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DEVELOPING DRUGS FOR CORE SOCIAL AND COMMUNICATION IMPAIRMENT IN AUTISM

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SYNOPSIS

There are many challenges to studying drug effects on core social and language impairment in autism. Drugs such as fenfluramine, naltrexone, and secretin do not appear to be efficacious for these core symptoms. Risperidone has led to improvement in some aspects of social relatedness when used to treat irritability in autism. More research is needed on the utility of selective serotonin reuptake inhibitors, cholinergic drugs, glutamatergic drugs, and oxytocin for core autistic symptoms.

Autistic disorder (autism) is defined by specific impairments affecting socialization, communication, and stereotyped behavior which together are called the “core symptoms” of autism. Another article in this issue addresses stereotyped and repetitive behavior (see Soorya et al.). This article focuses on the development of drugs for core social and communication impairment in autism and other pervasive developmental disorders (PDDs).

The impairment in reciprocal social interaction and communication in autism is severe and persistent and usually includes problems with eye-to-eye gaze, facial expression, body posture, and gestures. Some individuals may have little or no interest in establishing friendships. Others may have an interest in developing relationships, but lack understanding of how to go about it. Individuals with autism often exhibit a significant delay in language acquisition and have difficulty communicating even if language is obtained. Echolalia is also common. Persons with Asperger's disorder and PDD not otherwise specified (NOS) may have relatively intact language, but have difficulty with conversational or pragmatic language.

Finding drugs to effectively target socialization and communication has been challenging to say the least. Many of the drugs showing efficacy in autism are most helpful for symptoms distinct from the core symptoms. Risperidone, the only FDA approved treatment for autism, is specifically indicated for irritability associated with autism. Other associated symptoms that often cause clinically significant problems include inattention, hyperactivity, anxiety, and sleep

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disturbance.[1] Psychiatric drugs are frequently used to address these symptoms in children with autism,[2] although the evidence base supporting this clinical practice is still evolving. In contrast, there are no drugs that are commonly used or proven effective in treating the core social and communication impairments that are the hallmark of PDDs.

A number of challenges to developing drugs that effectively treat social and communication impairment in autism will be discussed in this article. We will also summarize past and recent research involving drugs to treat these core symptoms of autism.

CHALLENGES TO DRUG DEVELOPMENT

Researchers are just beginning to understand the neurobiology of autism and other PDDs. Early research focused on neurochemical abnormalities such as elevated whole blood serotonin (5-hydroxytryptamine [5-HT]), found in a large minority of children with autism. Twin studies have clearly indicated a high degree of heritability with one study finding a monozygotic concordance rate of 92% compared to a dizygotic concordance rate of 10%.[3] Structural neuroimaging has found that brain growth trajectory is altered in young children with autism.[4] Functional neuroimaging has begun to unravel some aspects of the social brain.[5] Despite these emerging findings, the lack of reproducible neurobiological findings has hampered translational research efforts.

Part of the difficulty in understanding the basic pathophysiology may be due to the heterogeneity of those classified as having a PDD. The consistent use of standardized semi-structured diagnostic measures such as the Autism Diagnostic Interview-Revised[6] in research studies has led to consistency across academic centers. However, within this group there continues to be significant differences between patients. Patients may differ widely in terms of the degree of impairment in various core symptoms, as well as intellectual and adaptive functioning. In addition, the number of patients diagnosed as having PDDs is rapidly increasing, owing partly to better recognition and the identification of milder cases which may further lead to this phenotypic heterogeneity.

Despite the increased prevalence of PDDs, these disorders are still relatively uncommon which leads to further challenges in conducting clinical trials of promising drugs. Recent epidemiologic research suggests that PDDs are present in 1 in 166 preschool children.[7] However, the rate of narrowly-defined autism may still only be 1 in 500. Timely recruitment of subject volunteers into clinical research protocols is difficult, but has been improved by the establishment of multi-site research networks such as the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network[8] and industry-sponsored multi-site studies. Identifying patients who are not taking concomitant psychotropic medications is challenging in a disorder where as many as 50% of patients are taking medications for associated symptoms like irritability or hyperactivity.[2]

The study of core social and communication difficulties brings additional challenges. In the majority of children with autism, these symptoms improve naturally over time. For example, some children who are not talking at age 3 years may begin talking by age 5 years. They continue to demonstrate impairment relative to unaffected peers, but the symptoms improve nevertheless. Assessing the efficacy of drugs on this moving developmental target can be difficult. Placebo-controlled studies are essential given improvement which occurs simply with the passage of time, education, and regular speech and language therapy.

Lastly, there is a lack of agreement on which outcome measures are best at assessing the core symptoms of autism and whether any of them will ultimately prove useful in clinical trials. Designing an ideal outcome measure is also challenging due to the heterogeneity of presentation discussed above.

DRUGS NOT EFFECTIVE FOR SOCIAL AND COMMUNICATION IMPAIRMENT

Fenfluramine

Fenfluramine is an indirect 5-HT receptor agonist with structural similarities to amphetamine that was a Food and Drug Administration (FDA)-approved treatment for obesity. In 1997, it was voluntarily withdrawn from the market because of concern that it contributed to the development of cardiac valvular disease.[9] In the 1980s, however, fenfluramine was the target of much interest as a potential treatment for autism because of preliminary reports of efficacy combined with its potential to decrease 5-HT blood levels.[10] Although a subsequent double-blind crossover study was positive,[11] more definitive studies failed to find consistent benefit and suggested that fenfluramine may adversely affect learning.[12]

Naltrexone

Naltrexone is an opioid receptor antagonist that is FDA-approved for the treatment of alcoholism and opioid dependence. It has also been studied as a potential treatment for self-injury and core autistic symptoms based on possible links between autism and opioid dysregulation.[13]

Several double-blind, placebo-controlled studies of naltrexone in autismhave been published. One of the larger of these was completed by Campbell et al. who randomly assigned 41 hospitalized young children (ages 2.9−7.8 years) with autism to either 3 weeks of naltrexone (1 mg/kg/day) or placebo treatment.[14] Naltrexone treated patients showed significant improvement in hyperactivity, but no improvement in learning or core autistic symptoms. Adverse effects were minimal. Another naltrexone (1.48−2.35 mg/kg/day) trial of similar design by Willemsen-Swinkels et al. replicated this in 23 children (ages 3−7 years) with autism.[15] Willemsen-Swinkels et al. also conducted a 4-week, double-blind, placebo-controlled crossover study in adults with mental retardation, 23 of whom had autism.[16] In this study, naltrexone (50 mg) was no better than placebo, and was actually worse on a staff-rated Clinical Global Impressions (CGI) scale.[17]

Double-blind, placebo-controlled studies have failed to support the initial hypothesis that naltrexone alters the core symptoms of autism, including social behavior. Although the drug may improve certain symptoms in some individuals with autism, its effectiveness in the majority of patients is questionable. The most consistent findings coming from these controlled studies is that naltrexone is well-tolerated and may be effective in reducing motor hyperactivity.

Secretin

Secretin is the most recent agent to receive attention as a possible pharmacological treatment for core symptoms of autism. Secretin is a gastrointestinal polypeptide hormone that is FDA-approved for use in the diagnosis of certain gastrointestinal diseases. It also has the distinction of being one of the best studied treatments for autism owing to widespread use following a well publicized case report of three patients with PDD who showed marked improvement when given it as part of a diagnostic evaluation for gastrointestinal problems.[18] As discussed in the article on complementary and alternative treatments by Levy & Hyman in this issue, none of the randomized placebo-controlled studies of secretin have confirmed any positive effect.

DRUGS WHERE MORE RESEARCH IS NEEDED

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are increasingly being prescribed to children with PDDs. Aman et al. recently compared two North Carolina community surveys of psychotropic medication use in autism and found a utilization of 21.4 % for all antidepressants,

the majority of which were SSRIs.[2] In the article by Soorya et al. in this issue, several potential reasons behind this widespread use of SSRIs in autism are discussed including documented abnormalities in 5-HT function in autism and the shared features with obsessive-compulsive disorder (OCD).

McDougle et al. treated 30 adults with autism with either fluvoxamine (276.7 mg/day) or placebo over the course of a 12-week double-blind study.[19] Eight of 15 (53 %) fluvoxamine-treated subjects were rated as responders compared to 0 of 15 placebo-treated subjects. Improvement was seen in repetitive thoughts and behavior, maladaptive behavior, and repetitive language usage. A subsequent unpublished 12-week, double-blind, placebo-controlled study in 34 children and adolescents (ages 5−18 years, mean age 9.5 years) with PDDs found that only 1 of 18 subjects treated with fluvoxamine (106.9 mg/day) responded.[20] There was also a high rate of adverse events including insomnia, hyperactivity, agitation and aggression despite using doses that are usually well tolerated in children with OCD. Thus, fluvoxamine may improve repetitive language or echolalia secondary to autism in adults, but should be used cautiously in children.

Hollander et al. administered fluoxetine to 39 children (ages 5−16 years, mean age 8.2 years) during a 20-week (8 weeks on drug) placebo-controlled crossover study.[21] Liquid fluoxetine was dosed starting at 2.5 mg/day and increased on a weekly basis to reach a maximal target dose of 0.8 mg/kg/day by week 4, if needed. The mean final dose was 0.4 mg/kg/day (mean dose 9.9 mg/day, range 2.4−20 mg/day). Fluoxetine was significantly better than placebo for reducing repetitive behaviors on the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) (Scahill et al., 1997). There was no improvement on measures of speech or social interaction. Side-effects were not significantly different between fluoxetine and placebo. Thus, fluoxetine may lead to a reduction in repetitive behavior or stereotypy in children with PDD.

Placebo-controlled trials support the use of fluvoxamine in adults with autism and fluoxetine in children with PDD for select symptoms, but to date these drugs have not been shown to significantly improve core social and language impairment in controlled studies. Additional uncontrolled reports have reported benefits from other SSRIs including sertraline, paroxetine, citalopram, and escitalopram.[22] Overall, improvements have been most commonly reported in symptoms of anxiety, mood disturbance, aggression, and repetitive behavior. A more optimistic view of the effectiveness of SSRIs has been put forth by De Long et al.[23] In their clinical treatment of 129 young children (ages 2−8 years) with autism, fluoxetine treatment (4−40 mg/day over 5−76 months) was associated with a positive response in 89 of 129 children (69 %). Their report is intriguing in that improvements in a number of core autistic symptoms were reported. However, the data is difficult to interpret in comparison to controlled studies given the lack of standardized outcome measures and placebo control.

Atypical Antipsychotics

Risperidone, an atypical antipsychotic, is the only FDA-approved treatment for autism. Specifically, it is approved for children, ages 5−16 years, with autism accompanied by irritability including aggression, self-injury, tantrums, and mood swings. Much of the research supporting its use has focused on children with high degrees of irritability (see article by Stigler & McDougle in this issue). However, some families report improvement in other symptoms including social interaction. Thus, it is informative to examine social and communication outcomes in these studies.

Risperidone—The first placebo-controlled trial of risperidone conducted in autism involved 31 adults (mean age 28.1 years) with autism or PDD NOS.[24] Risperidone (mean dose 2.9 mg/day) was significantly more efficacious than placebo, with 8 of 14 (57%) subjects being categorized as responders on the CGI-Improvement scale versus none of 16 in the placebo

group. Risperidone was beneficial for reducing interfering repetitive behavior as well as aggression, but did not lead to improvement in social relatedness or language.

The logical next step was to study risperidone in children with autism. The RUPP Autism Network randomized 101 children (mean age, 8.8 years) to 8 weeks of risperidone or placebo.[25] At baseline, all patients had significant irritability, aggression, or self-injury as rated by the Aberrant Behavior Checklist (ABC).[26] Risperidone led to significant reduction on all of the ABC subscales compared to placebo, but the reductions in social withdrawal and inappropriate speech were only significant at the p=0.03 level (insignificant following Bonferroni correction for multiple analyses). To further analyze the efficacy of risperidone on the core symptoms of autism in this group of highly irritable patients, McDougle et al.[27] examined secondary outcome measures that included a modified Ritvo-Freeman Real Life Rating Scale (R-F RLRS)[28] and modified Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).[29] On the R-F RLRS, significant improvement was seen on the following subscales: sensory motor behaviors, affectual reactions, and sensory responses. However, there was no significant change on the social relationship to people or language subscales.

A second multicenter, placebo-controlled study of risperidone in children with PDD was conducted in Canada.[30] Seventy-nine children (mean age 7.5 years) were randomized to either risperidone (mean dose 1.2 mg/day) or placebo for 8 weeks. Significant improvement ($p<0.05$) was seen on all subscales of the ABC, but were of greatest magnitude for irritability and hyperactivity. Social withdrawal decreased by 63% in the risperidone group compared to 40% for placebo ($p<.01$).

Studies have also examined risperidone in even younger children. Risperidone is occasionally needed in very young children due to the severity of the irritability and agitation, which can be extreme.[31] Nagaraj et al.[32] randomized 39 children (ages 2−9 years; mean age 5 years) to risperidone 1 mg/day or placebo and examined ratings on the Childhood Autism Rating Scale (CARS).[33] The children had variable presenting symptoms, but 36/39 (92%) were considered having problems with irritability. At 6 months, 12 of 19 (63%) children treated with risperidone showed a 20% improvement in CARS score compared to none of 20 (0%) treated with placebo. In a study by Luby et al.[34], 23 children (ages 2−6 years; mean age 4 years) also received risperidone (0.5−1.5mg/day) or placebo for 6 months. However, these investigators found risperidone only minimally efficacious compared to placebo at 6 months possibly owing to group differences at baseline or small sample size. In contrast to the study by Nagaraj et al.[32], high degrees of irritability were not required for study entry.

These studies suggest that risperidone may have modest benefit for reducing social withdrawal, repetitive language, and/or core symptoms of autism (as rated by CARS) in children with PDD exhibiting high levels of baseline irritability. It is unclear whether risperidone improves these symptoms in the absence of irritability.

Other atypical antipsychotics—Three prospective open-label trials[35-37] and one small placebo-controlled trial[38] of olanzapine in PDD have been published. All of these studies with the exception of the one from Kemner et al.[37] were positive in terms of olanzapine efficacy. In the latter study, only 3 of 25 (12%) children (mean age 11 years) with PDD receiving olanzapine (mean dose 10.7 mg/day) responded at three months. In contrast to the other studies, disruptive behavior or irritability was not an entry criterion. Potenza et al.[35] found improvement in core social and language impairment in addition to other disruptive behavior and irritability. Excessive weight gain was prominent in all four studies.

Quetiapine, ziprasidone, and aripiprazole have also been examined in pediatric and adult populations with PDD. All of these studies have been open-label in design and are described

by Stigler & McDougle in another article in this issue. None of them reported significant improvements in core social and language impairment in PDD. This is not surprising given the preliminary nature of the research, as well as its focus on the use of these drugs to treat irritability and disruptive behavior. Larger placebo-controlled trials of olanzapine and aripiprazole are underway[39] and will lead to more information on the effects of these medications on core social and language impairment in PDD, at least in the subset of patient with irritability and disruptive behavior.

Cholinesterase Inhibitors

Recently, several investigators have explored the use of four acetylcholinesterase inhibitors: tacrine, donepezil, rivastigmine, and galantamine. All of these drugs are FDA-approved to treat Alzheimer's disease. Tacrine was the first of these drugs to be marketed, but is less frequently prescribed given problems with dosing, tolerability, and safety. A brief case report found only modest benefit of tacrine in three patients with autism.[40]

Hardan & Handen[41] reviewed the charts of eight patients with autism (ages 7−19 years, mean age 11 years) treated with donepezil (modal dose 10 mg/day) and found that 4 of 8 (50%) showed significant improvement. Improvement was seen on ABC ratings of irritability and hyperactivity, but not social withdrawal, inappropriate speech, or stereotypy. Doyle et al.[42] also found open-label donepezil beneficial for attention-deficit/hyperactivity disorder symptoms in another eight youth (ages 10−17 years) with PDDs.

Results from a double-blind, placebo-controlled trial of donepezil have also been published.[43] In this study, 43 children (ages 2−10 years, mean age 7 years) with PDDs received either donepezil (2.5 mg/day) or placebo for six weeks in double-blind fashion. At least 28 (65%) of the subjects had nocturnal epileptiform activity on EEG, and the majority were taking concomitant psychotropic medications. During the first six weeks of the trial, donepezil treatment, but not placebo, was associated with a statistically significant improvement in standardized ratings of receptive and expressive language compared to baseline. However, an opposite effect was seen on other core symptoms of autism; placebo treatment, but not donepezil, led to significant improvement on the CARS compared to baseline. Irritability occurred in 5 of 23 (22%) of subjects initially receiving donepezil compared to none of 20 (0%) subjects receiving placebo.

The efficacy of 12 weeks of open-label rivastigmine (0.4−0.8 mg given twice daily) has also been examined in 32 children (ages 3−12 years; mean age 7 years) with PDDs.[44] The sample included 13 (41%) subjects who had nocturnal epileptiform activity and 23 (72%) who were taking concomitant medications with psychotropic activity. At weeks 6 and 12 of treatment, subjects showed improvement on the CARS compared to baseline. Measures of expressive language, but not receptive language, improved over time as well. However, caution in the interpretation of this is needed given the lack of a control group.

Finally, Nicolson et al.[45] recently published an open-label trial of galantamine in 13 drug-free children (ages 4−17 year, mean age 9 years) with autism. Galantamine was started at 2 mg/day and titrated up to a maximum dose of 24 mg/day. Three subjects withdrew due to either worsening target symptoms (n=2) or headache (n=1). Eight (62%) subjects were rated as responders by CGI. Treatment led to improvements in CGI global severity, ABC Irritability and Social Withdrawal subscales, and Children's Psychiatric Ratings Scale[46] Autism and Anger factors.

These preliminary studies of cholinesterase inhibitors are noteworthy. More rigorously controlled trials of donepezil and galantamine have been completed and will likely be published

shortly.[39] Until then, it is uncertain whether these drugs yet have any role in treating the core social and language impairment of autism.

Glutamatergic drugs

A role for glutamatergic dysfunction in the pathophysiology and treatment of autism has been proposed.[47, 48] Glutamate, the primary excitatory amino acid neurotransmitter in the brain, is important in neuronal plasticity and higher cognitive functioning.[49] Evidence for the role of glutamate in autism comes from several areas including peripheral glutamate study, post-mortem analysis, neuroimaging, and genetic studies.[48] Several reports have appeared that describe treatment of autistic individuals with drugs that affect the glutamate neurotransmitter system.

Lamotrigine—Lamotrigine, an anticonvulsant that attenuates glutamate release, resulted in improvement in "autistic symptoms" in 8 of 13 autistic children and adolescents during a study for intractable epilepsy.[50] Lamotrigine treatment of an 18-year-old female with profound mental retardation and a generalized seizure disorder led to improvement in irritability, sleep, social withdrawal, and emotional responsiveness.[51] Belsito et al.[52] conducted a double-blind, placebo-controlled trial of lamotrigine in 28 children with autism that was not as promising. In this study, lamotrigine (mean dose 5.0 mg/kg/day) was no better than placebo on any of the outcome measures, including the Autism Behavior Checklist,[53] Autism Diagnostic Observation Schedule[54] (Lord et al., 1989), ABC, or CARS.

D-cycloserine—D-cycloserine is an FDA-approved antibiotic used for the treatment of tuberculosis that also acts as a partial agonist at the NMDA subtype of glutamate receptor. Several studies in adults with schizophrenia found that D-cycloserine is beneficial for the treatment of the negative symptoms of schizophrenia.[55, 56] However, a large multi-site study has failed to confirm these finding.[57]

Because of overlap between the negative symptoms of schizophrenia and that of social impairment in autism, our group recently published results of a single-blind study of D-cycloserine directed toward the core social impairment of subjects with autism.[58] Following a 2-week, single-blind placebo lead-in phase, 12 drug-free subjects with autism were given three different ascending doses (30 mg/day, 50 mg/day, 85 mg/day) of D-cycloserine during each of three 2-week periods. Two subjects withdrew from the study after completing only the 2-week placebo lead-in phase. The remaining 10 subjects (8 male, 2 female) (ages 5−28 years, mean age 10 years) completed all 8 weeks of the study. Response rates on the global CGI for the placebo, low, medium and high dose phases were 0%, 30%, 40%, and 40%, respectively. A statistically significant improvement was seen on the ABC Social Withdrawal subscale. Two subjects experienced adverse effects (a transient motor tic and increased echolalia) at the highest dose they received. Results from a double-blind, placebo-controlled study of D-cycloserine monotherapy are currently being analyzed.[39]

N-methyl-D-Aspartate (NMDA) Antagonists—Amantadine, an uncompetitive antagonist at the NMDA subtype of glutamate receptor, has also been studied in autism. Open-label amantadine (dose range 3.7 to 8.2 mg/kg/day) led to improvement in 4 of 8 children with developmental disabilities and associated aggression, hyperactivity, or impulsivity.[59] In a subsequent double-blind, placebo-controlled study, 39 subjects with autism (ages 5 to 19 years) were given amantadine (5.0 mg/kg/day) or placebo.[60] Clinician ratings of hyperactivity and inappropriate speech showed statistically significant improvement and there was a trend towards greater response in the amantadine group, based on ratings on the CGI. There was no statistical difference between amantadine and placebo on parent ratings; amantadine was well tolerated.

Memantine is another uncompetitive NMDA antagonist that is FDA-approved for the treatment of Alzheimer's disease. Memantine has been the subject of a case report,[61] two retrospective reviews[62, 63], and two open-label evaluations[64, 65] in persons with autism and related PDDs. Over eight weeks of treatment with memantine (10 mg daily), a 23-year-old man with autism exhibited significantly reduced irritable behavior and social withdrawal.[61] The effects of open-label memantine (mean dose 10.1 mg/day) over a mean duration of 19.3 weeks in 18 patients (aged 6−19 years) with PDDs were also examined by this group.[62] Eleven (61%) of 18 patients were judged responders based on ratings of “much improved” or “very much improved” on the CGI. Improvement was primarily seen in social withdrawal and inattention. In another retrospective review, 150 children and adolescents (mean age 9 years) with PDDs received memantine (mean dose 12.7 mg/day) for 4−8 weeks. On the CGI, 105/150 (70%) were “much improved” or “very much improved” in terms of language; 106/150 (71%) showed improvement in social behavior. In both of these reviews, memantine was frequently given as an adjunct to other medications.

Niederhofer (2007) reported on an open-label trial of memantine (20 mg/day) in four persons with PDDs (mean age 17.2 years) who were medication-free for at least two weeks prior to the trial.[64] After four weeks of treatment, the irritability, hyperactivity, and inappropriate speech subscales of the ABC had significantly improved. In another open-label trial, 14 children (ages 3−12 years) with PDDs were enrolled in an 8 week study of memantine (0.4 mg/kg/day).[65] Four of 14 (29%) patients were continued on concomitant psychotropic medication during this trial. No patients were judged as “much improved” or “very much improved” on the CGI, although significant improvement was noted on the hyperactivity, social withdrawal, and irritability subscales of the ABC. The results of memantine studies in PDDs to date have been somewhat variable and warrant further, preferably placebo-controlled study to further elucidate the effects of this compound in PDDs.

Dextromethorphan, an antitussive drug with NMDA antagonism, has also been the subject of one placebo-controlled trial employing an ABAB design over 10 weeks in eight children (aged 9 to 17 years) with PDDs (7 with autism, 1 with PDD-NOS).[66] The authors reported no group effect associated with use of dextromethorphan (30−60 mg/12 hours), but they did postulate that the drug was potentially more effective in children who exhibited significant inattention and hyperactivity.

Oxytocin

Oxytocin is a neuropeptide that has been implicated in social affiliation and attachment. Several lines of evidence suggest that it may also play a role in the pathophysiology of autism.[67] In a placebo-controlled crossover study, Hollander et al.[68] infused synthetic oxytocin into 15 adults with Asperger's disorder or autism during a comprehension task where they had to identify the affect (happy, indifferent, angry, and sad) of an audiotaped speaker making neutral statements. The majority of subjects had average to above average IQ. The order of treatments was random; each treatment was conducted on separate days. The comprehension task was performed at baseline and at regular intervals during the 4-hour infusion. Both oxytocin and placebo infusions led to improvement in affective comprehension during the first of two trials. However, those receiving oxytocin first maintained this improvement at the time of the next baseline assessment, whereas those who received placebo first reverted back to their original baseline. This carryover effect makes interpretation of this crossover trial less straightforward, but suggests that further studies are warranted.

SUMMARY

Identifying effective drugs to treat core social and communication impairment in autism presents many challenges. Currently, no drug has been consistently proven to be effective for

the core social and communication impairment so central to the PDDs. Patients with autism exhibiting high levels of irritability may receive benefit in certain aspects of socialization and repetitive speech when prescribed risperidone. However, it is not clear whether this is an effect unique to risperidone or simply secondary to a reduction in irritability. A number of other drugs are promising and deserve further study. Most promising among these are the glutamatergic drugs and oxytocin. However, additional placebo-controlled trials are sorely needed before widely recommending these drugs for core symptom treatment. Conducting these trials is challenging, but significant progress toward the goal of identifying treatments for autism, particularly irritability, has been made over the past quarter century. The rate of progress should increase given the increased interest by society in studying the causes and treatments of autism.

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