism. However, double-blind, placebo-controlled studies of both porcine^[20-23,79,80] and human synthetic secretin^[20,24,76,81] have not demonstrated efficacy in autistic spectrum disorders.

Although there has been some disagreement about whether the dosage strategies used in the studies have been optimal, it was recently reported that an industry-sponsored^[76] multi-site study of synthetic human secretin failed to show superiority of the drug over placebo. This was a phase III study in which 132 autistic children aged 2.7–4.9 years received six injections of secretin or placebo over an 18-week period. The failure of this multi-site study to show efficacy, in conjunction with the negative results from previous studies, further suggests that secretin is not beneficial in this population.

2.2 Cholinesterase Inhibitors

Donepezil, a cholinesterase inhibitor used for treating dementing illnesses such as dementia of the Alzheimer's type, has been investigated in an open study^[82] in autism, but data to support such use are limited.

2.3 Oxytocin

Oxytocin is a neurohypophyseal peptide. It is thought to have central action as a neurotransmitter or neuromodulator and to influence the behaviours, such as social learning, that are abnormal in autism.^[83] Hollander et al.^[84] reported that an oxytocin challenge produced a brief decrease in repetitive behaviours in a sample of 15 adults with autism and Asperger's disorder. Adverse effects included drowsiness, anxiety, depression, headache, tingling, backache, trembling, restlessness, stomach cramps and enuresis. Oxytocin cannot be recommended for

clinical use in this indication without further significant study.

3. Alternative Treatments: Vitamins and Nutritional Therapies

3.1 Vitamin B6

Rimland and colleagues,^[85] one of the first groups to administer vitamin B6 to children with autistic symptoms, reported benefit. Since then, a number of studies with some controls have been conducted, also suggesting benefit.^[86,87] However, Findling and colleagues^[88] conducted a 10-week double-blind, placebo-controlled trial of pyridoxine and magnesium in ten patients and failed to find a treatment effect, replicating another controlled trial.^[89] A review of studies on the efficacy of vitamin B6 and magnesium in the treatment of autism concluded that the studies with positive findings had a number of methodological flaws, making interpretation of the results difficult.^[90] This conclusion is disputed by Rimland.^[91]

3.2 Gluten/Casein-Free Diet

The most frequently cited diet in the treatment of autism is the gluten/casein-free diet.^[92] Gluten and casein are dietary proteins found in wheat/barley and cow's milk, respectively. It is hypothesised that toxins released with the incomplete breakdown of gluten and casein cause autism. By excluding these proteins, gluten- and casein-free diets eliminate the toxins.^[93,94] However, data to support these claims are limited, coming from open trials and small controlled studies.^[94]

4. Conclusion

While there is currently no cure for autism, psychotropic drugs, when used appropriately, can alleviate a number of behavioural symptoms in children, such as ritualistic and perseverative behaviours, tantrums, hyperactivity and aggression. Symptom reduction enhances the quality of life for both the child and the family.

Among the drugs that have been studied for the treatment of children with autism, antipsychotics, namely haloperidol and risperidone, are the most widely studied agents. While these have been shown to be effective in at least five double-blind and placebo-controlled studies, a concern with haloperidol is that administration has been associated with dyskinesias in this population. Risperidone is likely to be associated with a lower risk for dyskinesias but may cause more weight gain.

Other drugs are less well studied than the antipsychotics in autism. SSRIs have provided mixed results in controlled studies and have not been shown to be globally effective in this population. Naltrexone has proven to have only minimal benefit. The stimulants may increase focus and decrease hyperactivity, but there is a risk of adverse events, including behavioural worsening.

It is important to note that for a variety of reasons, some novel treatments become widely used before definitive studies are conducted, and once critically studied, often prove to be largely ineffective. This was the case with secretin, which was widely publicised as a treatment for autism. However, controlled studies have not shown secretin to be more effective than placebo. Newer agents such as oxytocin have shown some promise, but should be further and more definitively studied before recommendations about their use in this population can be made.

Acknowledgements

Dr Malone is currently being funded by the US FDA (Orphan Product Development) and the National Institute of Mental Health (NIMH) to conduct a study of olanzapine in children with autism; the medication for this study is being provided by Eli Lilly. Dr Malone is also being funded by Pfizer to conduct a study of ziprasidone in adolescents with autism, and by Bristol Myers Squibb to conduct a study of aripiprazole in adolescents with autism. In the past, Dr Malone has conducted an investigator-initiated study of olanzapine in autism (funded by Eli Lilly) and was involved in a long-term study of haloperidol in autism funded by the NIMH (principal investigator: Magda Campbell, MD). Dr Delaney is a co-principal investigator on the aforementioned FDA, Pfizer and Eli Lilly studies. This work was supported in part by grants from the FDA Orphan Product Development (FD-R-002190) and the NIMH (R01MH073524).

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