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Treatment of Inattention, Overactivity, and Impulsiveness in Autism Spectrum Disorders

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Abstract

We reviewed the recent literature on medicines used to manage inattention, impulsiveness, and overactivity in children with pervasive developmental disorders (autistic disorder, pervasive developmental disorder not otherwise specified, Asperger's disorder) using computer searches of pharmacological studies. A substantial number of reports were identified and summarized. The literature tends to be dominated by uncontrolled studies, although the number of controlled trials is growing. The findings for psychostimulants, noradrenergic reuptake inhibitors, antipsychotics, alpha adrenergic agonists, antidepressants, anxiolytics, cholinesterase inhibitors, NMDA receptor blockers, and antiepileptic mood stabilizers are described. Evidence for a positive effect is strongest for psychostimulants, noradrenergic reuptake inhibitors, antipsychotics, and alpha adrenergic agonists; evidence for efficacy seems weakest for newer antidepressants, anxiolytics, and mood stabilizers.

Keywords

autism; pervasive developmental disorder—not otherwise specified; Asperger's disorder hyperactivity; ADHD; psychostimulant; atomoxetine; antipsychotics; alpha adrenergic agonists; antidepressants; anxiolytics; cholinesterase inhibitors; NMDA receptor blockers; mood stabilizers

Introduction

Research has shown that children with pervasive developmental disorders (PDDs) [autistic disorder, pervasive developmental disorder not otherwise specified (PDD—NOS) and Asperger's disorder] have very high rates of inattention, impulsivity, and overactivity

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(hereinafter called "attention-deficit/hyperactivity disorder (ADHD) symptoms"). For example, Lecavalier [1] surveyed parents and teachers of 487 Ohio school children with the Nisonger Child Behavior Rating Form (hereinafter called *NCBRF*) [2], an instrument for assessing problems in young people with developmental disabilities. The percentages reported as displaying ADHD symptoms at moderate or severe levels (parents and teachers, respectively) were as follows: *Difficulty concentrating,* 49 and 50%; *Easily distracted,* 60 and 59%; *Fidgets/wiggles/squirms,* 42 and 43%; *Overactive,* 41 and 29%; *High energy level,* 44 and 30%; and *Short attention span,* 54 and 47%. Most impressively, these were unselected children who were identified in the schools as having an autism spectrum disorder, not a clinical sample.

In this review, we summarize some of the key research that has been done in children with PDDs and ADHD symptoms. We conducted searches of Medline and Psycinfo using the following terms to capture reports on children with PDDs and ADHD symptoms: autism, PDD, Asperger's disorder, hyperactivity, and ADHD. We combined these terms with overarching drug categories, such as antidepressant, SSRI, and individual examples of generic drugs belonging to the medication group (e.g., imipramine, fluoxetine, venlafaxine). We then worked through the prominent groups of psychotropic agents with possible effects on ADHD symptoms (psychostimulants, noradrenergic reuptake inhibitors, antipsychotics, alpha adrenergic agonists, antidepressants, cholinergic and other Alzheimer treatments, and "other" drugs (anti-epileptic drug (AED) mood stabilizers, N-Methyl-D-Aspartate (NMDA) receptor antagonists).

Psychostimulants

Because of the volume of research on psychostimulants in patients with intellectual disability (ID) and ADHD symptoms and because of overlap of ID with patients having PDDs, we start with a brief comment on the ID/ADHD research. Arnold et al. [3] conducted an exhaustive review of stimulant effects and concluded that they do benefit many people with ID. They noted that most of the sound research was conducted with patients having mild and moderate ID and that efficacy in people with severe or profound ID has not been well demonstrated and may occur at lower rates. Aman et al. [4] studied 90 children with ID and ADHD, and reported that 44% of participants showed at least a 30% reduction compared with placebo on teacher ratings when treated once daily with a dose of 0.40 mg/kg methylphenidate (MPH). Using the same quantitative definition of response, Pearson et al. [5] found that 38% of children with ID receiving 0.30 mg/kg b.i.d. MPH and 55% of those receiving 0.60 mg/kg b.i.d. showed a 30% advantage over placebo as rated by teachers on Conners' Abbreviated Symptom Questionnaire (henceforth called *CASQ).*

Group studies of psychostimulant treatment in young people with PDDs and ADHD are presented in Table 1. The earliest studies [6,7] were conducted with preschoolers with autism (but not necessarily with ADHD symptoms) and therapeutic effects on ADHD symptoms were not observed. Furthermore, a variety of adverse events including irritability, worse stereotypies, and increased hyperactivity occurred in some children. However, we should not be overly influenced by these reports, as the children were not selected for ADHD symptoms and most of them were preschoolers; we now know that typically-developing preschoolers often show a muted response to stimulants [8]. Five modest studies ran the gamut from totally uncontrolled [9], to confounded with time due to open-label design [10,11], to well controlled [12,13]. All of these reported at least some benefit in ADHD symptoms, and most also reported a variety of adverse events including irritability, self injury, social withdrawal, and insomnia. Response rates in these trials ranged from 46% [11] to 62% [13].

Santosh et al. [14] reported two comparisons involving children with ADHD plus autism spectrum disorder (ASD). In the first retrospective comparison of 113 children with "pure" ADHD (no ASD) and 61 children with ADHD plus ASD, the percentage of responders [Clinical Global Impression Improvement (CGI—I) [15] scores of 1 or 2] [15] was 66.3% and 51%, respectively, which did not differ significantly. Remarkably, only 1.6% of the ADHD plus ASD group had bedwetting problems, and only 21.3% had "learning difficulties" (often used in the UK to refer to intellectual disability). In a companion trial that was part of the same publication, Santosh et al. [14] compared the progress of 25 "pure" ADHD patients with that of 27 ASD plus ADHD patients. They claimed more-or-less equivalent gains in both groups, although they did not report response rates and used independent *t*-tests where a 2-way ANOVA model would have been more appropriate. They reported IQs as 95 for "pure" ADHD and 84 for ASD plus ADHD. These and the low rates of bedwetting (1.6%) and learning difficulties (21.3%) in the first study raise questions about the representativeness of participants with ASDs in these studies since they may have been quite "high-functioning."

The largest and best controlled trial of stimulant treatment was conducted by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network [16,17] (see Table 1). Autistic disorder was the predominant diagnosis (74% of sample), but 26% of the sample had PDD-NOS or Asperger's disorder (RUPP, 2005). Placebo and methylphenidate doses approximating 0.125, 0.25, and 0.50 mg/kg were given b.i.d. with a third, smaller, dose given late afternoon. As assessed by the Aberrant Behavior Checklist (henceforth called *ABC*) [18,19] Hyperactivity subscale, parents rated their children as significantly improved compared with placebo on the low, medium, and high doses (with effect sizes, *d,* of 0.29, 0.54, and 0.40, respectively). The Parent-rated Social Withdrawal subscale on the ABC was significantly *worse* on the high dose. Thirty-five of the 72 participants (49%) were classified as clinical responders to MPH, whereas 13 participants (18%) exited the study because of intolerable side effects. Irritability, emotional outbursts, and initial insomnia were the most problematic adverse events (AEs).

Posey et al. [17] reported additional findings from the RUPP study. On the Swanson, Nolen, and Pelham (SNAP) rating scale (http://www.adhd.net/snap-iv-instructions.pdf) [20], parents rated the children as significantly improved on all three doses. On the teacher-rated SNAP Hyperactivity subscale, the medium and high doses produced significant improvement compared with placebo; the low dose failed to separate from placebo. Posey et al. examined age, IQ, and autism versus other PDDs as possible moderators, but none of them influenced outcome.

All in all, the stimulants tend to produce highly variable responses in children with PDDs and ADHD symptoms. Such responses range from substantial improvement with minor side effects through to more problematic behavior and physical and/or behavioral side effects. Given what we know, stimulants would still be a reasonable first therapeutic choice for previously-untreated children with PDDs and uncomplicated ADHD, even though they do not work as well, *on average,* as they do in typically-developing children. Any side effects should be reversible on discontinuing the drug. Clinicians should be candid with parents about the lower likelihood of a positive clinical response and elevated risk of AEs. Treatment should proceed with low initial doses, small dose increments, and a data-based approach. Both clinicians and parents should be prepared to stop the trial if there is clear evidence of behavioral deterioration and/or unacceptable AEs.

Atomoxetine

Atomoxetine (Strattera) is a relatively new noradrenergic reuptake inhibitor frequently used to control symptoms of ADHD in typically-developing children. Jou et al. [21] were first to report on the effects of atomoxetine on hyperactivity and inattention in children with PDDs. Twenty patients (10 dually-diagnosed with mental retardation; 16 with autism, 2 with Asperger's disorder, and 2 with PDD—NOS) were openly treated with atomoxetine for an average of 19.5 weeks. Sixteen (80%) received concomitant medications but no changes in dose or titration in co-therapy were made during the course of the study. Conners' Parent Rating Scale (Conners' PRS) [22] was the main outcome measure. Significant improvement between baseline and endpoint was reported for the Hyperactivity and Inattention subscales. The average baseline Hyperactivity score of 17.1 improved to 13.0 ($t = 3.86$, $p < 0.001$, $d = 1.77$), while baseline and endpoint Inattention scores were 7.5 and 5.8, respectively ($t = 3.1$, $p = 0.01$, $d = 1.42$). Twelve (60%) of the participants were responders to atomoxetine based on the CGI—I scores of 1 or 2.

Troost et al. [23] did a pilot study of atomoxetine in 12 children with PDD (6 with autism, 5 with PDD-NOS, and 1 with Asperger's disorder). Patients were washed out of psychoactive drugs and treated openly with atomoxetine. Five subjects (42%) discontinued after at least 6 weeks due to side effects including gastrointestinal complaints. The parent-rated, investigator scored ADHD Rating Scale-IV (ADHD-RS) [24], Conners' PRS and the ABC were outcome measures. The endpoint Total Score of the ADHD-RS significantly decreased from a baseline average of 40.33 to 22.42 ($p = 0.003$, $d = 2.30$). A significant improvement occurred in the Conners' PRS ADHD Index between baseline and endpoint (24.25 and 18.67, respectively; $p = 0.023$, $d = 0.65$). The Hyperactivity subscale of the Conners' PRS showed a significant reduction from 9.83 to 6.67 ($p = 0.03$, $d = 0.63$); but the change on the ABC Hyperactivity subscale failed to reach significance (baseline 23.58; endpoint 18.67; $p = 0.07$). The authors felt that gastrointestinal symptoms were more severe in their participants than observed in typically-developing children, and they speculated that children with PDD may be more susceptible to such effects.

Posey et al. [25] conducted an 8-week open-label pilot study included 16 children with PDDs (7 with autism, 7 with Asperger's disorder, and 2 with PDD-NOS), hyperactivity, and a nonverbal IQ of at least 70. Participants began with a dose of 0.5 mg/kg/day, which was titrated to 1.2 mg/kg/day in the third week. The CGI—Severity subscale was the primary outcome measure; secondary measures included (a) the ABC, (b) the SNAP, and (c) Conners' Continuous Performance Test (CPT) [26]. After 8 weeks, there was a significant reduction on the CGI—S (5.1 to 3.9; F (1,15) = 17.86, $p = 0.001$; $d = 1.09$). The ratings of both parents and teachers on the SNAP-IV decreased significantly (44.4 to 22.6, $d = 1.9$; 29.6 to 14.7, $d = 1.4$, respectively; $p < 0.0001$). In addition to decreases on several other subscales of the ABC, both parents and teachers saw improvement on the Hyperactivity subscale (28.4 to 14.2, $p = 0.0004$, $d = 1.9$; 18.2 to 8.4, $p < 0.0001$, $d = 1.0$, respectively). No differences were found on the Conners' CPT, consistent with a study in typically-developing adults with ADHD [27].

Arnold et al. [28] completed the first placebo-controlled trial of atomoxetine in children with PDDs. This double-blind pilot study used a crossover design where each condition lasted for 6 weeks (3 week titration), followed by a one-week washout period. The primary outcome measures were the ABC Hyperactivity subscale, the CGI—I, CGI—S, and SNAP Hyperactivity subscale (each rated on a scale of 0–3). Sixteen children were randomized, and three terminated early (2 due to lack of effect with placebo, 1 due to AE with atomoxetine). "Responder" status was achieved by a 25% decrease on ABC Hyperactivity subscale and a 1 or 2 on the CGI-I. Nine children (56%) responded to atomoxetine, whereas

four (25%) responded to placebo. This response rate is lower than that found in studies with typically-developing children, although slightly better than the response rate found in the RUPP study using methylphenidate in children with PDD[16]. The slope of response on time was compared for the outcome measures. The slopes for atomoxetine and placebo were significantly different on the ABC Hyperactivity subscale (−5.00 vs. 0.56, respectively, $p = 0.04$; $d = 0.90$) and SNAP Hyperactivity (−5.87 vs. −0.82, $p = 0.005$, $d = 1.27$). The effect sizes of the placebo-controlled impact of atomoxetine on ADHD symptoms were comparable to those found in typically-developing children[29,30,31]. The low incidence of AEs was impressive; two of the three individuals who terminated early were in the placebo group. The authors suggested that future research include a parallel group design to alleviate carry-over effects.

Together, these studies suggest that atomoxetine may be useful for controlling ADHD symptoms in children with PDD. Although effect sizes were generally large, this likely was due in part to the open-label design of most studies. In general, the side effects profile appeared to be mild, including mostly tolerable gastrointestinal effects. However, this evidence is preliminary; no large, placebo-controlled, parallel design trials have been published. To our knowledge, no study thus far (either with children having a form of PDD or in typically-developing children with ADHD) has demonstrated significant effects of atomoxetine on cognition [25,28,32]. If correct, this stands in contrast to psychostimulants, where enhancement of sustained attention and other performance tests is the norm. This would reflect a true qualitative difference in mode of action between atomoxetine and psychostimulants. It may be tempting to discount atomoxetine because of this, but it is well to remember that no long-term study of the psychostimulants in typically-developing children has demonstrated academic gains due to active treatment.

Antipsychotics

Classical Antipsychotics

Predictably, most of the work on classical antipsychotics used small sample sizes, and much of it was poorly designed. Waiser et al. [33] assessed open-label thiothixene in 18 outpatient “schizophrenic” children diagnosed with Creak’s criteria. The children (ages 5 to 13 years, mean 9.4) were rated as significantly improved on ratings of psychomotor activity (36% reduction) and concentration (9%) with a mean dose of 17 mg/day.

Probably the best study of classical antipsychotics came from Magda Campbell’s laboratory at New York University [34]. In this investigation, 40 inpatient children, ages 2 to 6 years (mean 4.6 years) with autism were treated with one of two sequences of medication: haloperidol (HAL), placebo, HAL; or placebo, HAL, placebo, each of which lasted 4 weeks. Outcome measures included the Children’s Psychiatric Rating Scale (hereinafter, *CPRS*) [35], CASQ, and the CGI. On the CPRS, the children were rated by clinicians as having significantly less hyperactivity and fidgetiness (both *P*s <.01) with HAL. The children were rated by their teachers as having significantly lower CASQ scores with HAL, and clinicians rated the children as more improved with HAL on both the CGI—S and CGI—I. Unfortunately, 11 of the 40 participants (28%) developed dystonic reactions at some stage. In one follow-up study of 118 autistic children who were treated for 6 to 12 months, Campbell et al. [36] found that 34 subjects (29%) showed withdrawal dyskinesias on placebo substitution and 4 subjects (3.4%) showed tardive dyskinesia [total prevalence of dyskinesia of 38 (32.2%)]. Despite the positive effects on ADHD symptoms in the acute study, one would want to be very conservative and use HAL only where target symptoms are quite extreme in young patients with PDDs.

Atypical antipsychotic (AAPs)

We begin with risperidone and then we address the other AAPs.

Risperidone—In contrast to conventional antipsychotics, novel agents are reported to activate dopamine neurons in prefrontal cortex and limbic regions (e.g., nucleus accumbens) with lower effect in the striatum [37]. In addition to this, risperidone has greater 5-HT_2 blockade than D_2 blockade. Because risperidone is better researched than the others, we present only controlled studies with risperidone.

Currently there are four controlled studies of risperdone in children with PDDs that have targeted inattentiveness and hyperactivity (Table 2). The RUPP Autism Network [38] conducted a randomized controlled study of 101 children with autism and disruptive behavior, including hyperactivity. Scores on the ABC Hyperactivity subscale were markedly and significantly lower for risperidone compared with placebo after 8 weeks of treatment (d= 1.00). Shea et al. [39] also conducted an 8-week, controlled trial and reported significant ABC Hyperactivity subscale reductions. On the parent-rated NCBRF Hyperactive subscale, risperidone produced significant reductions. The effect sizes were smaller in Shea et al. than in the RUPP study, probably because subjects were not selected for extreme behavior in Shea et al.

Hellings et al. [40] randomized subjects first to placebo and then to two risperidone dosing schedules (low and high). In this double-blind placebo-controlled crossover study, the ABC Hyperactivity subscale showed moderate improvements at both low (d= 0.58) and high dose (d= 0.41) of risperidone (Table 2). Finally, Troost et al. [41] conducted an open-label study of risperidone with a double-blind placebo-controlled discontinuation phase. The outcome measures were from focused attention and divided attention tasks. At endpoint of the open-label (Week 24), half of the subjects were tapered off risperidone to placebo over an 8-week period. There were no significant drug group differences on focused attention, but the risperidone group performed better on the divided attention task in reaction time hits and reaction time for correct rejections. However, the parent-rated ABC Hyperactivity subscale showed no significant group differences [42].

When participants were admitted because of extreme behavior, risperidone had significant and important effects on ADHD symptoms. The effects on attention tests require replication, but they also suggested improvement.

Other AAPs—Unfortunately there is no well-controlled research known to us that addresses the effects of other AAPs on hyperactivity. We summarize the evidence on quetiapine, ziprasidone, and aripiprazole (see Table 2). The two retrospective reports on quetiapine reported overall gains on the CGI—I, which was based in part on hyperactivity [43], and CPRS parent ratings of Inattention and Hyperactivity [44]. One very small open-label study of ziprasidone found significant improvement on the ABC Hyperactivity subscale but not on the CPRS Hyperactivity scale [45]. Valicenti-McDermott and Demb [46] described outcomes for a heterogeneous group of young people with “developmental disabilities.” Improvement in hyperactivity occurred for 10 of 21 children (48%) with ADHD symptoms as a target of treatment; the authors felt that children with PDDs responded less well than the other participants.

Alpha2 Adrenergic Agonists

Clonidine and guanfacine act on α2-adrenergic presynaptic receptors to inhibit noradrenergic release and synaptic transmission [37]. Guanfacine has a longer action than clonidine.

Clonidine

Two small studies have investigated clonidine for hyperactivity in autistic disorder. Fankhauser et al. [47] conducted a double-blind placebo-controlled crossover study of the clonidine transdermal patch (approximately 0.005 mg/kg/day) in 7 autistic males ages 5 to 33 years (mean age 12.9) exhibiting "hyperarousal." The parent-rated CASQ did not show a significant difference between groups in hyperactivity and inattentiveness at endpoint. However, CGI—Improvement ratings showed significant gains (p <0.0001). Jaselskis et al. [48] conducted a 12-week double-blind placebo-controlled crossover study of clonidine (0.15–0.20 mg/day) in 8 males with autistic disorder and hyperactivity. The results were mixed, showing a significant improvement in ADHD symptoms on the parent-rated CASQ (p = 0.03; d = .57) and the teacher-rated ABC Hyperactivity subscale (p = 0.03; d = .34), but not on the clinician rated CPRS Hyperactivity subscale.

Guanfacine

Two studies have been reported. Posey et al. [49] conducted a retrospective study of guanfacine in children with target symptoms including inattentiveness and hyperactivity. Eighty subjects (10 female, 70 males), with a mean age of 7.7 years, met the criteria of a PDD diagnosis and history of guanfacine pharmacotherapy. A determination of global severity and global improvement (based on interfering behaviors including ADHD symptoms) was made by subjects' treating psychiatrists. Guanfacine was associated with a statistically significant improvement in CGI Severity ratings (p < 0.001; d= 0.58).

Scahill et al. [50] conducted an 8-week open trial of guanfacine in 25 children (23 boys and 2 girls) with a mean age of 9.0 years and a diagnosis of PDD accompanied by hyperactivity. All 25 had failed to respond or could not tolerate MPH. Outcome measures included parent and teacher ratings on the ABC, SNAP-IV, 2001), and CGI—I. Dosage ranged from 1.0–3.0 mg/day, split into 2 or 3 doses. The results showed significant improvement on the parent-rated ABC Hyperactivity subscale (p <0.001; d = 1.4) and the SNAP-IV Hyperactivity subscale (p <0.0001; d =1.5). Teacher ratings also reflected significant improvement on ABC Hyperactivity (p <0.01; d = 0.83) and on the SNAP-IV (p= 0.01; d = 0.56). Forty eight percent of subjects were rated *much improved* or *very much improved* on the CGI-I. Four subjects terminated early due to irritability and one due to agitation.

Antidepressants

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) have a long history of use for ADHD symptoms in typically-developing children [51] and in adults. In recent years, however, growing concern about potentially-serious cardiovascular effects has curbed the use of this class in children. The literature regarding TCAs in children with developmental disabilities is limited. Gordon et al. [52] compared the use of clomipramine and desipramine to treat the associated behaviors of autism in seven children with the disorder. The subjects took part in a 10-week, double-blind, randomized, crossover trial, following two weeks of a single-blind placebo period. On the CPRS Hyperactivity subscale, the effects of clomipramine and desipramine after 5 weeks were significantly different from placebo (115% improvement, 80% improvement, and 2% improvement, respectively; F = 4.62, p = 0.05, d = 1.11), but not from each other.

Gordon et al. followed the 1992 report with a larger, double-blind comparison of clomipramine, desipramine, and placebo [53]. Twelve children with autism completed a 10-week, double-blind, crossover study of clomipramine and placebo, and twelve different subjects with autism participated in an identical study of clomipramine and desipramine.

The same pattern of results as the earlier report was found; both desipramine and clomipramine had significantly greater effects than placebo on hyperactivity ($F = 14.4$, $p=0.0001$, $d = 1.32$), but they were not significantly different from one another. Medication was reduced for two patients who experienced cardiac effects with clomipramine (one experienced tachycardia, another delayed conduction). A third subject had a generalized tonic-clonic seizure. To the best of our knowledge, these promising effects on ADHD symptoms have not been pursued in subsequent research.

Selective Serotonin Reuptake Inhibitors (SSRIs)

There are several older reports of fluoxetine (Prozac) for depression in adolescents and adults with autism [54,55] although the only purely adolescent sample was that of Fatemi et al. [56]. This open trial included seven patients with autism who had been treated with fluoxetine in the previous six years (for an average of 18 months). Mean baseline and endpoint scores on the ABC were compared, and a significant drop was observed in all subscales *except* Hyperactivity, which increased by 14% (22.21 to 25.80, significance not reported). Although fluoxetine seemed to be beneficial for some autism symptoms, the increase in hyperactivity may be a limiting factor.

There are several reports that venlafaxine, a serotonin-norepinephrine reuptake inhibitor, was useful in young adults with PDD. However, these effects did not seem to appear in children. Hollander et al. [57] completed an open-label study of 10 individuals with PDDs. The sample included 8 children (1 with PDD-NOS, 4 with Asperger's disorder, and 3 with autism) and 2 adults. Results were presented qualitatively; 4 of the 8 children experienced significant hyperactivity/restlessness as an AE of the drug, although 6 of 8 were considered responders (i.e., a "Much improved" or "Very much improved" rating on the CGI—I addressing the core symptoms of autism). The authors concluded that venlafaxine may cause some improvement to the core symptoms of autism, although it appeared to exacerbate hyperactivity.

The remaining reports of SSRIs in individuals with autism were specific to symptoms of depression and/or did not include children. It appears that TCAs may have some role in managing ADHD symptoms in children with PDDs, although potential cardiac effects warrant cautious use. There is little reason to believe that the SSRIs or venlafaxine have utility for managing ADHD symptoms in young people with PDDs and, in fact, they may exacerbate ADHD symptoms.

Anxiolytic Agents

The literature on use of anxiolytic agents to control ADHD symptoms in typically-developing children is both sparse and weak [58]. Benzodiazepine anxiolytics may produce significant side effects as well as dependence, withdrawal, and rebound symptoms. Not surprisingly, there are no respectable studies of these drugs in children with PDDs.

Two reports of buspirone, which has mixed pharmacologic action on dopamine and serotonin receptors and is marketed as an anxiolytic, were located. Realmuto et al. [59] published a case study of four subjects with autism and mild-to-moderate mental retardation. Hyperactivity was a target symptom for three. Each child received 5 mg of buspirone, open-label, three times daily for four weeks, followed by methylphenidate or fenfluramine for four more weeks. Parents completed the ABC, and teachers completed Conners' Teacher's Rating Scale (hereinafter, *Conners' TRS*) [60]. Only qualitative data were reported; two children showed "improvement" in hyperactivity. Another child did not respond to initial treatment; when switched to fenfluramine, he experienced worsening of ADHD symptoms, which improved again when returned to buspirone.

In a "single-subject study" [61] a child with autism and ADHD symptoms received three weeks of placebo, followed by washout and three weeks of buspirone (10 mg/day). Improvements on blinded ratings on the CASQ failed to reach significance, although a reliable linear improvement was seen in the number of daily performance tasks completed at school with buspirone.

We were able to find only one other study examining the use of anxiolytic agents in children with PDD, this being with a benzodiazapine. Marrosu et al. [62] administered diazepam to seven children with infantile autism (DSM III) and disruptive anxiety attacks. Diazepam was given intramuscularly when the children experienced anxiety attacks significant enough to disrupt the class they were attending. Children were rated on the "Children's Diagnostic Scale" in the hour following the administration of the drug. Ratings of hyperactivity *worsened* for six of the seven participants.

The lack of studies in children with PDD may well be due in part from known effects of anxiolytic agents in typically-developing children, where true anxiolytic agents have been shown to cause dysinhibition and sometimes increased activity and impulsiveness [58]. There is little reason to assume that they will be helpful in children with PDDs and ADHD symptoms, and they may have adverse effects.

Cholinesterase Inhibitors

Cholinesterase inhibitors increase acetylcholine levels in the brain through the inhibition of the enzyme cholinesterase and have been used for Alzheimer's disease [37]. Post-mortem studies have found significant abnormalities of the cholinergic system and its nicotinic receptors in the brains of individuals with autism [63,64].

Donepezil

Very few studies of donepezil have been attempted in autism spectrum disorders (ASD). Hardan and Handen [65] conducted a retrospective study of donepezil and its effects on core symptoms of autism and disruptive behavior in 8 young people. Significant improvement was reported for the CGI severity ratings and on the ABC Hyperactivity and Irritability subscales. To date, there is no compelling argument for advocating donepezil for treating either the secondary symptoms or the core features of autism. Rigorous exploratory studies are needed.

Galantamine

Neiderhofer [66] tested the effects of galantamine in a randomized placebo-controlled crossover study of 20 outpatient boys (mean age 7.4 years) with autism diagnosed by ICD-10 criteria. After combining parent and teacher ratings, the investigators found significant differences favoring galantamine on ABC Irritability, Hyperactivity, and Inappropriate Speech subscales. No side effects were reported. Neiderhofer concluded that galantamine is well tolerated and may be beneficial for treating irritability in children with autism.

Nicolson et al. [67] conducted a 12-week open-label study of galantamine in 13 children and adolescents with autism, ages 4–17 years. Significant improvement was noted on the ABC for the Irritability and Social Withdrawal subscales, but not for Hyperactivity. Clinician ratings on the CPRS showed significant improvement over time on the Autism and the Anger subscales but not the Hyperactivity subscale. Clinician ratings showed a significant reduction in the autism severity on the CGI-S. This study suggests possible benefit of galantamine for interfering behaviors in children with PDDs, although there was no indication of benefit for ADHD symptoms.

Rivastigmine Tartrate

Rivastigmine tartrate has dual actions, inhibiting both acetylcholinesterase and butyrylcholinesterase and enhancing cholinergic function at the synaptic cleft [37]. Chez et al. conducted a 12-week open-label study of rivastigmine tartrate in 32 children with PDDs, ages 2–12 years [68]. Paired *t* tests indicated significant improvements over time on the Childhood Autism Rating Scale and Conners' PRS—R [69]. It was not clear from this report whether the change occurred on the Hyperactivity subscale or on the total score from the Conners'.

NMDA receptor Antagonists

Amantadine Hydrochloride

Amantadine has been found to have noncompetitive NMDA (n-methyl-d-aspartate) antagonist activity and has moderate NMDA receptor-blocking properties at doses routinely used for its prescribed indications (i.e., influenza, herpes zoster, and Parkinson disease) [70]. It also exerts its activity by increasing dopamine at the receptor [37].

King et al. [70] conducted a double-blind placebo-controlled multicenter study of amantadine hydrochloride in 39 subjects with autistic disorder, ages 5–19 years. There were no clinically-significant differences between treatments on the parent-rated ABC Irritability or Hyperactivity subscales. Investigator-rated ABC scores did reveal a significant treatment difference on Hyperactivity. There were no significant differences on the CGI—S at the final visit. Amantadine was well tolerated. The investigators concluded that the dose range of 90–200 mg (below the recommended 200-mg dose for treatment of influenza) may have been too low to elicit a treatment effect even if amantadine has clinical potential.

Memantine

Memantine is an NMDA antagonist that is thought to preserve neuronal function. It selectively blocks the excitotoxic effects associated with abnormal glutamate transmission by modulating calcium channels[37]. It has been hypothesized that glutamate is involved in the pathophysiology of PDDs [71,72]. Owley et al. [73] conducted an open-label trial of memantine in 14 children with PDDs. There were no significant differences between baseline and endpoint on measures of expressive language, receptive language, nonverbal IQ, or CGI—S. Significant differences were found on a memory test (p=0.02) and on all subscales of the ABC (especially the Social Withdrawal and Hyperactivity subscales). Conversely, hyperactivity was an AE for 5 subjects (36%). The investigators called for double-blind placebo-controlled studies of memantine.

Erickson et al. [74] conducted a retrospective chart review of memantine in 18 children (15 male, 3 female; ages 6–19 years) with PDDs. As part of routine care, the treating physician completed the CGI—S and the CGI—I scales. Six subjects also had ABC baseline and endpoint data available. Eleven of the 18 (61%) were considered responders on the CGI-I, and on the ABC there was a significant improvement on the Hyperactivity subscale.

There are enough positive data to warrant controlled trials of memantine. Hyperactivity was reported as both a side effect and as an area of therapeutic change. Thus, treatment with memantine is clearly experimental at this time.

AED Mood Stabilizers

Many children with autism spectrum disorders are also diagnosed with epilepsy, and receive antiepileptic drugs. Hollander et al. [75] reported that five of fourteen (36%) autistic individuals aged 5 to 40 years became less impulsive after treatment with divalproex

sodium, although side effects (fatigue, sedation, behavioral activation) were severe enough for two participants to terminate. Uvebrant and Bauziene [76] published an anecdotal report of 50 children treated with lamotrigine. They reported that the children experienced an increase in attention span; however, only 13 of the children (26%) were diagnosed with autism, so it is not clear if these results were true of autism. Belsito et al. [77] explored lamotrigine for symptoms of autism in a double-blind, placebo-controlled trial. Twenty-eight children with autism were treated with lamotrigine for eight weeks, followed by a four-week maintenance period. The main outcome measures, the Autism Behavior Checklist [78] and the ABC, showed no differences between placebo and lamotrigine. The authors concluded that lamotrigine is probably not helpful in treating core symptoms of autism; an effect on ADHD symptoms seems unlikely.

Hardan et al. [79] conducted an open-label retrospective chart-review of topiramate in children with PDDs. Fifteen patients were included in the sample (11 with autism, 2 with Asperger's disorder, and 2 with PDD-NOS), and hyperactivity was a target symptom for eight. Eight of the children (53%) were considered responders after achieving a "Much improved" or "Very much improved" rating on the CGI—I. The children displayed significant reductions on several subscales of Conners' PRS [22]: Inattention declined from 8.5 to 5.3 ($t = 3.11$, $p = 0.008$, $d = 1.66$), and Hyperactivity decreased from 17.9 to 12.5 ($t = 4.30$, $p = 0.001$, $d = 2.30$). There is a need for a double-blind placebo-controlled trials to confirm these impressions.

Overall, there are few studies and limited evidence for the use of antiepileptic mood stabilizers in improving symptoms of ADHD in children with PDDs and the positive studies in ASD are all uncontrolled. Despite some positive carbamazepine studies in typically developing children, clinical use of these agents for ADHD symptoms in children with PDDs must be considered a personal experiment and should be guided by clinical data.

Opiate Blockers

Several studies of naltrexone were conducted in children with autism, usually with the hope of reducing core features of autism [80,81,82,83,84,85,86]. No effects were consistently found in autism symptoms; what is intriguing is that all of these studies observed reductions in hyperactivity, an often unanticipated finding [87].

Conclusions

Unfortunately, case series, open label trials, and retrospective reports still dominate the autism field, and blinded placebo-controlled studies make up a small minority of the literature. Although uncontrolled studies *may* reflect true effects, it is equally true that "significant" changes may be due to the passage of time, placebo effects, or the well-known tendency of higher scores to regress to the mean. Such uncontrolled studies may exaggerate effect sizes. Hence, the brunt of the evidence presented here is only suggestive, and awaits true assessment in properly-controlled studies. At this point, the evidence for a therapeutic effect on hyperactivity and inattention seems best for methylphenidate (although other stimulant preparations probably also work about as well), atomoxetine, certain atypical antipsychotics, and alpha-2 adrenergic agonists. There is not much to commend the SSRIs, venlafaxine, benzodiazepines, or AED mood stabilizers for these symptoms. The case still needs to be made for tricyclic antidepressants, cholinesterase inhibitors, and NMDA receptor blockers, whose use for hyperactivity should be viewed as experimental.

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Table 1

Studies of Psychostimulants in Young People with PDDs

Authors	Subjects	Treatment and Design	Outcome by Variable
Campbell et al., 1972	16 children, ages 3 to 6 years (mean 4.3), with autistic disorder, treated as inpatients. Subjects not selected for ADHD symptoms. IQ ranged from 28–96.	Open-label trial, lasting 3–4 days, comparing baseline with d-amphetamine (mean dose = 4.8 mg)	Nonsignificantly worse behavior on CGI (No drug > d-AMPH). Nonsignifcantly worse behavior on Fish Symptom Severity Scale (No drug > d-AMPH). AEs reported: Irritability, hyperactivity, and appetite loss commonly occurring.
Campbell et al., 1976	11 children, ages 3 to 6 years (mean 5.4), with autistic disorder, treated as inpatients. IQ ranged from 36–90.	Levoamphetamine (L-AMPH) (crossed with levodopa) and with 4-week washout between active drugs. L-AMPH dose ranged from 3.5 to 42 mg/d (mean = 13.4 mg/d). Duration of L-AMPH ranged from 4–12 weeks (mean 8.3).	On CGI—I subscale, 7 subjects rated worse, 2 rated as unchanged, and 2 as minimally improved. No change on Symptom Severity scale. Hyperactivity declined in 5 of 7 subjects with the symptom. AEs reported: Loss of appetite (n=7), weight (n=6), worsening of preexisting and de novo stereotypies (n=9), worsening of self injury (n=3) worsening of excitability (n=1).
Hoshino et al., 1977	15 children with autism, ages 2 to 13 years (mean = 7.0 years). All but one were boys. Not clear whether ADHD symptoms problematic at outset.	Open-label, variable duration (2 weeks to 1 year) trial of MPH (0.3 to 1.0 mg/kg/d). Average treatment duration was 6.5 months. No inferential statistics.	Werry, Weiss, Peters Activity Scale (parent rated): Baseline score = 29.9; endpoint = 21.9. 6 subjects rated as substantially improved on WWPAS. 9 cases (60%) considered substantially improved clinically. Adverse events; 6 (40%), irritability; 5 (33%), insomnia; 4 (27%), self injury or aggression; 3 (20%) diarrhea
Birmaher et al., 1988	9 children, ages 4–16 years (mean not reported), with autism and significant ADHD symptoms.	Uncontrolled group study comparing 1-week baseline (no drug) with MPH given in doses of 10–50 mg/d (mean dose = 25 mg) on b.i.d. basis for 2 weeks.	Conners' Parent Rating Scale: MPH > BL Conners' Teacher Rating Scale: MPH > BL Children's Psychiatric Rating Scale (total score): MPH > BL AEs reported: mild initial insomnia
Quintana et al., 1995	10 children with autism and symptoms of ADHD. Developmental quotient ranged from 50 to 84 (mean = 64.3). Age ranged from 7 to 11 years (mean = 8.5 years).	Double blind, PBO controlled, X-over, with 2 weeks on each drug condition. Dose was 10 mg MPH bid in first week and 20 mg in second week. No drug confounds.	Conners' Parent Rating Scale: BL= MPH Doctor-completed ABC Hyperactivity: MPH > PBO Doctor-completed CTQ: MPH > PBO Number of clinical responders not reported. Authors characterized findings as significant but modest.
Handen et al., 2000	13 children with PDDs and symptoms of ADHD. 9 had autism and 4 had PDD-NOS. 10 were boys and 3 girls. Age ranged from 5.6 to 11.2 years (mean = 7.4). 11 of 13 had intellectual disability.	Double blind, PBO controlled, X-over, with treatment trials of 1 week. PBO compared with MPH 0.3 mg/kg/d and 0.6 mg/kg/d, given 2 or 3 times/day. High dose always followed low dose.	Conners' Abbreviated Symptom Questionnaire (CASQ): High, Low> PBO IOWA Conners' Scale: Low > PBO ABC, Hyperactivity: High > PBO ABC, Inappropriate Speech: Low, High > PBO All comparisons based on teacher ratings. AEs associated with MPH: social withdrawal, dullness, sadness, and irritability. One child unable to tolerate MPH. 8 (62%) participants subsequently treated clinically with 0.2 to 0.6 mg/kg/d MPH
Di Martino et al., 2004	13 children with autism (n = 7), PDD-NOS (n = 3), or Asperger's disorder (n = 3), all with ADHD symptoms. Moderate or greater hyperactivity on Hyperactivity subscale of CPRS and T-score ≥ 60 on Conners' Parent and Teacher Revised Scale. Age ranged from 5 to 13 years (mean = 7.9).	Test trial: Acute 1-hour open trial with 0.4 mg/kg MPH. Efficacy trial: Open label trial, extending from 1 week (non-responders) to 3 months (responders).	Test trial: On CGI-I, 5 children were terminated. 2 had worse hyperactivity, 1 had worse stereotypic behavior, 1 had dysphoria, and 1 had motor tics. 8 children entered remainder of trial. Week 1: 6 of 8 subjects rated 2 or 3 on CGI and followed for 3 months. 2 subjects unchanged on CGI-I and terminated. 3 Month Comparison: Conners' Parent/Teacher Rating Scales-R: Hyperactivity MPH > PBO. ADHD Index MPH > PBO. ADHD/DSM Total MPH> PBO (all findings true of parent and teacher ratings).

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Authors	Subjects	Treatment and Design	Outcome by Variable
			As 5 subjects terminated after test dose and 2 terminated after 1 week, only 6 subjects completed trial. Six of original 13 subjects (46%) had positive response to MPH
RUPP, 2005	72 children with PDD and ADHD symptoms, ages 5–14 years (mean, 7.5). 47 (65%) had autism, 14 (19%) had PDD—NOS, and 5 (7%) had Asperger's disorder	MPH; low, medium, high doses (approx. 0.125, 0.250, 0.500 mg/kg) given 3 times daily (last dose about ½ morning and midday doses). Double blind, X-over, PBO controlled, 1-week treatment phases.	Six subjects (8.3%) did not survive test-dose phase. One dropped out before X-over. Parent-rated ABC Hyperactivity; low, medium, high > PBO. Effect sizes = 0.29 (low), 0.54 (medium), and 0.40 (high) Parent-rated ABC Social Withdrawal: PBO > High dose (indicates worsening with MPH; E.S. =0.37) 35 of 72 subjects (49%) were responders. CGI-I: Medium dose > PBO
Santosh et al., 2006 (a)	113 children with "pure" ADHD and 61 children with ASD (by consensus) and ADHD. Mean ages were 13.14, and 12.43, respectively.	Open-label, of variable duration, no controls with retrospective ratings from clinical notes. Doses did not differ between groups. No data about concomitant treatment or drugs.	CGI-I: Did not differ statistically between groups, CGI-I =1 or 2 for 63% and 51% of ADHD-only and ADHD + ASD groups (p not reported). Efficacy Index, taken from CGI: Although marginal difference ($p = 0.06$) favoring ADHD + ASD, the index did not correspond to the official NIMH form.
Santosh et al., 2006 (b)	25 children with "pure" ADHD and 27 children with ADHD + ASD. Mean ages were 11.6 and 10.6 years, respectively. Mean IQs were 95.2 and 84.3, respectively.	Open-label trial, of variable duration, with prospective ratings done at baseline and "follow-up" (1–6 months later; mean 87 days). No control condition or blindness. No data on concomitant treatment or drugs.	Internet-based "profile of neuropsychiatric symptoms" (POMS) used. As assessed by separate t-tests, both groups improved on hyperactivity, impulsivity, inattention, oppositionality, aggression, and intermittent explosive rage. To properly test for differential effect, 2 × 2 ANOVA should have been used. CGI, inappropriately analyzed by t-tests, improved in both groups. Response rates not reported.
Posey et al., 2007	66 children (of 72 reported in RUPP, 2005) with PDD and ADHD symptoms, ages 5–14 years (mean, 7.5)	MPH; Low (0.125 mg/kg), Medium (0.25 mg/kg), and High (0.50 mg/kg) dose conditions. Double-blind, PBO controlled, X-over, 1-week treatment phases.	Parent-rated SNAP Hyperactivity: Low, medium, high > PBO Teacher-rated SNAP Hyperactivity: Medium, high > PBO; low = PBO Parent-rated SNAP ODD: Low, medium, high = PBO Teacher-rated SNAP ODD: Low, medium, high = PBO IQ, age, type of PDD did not moderate outcome

Note. AE, Adverse event; AMPH, Amphetamine; ASD, Autism spectrum disorder; E.S, Effect size; MPH, methylphenidate; SNAP, Swanson, Nolan, and Pelham scale; >, Better response than; =, No change

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Table 2

Studies of Antipsychotics in Young People with PDDs

Authors	Subjects	Treatment and Design	Outcome by Variable
RUPP, 2002	Children; ages 5–17 years (mean, 8.8); 82 males & 19 females; Autistic Disorder and serious behavioral problems. N=101	Double Blind, PBO controlled, parallel groups; mean daily dose of RIS at endpoint was 1.8 mg (range 0.5 to 3.5); 8-week acute trial	Thirty four of 49 subjects (69.4%) were risperidone responders Parent rated ABC, Hyperactivity; RIS > PBO; E.S= 1.0 Parent rated ABC, Irritability; RIS > PBO; E.S.=1.2 Parent rated ABC Stereotypy; RIS > PBO; E.S.=0.8 Clinician rated CGI-I; RIS > PBO
Shea et al., 2004	Children; ages 5–12 years (mean, 7.45); 61 males & 18 females; with PDDs; no specific behavioral entry criteria; N=79	Double blind, PBO controlled, parallel groups; mean daily dose at endpoint 1.48 mg/day RIS oral solution; 8-week acute trial	77 subjects were included in the ITT efficacy sample. RIS-treated subjects given lower (better) scores Parent-rated ABC, Hyperactivity; RIS > PBO; ($p \leq .001$) Parent-rated NCBRF, Hyperactive; RIS > PBO; ($p \leq .05$) Clinician rated CGI-C RIS > PBO
Troost et al, 2005	Children; ages 5–17 years (mean, 9.1); 22 males & 2 females; with PDDs and serious behavioral problems; N=26	24 weeks of open-label RIS followed by an 8-week double blind, PBO-controlled, discontinuation of RIS; mean daily dose 1.7 mg/day.	26 subjects met criteria as RIS responders; 2 subjects terminated early due to weight gain. Parent-rated ABC, Hyperactivity subscale, RIS= PBO (p =.12)
Hellings et al., 2006	Children, adolescents, adults; ages 8–56 years (mean, 22.0) 23 males & 17 females with PDD (n=36) or ID (n=4); presence of serious behavioral problems; N=40	Double Blind, PBO controlled, X-over with discontinuation to PBO; low dose = 1 mg b.i.d and high dose = 2 mg/d given b.i.d.; mean daily dose at endpoint for children and adolescents was 1.67 mg and for adults 1.52 mg RIS oral solution	87.5% of subjects met the criteria as partial or full RIS responders Parent-rated ABC, Hyperactivity; RIS low dose > PBO 1&2 (Averaged E.S. = 0.58) Parent-rated ABC, Hyperactivity; RIS high dose > PBO 1&2 (Averaged E.S. = 0.41) Unable to locate *P* values for ABC Hyperactivity subscale.
Troost et al., 2006	Children; 5–17 years (mean 10.1); 22 males & 2 females; with PDDs and serious behavioral problems; N=24	24 weeks of open-label RIS followed by 8-week double-blind, PBO-controlled, discontinuation of RIS; mean dose =1.7 mg./day	12 – 14 subjects provided valid measures for focused attention task and divided attention task following discontinuation phase. Significant differences between treatment groups on divided attention task and reaction time hits under lighter of two memory loads, RIS > PBO (η^2 =0.36). Significant difference between groups in reaction time correct rejections during lighter memory load, RIS > PBO η^2= 0.37. Focused attention task, PBO = RIS.

Authors	Subjects	Drug and Design	Results By Outcome Variable
Corson et al., 2004	20 young people with autism, ages 5 to 28 years (mean, 12.1), 16 males and 4 females; 12 with autism and 8 with PDD-NOS.	Retrospective, non-blinded clinical trials with **quetiapine** (25–600 mg/d; mean 198 mg/d) over a time ranging from 4 to 180 weeks (mean, 60 weeks). Five subjects received other medication.	CGI, based on composite of aggression, self injury, irritability, and hyperactivity: 8 of 20 participants (40%) regarded as responders based on CGI—Improvement score of much improved (n=6) or very much improved.
Hardan et al., 2005	10 young patients, ages 5–19 years (mean, 12.0) with autism (n=7) or PDD-NOS (n=3). 8 males and 4 females.	Retrospective, non-blind chart review of consecutive patients treated with **quetiapine (QTP)** (200–800 mg/day; mean, 477 mg). Six subjects received constant doses of other psychotropic drugs. Duration of trials ranged from 10–48 weeks (mean, 22.0).	Parent ratings on Conners' Parent Rating Scale (PRS) (Goyette et al., 1978): Conduct problem, QTP > PBO, E.S.=0.49 Inattention, QTP > PBO, E.S.=0.93 Hyperactivity, QTP > PBO, E.S.=0.63 No effects on Psychosomatic, Learning, or Anxiety subscales.
Malone et al., 2007	12 adolescents with autism, ages 12–18 years (mean, 14.5). 2 enrolled as inpatients, 10 as outpatients	Open-label, 6 week trial of **ziprasidone (ZPD),** at 40–160 mg/d (mean 98.3). No other medicines permitted. Non-blind.	ABC Hyperactivity, ZPD > BL; E.S.=0.36 CPRS Hyperactivity, ZPD = BL Other:

Authors	Subjects	Drug and Design	Results By Outcome Variable
			BMI declined non-significantly QTC increased by 14.7 msec, p=0.04, not clinically significant.
Valicenti-McDermott & Demb, 2006	32 young people, ages 5–19 years (mean, 10.9). 23 (72%) were males, and 9 (28%) were females. Participants were chosen for a multitude of “developmental disabilities,” including mental retardation (n=18), autism (n=15), and PDD (n=3).	Retrospective chart review of patients who were switched to **aripiprazole (APZ)** from multiple other drugs or initiated de novo (n=4) on APZ. Duration of treatment ranged from 6 to 15 months. No standardized behavioral instruments used during treatment.	Improvement in hyperactivity occurred in 10 of 21 with the target symptom (48%) and in 5 of 13 children (38%) with a target symptom of impulsivity (disorder not specified). APZ effective in 9 of 24 children (37%) with “autism spectrum disorder,” including 4 of 5 children (80%) with “multiple complex developmental disorder.” Approximately half of children with PDDs (6 of 12) with hyperactivity listed as a target symptom were regarded as improved.

ABC = Aberrant Behavior Checklist. CPRS = Children’s Psychiatric Rating Scale. “>” indicates that the effect was statistically greater than; “=” indicates that the effect was not statistically different.

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