

Genetics of Childhood Disorders: XLIV. Autism, Part 3: Psychopharmacology of Autism

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The pharmacotherapy of autistic disorder (autism) and other pervasive developmental disorders (PDDs) currently involves the treatment of target symptoms including hyperactivity, inattention, interfering repetitive thoughts and behavior, and aggression toward self, others, or the environment. Although studies in laboratory animals have identified neuropeptides, including oxytocin and vasopressin, that mediate some elements of affiliative behavior, drugs that have consistent, primary effects on the core social and communication disability of autism have not yet been developed.

Elevated levels of whole blood serotonin (5-HT) have long been known to be associated with autism. Following reports that fenfluramine, an indirect 5-HT agonist, decreased blood and brain 5-HT in animals, this drug received considerable attention and some systematic investigation. Despite early enthusiasm, most controlled studies found no consistent efficacy for fenfluramine. Furthermore, the association of fenfluramine with primary pulmonary hypertension and (in combination with phentermine) valvular heart disease has eliminated its use as a safe agent.

Most of the typical antipsychotic drugs have been studied in heterogeneous groups of children that included autistic subjects. These trials were often direct comparisons of two low-potency drugs and did not include a placebo control. A number of these agents were found to be effective for reducing hyperactivity, agitation, and stereotypies. Because of significant sedation and adverse cognitive effects, however, studies of higher-potency conventional antipsychotics were next pursued.

Several well-designed controlled studies of haloperidol were conducted. In doses of 1 to 2 mg/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 treatment for autism. Results from initial open-label reports and small controlled studies suggested possible effectiveness, although more recent large controlled investigations have failed to demonstrate improvement in the majority of target symptoms or social behavior. The most consistent findings from these studies were that naltrexone is well tolerated and may be effective for reducing hyperactivity.

A number of other drugs, including β -adrenergic antagonists and the 5-HT_{1A} partial agonist bupropion, have been stud-

ied, although most of these trials were either uncontrolled or contained a small number of subjects. Controlled investigations of mood stabilizers, including lithium, valproic acid, carbamazepine, and gabapentin, have not been reported in well-defined groups of autistic subjects.

The pharmacological management of hyperactivity and impaired attention has proven particularly challenging. These symptoms are most prominent in younger autistic children when educational programming and interventions are most critical. Anecdotal reports from physicians in clinical practice and in academic centers commonly describe the onset or exacerbation of irritability, insomnia, and aggression with psychostimulants. Early controlled studies with these agents produced mixed results at best. In a recent double-blind crossover study of methylphenidate and placebo in 10 autistic children, modest improvement was seen on measures of hyperactivity and irritability, and adverse effects were minimal. After completion of the study, however, it was necessary to add haloperidol to the treatment of 2 of the 10 children because of persistent aggression. In a more recent study, 8 of 13 children responded to methylphenidate in a double-blind, placebo-controlled crossover study. Adverse effects were more frequent at higher doses and included social withdrawal, dullness, sadness, and irritability. A larger controlled study of methylphenidate is currently being conducted by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network to determine whether age, diagnosis, cognitive function, or other factors are related to response to psychostimulants.

The α_2 -adrenergic agonist clonidine has been shown to be modestly effective for treating hyperactivity in small samples of autistic children. A recent open-label, retrospective study of guanfacine, an α_2 -adrenergic agonist with a longer half-life than clonidine, which may be less sedating and cause less pronounced hypotension, found that approximately one quarter of children showed significant improvement in hyperactivity, inattention, and insomnia. Those with PDD-not otherwise specified (NOS) and Asperger's disorder showed a greater rate of response than those with autism.

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. Based on the efficacy of serotonin reuptake inhibitors (SRIs) in the treatment of obsessive-compulsive disorder, the high prevalence of interfering repetitive thoughts

Thalamic afferents / Prefrontal Cortex

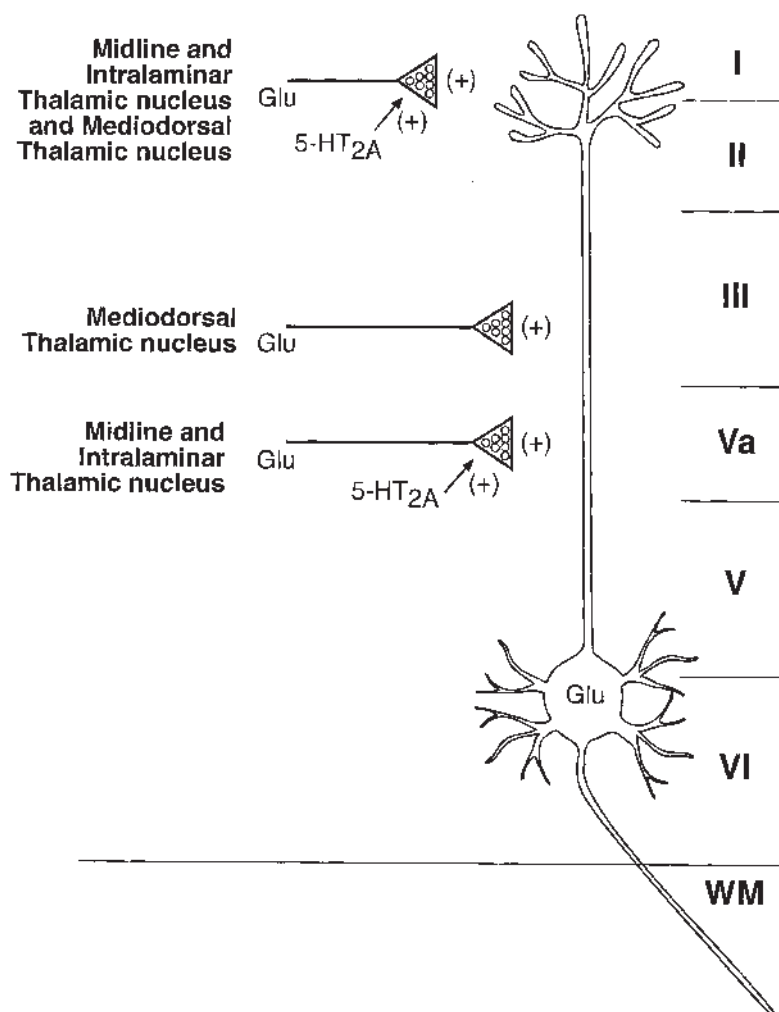


Fig. 1 Model describing the interaction of 5-HT_{2A} receptors and thalamocortical afferents terminating on layer V pyramidal cells. The layer V pyramidal cell extends its apical dendrite toward the pial surface. Thalamocortical afferents from the midline and intralaminar thalamic nuclei primarily terminate in layers I and Va of the medial prefrontal cortex. Thalamocortical afferents from the mediodorsal nucleus primarily terminate in layers I and III of the medial prefrontal cortex. Activation of the 5-HT_{2A} receptor appears to release glutamate from afferents originating in the midline and intralaminar thalamic nuclei since (1) medial thalamic lesions decrease the frequency of 5-HT-induced excitatory postsynaptic potentials by 60% and (2) the highest density of 5-HT_{2A} receptors are found in layers I and Va. The cortical laminae are listed at the right. WM = white matter.

and behavior in subjects with PDDs, and evidence for a dysregulation in 5-HT function in autism, researchers have been studying the clinical response and side effect profile of SRIs in this population.

A large double-blind comparison of the potent but nonselective SRI clomipramine, the relatively selective norepinephrine reuptake inhibitor desipramine, and placebo was conducted

in children and adolescents. Clomipramine was superior to both desipramine and placebo 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 hyperactivity. One child developed QT prolongation on electrocardiogram, another developed severe

tachycardia, and a third had a grand mal seizure. Subsequent open-label trials of clomipramine have suggested that younger children may tolerate clomipramine less well and show a decreased response compared with adolescents and adults with PDDs.

Because of their better side effect profile compared with clomipramine, selective SRIs (SSRIs) have been receiving increasing attention for the treatment of interfering repetitive behavior and other symptoms. To date, only one double-blind, placebo-controlled study of an SSRI has been published. 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 versus none given placebo were responders. Fluvoxamine was effective for reducing repetitive thoughts and behavior, aggression, and inappropriate repetitive language use. Adverse effects included transient nausea and sedation.

In contrast, a study of similar design in children and adolescents found the drug (mean dose, 106.9 mg/day) to be poorly tolerated with only limited efficacy. Only 1 of 18 of the fluvoxamine-treated children improved with the drug. Fourteen of the children randomly assigned to fluvoxamine demonstrated adverse effects, typically behavioral activation.

To date, there have been no published controlled studies of fluoxetine, sertraline, paroxetine, or citalopram. Results from open-label studies have been mixed. Trials conducted in adolescents and adults have generally yielded more positive findings than those in children.

The results from many of these studies suggest that SRIs may be less well tolerated and less effective in younger (*prepubertal*) autistic subjects compared with autistic adolescents and adults (*postpubertal*). Recent data indicate that significant changes in measures of 5-HT function occur during puberty in autistic individuals. For example, it was found that mean platelet 5-HT levels were significantly higher in prepubertal autistic children than prepubertal normal controls, but no difference was found between postpubertal male autistic subjects and postpubertal normal controls. Furthermore, results from a positron emission tomography brain imaging study showed that changes in brain 5-HT synthesis capacity which normally occur in developing humans are disrupted in autistic children. Thus, pre- and postpubertal autistic subjects may have significant differences in brain 5-HT function which 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.

Considerable interest has been generated by the introduction of the atypical antipsychotics. These agents appear to be better tolerated and have a lower risk of acute and tardive dyskinesias compared with conventional antipsychotics. In addition, these drugs have been shown to improve both the "positive" and "negative" symptoms of schizophrenia. A number of investigators have suggested that the negative symptoms of schizophrenia are comparable with those that characterize the social

impairment of autism. These agents have largely been targeted toward the treatment of aggression in subjects with PDDs.

There have been only two reports describing the use of clozapine in autism. 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/day. More recently, the case of a 17-year-old male with autism who showed a significant reduction in signs of "overt tension," hyperactivity, and repetitive motions in response to clozapine 275 mg/day was described. The scarcity of reports on the use of clozapine might reflect concern regarding the risks of agranulocytosis and seizures associated with the drug. Because autistic individuals typically have an impaired ability to communicate and often a high pain threshold, infections secondary to a decreased white blood cell count may not be identified in a timely manner. In addition, clozapine can lower the seizure threshold and up to one third of individuals with autism have seizures. Furthermore, the necessary frequent blood draws are not ideal for children, particularly those with autism.

A number of open-label reports with risperidone describing improvement in aggression, self-injury, ritualistic behavior, irritability, impulsivity, hyperactivity, and social relatedness have appeared. In the only published controlled study to date, 8 of 14 adults with autism or PDD-NOS treated with risperidone for 12 weeks responded compared with none of 16 given placebo. Risperidone reduced interfering repetitive behavior, as well as aggression toward self, others, and property. In general, the drug was well tolerated. The weight gain that has been observed with risperidone and other atypical antipsychotics in the treatment of some children and adolescents with PDDs did not occur to the same degree in this study of adults.

The RUPP Autism Network recently completed an 8-week, double-blind, placebo-controlled study of risperidone in 101 children with autism. Risperidone resulted in a significant decrease in self-injury, aggression, and agitation compared with placebo. Nearly 70% of children given risperidone responded compared with a placebo response rate of 11.5%. Increased appetite with associated weight gain, transient sedation, tremor, and drooling were more common with risperidone than placebo. Results from a longer-term treatment extension phase of this study will be forthcoming.

Case reports, an open-label case series, and a prospective comparison with haloperidol have described positive responses to olanzapine. In a recently published study using a parallel-groups design, 12 children with autism were randomly assigned to 6 weeks of open-label treatment with olanzapine or haloperidol. Both groups showed symptom reduction. Five of six subjects in the olanzapine group and three of six in the haloperidol group were rated as responders. Weight gain was significantly greater in the olanzapine group, whereas extrapyramidal symptoms occurred more frequently in children treated with haloperidol.

Only one report of quetiapine in the treatment of autism has been published. Two subjects completed the entire 16-week trial and both were considered responders. However, only one of these two subjects continued to benefit from longer-term treatment. Three subjects dropped out because of lack of response and sedation and a fourth because of a seizure. Other significant side effects included behavioral activation, increased appetite, and weight gain.

New directions in drug development are beginning to emerge. The *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor, which is central to developmental processes including neuronal migration, differentiation, and plasticity, is receiving increasing attention. Preliminary results from studies of drugs that modulate glutamate neurotransmission have been published. In an open-label study, 8 of 13 subjects given lamotrigine for intractable epilepsy showed a decrease in "autistic symptoms." Lamotrigine attenuates some forms of cortical glutamate release via inhibition of sodium channels, P- and N-type calcium channels, and potassium channels. In a controlled study of the NMDA receptor antagonist amantadine, no difference was found between drug and placebo on parent ratings, although clinician-rated measures of hyperactivity and inappropriate speech showed significant improvement. A trend toward greater percentage of responders was observed in the amantadine group and the drug was well tolerated.

On the basis of these preliminary results, and reports that the "negative" symptoms of schizophrenia improve with drugs active at the NMDA receptor, additional research with agents affecting the glutamatergic systems appears warranted. The group II/III metabotropic-glutamate receptor agonists and modulators of AMPA receptors may hold promise in this regard. Of interest, one mechanism of action underlying the relative efficacy of atypical antipsychotics, such as risperidone, for autism may be the suppression of glutamate release via 5-HT_{2A} antagonism. A model describing the interaction of 5-HT_{2A} receptors and thalamocortical glutamatergic neurons, which may underlie this effect, is presented in Figure 1.

Neuroimmunological dysfunction has also been implicated in the pathophysiology of autism. 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. Thus neuroimmune dysregulation in autism would not be inconsistent with altered glutamatergic function, as described above. Results from small open-label studies of intravenous immunoglobulin and oral vancomycin have suggested that these interventions may be helpful in some subjects. Controlled studies of agents with direct effects on immune function, however, have not been conducted.

Significant progress has been made in the psychopharmacology of autism. As in more recently conducted studies, inves-

tigators should continue to include subjects who demonstrate severity in a particular symptom domain as it is unlikely that any one drug will benefit the wide range of maladaptive behaviors seen in autism. Future research should include longer-term studies of atypical antipsychotics to gather longitudinal efficacy and safety data. Larger controlled trials of SRIs in pre-versus postpubertal individuals, as well as studies designed to determine the effects of these drugs in subjects with different subtypes of PDD, including Asperger's disorder, 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. Finally, exploration of promising 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.

WEB SITES OF INTEREST

<http://www.autism-pdd.net/autism.htm>
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ADDITIONAL READINGS

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