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CURRENT AND EMERGING THERAPEUTICS OF AUTISTIC DISORDER AND RELATED PERVASIVE DEVELOPMENTAL DISORDERS

CHRISTOPHER J. McDOUGLE

DIAGNOSIS OF PERVASIVE DEVELOPMENTAL DISORDERS

Pervasive developmental disorders (PDDs) are characterized by severe and pervasive impairment in several areas of development, including reciprocal social interaction skills, communication skills, and the presence of stereotyped behavior, interests, and activities (1). The qualitative impairments that define these disorders are abnormal relative to the individual's developmental level or mental age. These conditions are typically evident in the first 1 to 3 years of life and are usually associated with some degree of mental retardation. The PDDs are sometimes observed among a diverse group of identifiable biological abnormalities (e.g., chromosomal abnormalities, congenital infections, structural abnormalities of the brain). In the majority of cases, however, a specific etiologic factor is not found. Previously, terms like *psychosis* and *childhood schizophrenia* were used to refer to individuals with these conditions. However, there is now considerable evidence to demonstrate that PDDs are distinct from schizophrenia. There are five subtypes of PDD in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (1). They include autistic disorder, Rett syndrome, childhood disintegrative disorder, Asperger's syndrome, and PDD not otherwise specified (NOS) (Table 42.1).

Autistic Disorder

The essential features of autistic disorder are the presence of markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interests. The clinical presentation of the disorder varies significantly depending on the developmental level and chronologic age of the individual. In the past, autistic disorder was referred to as early infantile autism, childhood autism, or Kanner's syndrome.

The clinical features must include delays or abnormal functioning in social interaction, in language as used in social communication, or in symbolic or imaginative play prior to the age of 3 years. There is usually no period of clearly normal development, although 1 or 2 years of relatively normal progression can occur. In some instances, regression in language development, typically manifest as a complete loss of speech after a child has acquired from five to ten words, has been reported. If there is a period of normal development, it cannot extend past the age of 3 years.

In approximately 75% of cases, there is an associated diagnosis of mental retardation, commonly in the moderate range (IQ 35 to 50). A number of behavioral symptoms, including hyperactivity; inattention; impulsivity; aggression toward self, others, or property; and interfering repetitive thoughts and behavior are often present. The disorder is sometimes observed in association with an identifiable medical condition (e.g., herpes encephalitis, phenylketonuria, tuberous sclerosis, fragile X syndrome, anoxia during birth, maternal rubella). Seizures may develop, particularly in adolescence, in up to 25% to 33% of cases. The disorder is four to five times more common in males than in females, although females often have a more severe cognitive disability. Epidemiologic studies have identified rates of autistic disorder of two to five cases per 10,000. Language skills and IQ are the strongest predictors of eventual outcome.

Rett Syndrome

Rett syndrome differs from autistic disorder in its characteristic sex ratio and distinctive pattern of abnormal develop-

Christopher J. McDougle: Department of Psychiatry, Section of Child and Adolescent Psychiatry, Indiana University School of Medicine; James Whitcomb Riley Hospital for Children, Indianapolis, Indiana.

TABLE 42.1. DSM-IV PERVASIVE DEVELOPMENTAL DISORDERS (1)

Autistic disorder
Rett syndrome
Childhood disintegrative disorder
Asperger's syndrome
Pervasive developmental disorder not otherwise specified

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, fourth ed.

mental progression. The syndrome is much less common than autistic disorder and has been diagnosed almost exclusively in females. Following apparently normal prenatal and perinatal development, and a period of normal psychomotor development through the first 5 months of life, there is a characteristic pattern of head growth deceleration, loss of previously acquired purposeful hand skills, intermittent hyperventilation, and the appearance of ataxic gait or trunk movements. Individuals with Rett syndrome may exhibit difficulties in social interaction, particularly during the preschool years, but these may improve somewhat over time. Severe or profound mental retardation, seizures, and significant expressive and receptive language impairment are typical. Recently, a mutation in the gene (*MECP2*) encoding X-linked methyl-CpG-binding protein 2 (MeCP2) has been identified as the cause of some cases of Rett syndrome (2).

Childhood Disintegrative Disorder

Childhood disintegrative disorder contrasts with autistic disorder in that there is a distinctive pattern of developmental regression following at least 2 years of normal development. In autistic disorder, some developmental abnormalities are usually noted within the first year of life. After the first 2 years of life (but before the age of 10 years), the child with childhood disintegrative disorder has a clinically significant loss of previously acquired skills in at least two of the following areas: expressive or receptive language, social skills or adaptive behavior, bowel or bladder control, play, or motor skills. The onset, in most cases, is between the ages of 3 and 4 years and may be insidious or abrupt. To date, an underlying pathologic mechanism has not been identified. The disorder has been reported in association with metachromatic leukodystrophy and Schilder's disease, in some cases. Childhood disintegrative disorder is usually associated with severe mental retardation. It appears to be very rare, much less frequent than autistic disorder, and more common among males. The disorder has also been termed Heller's syndrome, dementia infantilis, or disintegrative psychosis.

Asperger's Syndrome

Asperger's syndrome can be distinguished from autistic disorder by the lack of delay in language and cognitive development, in addition to no significant abnormality in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood. Motor milestones may be delayed, and motor clumsiness is often observed. The syndrome appears to be more common in males. Asperger's syndrome is usually recognized somewhat later than autistic disorder, frequently in the context of school. All-encompassing preoccupations or circumscribed interests are typically present and can contribute to significant functional impairment.

Pervasive Developmental Disorder Not Otherwise Specified

PDD NOS is diagnosed when there is a severe and pervasive impairment in the development of reciprocal social interaction or verbal and nonverbal communication skills, but the criteria are not met for a specific PDD, schizophrenia, schizotypal personality disorder, or avoidant personality disorder. Stereotyped behavior, interests, and activities are often present. This category includes presentations associated with late age at onset, atypical or subthreshold symptoms, or both.

PHARMACOTHERAPY OF PERVASIVE DEVELOPMENTAL DISORDERS

The treatment of autistic disorder and related PDDs is multimodal and largely based on educational interventions and behavior management principles. Speech therapy is usually indicated, and physical and occupational therapy are often needed as well. Despite educational and behavioral strategies, many children, adolescents, and adults with PDDs remain significantly impaired. Under these circumstances, pharmacologic treatment is often appropriate and warranted.

Adequate drug treatment studies that have been focused on subjects with particular subtypes of PDD, other than autistic disorder, have not been conducted. Many investigations have included mixed samples of subjects with autistic disorder, Asperger's syndrome, and PDD NOS. Because of the extreme rarity of Rett syndrome and childhood disintegrative disorder, essentially no systematic psychopharmacologic treatment research has occurred in subjects with these subtypes of PDD. More recently, researchers have been conducting drug studies in adults with PDDs, in addition to those in children and adolescents with these disorders. The results from these investigations have allowed for some assessment of the impact of developmental factors on drug efficacy and tolerability.

Drugs that have consistent, primary effects on the core social disability of autistic disorder have not yet been developed. Studies in laboratory animals have identified particu-

lar neurochemical systems that mediate some elements of affiliative behavior (3,4). The translation of these findings into investigational applications in humans, however, has not yet occurred. The pharmacotherapy of autistic disorder currently involves the identification and treatment of symptoms including motor hyperactivity (primarily in prepubertal autistic individuals); inattention; aggression directed toward self, others, or the environment; and interfering repetitive thoughts and behavior. With reduction in these associated target symptoms, improvement in some aspects of social behavior can result secondarily.

Following a brief review of earlier drug studies, results from more current investigations, including those of atypical antipsychotics and serotonin reuptake inhibitors (SRIs), will be presented in some detail. For a more comprehensive review of drug treatment of PDDs, the reader is referred to other sources (5,6).

Early Drug Treatment Studies

Beginning in the 1960s, numerous agents, including lysergic acid diethylamide, methysergide, levodopa, triiodothyronine, imipramine, and 5-hydroxytryptophan were studied in autistic disorder. Many of these investigations were limited by a lack of diagnostic precision and inadequate methodologic design. In general, these initial studies identified no drug that resulted in consistent target symptom reduction.

Elevated levels of whole blood serotonin (5-hydroxytryptamine, 5-HT) have long been associated with autistic disorder in a large minority of subjects (7). Following reports that fenfluramine, an indirect 5-HT agonist, decreased blood and brain 5-HT in animals, this drug received extensive investigation. Despite early enthusiasm generated by small open-label reports, most controlled studies found no consistent efficacy for fenfluramine as a treatment for autistic disorder (8). Furthermore, increasing evidence of possible neurotoxic effects of the drug on 5-HT neurons in animals and the association of fenfluramine with primary pulmonary hypertension and (in combination with phentermine) valvular heart disease have eliminated its use as a safe agent.

Most of the available typical antipsychotic drugs were studied in heterogeneous groups of children that included autistic subjects. Many of these early investigations suffered from the lack of adequate diagnostic methods and nonstandardized outcome measures. Most of these trials were direct comparisons of two drugs, usually low-potency antipsychotics, and did not include a placebo control. A number of these agents were found to be effective for behavioral symptoms including motor hyperactivity, agitation, and stereotypies. Due to significant sedation and adverse cognitive effects secondary to the low-potency drugs, however, studies of higher potency conventional antipsychotics were next pursued.

Campbell and co-workers (9–12) conducted several well-designed controlled studies of haloperidol in autistic children. In doses of 1.0 to 2.0 mg per day, haloperidol was found to be more efficacious than placebo for withdrawal, stereotypy, hyperactivity, affective lability, anger, and temper outbursts. However, acute dystonic reactions along with withdrawal and tardive dyskinesias were not infrequent.

Beginning in the late 1980s, the opioid antagonist naltrexone was investigated as a potential treatment for the associated behavioral symptoms of autistic disorder, as well as the core social deficits. Again, results from initial open-label reports and small controlled studies suggested possible effectiveness for naltrexone. More recent large well-designed controlled investigations involving children, adolescents, and adults with autistic disorder, however, have failed to demonstrate improvement in the majority of target symptoms or social behavior (13,14). The most consistent findings from these controlled studies were that naltrexone is well tolerated and may be effective for reducing motor hyperactivity.

A number of other drugs have been studied in autistic disorder, although most of the trials were either uncontrolled or contained a small number of subjects (5,6). For example, β-adrenergic antagonists have been reported to reduce aggression and self-injury in some small open-label pilot trials in adults with autistic disorder. Hypotension and bradycardia were common dose-related adverse effects. Case reports and small open-label studies have described mixed results with the 5-HT$_{1A}$ partial agonist buspirone. Controlled investigations of mood stabilizers, including lithium, valproic acid, carbamazepine, and gabapentin, have not been reported in well-defined groups of autistic subjects.

The pharmacologic management of motor hyperactivity and impaired attentional mechanisms in individuals with PDDs has proven particularly challenging to clinicians and researchers. These symptoms are most prominent in younger-aged autistic children. Thus, these symptoms are largely present during a time when educational programming and interventions are most critical. The psychostimulants, such as methylphenidate and dextroamphetamine, are effective treatments for these symptoms in individuals with attention-deficit/hyperactivity disorder (ADHD). Early controlled studies of these agents in autistic children, however, produced mixed results at best (15,16). In a more recent double-blind crossover study of methylphenidate and placebo, ten autistic children, ages 7 to 11 years, received doses of 10 or 20 mg twice daily for 2 weeks (17). Statistically significant improvement was seen on the Conners Teacher Questionnaire (18) and on the hyperactivity factor, irritability factor, and total score of the Aberrant Behavior Checklist (19). Adverse effects were minimal. The authors' impression was that the effects of methylphenidate were modest. Following completion of the study, it was necessary to add haloperidol to the treatment regimen of two of the ten children due to continued symptoms of aggression. Anecdotal reports from physicians in clinical practice and in

academic centers commonly describe the onset or exacerbation of irritability, insomnia, and aggression in individuals with PDDs with psychostimulant treatment.

The α_2-adrenergic agonist clonidine has been shown to be an effective treatment for some individuals with ADHD. In a small double-blind, placebo-controlled study of clonidine (4 to 10 μg per kg daily) in eight children with autistic disorder, statistically significant improvement was recorded in hyperactivity and irritability on some teacher and parent ratings (20). No significant drug–placebo differences were identified on clinician ratings of videotaped observations, however. Adverse effects included hypotension, sedation, and irritability. In contrast, transdermal clonidine (5 μg per kg daily) was reported to be effective in a double-blind, placebo-controlled crossover study (4 weeks in each treatment phase) involving nine males (ages 5 to 33 years) with autistic disorder (21). Significant improvement was seen on the Clinical Global Impression Scale (CGI) (22), and hyperactivity and anxiety were also reduced. The most common adverse effects were sedation and fatigue.

Guanfacine is an α_2-adrenergic agonist with a longer half-life than clonidine that may be less sedating and cause less pronounced hypotension (23). No open-label or controlled studies have been published on the use of guanfacine in PDDs.

To more rigorously address the pharmacotherapy of symptoms of hyperactivity and inattention in PDD, the National Institute of Mental Health (NIMH)-sponsored Research Units on Pediatric Psychopharmacology (RUPP) Autism Network is planning a controlled investigation of a methylphenidate vs. placebo in children with PDDs.

Current Drug Treatment Studies

Atypical Antipsychotics

Over the past 5 to 10 years, considerable interest has been generated by the introduction of the atypical antipsychotics (24). These drugs appeared to have potential as a treatment for autistic disorder for a number of reasons. Initial studies in schizophrenia indicated that these agents were better tolerated and had a lower risk of acute and tardive dyskinesias compared with conventional antipsychotics. In addition, these drugs were shown to improve both the "positive" (hallucinations and delusions) and "negative" symptoms of schizophrenia. The negative symptoms include blunted affect, emotional and social withdrawal, lack of interest in interpersonal relationships, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking (25). A number of investigators suggested that the negative symptoms of schizophrenia were comparable to those that characterize the social impairment of autistic disorder. To date, reports have appeared in which clozapine, risperidone, olanzapine, or quetiapine was used in the treatment of autistic disorder and other PDDs. The reader

is referred to a recent publication that provides a comprehensive review of atypical antipsychotics in autistic disorder (26).

Clozapine

Clozapine has been shown to be effective for treatment-refractory schizophrenia (27). The drug's ability to block 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_3$, and dopamine D$_1$-D$_4$ receptors has been proposed as its mechanism of action. There has been only one report to date describing the use of clozapine in autistic disorder (28). Three children with significant hyperactivity or aggression were given clozapine after they had not responded to typical antipsychotics. Improvement was observed in the three subjects after 3 months' treatment at dosages up to 200 mg per day. The scarcity of reports describing the use of clozapine in autistic disorder might reflect concern regarding the risk of agranulocytosis or seizures in children or adolescents that are associated with the drug. Because autistic individuals typically have an impaired ability to communicate effectively and often a high pain threshold, infections secondary to a decreased white blood cell count may not be identified in a timely manner. Additionally, as mentioned above, many individuals with autistic disorder have comorbid seizure disorders. Furthermore, the necessary frequent blood draws are not ideal for children, particularly those with autistic disorder.

Risperidone

Risperidone is a highly potent 5-HT$_{2A}$/D$_2$ antagonist that has been shown in controlled trials to improve both the positive and negative symptoms of schizophrenia (29). A number of open-label reports describing improvement in aggression, self-injury, ritualistic behavior, irritability, impulsivity, hyperactivity, and social relatedness in children, adolescents, and adults with autistic disorder have appeared (26). Only one controlled study of risperidone, or any atypical antipsychotic for that matter, has been published in individuals with autistic disorder and related PDDs (30) (Table 42.2). In that study, 31 adults (mean age, 28.1 years) with autistic disorder ($n = 17$) or PDD NOS ($n = 14$) entered the 12-week trial. For subjects completing the study, eight (57%) of 14 treated with risperidone [mean $\pm$ standard deviation (SD) dose, 2.9 $\pm$ 1.4 mg daily; range 1 to 6 mg per day] were categorized as responders compared with none of 16 in the placebo group based on the CGI. Nine (60%) of 15 subjects who received open-label risperidone following the double-blind placebo phase responded. Specifically, risperidone was effective for reducing interfering repetitive behavior, as well as aggression toward self, others, and property.

Although risperidone was better than placebo for decreasing the overall maladaptive behaviors of autistic disorder, as measured by the Ritvo-Freeman Real Life Rating Scale overall score (31), this finding was largely accounted

TABLE 42.2. CONTROLLED TRIALS OF CURRENT DRUG TREATMENTS FOR AUTISTIC DISORDER

Drug	Reference	Sample and Design	Results
Atypical antipsychotics			
Risperidone	McDougle et al. (30)	31 adults, autistic disorder (*n* = 17), pervasive developmental disorder not otherwise specified (PDD NOS) (*n* = 14), 12-week double-blind, placebo-controlled	Risperidone—8 of 14 (57%) responders Placebo—0 of 16 responders
SRIs			
Clomipramine vs. Desipramine	Gordon et al. (40)	7 children and adolescents with autistic disorder, 10-week double-blind crossover following 2-week single-blind placebo phase	Clomipramine > desipramine for obsessive-compulsive symptoms and autistic symptoms Clomipramine = desipramine for hyperactivity
Clomipramine vs. Placebo	Gordon et al. (41)	12 children and adolescents with autistic disorder, 10-week double-blind crossover following 2-week single-blind placebo phase	Clomipramine > placebo for obsessive-compulsive symptoms, autistic symptoms and hyperactivity
and Clomipramine vs. Desipramine		12 children and adolescents with autistic disorder, 10-week double-blind crossover following 2-week single-blind placebo phase	Clomipramine > desipramine for obsessive-compulsive symptoms and autistic symptoms Clomipramine = desipramine for hyperactivity
Fluvoxamine	McDougle et al. (48)	30 adults with autistic disorder, 12 week double-blind, placebo-controlled	Fluvoxamine—8 of 15 (53%) responders Placebo—0 of 15 responders

SRI, serotonin reuptake inhibitor.

for by significant changes in sensory motor behaviors (e.g., rocking, flapping), affectual reactions (e.g., temper outbursts), and to some extent sensory responses (e.g., spinning objects, sniffing self or objects). Significant differences between risperidone and placebo were not captured on subscales of the Ritvo-Freeman Scale that measure social relationships to people and language. For many subjects, however, clinicians, parents, and other members of the treatment teams had the impression that anxiety associated with social interactions was reduced, allowing for enhanced social function. It may be that the rating scales used to assess social relatedness in this study were not sensitive enough to detect changes in this complex aspect of behavior.

In general, risperidone was well tolerated. Thirteen (87%) of 15 subjects randomized to risperidone had at least one adverse effect, although this included only mild, transient sedation in five subjects, compared with five (31%) of 16 subjects given placebo (agitation in all five cases). Interestingly, the weight gain that has been observed with risperidone in the treatment of some children and adolescents with PDDs did not occur to the same degree in this study of adults.

Based on these results and other clinical, preclinical, and safety data, the RUPP Autism Network chose risperidone as the first drug to study in children and adolescents with autistic disorder (26). When completed, this investigation will be the largest controlled drug trial conducted to date in autistic disorder.

Olanzapine

Three case reports and an open-label case series have described positive responses to the atypical antipsychotic olanzapine in subjects with PDDs. In the case series, six of seven children, adolescents, and adults with autistic disorder and other PDDs (mean ± SD age, 20.9 ± 11.7 years; range 5 to 42 years) who completed the 12-week open-label trial were responders based on the CGI (32). Significant improvement in overall symptoms of autistic disorder, motor restlessness or hyperactivity, social relatedness, affectual reactions, sensory responses, language usage, self-injurious behavior, aggression, irritability or anger, anxiety, and depression was observed. Significant changes in repetitive behavior did not occur for the group. The mean ± SD dose of olanzapine was 7.8 ± 4.7 mg daily (range 5 to 20 mg per day). The drug was well tolerated, with the most significant adverse effects being increased appetite and weight gain in six subjects and sedation in three.

Quetiapine

Only one report of quetiapine in the treatment of autistic disorder has been published (33). Six males with autistic disorder, 6.2 to 15.3 years of age (mean ± SD age, 10.9

± 3.3 years), entered a 16-week open-label trial of quetiapine. The mean ± SD daily dose of quetiapine was 225 ± 108 mg (range 100 to 350 mg per day). Overall, there was no statistically significant improvement for the group as a whole on various behavioral rating scales. Two subjects completed the entire 16-week trial; both were considered responders based on CGI scores. However, only one of these two subjects continued to benefit from longer term treatment with the drug. The other four subjects dropped out due to lack of response and sedation (three subjects), and a possible seizure during the fourth week of treatment (one subject). Other significant side effects included behavioral activation, increased appetite, and weight gain (range 0.9 to 8.2 kg). The authors concluded that quetiapine was poorly tolerated and ineffective in most subjects, although the sample size was small. More studies of quetiapine in autistic disorder and related PDDs are needed before definitive conclusions about its effectiveness and safety can be made.

Summary

The atypical antipsychotics have potent effects on 5-HT and dopamine neuronal systems, both of which have been implicated in the pathophysiology of PDDs. Unlike the typical antipsychotic, haloperidol, which has been shown to be effective for reducing many of the maladaptive behaviors associated with PDDs, the atypical agents' 5-HT$_{2A}$/D$_2$ ratio of receptor blockade appears to produce a lower risk of acute and chronic extrapyramidal side effects, as well as enhanced efficacy for the "negative" symptoms of PDD. Because most of the studies of this class of drugs have been short-term open-label trials in small samples, larger scale controlled investigations are needed to confirm these preliminary results. Due to the possibility that many children and adolescents who demonstrate short-term benefit from these drugs will remain on them indefinitely, the longer term safety and efficacy of atypical antipsychotics in this population also needs to be determined.

Serotonin Reuptake Inhibitors

In Kanner's 1943 landmark description of 11 autistic children, the repetitive natures of behavior, speech, and modes of social interaction were designated as core clinical elements of the syndrome (34). Verbal and motor rituals, obsessive questioning, a rigid adherence to routine, a preoccupation with details, and an anxiously obsessive desire for the maintenance of sameness and completeness were all noted. Religious and somatic obsessions, repetitive hand washing, and tics were identified in family members.

Results from a more recent study indicated that adults with autistic disorder and obsessive-compulsive disorder (OCD) can be distinguished on the basis of their current types of repetitive thoughts and behavior (35). Compared with the OCD group, the autistic subjects were significantly less likely to have aggressive, contamination, sexual, religious, symmetry, and somatic thoughts. Repetitive ordering, hoarding, telling or asking (trend), touching, tapping, or rubbing, and self-damaging or self-mutilating behaviors were reported significantly more frequently in the autistic subjects, whereas cleaning, checking, and counting behaviors were less common in the autistic group compared with the OCD subjects.

The clear efficacy of potent SRIs in OCD and their differential effects when directly compared to drugs that potently inhibit norepinephrine (NE) uptake support the hypothesized importance of 5-HT in the treatment of obsessive-compulsive symptoms (36). Consistent with these drug response data is the hypothesis that a dysregulation of 5-HT function might contribute to the pathophysiology of at least some individuals with OCD (37). Abnormalities in 5-HT function have also been identified in subjects with autistic disorder and other PDDs (38). Based on the efficacy of SRIs in the treatment of OCD, the high prevalence of interfering repetitive thoughts and behavior in subjects with PDD, and evidence indicating that a dysregulation in 5-HT neurotransmission may contribute to the pathophysiology of some individuals with autistic disorder, researchers have been studying the clinical response and side effect profile of SRIs in children, adolescents, and adults with PDDs.

Clomipramine

Clomipramine, a tricyclic antidepressant (TCA) and potent, but nonselective, inhibitor of 5-HT uptake, has been shown to be more efficacious than the relatively selective NE uptake inhibiting TCA desipramine in the treatment of children and adolescents with OCD (39). In the first controlled investigation of clomipramine in autistic disorder, the drug was found to be more efficacious than desipramine and placebo on standardized ratings of autistic disorder and anger, as well as ratings of repetitive and compulsive behaviors (40). Seven subjects with autistic disorder, ages 6 to 18 years (means age, 9.6 years), completed the 10-week double-blind crossover trial of clomipramine (mean dose, 129 daily) and desipramine (mean dose, 111 mg daily) following a 2-week single-blind placebo phase. In general, the side effects were relatively minor and did not differ between the two drugs. Mild sleep disturbance, dry mouth, and constipation were observed, and one patient developed a minor tremor on clomipramine. Two subjects taking desipramine developed uncharacteristic and severe irritability and temper outbursts. The parents of all seven subjects chose to have their children continue on clomipramine after completion of the study.

As a follow-up to this pilot study, a larger double-blind comparison of clomipramine, desipramine and placebo was conducted in children and adolescents with autistic disorder (41). Following a 2-week single-blind placebo phase, 12 subjects completed a 10-week double-blind crossover comparison of clomipramine and placebo, and 12 different subjects completed a similar comparison of clomipramine and

desipramine. The latter study included data from the seven subjects who participated in the original pilot study described above. Clomipramine (mean dose, 152 mg daily) was superior to both placebo and desipramine (mean dose, 127 mg daily) on ratings of autistic symptoms, including stereotypies, anger, and ritualized behaviors, with no difference between desipramine and placebo. Clomipramine was equal to desipramine and both drugs were superior to placebo for reducing motor hyperactivity. One child developed prolongation of the corrected QT interval (0.45 seconds) and another developed severe tachycardia (resting heart rate, 160 to 170 beats per minute) during clomipramine treatment. A third child experienced a grand mal seizure.

Subsequent open-label studies of clomipramine have been published with mixed results and increased recognition of adverse effects. Clomipramine treatment of five young adults (ages 13 to 33 years) with autistic disorder led to ratings of "much improved" on the CGI in four patients, with improvement seen in social relatedness, obsessive-compulsive symptoms, aggression, and self-injurious behavior (42). In another study, 11 consecutively referred children and adolescents with developmental disabilities and chronic stereotypies or self-injurious behavior were treated with clomipramine (43). Four of the subjects (ages 13 to 20 years) had been diagnosed with autistic disorder and of them, three had a significant reduction in stereotypic, self-injurious behavior with clomipramine at doses of 50 to 125 mg daily. Adverse effects included constipation, aggression, rash, and enuresis. In another open-label study, clomipramine 200 mg daily, was associated with decreased abnormal motor movements and compulsions in five autistic boys ages 6 to 12 years (44).

A large prospective open-label study of clomipramine (mean dose, 139 mg daily) treatment of 35 adults diagnosed with different subtypes of PDD was described (45). Of the 33 subjects who completed the 12-week study, 18 (55%) were judged responders on the CGI with improvement seen in aggression, self-injury, interfering repetitive thoughts and behavior, and social relatedness. Thirteen of the 33 subjects had significant adverse effects including seizures (in three patients, including two who had preexisting seizure disorders stabilized on anticonvulsants), weight gain, constipation, sedation, agitation, and anorgasmia.

A number of studies have suggested that younger children may tolerate clomipramine less well and show a decreased response compared to adolescents and adults with PDDs. In one report, eight children (ages 3.5 to 8.7 years) were given clomipramine (mean dose, 103 mg daily) for 5 weeks in a prospective open-label manner (46). Among the seven children who completed the trial, only one child was rated as moderately improved on a clinical global consensus measure. Adverse effects were frequent and included urinary retention requiring catheterization, constipation, drowsiness, and increased aggression and irritability. In a follow-up report to the study described above, in which five autistic children had an initial positive response to clomipramine (44), it was noted that the drug was eventually discontinued in all cases due to adverse effects or continued maladaptive behavior (47). Adverse effects included the serotonin syndrome, increased seizure frequency, and exacerbation of agitation and aggressiveness that required hospitalization.

Because of their better side effect profile compared with clomipramine, including their lower propensity to decrease the seizure threshold, selective SRIs (SSRIs) have been receiving increasing attention as a potential treatment for the interfering symptoms associated with autistic disorder and other PDDs.

Fluvoxamine

To date, only one double-blind, placebo-controlled study of an SSRI in subjects with autistic disorder has been published (48). Fluvoxamine (mean dose, 276.7 mg daily) or placebo was given to 30 autistic adults for 12 weeks. Eight of 15 subjects who received fluvoxamine vs. none who received placebo were categorized as "much improved" or "very much improved" on the CGI. Fluvoxamine was significantly more effective than placebo for reducing repetitive thoughts and behavior, maladaptive behavior, and aggression. In addition, fluvoxamine reduced inappropriate repetitive language usage. Adverse effects included nausea and sedation, which were transient and of minor severity.

In contrast to the encouraging results from this study of fluvoxamine in autistic adults, a 12-week double-blind, placebo-controlled study in children and adolescents with autistic disorder and other PDDs found the drug to be poorly tolerated with limited efficacy at best (McDougle and co-workers, unpublished data). Thirty-four patients (five female, 29 male; age range 5 to 18 years, mean age, 9.5 years), 12 of whom met criteria for autistic disorder, eight for Asperger's syndrome, and 14 for PDD NOS, participated. Of the 16 subjects randomized to placebo, none demonstrated any significant change in target symptoms. Adverse events that occurred in the placebo-treated subjects included increased motor hyperactivity ($n = 2$), insomnia ($n = 2$), dizziness and/or vertigo ($n = 1$), agitation ($n = 1$), diarrhea ($n = 1$), decreased concentration ($n = 1$), and increased self-stimulation ($n = 1$). Eighteen of the subjects were randomized to fluvoxamine (range 25 to 250 mg daily; mean dose, 106.9 mg per day). The drug was begun at 25 mg every other day and increased by 25 mg every 3 to 7 days as tolerated. Only one of the fluvoxamine-treated children demonstrated a significant improvement with the drug. Fourteen of the children randomized to fluvoxamine demonstrated adverse effects [insomnia ($n = 9$), motor hyperactivity ($n = 5$), agitation ($n = 5$), aggression ($n = 5$), increased rituals ($n = 2$), anxiety ($n = 3$), anorexia ($n = 3$), increased appetite ($n = 1$), irritability ($n = 1$), decreased concentration ($n = 1$), and increased impulsivity ($n = 1$)].

The marked difference in efficacy and tolerability of fluvoxamine in children and adolescents with autistic disorder

and other PDDs in this study, compared with that of autistic adults, underscores the importance of developmental factors in the pharmacotherapy of these subjects. This differential drug response is consistent with the hypothesis that ongoing brain development has a significant impact on the subjects' ability to tolerate and respond to a drug, at least with respect to fluvoxamine and possibly other SSRIs. Developmental changes in brain 5-HT function may contribute to these widely varying clinical responses between subjects with autistic disorder and other PDDs of different age groups.

Fluoxetine

Several case reports have described fluoxetine treatment of autistic subjects although, to date, no controlled studies have appeared.

In a large case series, Cook and associates (49) found fluoxetine (10 to 80 mg daily), given in an open-label manner, effective in 15 of 23 subjects (ages 7 to 28 years) with autistic disorder as determined by the CGI (49). Intolerable side effects, including restlessness, hyperactivity, agitation, elated affect, decreased appetite, and insomnia, occurred in six of 23 subjects.

In a retrospective investigation, fluoxetine (20 to 80 mg daily) and paroxetine (20 to 40 mg daily) were found to be effective in approximately one-fourth of adults (mean age, 39 years) with "intellectual disability" and autistic traits (50). The sample included all intellectually disabled subjects who had been treated with an SSRI over a 5-year period within a health care service in Great Britain. The mean duration of treatment was 13 months. Target symptoms were perseverative behaviors, aggression, and self-injury. Six of 25 subjects treated with fluoxetine and three of 12 subjects given paroxetine were rated as "much improved" or "very much improved" on the CGI.

In another study, 37 children (ages 2.25 to 7.75 years) with autistic disorder were treated with fluoxetine in an open-label fashion at doses ranging from 0.2 to 1.4 mg per kg daily (51). Eleven of the children had an "excellent" clinical response and 11 others had a "good" response. Improvement was seen in behavioral, cognitive, affective, and social areas. Interestingly, language acquistion seemed to improve with fluoxetine treatment. Drug-induced hyperactivity, agitation, and aggression were frequent causes of discontinuation of fluoxetine.

Sertraline

To our knowledge, no controlled studies of sertraline in subjects with autistic disorder or other PDDs have been published, although a number of open-label reports have appeared. In a 28-day trial of sertraline (at doses of 25 to 150 mg daily) in nine adults with mental retardation (five of whom had autistic disorder), significant decreases in aggression and self-injurious behavior occurred in eight as rated on the CGI severity rating (52). In a case series of

nine autistic children (ages 6 to 12 years) treated with sertraline (25 to 50 mg daily), eight showed significant improvement in anxiety, irritability, and "transition-induced behavioral deterioration" or "need for sameness" (53). In three of the responders, a return of symptoms occurred after 3 to 7 months. Two children demonstrated agitation when the dose was raised to 75 mg daily.

A large prospective open-label study of 42 adults with PDDs (including subjects with autistic disorder, Asperger's syndrome, and PDD NOS) found sertraline (mean dose, 122 mg per day) effective for improving aggression and interfering repetitive behavior, but not impaired social relatedness as assessed by various rating scales over the course of the 12-week study (54). As determined by a CGI global improvement item score of "much improved" or "very much improved," 15 of 22 subjects with autistic disorder, none of six with Asperger's syndrome, and nine of 14 with PDD NOS were judged responders. Those subjects with autistic disorder and PDD NOS showed significantly more benefit from sertraline than those with Asperger's syndrome; the authors hypothesized that this might have been because those diagnosed with Asperger's syndrome were less symptomatic at baseline. Three of the 42 subjects dropped out of the study due to intolerable agitation and anxiety.

Paroxetine

Only a few reports, none of them controlled, have appeared on the use of paroxetine in autistic disorder. Paroxetine 20 mg per day decreased self-injury in a 15-year-old boy with "high-functioning" autistic disorder (55). In another report, paroxetine resulted in a reduction of irritability, temper tantrums, and interfering preoccupations in a 7-year-old boy with autistic disorder (56). The optimal dose of paroxetine was 10 mg daily; an increase of paroxetine to 15 mg per day led to agitation and insomnia. As described earlier, a retrospective case analysis found paroxetine to be effective in approximately 25% of adults with PDD NOS (50).

In a 4-month open-label study of 15 adults with severe and profound mental retardation (seven with PDD), paroxetine at doses of 20 to 50 mg daily was effective for symptoms of aggression at 1 month, but not at 4-month follow-up (57). The investigators hypothesized that adaptive changes may have occurred in 5-HT receptor density, availability of 5-HT, or in 5-HT transporter sensitivity.

Citalopram

To date, there have been no published reports on the effects of citalopram, an SSRI that has been recently introduced in the United States, in patients with autistic disorder or other PDDs.

Summary

Recent work has determined that the types of repetitive phenomena associated with autistic disorder are different from those that characterize OCD. Nevertheless, these signs

and symptoms can interfere with the autistic individual's quality of life. Studies of SRIs, the mainstay of treatment for the obsessions and compulsions of OCD, have yielded mixed results in autistic disorder. To date, only three controlled studies of SRIs in autistic disorder have been published, as reviewed above (Table 42.2). All three of these studies found the SRI to be helpful for the interfering repetitive phenomena associated with autistic disorder, as well as for aspects of aggression, self-injury, and impaired social relatedness. On the other hand, results from an unpublished controlled study of fluvoxamine in children and adolescents with autistic disorder and other PDDs indicated that the drug was poorly tolerated and of limited efficacy. The results from that study are consistent with those from a number of open-label reports suggesting that SRIs may be less well tolerated and less effective in younger (prepubertal) autistic subjects compared with autistic adolescents and adults (postpubertal). Although this developmental difference in tolerability and response to SRIs may be a dose-related phenomena, other factors need to be considered. Recent data indicate that significant changes in measures of 5-HT function occur during puberty in autistic individuals. For example, McBride and co-workers (58) found that mean platelet 5-HT levels were significantly higher in prepubertal autistic children than prepubertal normal controls, but no significant difference was found between postpubertal male autistic subjects and postpubertal normal controls (58). Furthermore, Chugani and associates (59) reported results from a positron emission tomography brain imaging study showing that changes in brain 5-HT synthesis capacity that normally occur in developing humans are disrupted in autistic children (59). Thus, pre- and postpubertal autistic subjects may have significant differences in brain 5-HT function that influence their ability to tolerate and respond to SRIs. Pharmacogenetic differences among autistic individuals, which may affect SRI tolerability and responsivity, will also require more investigation (60).

Novel Therapeutic Strategies

Secretin

Secretin is a polypeptide hormone secreted primarily by the endocrine cells in the upper gastrointestinal (GI) tract that is involved in regulating pancreatic exocrine secretion. A synthetic form of secretin is Food and Drug Administration (FDA) approved for use in the diagnosis of particular GI diseases. In 1998, Horvath and co-workers (61) published a report that described marked improvement in language and social behavior in three children with autistic disorder who received secretin as part of a routine diagnostic workup for GI problems.

These encouraging yet preliminary results, coupled with enthusiastic media reports, led to widespread excitement and optimism among many family members of autistic individuals about a potential "cure" for the disorder. In response, researchers began conducting controlled studies of secretin in autistic children. A double-blind, controlled study of single-dose intravenous secretin (0.4 µg per kg) or placebo administration was conducted in 60 children, ages 3 to 14 years, of whom 40 had autistic disorder and 20 had PDD NOS (62). No significant differences were found between secretin and placebo on primary outcome measures that assessed changes in autistic behaviors and adaptive functioning at days 1 and 2 and weeks 1, 2, and 4 following the infusion. No significant difference was found in adverse effects between secretin and placebo. Two additional controlled studies have reported similar findings (63,64). Based on the results of these systematic investigations, secretin cannot be recommended as a treatment for the target symptoms associated with autistic disorder.

Glutamatergic Agents

The *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor is central to developmental processes including neuronal migration, differentiation, and plasticity (65). Disturbances in glutamatergic function, via reduced neurotropic actions of glutamate or excessive neurotoxic effects, could alter neurodevelopment substantially (66). During the past 5 to 10 years, significant advances have been made in the identification of potential pharmacotherapies affecting glutamatergic function for a number of neuropsychiatric disorders (67).

Hypotheses regarding glutamatergic dysfunction in autistic disorder have been proposed (68). In addition, preliminary results from studies of drugs that modulate glutamate neurotransmission in autistic disorder have been published. Lamotrigine is a drug that attenuates some forms of cortical glutamate release via inhibition of sodium channels, P- and N-type calcium channels, and potassium channels. In one study, eight of 13 children and adolescents with autistic disorder given lamotrigine for intractable epilepsy showed a decrease in "autistic symptoms" (69). Another report described improvement in self-injurious behavior, irritability, and disturbed sleep in an 18-year-old woman with profound mental retardation and a generalized seizure disorder who was given open-label lamotrigine (70). Interestingly, the subject showed improvement in measures of "fixed facial expression, lacks emotional responsivity," "resists any form of physical contact," and "inactive, never moves spontaneously." The authors suggested that these changes might represent a "prosocial" effect of the drug. In a double-blind, placebo-controlled study, 39 subjects with autistic disorder, ages 5 to 19 years old, were given placebo or the NMDA receptor antagonist amantadine (71). The design included a single-blind placebo lead-in, followed by a single daily dose of amantadine (2.5 mg per kg) or placebo for the next week, and then twice daily dosing for the subsequent 3 weeks. No significant difference was found between drug

and placebo on parent ratings, although clinician-rated measures of hyperactivity and inappropriate speech showed statistically significant improvement. A trend toward greater response in the amantadine group, based on CGI ratings, occurred. Amantadine was well tolerated.

Based on these preliminary results, and reports that the "negative" symptoms of schizophrenia can be improved with drugs active at the NMDA receptor (72), additional research with these and other agents affecting the glutamatergic systems appears warranted. The group II/III metabotropic-glutamate receptor (mGluR II/III) agonists (73) and the positive allosteric modulator of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, CX516 (Ampakine) (74) may hold promise in this regard. Interestingly, one mechanism of action underlying the relative efficacy of atypical antipsychotics, such as risperidone, for autistic disorder (30) may be the suppression of glutamate release via 5-HT$_{2A}$ antagonism (75).

Neuroimmune Modulation

Neuroimmunologic dysfunction has been implicated in the pathophysiology of autistic disorder (76) and other neuropsychiatric conditions (77). To date, no consistent immunologic abnormalities have been found in autistic disorder, although viral and autoimmune hypotheses, among others, have been posited (76). Neurovirologic disease and other insults to the immune system can lead to increased production of catabolites of tryptophan, including quinolinate and kynurenate, which can cause significant neurotoxicity via activity at the NMDA receptor complex (78). Thus, neuroimmune dysregulation in autistic disorder would not be inconsistent with altered glutamatergic function, as described above. Results from small open-label studies of intravenous immunoglobulin have suggested that this intervention may be helpful in only a limited minority of subjects, if at all (79). Controlled studies of agents that have direct effects on immune function, however, have not been conducted in autistic disorder. Such research on neuroimmune interactions may yield important data on pathophysiology, if not etiology, in a subset of autistic subjects.

CONCLUSION

Significant progress in the neuropsychopharmacology of autistic disorder and related PDDs has been made since the fourth edition of this text (80). Future research in this area should include controlled studies of atypical antipsychotics in children and adolescents with autistic disorder and other PDDs, such as that being conducted by the NIMH-sponsored RUPP Autism Network (26). Longitudinal efficacy and safety data will need to be gathered on atypical antipsychotics in this population, as well. Larger double-blind, placebo-controlled trials of SRIs in pre- vs. postpubertal indi-

viduals with autistic disorder, as well as studies designed to determine the effects of these drugs on the target symptoms of subjects with different subtypes of PDD, including Asperger's syndrome, are also needed. In these studies, the optimal dosage for age and developmental level and the duration of adequate treatment should be determined. In addition, genetic predictors of treatment response, such as 5-HT transporter protein genotype, should be sought (60). The scientific community needs to continue to respond to reports of putative "cures" for autistic disorder, such as those that surrounded secretin, by conducting controlled studies of such agents. Accepting this responsibility will contribute to ensuring the continued safety of autistic subjects and provide family members with data on which to base informed decisions regarding their child's medical care. Finally, exploration of promising novel therapeutic strategies, such as those affecting glutamatergic and neuroimmune function, may provide new insights into the neurobiology and treatment of this devastating group of disorders.

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