UNDERSTANDING THE CAUSES AND IMPLEMENTING THE INTERVENTIONS FOR AUTISM SPECTRUM DISORDERS

A cure for autism remains on the distant horizon; however, a number of interventions exist today that address coexisting problems as well as possible comorbid psychiatric disorders. Although treating "around the edges" may not improve core symptoms of autism per se, this approach can certainly improve the quality of life for persons with autism and the families who care for them. This chapter aims to address several common problems associated with autism spectrum disorder (ASD) that impair the delivery of optimal care in the medical setting.

Aggression and Self-Mutilation

First, aggression and self-mutilation occur frequently in persons with autism, and the *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV-TR) (APA, 2000) conceptualized these behaviors as core stereotypical symptoms. Nonetheless, such behaviors often increase during periods of medical illness, thereby serving as a sentinel of an underlying disease process. An exacerbation in self-injurious or aggressive behaviors without any recent change in the environment should warrant a medical work-up. The aggression and self-mutilation may be driven by the patient's need for medical attention, since he or she may not be able to communicate pain or distress verbally. As with delirium, the definitive treatment lies in treating the underlying medical condition as soon as possible.

Assessment of Comorbid Psychiatric Conditions

Second, assessing and treating comorbid conditions will be discussed. Failure to treat comorbid psychiatric conditions often sabotages medical treatments because far too often they go undiagnosed. Part of the problem lies in the tendency to attribute many difficult behaviors or

other psychiatric symptoms to the PDD. Perhaps the term *pervasive developmental disorder* tricks one into thinking that every symptom or problem must be attributed to the pervasive nature of autism. Of course, teasing out the symptoms of other comorbid psychiatric disorders from a morass of autistic symptoms is more tedious than diagnosing these conditions in normally developing individuals, but the approach pays off with a better quality of life once the psychiatric condition is in remission. Consider the burden of untreated depression in persons with diabetes. That burden of illness becomes magnified if the person has autism in addition to the depression and diabetes, because the depression often goes unrecognized.

Insomnia

Insomnia is a third area that can complicate medical treatment. Sleep problems can be part of a comorbid psychiatric disorder, but most of the time insomnia occurs in the absence of comorbid psychopathology. Poor sleep leads to low energy, poor concentration, and, sometimes, increased irritability, so correcting sleep problems can be crucial to providing optimal medical care.

Before beginning, the clinician must be aware that persons with autism frequently exhibit finicky eating patterns. Sometimes these relate to sensory integration issues, as in the case of the sisters already mentioned. At other times, restricted or repetitive behaviors at the core of autism might result in a peculiar dietary regimen. For instance, a person with autism may be stuck on eating foods of a certain color and stick to a “beige” diet. Such restricted diets can lead to dietary deficiencies or slow recovery from medical illness.

Sensory Integration Issues

Children with autism sometimes have symptoms that are thought to be related to disruptions in how the children process and integrate information from other senses. Sensory integration theory suggests that inappropriate or deficient sensory processing is a developmental disorder or part of

a developmental disorder amenable to treatment, and often referred to occupational therapists. A standard profile reporting children's sensory experiences illustrate how these symptoms present in children. Both social and non-social dimensions are noted. On the hyposensory-social dimension, children do not respond to their name, ignore new persons, or seek rough-housing play. On the hyposensory-non-social dimension, children stare at lights or objects; flap their arms, do not pay attention to novel objects, mouth objects, ignore loud noises, smell objects, do not respond to pain, and crave movement. The hypersensory-social dimension is captured in children who dislike being held, are distressed during grooming, are averse to social touch, avoid eye contact, and dislike tickling. The hypersensory-non-social children are sensitive to loud noises, avoid textures, are sensitive to light, averse to water, and avoid food with a strongtaste/texture (Baranek, 2006). In order to deliver medical care to patients with milder forms of sensory idiosyncrasies, these traits can be taken into consideration. Patients may have distinct responses to restraints, to touching, to specific types of foods. Understanding this aspect of their makeup can facilitate care.

Occupational therapists have developed treatments for these symptoms. They use brushes, swings, balls, and other equipment with the hope of organizing sensory inputs and clarifying their role in developmental disorder and adaptation. The American Academy of Pediatrics (AAP) has written a policy statement to clarify the role of these treatments (AAP, 2012).

Difficulty Expressing Inner States

Since autism runs the range from nonverbal to the precocious verbal skills that some persons with Asperger's disorder exhibit, a clinician may struggle to obtain information from most patients. Even those with impressive vocabularies might have great difficulty expressing their

feelings or internal states. Any technique or technology that facilitates communication will make history-taking easier. This is not to be confused with “facilitated communication,” a therapy that once seemed to be a breakthrough in autism. “Facilitated communication” trained therapists to help guide the patient’s hand over a keyboard so that thoughts that could not be expressed verbally could be typed. The rationale was that the therapist could help the patients compensate for their fine motor deficits, but “facilitated communication” eventually fell from favor after scientific scrutiny showed significant flaws in its effectiveness. Nevertheless, numerous electronic devices have been invented to help nonverbal or nearly nonverbal persons with autism express themselves. As technology advances, these devices are becoming less expensive, more reliable, more compact, and easier to operate. At first, these devices were designed specifically for persons with communication problems and were limited to this application. Now, software programs can be downloaded into electronic pads and even pocket-sized smartphones with touchpad technologies. These can help in gathering more accurate histories and augment incomplete information provided by caregivers.

Concrete Thinking Patterns

Even persons on the autism spectrum without speech delays might still struggle with communication issues, given their concrete thinking patterns. Clinicians should remain aware that their patients with higher functioning autism are likely to interpret conversations in literal terms. I recall an interview in medical school in which the silver-haired and seasoned psychiatrist asked a patient if he heard voices. The patient responded, “Of course I do, how else could I be answering all your questions?” Although concrete and literal ways of thinking make for amusing moments, this sort of thinking may result in unintentional miscommunication of relevant clinical information. Therefore, carefully framing questions and accepting that responses may come from

a person with a different frame of mind makes for more effective communication with the patient.

Problems in the Literature

Even though research into ASDs has made many recent gains, most of the literature on treatment interventions suffers from a number of shortcomings. For instance, many studies include heterogeneous groups of patients on the autism spectrum, and the heterogeneity waters down results, thereby obscuring conclusive evidence that a homogeneous selection of patients would offer. Other studies are too poorly powered to make any clear assumptions about effectiveness, so the literature limps along, only hinting at the benefits of one treatment over another. Another common problem, which is magnified in poorly designed studies, is the high rate of placebo response in the autistic population. Several factors, such as reliance on caregiver's reports and using inadequate rating scales that cannot accurately capture changes in autism over the short term of a clinical trial, contribute to the placebo response problem. Some studies attempt to assess the treatment outcomes of comorbid conditions, such as depression or anxiety, but the standard rating scales that work well for the general population with depression or anxiety have not been validated in the autistic population. Moreover, most of the research into autism focuses on younger populations. Many other deficiencies exist; however, a few studies have met the gold standard seen in other areas of psychiatric research. These studies have provided the first two FDA-approved treatments for people with autism, even though these treatments do not treat the core symptoms of autism.

Medications

Irritability, Aggression, Self-Injurious Behaviors

Two atypical antipsychotic agents, risperidone and aripiprazole, are approved for the treatment of "irritability," defined as tantrums, aggressive behaviors, and self-mutilation in children with autism. These medications have improved the quality of life for these children and their families, but the core symptoms of autism, for the most part, remain unchanged. Although risperidone and aripiprazole do not improve the social and communication problems common to autism, one might argue that a reduction in certain forms of aggression or self-mutilation represents an improvement in stereotypical behaviors. Nevertheless, the medications target irritability, and some aspects of irritability are rhythmic and repetitive in the realm of stereotypies, or occur if such stereotypical behaviors are blocked (Aman et al., 2009; Marcus et al., 2009; Owen et al., 2009; Stigler et al., 2009). Take, for example, head banging, which fits criteria for stereotypy and improves with atypical neuroleptic treatment.

Atypical Neuroleptics

Risperidone

Risperidone was the first medication approved specifically for patients with autism. Information from several case series and double-blind, placebo-controlled studies indicated that risperidone was effective in reducing irritability in children and adolescents with autism and related disorders (Posey&McDougle, 2008). The Research Units of Pediatric Psychopharmacology (RUPP) Autism Network showed foresight in conducting the first double-blind, placebo-controlled trial of risperidone in children and adolescents with autism. The eight-week study followed 101 youths (mean age, 8.8 years) who were randomly assigned to either risperidone or placebo. Subjects had "significant irritability," defined by a score of 18 or greater on the Aberrant Behavior Checklist (ABC) Irritability subscale. A mean dosage of 1.8 mg per day provided a 57% reduction on the ABC Irritability subscale score, compared with a 14% in the

placebo group (Network RUoPPA, 2008; Aman et al., 1985). With “response” defined as greater than 25% improvement on the ABC Irritability subscale score and a rating of “much improved” or “very much improved” on the Clinical Global Impressions–Improvement (CGI-I) scale, 69% on risperidone and 12% on the placebo were responders. An effect size of d = 1.2 in favor of risperidone on the main outcome measure was documented by the Research Units in Pediatric and Psychopharmacology (RUPP)Autism Network (Arnold et al., 2010). Even though improvements were seen on the Social Withdrawal and Inappropriate Speech subscales, these were [not] statistically significant. Risperidone was associated with a mean weight gain of 5.8 lbs., while the placebo group experienced a mean weight gain of 1.8 lbs. Drooling occurred more frequently with risperidone, yet extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) showed no significant differences between the risperidone- and placebo-treated groups (Network RUoPPA, 2005a).

An analysis of secondary outcome measures showed significant improvements in sensorimotor behaviors, affective reactions, and sensory responses on the modified Ritvo-Freeman Real Life Rating Scale (R-F RLRS), but no significant change appeared on the Social Relationship to People or Language subscales (McDougle et al., 2005; Freeman et al., 1986). The analysis of the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS) found risperidone to be more efficacious than placebo for reducing interfering repetitive behaviors (Scahill et al., 1997).

After the acute eight-week phase of the study, 63 responders entered the extended 16-week, open-label phase of the study (NetworkRUoPPA, 2005a). Over the course of 16 weeks, two subjects discontinued taking the drug due to loss of effectiveness, and one due to an adverse event. The remainder of the subjects showed no clinically significant worsening of target

symptoms while the mean dosage remained stable. Weight gain averaged 11.2 lbs. during the six months of risperidone treatment. Following the 16-week open-label phase, the 32 subjects who continued to be responders were randomized to either continued risperidone treatment or gradually switch to placebo over the course of three weeks. Of the 16 subjects switched to placebo, 62.5% showed significant worsening of symptoms, while only 12.5% of those continuing on risperidone worsened. Therefore, these results, along with those of another placebo-controlled discontinuation study, suggest that risperidone treatment beyond six months is probably necessary to prevent relapse (Network RUoPPA, 2005).

Recently, intention-to-treat (ITT) analyses were performed with suspected moderators and mediators entered into the regression equations (Arnold et al., 2010). The benefit–risk ratio of risperidone appeared better with greater symptom severity prior to treatment. Weight gain was not required for risperidone response, and it might even detract from it. Also, socioeconomic advantage, low prolactin, and absence of comorbid problems non-specifically gave better outcome (Arnold et al., 2010).

In addition to the RUPP study, a second multicenter, placebo-controlled study of risperidone in children and adolescents with PDDs completed the database needed to demonstrate requisite efficacy and tolerability to secure FDA approval (Posey&McDougle, 2008; Shea et al., 2004). This second study included 79 youths (mean age, 7.5 years) randomly assigned to risperidone (mean dose, 1.2 mg/d) or placebo (Shea et al., 2004). All subjects met criteria for PDD and scored greater than 30 on the Childhood Autism Rating Scale (CARS) (Shea et al., 2004; Shopler et al., 1980). The mean baseline score on the ABC Irritability subscale was 20. Risperidone-treated subjects experienced a 64% reduction in the ABC Irritability subscale score, while scores for subjects on placebo only decreased by 31%.

Moreover, 53% of subjects on risperidone versus 18% on placebo showed an adequate response to the assigned treatment. Subjects given risperidone gained more weight than those given placebo (5.9 lbs. versus 2.2 lbs.), but extrapyramidal symptoms did not differ between groups over the eight-week study period (Shea et al., 2004).

In smaller study of 30 youths (ages, 8–18 years) treated with risperidone (0.01 mg/kg/d) versus haloperidol (0.01 mg/kg/d) under double-blinded conditions, the risperidone group showed significantly greater reductions in the total ABC scores, along with greater improvements in general behavior compared to a haloperidol group (Posey&McDougle, 2008; Miral et al., 2008). Subjects on risperidone experienced significant increases in prolactin levels (Posey&McDougle, 2008; Miral et al., 2008).

Although controlled studies of risperidone in adults with ASDs are needed, a placebo-controlled study of risperidone did focus on children down to the very young age of two years old (Nagaraj, Singhi&Malhi , 2006). Children aged two to nine years received risperidone (1 mg/day) or placebo. Scores on the CARS and Children's Global Assessment Scale showed risperidone to be highly efficacious (Posey&McDougle, 2008; Nagaraj, Singhi&Malhi , 2006). On the other hand, a six-month, placebo-controlled study of 24 children with PDDs under six years old showed the risperidone dose range of 0.5–1.5 mg/day to be only minimally efficacious compared to placebo (Posey&McDougle, 2008; Luby et al., 2006). The low level of baseline irritability may have dampened the effect seen in other studies in which baseline irritability started substantially higher (Posey, 2008).

Emerging research involving 45 autistic patients treated for up to a year with risperidone monotherapy suggests that polymorphisms on certain candidate genes may help predict clinical improvement with risperidone (Corriea et al., 2010). Corriea and colleagues also found that

polymorphisms on particular genes were associated with risperidone-induced increases in prolactin levels and body mass index (BMI) (Corriea et al., 2010). These associations will require replication, but this early work may eventually lead to routine clinical tests that identify the drug that will work best with the fewest risks of adverse events for a given individual with autism.

Aripiprazole

The second medication approved for aggression and irritability in children with PDDs was aripiprazole. To evaluate the short-term efficacy and safety of aripiprazole in the treatment of irritability associated with autism, 218 children and adolescents (aged 6–17 years) were randomized 1:1:1:1 to aripiprazole (5, 10, 15 mg/day) or placebo in a double-blind, randomized, placebo-controlled, parallel group, eight-week study (Marcus et al., 2009). The efficacy was assessed with the (ABC) Irritability subscale (primary efficacy measure) and the clinician-rated Clinical Global Impression–Improvement score. All aripiprazole doses showed significantly better ABC Irritability subscale scores (5 mg/day, –12.4; 10 mg/day, –13.2; 15 mg/day, –14.4; versus placebo, –8.4; all, $p < 0.05$). Additionally, all aripiprazole doses delivered significantly greater improvements in the mean Clinical Global Impression–Improvement scores than the placebo group at week 8. Sedation was the most common cause for discontinuation. Mean weight gain was approximately 1 kg greater in each aripiprazole group (5 mg/day, 1.3 kg; 10 mg/day, 1.3kg; 15 mg/day, 1.5 kg) compared to placebo (0.3 kg). Two serious adverse events—presyncope (5 mg/day) and aggression (10 mg/day)—occurred during the treatment phase. Overall, aripiprazole showed efficacy and was generally well tolerated (Marcus et al., 2009).

An eight-week double-blind, placebo-controlled trial of aripiprazole in 98 youths (aged 6–17 years) showed significantly greater improvement on the ABC Irritability subscale with aripiprazole treatment in a flexible dose range of either 5, 10, or 15 mg/day (Owen et al., 2009).

In a 14-week prospective open-label trial in patients with PDD NOS or Asperger's disorder, Stigler and colleagues noted significant improvement in 22 of 25 (88%) subjects with a dose range of 2.5 to 15 mg in 5–17-year-olds (Stigler et al., 2009). The ABC Irritability subscale dropped from a mean score of 29 at study start to 8.1 at study endpoint (Stigler et al., 2009). Weight gain was the most common adverse event (19/25 subjects, mean +2.3 lbs.) followed by tiredness (16/25 subjects, mild; 1/25 subjects, moderate) and extrapyramidal side effects (EPS) (9/25 subjects, mild) (Stigler et al., 2009).

The RUPP Autism Network implemented an elegantly designed multiple-site study with 124 children aged 4 to 13 who were diagnosed with PDDs accompanied by frequent tantrums, aggression, or self-injury (Aman et al., 2009. Subjects were randomly assigned to either risperidone monotherapy ranging from 0.5 to 3.5 mg/day (MED) or risperidone along with an average of 10.9 sessions of parent training (COMB). A positive clinical response was defined as a rating of "much or very much improved" on the Clinical Global Impression–Improvement subscale plus at least 25% reduction on the ABC Irritability subscale. If clinical response was not reached by week 8, the risperidone was phased out and replaced with aripiprazole. The study sample was composed of 105 (85%) boys and 19 (15%) girls, with groups similar in terms of household income, parental education, and educational placement; however, the MED group had lower functional skills and was more likely to be treated with anticonvulsants. The COMB group's Home Situations Questionnaire Severity score decreased 71% compared to the MED groups score, resulting in an effect size of 0.34 by week 24. The effect-size differences between

the MED and COMB groups were small up to week 16, but by week 24, the effect-size differences were in the medium range and favored the COMB group for the ABC Irritability and Hyperactivity/Noncompliance subscales (Aman et al., 2009a).

Olanzapine

Evidence for olanzapine's effectiveness is limited to one small placebo-controlled study and three open-label trials (Posey, 2008). The small, eight-week, placebo-controlled study enrolled 11 subjects (aged 6–14) randomly assigned to olanzapine (mean dose, 10 mg/day) or placebo (Hollander et al., 2006). While three of six (50%) subjects on olanzapine responded, one of 5 (20%) on placebo met response criteria. The olanzapine group gained substantially more weight (mean weight gain, 7.5 lbs., versus 1.5 lbs. on placebo) (Hollander et al., 2006).

A 12-week open-label study of olanzapine (mean dose, 7.8 mg/day) in eight individuals (mean age, 20.9 years; age range, 5–42 years) reported significant improvement irritability in six of the seven (86%) subjects completing the study (Potenza et al., 1999). Weight gain was significant in six subjects (mean weight gain, 18.4 lbs.), while three subjects experienced sedation (Potenza et al., 1999). Another six-week open-label study used a parallel group design to compare olanzapine (mean dose, 7.9 mg/day) versus haloperidol (mean dose, 1.4 mg/day) in 12 children with autism (mean age, 7.8 years) (Malone et al., 2001). Five of six (83%) subjects on olanzapine responded to treatment, whereas three of six (50%) improved on haloperidol. The olanzapine-treated subjects gained more weight (mean, 9 lbs.; range 5.9 to 15.8 lbs.) compared to those on haloperidol (mean 3.2 lbs.; range, –5.5 to +8.8 lbs.) (Malone et al., 2001).

On the other hand, a three-month open-label study of olanzapine (mean dose, 10.7 mg/day) in 25 children (mean age, 11.2 years) with PDD found it to be effective in only three (12%) subjects. As was the case in preschool-aged children treated with risperidone, low

baseline scores on the ABC Irritability subscale may have contributed to the limited improvement in this study (Posey, 2008).

Quetiapine

Only two prospective and two retrospective studies have examined the benefits of quetiapine in persons with PDD (Posey&McDougle, 2008). In a 16-week open-label study (mean dose, 225mg/day), two of six (33%) of the youths (ages, 6–15 years) responded to treatment (Martin et al., 1999). Of the nine subjects originally enrolled, two discontinued due to sedation or lack of response, and one due to a possible seizure (Martin et al., 1999). Weight gain ranged from 2 to 18 lbs. The other prospective study enrolled nine adolescents (age range, 12–17 years) for a 12-week trial on quetiapine (mean dose, 292 mg/day). Again, only six of nine subjects completed the study, with a mere two (22%) subjects considered responders (Findling et al., 2004). One of the subjects discontinued due to agitation and aggression, and weight gain and sedation were the most common adverse events in other subjects (Findling et al., 2004).

In the first published retrospective study, 20 subjects (mean age, 12.1 years; range 5–28 years) received monotherapy with quetiapine (mean dose, 249 mg/day; range, 25–600 mg/day) for at least four weeks (mean duration, 59.8 weeks; range, 4–180 weeks) (Corson et al., 2004). Although eight (40%) subjects responded, 15% of the subjects discontinued, while 50% reported adverse events (Corson et al., 2004). The other retrospective review included ten subjects (ages, 5–19 years) who were diagnosed with PDD and mental retardation (MR) (Hardan, Jou&Handen, 2005). The mean dose of quetiapine was 477 mg/day, and concomitant medications were allowed as long as the dosages did not change during the period of observation on quetiapine. A response rate of 60% resulted from the intervention, with mild sedation, excessive salivation, and weight gain reported as adverse events (Hardan, Jou&Handen, 2005).

Ziprasidone

Evidence for ziprasidone in treating irritability associated with PDD is limited to three published papers (Posey&McDougle, 2008). One six-week, prospective, open-label study of ziprasidone enrolled 12 adolescents (mean age, 14.5 years; range 12–18 years) with autism who were treated with ziprasidone (mean dose, 98.3 mg/day; range 20–160 mg/day) (Malone et al., 2007). At the study endpoint, 9 of the 12 subjects responded to treatment with reduction in irritability, aggression, and hyperactivity. Acute dystonic reaction occurred in two subjects, but ziprasidone treatment appeared to be weight-neutral. Electrocardiography recorded a mean prolongation in QTc of 14.7 milliseconds which should be considered in the context of the FDA warning about using ziprasidone with other drugs that may prolong QTc in individuals with known cardiac arrhythmias or a long QT syndrome. Total cholesterol decreased without any change in prolactin levels (Posey&McDougle, 2008; Malone et al., 2007).

The first retrospective review reported on 12 subjects (mean age, 11.6 years; range 8–20 years) receiving open-label treatment with ziprasidone (mean dose, 59.2 mg; range, 20–120 mg/day) for at least six weeks (mean duration, 14.2; range, 6–30 weeks) (McDougle, Kem& Posey, 2002). Aggression, agitation, and irritability improved in six (50%) of the 12 subjects. Transient sedation was the most common adverse event, and no untoward cardiac effects were reported or observed. Although a mean weight loss of 5.8 lbs. (range, –35 to +6 lbs.) was documented, this probably occurred as a result of subjects' being switched from other medications known to cause significant weight gain (McDougle, Kem& Posey, 2002). The second retrospective study involved ten adults with autism and mental retardation who switched from clozapine, risperidone, or quetiapine to ziprasidone (Cohen et al., 2004). Weight gain most often prompted the switch, and ziprasidone resulted in a significant mean weight loss of 9.5 lbs.

after six months of treatment. Maladaptive behaviors improved in six subjects, while three subjects experienced worsening, and one remained unchanged with respect to the maladaptive behaviors (Cohen et al., 2004).

Paliperidone

Paliperidone, approved by the FDA for schizophrenia in adults, is the major active metabolite of risperidone and the only atypical antipsychotic agent to use the Osmotic [Controlled] Release Oral System (OROS™) technology (Stigler et al., 2010). Unlike risperidone, cytochrome P450 2D6 (CYP2D6) has a limited role in the elimination of paliperidone, and most of the drug is excreted mainly unchanged in the urine. Recently, case reports of a 16-year-old Caucasian female and a 20-year-old Caucasian male with DSM-IV-TR–defined autism suggested that paliperidone may be an effective and well-tolerated treatment for severe irritability in adolescent and adult patients with autism (Stigler et al., 2010).

Clozapine

At the end of the list of atypical antipsychotic agents is clozapine. It rounds off the list as one the last medications to try, due to factors that make it an end-of-the-line treatment for schizophrenia. The main reason it is reserved as a last-ditch treatment is the risk of agranulocytosis. Many patients with autistic spectrum disorder struggle with venipuncture in conjunction with their yearly physical, so biweekly blood work would be out of the question. Since the prevalence of seizures ranges between 20% and 35% in adults and 17% and 14% in children and adolescents with ASD (Minshew, Sweeney, & Bauman, 1997;Rapin, 1996), clozapine would not be a first-line choice given its propensity to lower the seizure threshold (Posey&McDougle, 2008). Moreover, the literature only documents three reports of the use of clozapine in individuals with ASD. Three children ages 8 to 12 received treatment with clozapine 200-450 mg/day after they

failed haloperidol treatment for eight months. Zudda and colleagues reported that decrease in aggression, hyperactivity, and negativism was sustained in two of the children, while the third child relapsed after five months (Zudda et al., 1996). These three children experienced transient sedation and enuresis (Zudda et al., 1996). Chen and colleagues treated a 17-year-old male inpatient with clozapine 275 mg/day and showed significant reduction in "overt tension," hyperactivity, and stereotypies; however, the period of observation was only 15 days (Chen et al., 2001). A case report on a 32-year-old male patient with autism and profound mental retardation treated with clozapine 300 mg/day showed marked improvement in treatment-refractory aggression and social interactions over two months, with further improvements over five years of treatment (Gobbi&Pulvirenti, 2001). This individual did not develop extrapyramidal syndrome (EPS) or agranulocytosis over the five years of treatment, but literature on clozapine's use in autistic spectrum disorder is scant and the risk of agranulocytosis serious, albeit uncommon, so it should remain delegated to a last-resort treatment until more substantial data are available.

On the other hand, EPS is much more common with typical antipsychotic agents, but they have been a mainstay of managing certain psychiatric conditions in the medical setting. The typical antipsychotic agents have a track record for rapid and reliable treatment stretching back decades. The typical antipsychotic agents often served as first-line treatments for aggression and agitation associated with delirium, psychotic disorders, and mania in the medical setting, given that they were less expensive than their non-generic atypical counterparts. In recent years, generic versions of atypical neuroleptics narrowed the price gap between the typical and atypical antipsychotic agents, so hospital formularies usually offer easy access to first-generation atypical agents, from aripiprazole to ziprasidone. Nonetheless, the typical antipsychotic agents still

maintain an edge in the medical setting, because they can be rapidly titrated, and, in certain situations, intramuscular formulations can be used to expedite an effective dosage and thereby reduce patients' length of stay.

Typical Neuroleptics

Haloperidol

In hindsight, many of the earliest studies using typical antipsychotic agents to treatSIBand aggression in autistic individuals contained flaws in methodology or diagnostic accuracy. The first well-designed research studies in this vein came from Campbell and colleagues, who systematically evaluated haloperidol in children with autism (Campbell et al., 1978). They first studied children with autism aged 2.6 to 7.2 years treated with haloperidol (mean dosage 1.7 mg/day) versus placebo in combination with one of two language-based training groups. Although sedation occurred in 12 and dystonia in 2 of the 20 subjects on haloperidol, significant improvement was noted in symptoms of withdrawal and stereotypy in the youths aged 4.5 years and older who were randomized to medication treatment (Campbell et al., 1978). Other studies showed that haloperidol targeted a range of maladaptive behaviors in youths, but acute dystonic reactions and dyskinesias consistently appeared in this treatment population (Posey&McDougle, 2008). Two larger studies focused on the association between haloperidol treatment and the frequency of dyskinesias. One study enrolled 60 children aged 2.3 to 7.9 years and randomly assigned them to either continuous or discontinuous (5 days on and 2 days off) treatment with haloperidol for six months, followed by one month on placebo. The other treated 118 children aged 2.3 to 8.2 years with haloperidol for six months, followed by one month on placebo. In both studies, withdrawal dyskinesias occurred more frequently and tended to be reversible; however, nine of ten subjects treated with the higher mean dosage of haloperidol 3.4 mg/day developed

dyskinesias in the latter study (Posey, 2008). In general, children and adolescents experience more movement disorders with the high-potency typical antipsychotic agents than do adult patients. Unfortunately, the high-potency typical neuroleptics such as haloperidol have not been studied systematically in adults with autism. Poor tolerability in terms of dyskinesias limits the use of high-potency and sedation the use of low-potency antipsychotic agents in children; however, the high-potency typical neuroleptics may have a role in the treatment of adults with autism, given that they have a long and successful history of treating other agitation and aggression secondary to other conditions in adults.

Alpha-2 Adrenergic Agonists

Guanfacine and Clonidine

Since irritability, agitation, and self-injurious behaviors cause such problems for persons with autism or those who care for them, a number of other medications have been studied. These medications may have offered a better side effect profile, but they proved to be less effective than the two FDA-approved atypical neuroleptics. Moreover, shortcomings in the design of these published reports limit one's ability to generalize the results. The largest of these studies retrospectively analyzed guanfacine (mean dosage 2.6 mg/day) treatment in 80 subjects aged 3 to 18 years (mean age 7.7 years) with PDD(Posey et al., 2004). Subjects diagnosed with Asperger's disorder or PDD NOS showed a greater response than those with autism; however, guanfacine was only effective in 10 of 69 (14%) subjects with significant aggression (Posey et al., 2004). In a six-week, double-blind, placebo-controlled crossover trial of clonidine (dosage range 0.04–0.10 mg/kg/day) in eight youths aged 5 to 13 (mean age, 8.1 years) with autism, significant improvements were noted on the Autism Behavior Checklist by teacher and parent ratings, but not by the clinician (Posey, 2008). A similarly designed four-week study with transdermal

clonidine (dosage range 0.16 to 0.48 mg/day) in nine individuals aged 5 to 33 (mean age, 12.9 years) appeared beneficial for impulsivity, hyperarousal, and self-stimulation (Posey&McDougle, 2008). Sedation was the most common side effect in all the above studies with alpha-2 adrenergic agonists (Posey, 2008). Presently, long-acting formulations of guanfacine and clonidine have been approved for the treatment of attention-deficit hyperactivity disorder (ADHD) in children, and these may offer a better pharmacokinetic profile for individuals with autism. Nevertheless, these long-acting alpha-2 adrenergic agonists have not been systematically studied in the autistic population. Again, except for the few adult patients in the transdermal clonidine study above, the literature remains limited to the children and adolescents with autism.

Anticonvulsants and Mood Stabilizers

Divalproex

Given that mood stabilizers and certain anticonvulsants show efficacy in controlling agitation in manic states, these were a logical choice for possibly controlling agitated, aggressive states in persons with autism. The most well-designed study of this group was an eight-week double-blind, placebo-controlled study of divalproex sodium in 30 subjects aged 6 to 20 years with PDD and significant aggression. Despite a mean serum trough level of 77.8 ug/mL, no significant difference between treatment and placebo groups was noted on the ABC Irritability subscale (Hellings et al., 2005). A smaller, open-label study of divalproex sodium (mean dosage, 768 mg/day) resulted in CGI-I ratings of “much improved” or “very much improved” in 10 of 14 subjects. Improvement was noted in impulsivity, aggression, and affective instability (Posey, 2008).

Lamotrigine

Although 8 of 13 (62%) youths initially prescribed lamotrigine for intractable epilepsy experienced a reduction in interfering behavioral symptoms, a double-blind, placebo-controlled trial in 14 youths aged 3 to 11 with autism demonstrated no differences between lamotrigine (5 mg/kg/d) and placebo groups on the Autism Behavior Checklist over the four weeks of treatment (Posey, 2008). In a small, naturalistic study of five patients aged 9 to 13 treated from 10 to 33 weeks (mean duration, 22 weeks) two of five responded with CGI-I ratings of "much improved" or "very much improved" for irritability, anger, and hyperactivity. Of note, two study patients received add-on sertraline at six months for obsessive behaviors, while another one was on long-term treatment with risperidone (Mazzone et al., 2006).

Levetiracetam

Rugino and colleagues investigated levetiracetam for the treatment of aggression, hyperactivity, mood lability, and impulsivity in ten children aged 4 to 10 with autism (Rugino&Samsock, 2002). Over the course of four weeks of treatment, only the subjects who were not recently weaned from drugs targeting aggression showed significant improvement in aggression. Nevertheless, a ten-week, double-blind, placebo-controlled study of levetiracetam (mean dosage, 862.5 mg/day) in 20 youths (age range, 5–17 years) with autism found no significant difference in parent and teacher ratings on the Autism Behavior Checklist between the levetiracetam and placebo group (Wasserman et al., 2006).

With estimates of seizure disorders of up to 35% of adults and 14% of children with autism, the appropriate anticonvulsant can be life-saving and offer improvement in functioning, but as a treatment solely targeting aggression and self-injurious behaviors without a comorbid seizures, these medications have shown inconsistent results (Bauman, 2010). At any rate, new-onset disruptive behaviors should make one consider the possibility that a seizure disorder might

be emerging, particularly if caregivers cannot identify any changes in the environment or clinicians do not observe any other common medical issues that might provoke the change in behavior. Sensory issues may pose challenges to obtaining electroencephalography (EEG) in some individuals with autism, but the results can be a useful guide to the type of medication that should be employed, if EEG abnormalities appear. Be aware that the partial complex seizures occur most frequently in individuals with ASD, and atypical behaviors and body movements associated with this type of seizure may be attributed to ASD. Temporal lobe seizures sometimes escape detection on regular EEG recordings, so clinical judgement should guide whether the patient could tolerate continuous monitoring with videography or the use of nasopharyngeal leads to confirm seizure activity.

Nonetheless, not all odd movements and mannerisms arise from abnormal EEG activity or stereotypical ASD symptoms. Other medical conditions, such as gastroesophageal reflux disease (GERD) or sinusitis, could manifest in abnormal behaviors, particularly if the person with ASD struggles with expressing their distress (Buie, 2005).

Lithium

Lastly, one case report of lithium (900 mg/day) augmenting fluvoxamine therapy in an autistic patient without comorbid mania or bipolar disorder resulted in a marked decrease in aggression and impulsivity after two weeks of treatment (Epperson et al., 1994).

Comorbidity

Often, autistic symptoms predominate in the clinical picture, which causes clinicians and caregivers to overlook comorbid psychiatric and medical conditions and mistakenly attribute these to autism. A condition that could be addressed in conventional ways goes unrecognized and untreated. In the case of psychiatric disorders, a strong family history of mood, anxiety, or

psychotic disorders should make clinicians vigilant to the emergence of such disorders in their patient with ASD.

For persons of normal intelligence with ASDs, estimates of coexisting psychiatric conditions vary considerably, from 9% to 89% (Hofvander et al., 2009). Hofvander and colleagues examined a sample of normal-intelligence individuals with ASD (n = 122) and noted that 80% of the of adult subjects met criteria for at least one other major Axis-I disorder, whereas all subjects in the Asperger's syndrome and PDD NOS subgroups carried at least one other comorbid Axis-I diagnosis (Hofvander et al., 2009). Several studies cite mood disorders along with anxiety disorders as the morbid psychiatric conditions (Hofvander et al., 2009). A lifetime incidence of mood disorder ranked highest of the comorbid psychiatric conditions (n = 65, 53%) with a third of the subjects (n = 42, 34%) having been prescribed antidepressant medications at least once in their lives, according to Hofvander's more recent work (Hofvander et al., 2009). Approximately 8% (n = 10) of the subjects with AS or PDD NOS in Hofvander's sample met criteria for bipolar disorder (Hofvander et al., 2009). The small samples size (n = 5) of subjects with AD prevented any prediction of incidence rates of bipolar disorder in this study.

Anxiety disorders followed as the second most commonly encountered DSM-IV condition in individuals with normal intelligence and ASDs in Hofvander's study (Hofvander et al., 2009). The anxiety disorders in this sample included: generalized anxiety disorder (n = 18, 15%), social phobia (n = 16, 13%), panic disorder (n = 13, 11%), specific phobia (n = 7, 6%), post-traumatic stress disorder (PTSD) (n = 2, <2%), and anxiety disorder NOS (n = 1, <1%). Other studies note high rates of tic disorders, but tics are sometimes difficult to distinguish from stereotypical movements associated with ASDs (Posey, 2008). Substance use disorder (SUD) was more common in the PDD NOS group than the AD group, with alcohol listed as the most

frequently abused substance (Hofvander et al., 2009). Fifteen percent (*n* = 19) of the subjects met criteria for SUD, while 12% (*n* = 15) reported alcohol as the substance of choice (Hofvander et al., 2009). Intermittent explosive disorder ranked at the top of the list for impulse control disorders, with an incidence rate of 6% (*n* = 7) (Hofvander et al., 2009). According to Hofvander and colleagues, about 12% (*n* = 15) of the adults in this sample met criteria for a psychotic disorder, and 15% (*n* = 18) had received neuroleptic medication at least once in their lives (Hofvander et al., 2009). In Hofvander and colleagues' sample, a substantial proportion (*n* = 52, 43%) met DSM-IV criteria for ADHD. The PDD NOS subgroup exhibited more symptoms of inattention and hyperactivity/impulsivity than their AS counterparts. About 14% (*n* = 16) had a reading disorder in combination with a disorder of written expression.

Larger prospective studies may provide more precise estimations of comorbid conditions in the future. At the present time, clinicians should be aware that comorbid conditions are a logical target for psychopharmacological interventions, even if this means extrapolating information from treatment studies performed on persons with various psychiatric disorders who were not diagnosed with an ASD.

Sometimes sorting out symptoms related to autism and those related to other comorbid conditions proves difficult. For instance, restrictive, repetitive behaviors and interests (RRBIs) resemble obsessions and compulsions typical of obsessive-compulsive disorder (OCD). The DSM-IV defines RRBIs as follows:

> A preoccupation with stereotyped and restricted patterns of interest;
>
> Inflexibility in adhering to routines and rituals;
>
> Stereotyped and repetitive motor mannerisms;
>
> Persistent preoccupations with parts of objects.

(Soorya, Kiarashi, & Hollander, 2008)

Neuropsychological, behavioral, and biological theories have been proposed to explain repetitive and restrictive behaviors in ASD. This chapter focuses on the biological theories, since double-blind, placebo-controlled trials of medications have tried to target the proposed dysregulation of serotonin or sensitivity to dopamine or endogenous opioids.

As for the RRBIs seen in autism, McDougle and colleagues reported differences in the Yale-Brown Obsessive Compulsive Scale (YBOCS) in autistic adults compared to those with OCD (Soorya, Kiarashi, & Hollander, 2008). Those with autism exhibited more compulsive behaviors than obsessions, and their obsessions were less likely to involve sex, religion, symmetry, contamination, and aggression compared to adults with only OCD (Soorya, Kiarashi, & Hollander, 2008). With the similarities between RRBIs and OCD symptoms, drugs used for OCD treatment were tried for RRBIs in autistic individuals. A study by Shain, Freedman, and colleagues as well as other subsequent studies indicate that approximately a third of individuals with autism express elevated platelet levels of serotonin (Soorya, Kiarashi, & Hollander, 2008; Cook & Leventhal, 1996). McDougle and colleagues demonstrated that tryptophan depletion in adults with autism led to their exhibiting more repetitive behaviors such as whirling, flapping, pacing, banging, rocking, and self-injury. In addition, they showed that the sensitivity of the 5-HT1d receptor positively correlated with the severity of repetitive behaviors (Soorya, Kiarashi, & Hollander, 2008). With this evidence, serotonin-reuptake inhibitors (SRIs) and selective serotonin-reuptake inhibitors (SSRIs) reuptake inhibitors received attention as possible interventions for the RRBIs associated with autism.

Serotonin-Reuptake Inhibitors

Despite significant improvement in RRBIs in the double-blind, placebo-controlled trials of clomipramine, they lack approval for the treatment of the repetitive and restrictive aspects of autism due to the small size of the studies and tolerability issues. An early randomized, crossover study of children with autism started with a two-week single-blind placebo phase followed by a crossover to ten weeks in either the clomipramine/placebo (n = 12) or the clomipramine/desipramine arm (n = 12). Clomipramine performed better than desipramine and placebo, as measured by the Autism subscale of the Children's Psychiatric Rating Scale and several outcome measures of OCD (Gordon et al., 1993). Although adverse events paralleled those seen in the treatment of OCD, one subject was dropped due to a seizure (Gordon et al., 1993). Other open-label and placebo-controlled studies showed less favorable outcomes (Posey, 2008). For example, clomipramine failed to separate from placebo in terms of decreased stereotypy on the ABC in a double-blind, placebo-controlled crossover trial of clomipramine, haloperidol, and placebo (Remington et al., 2001). High dropout rates occurred, with 20 of 32 subjects prematurely terminating in the clomipramine arm, vs. 10 out of 32 of those receiving haloperidol (Remington et al., 2001). Those receiving clomipramine reported high rates of fatigue, tremors, tachycardia, diaphoresis, and behavior problems (Remington et al., 2001). The need to monitor serum levels and electrocardiograms during treatment especially complicates treatment with SRI agents.

Selective Serotonin-Reuptake Inhibitors

Since SSRI medications offered a more favorable side effect profile, a number of open-label studies with sertraline, citalopram, escitalopram, fluvoxamine, and fluvoxetine attempted to demonstrate improvement in RRBIs associated with autism (Posey&McDougle, 2008). These open-label studies incorporated various designs, sample sizes, and durations of treatment, but

results tended to be positive in terms of decreasing RRBIs (Posey&McDougle, 2008). Of note, the literature lacks studies of citalopram and escitalopram in adults with ASDs.

At present, double-blind placebo-controlled trials of fluvoxamine (n = 30) and fluoxetine (n = 6) in adults and fluoxetine (n = 45) in children and adolescents reported significant improvement in repetitive behaviors on YBOCS or Children's YBOCS (C-YBOCS), depending on the age group (Posey&McDougle, 2008). However, a double-blind, placebo-controlled study of fluvoxamine in children and adolescents (n = 18, mean age 9.5 years) with ASDs showed a poor response, with 14 of the subjects reporting notable adverse events (Posey&McDougle, 2008).

Unfortunately, limited information is available about the effect size, response rates, and other clinically pertinent points related to SSRIs in the treatment of major depression and other anxiety disorders. The same holds true for other classes of medications approved for mood and serotonin norepinephrine-reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors. Although not specifically studied in individuals with autism, the sedating properties of some of these classes of medication may address insomnia. For example, fluvoxamine, mirtazapine, and other medications could improve insomnia; however, trazodone probably should be avoided in males who cannot communicate, given the risk that priapism could occur and go untreated.

Benzodiazepines

Clonazepam can be effective for non–rapid-eye-movement (REM) arousal disorders. It may be particularly helpful for individuals who exhibit repetitive, stereotyped, and rhythmic motor behaviors that impair their transition to sleep. Even though clonazepam does not always improve non-REM sleep disorder behaviors, it often helps REM sleep behavior disorders. Nonetheless,

the use of benzodiazepines has not been extensively studied in persons with autistic spectrum disorders. Therefore, one must infer the benefits of benzodiazepines from studies performed with persons without autism. On the other hand, the risks, such as dependence, cognitive slowing, and reduced respiratory drive, are assumed to be at least as prevalent in persons with autism as in those without PDD. Paradoxical reactions can occur with benzodiazepines, and this may happen somewhat more frequently in persons with autism. Therefore, start benzodiazepines at a low dosage, and watch for disinhibition as the medication is slowly titrated.

Of course, non-pharmacological approaches to insomnia, such as attention to sleep hygiene, should be tried before turning to medications. Should these fail, a number of other prescription medications are now FDA-approved for the treatment of insomnia in adults, but few if any of the subjects in the studies had an ASD. Although no medication has FDA approval for the treatment of insomnia in children, two open-label trials of melatonin, one with immediate release (3 mg, $n = 15$), another combining immediate and controlled release (3–6 mg, $n = 16$), and a retrospective trial of melatonin ($n = 100$) in children with ASD suggest that this supplement could reduce time to sleep onset and increase total sleep time (Posey, 2008). Like other over-the-counter supplements and herbal remedies, the purity and bioavailability of melatonin products may vary widely, as these are not regulated by the FDA.

Dietary Supplements

Thus far, the literature on dietary supplements appears weak, and the few positive studies usually suffer from methodological flaws or small sample sizes. One of the better studies was a double-blind, placebo-controlled trial of l-carnitine 800 mg/day in 31 children with autism. In this study, a subjective improvement on the Gilliam Autism Rating Scale was seen over the eight-week trial (Crill& Helms, 2007). A 30-week, double-blind, placebo-controlled trial of vitamin C in 18

children with ASD showed positive results. Although tryptophan depletion in adults diagnosed with autism resulted in worsening of their symptoms, no convincing evidence exists to suggest that supplementing with tryptophan or other amino acids improves autism symptoms. A double-blind, placebo-controlled trial (n = 18 children) of supplementation with vitamin C for 30 weeks resulted in a reduction in stereotyped behaviors (Dolske et al., 1993). Another randomized, double-blind, placebo-controlled trial (n = 13 children) of omega 3 fatty acids reduced severe behavioral difficulties (Amminger et al., 2007). Supplementation with vitamin B_6 plus magnesium showed improvement in IQ and social quotient in one small study (n = 8); no change was noted in a slightly larger randomized, double-blind, placebo-controlled study (n = 12). Even though an open-label study of 33 children also showed improvement, all three studies contained methodological shortcomings (Posey&McDougle, 2008). Moreover, studies with supplements primarily focused on children, so even less is known about the use of dietary supplements in adults with autism. On the other hand, the use of vitamins and other supplements whenever a specific deficiency is present makes good clinical sense.

Psychostimulants

In general, psychostimulants lack the robust effectiveness in treating attention deficits and impulsive behaviors in persons with ASD compared to those with typical ADHD, and side effects tend to be more common in the ASD group. Nonetheless, psychostimulants could improve adherence to treatment and increase functioning in some individuals on the ASD spectrum. Given the problems with tolerability, trials with psychostimulants should be deferred until after episodes of acute medical illness resolve. Patients in pain or distress from acute illnesses typically exhibit a reduced capacity for concentration, and their hyperactivity might be an attempt to find a body position that minimizes their physical discomfort. As always, clinicians

should use every means available to ascertain whether a patient with ASD is suffering, then make every effort to relieve the physical pain. Once the patient is fully recovered from an illness, a reexamination of his level of inattention, hyperactivity, and impulsivity can be considered.

The preponderance of studies on the benefits of stimulants in children with ASD was done with younger subjects, and there is scant information available about the ways adults with ADHD respond to this class of medication. The RUPP Autism Network conducted the best of these studies to date. The RUPP study sample included 72 youths between the ages of 5 and 14 years (Network RUoPPA, 2005). About 74% of the sample carried the diagnosis of autism, while another 26% had PDD NOS or Asperger's disorder as their diagnosis (Network RUoPPA, 2005). This double-blind, crossover, placebo-controlled study used one-week treatment phases with doses of methylphenidate (immediate release) approximating 0.125, 0.25, and 0.5 mg/kg (Network RUoPPA, 2005). The first two doses of the day were the same, while the last dose, given in the late afternoon, was smaller to improve tolerability (Network RUoPPA, 2005). The ABC as scored by parents served as the main outcome measure (Network RUoPPA, 2005). About half of the subjects (39/72) responded favorably to the methylphenidate, whereas 18% (13/72) dropped out of this study due to side effects (Network RUoPPA, 2005). Parent ratings showed significant improvement in their children on the Hyperactivity subscale, while their ratings on the Withdrawal subscale of the ABC was significantly worse on the higher dosage (Network RUoPPA, 2005). A subsequent analysis by Posey and his colleagues of those who completed the Swanson, Nolen, and Pelham (SNAP) rating scale reported that parents saw significant improvement at all three dosages, while teachers only appreciated significant improvement in the youths at the medium and high dosages on the Hyperactivity subscale

(Posey, 2008). Irritability, emotional outbursts, and initial insomnia associated with methylphenidate caused the most problems for those who experienced side effects (Posey, 2008)

Beyond the RUPP study, the literature remains weak, with two small double-blind, placebo-controlled, crossover studies of methylphenidate (n = 10, mean age 8.5 years; n = 13, mean age 7.4 years), which suggested a trend toward improvement compared to placebo (Posey, 2008). In the smaller study of the two, a significant but modest improvement was noted on the Conners' Parent and Teacher Rating Scales and the clinician-completed ABC Hyperactivity subscale (Posey, 2008). The other study focused on results from the Conners' Abbreviated Symptom Questionnaire and the ABC Hyperactivity subscale completed by teachers (Posey, 2008). A few other small (n = 9 to 15), open-label studies with methylphenidate using Conners' Rating Scales or other instruments reported similar results compared to those above (Posey, 2008). Of note, two older studies in children ages 3 to 6 years using amphetamines (d-amphetamine, n = 16; and l-amphetamine, n = 11) were conducted with autistic children during inpatient hospitalizations (Posey, 2008). The d-amphetamine study employed an open-label design, while the l-amphetamine used a crossover design with levodopa; however, both studies showed worsening in the majority of the patients on the CGI scale (Posey&McDougle, 2008).

About half of the individuals with "ADHD but not PDD" continue to have symptoms as adults. With this in mind, one could expect that a number of adults with PDD and ADHD symptoms would follow a similar pattern and perhaps require treatment into adulthood. The bulk of research on stimulant use in persons with PDD focused on children and adolescents. If using stimulants in adults with PDD, be aware that this class of medication reliably increases blood pressure and pulse. This may cause problems in individuals with hypertension or borderline hypertension. The elevated heart rate could be construed as an anxiety symptom as well.

Nevertheless, carefully monitoring adult patients who are prescribed stimulants provides the optimal level of care and predicts a better outcome.

Atomoxetine

The norepinephrine-reuptake inhibitor atomoxetine offers another approach to treating ADHD symptoms in the context of PDD. Arnold and colleagues used a randomized, double-blind, placebo-controlled, crossover design to study with a one-week washout period (Posey&McDougle, 2008). Of the 16 children enrolled, one discontinued early due to adverse events, and two others due to lack of effect (Posey, 2008). Responder status (25% reduction on the ABC Hyperactivity subscale and a 1 or 2 on the CGI) was achieved by 56% (n = 9) of the children while 25% (n = 4) responded to placebo (Posey&McDougle, 2008). Although the response rate was lower than that found in larger studies of children with ADHD who did not have PDD, it produced a slightly better response rate than the RUPP study using methylphenidate cited above (Posey, 2008). Several small open-label studies using atomoxetine in children with ASD showed significant improvement on the Conners' Parent Rating Scale (Jou, Harden&Handen, 2005), the parent-rated investigator-scored ADHD Rating Scale–IV (ADHD RS), and the ABC (Troost et al., 2006), and the CGI and SNAP (Posey, Wiegan& Wilkerson , 2006). Although the literature is limited and mainly confined to studies of younger subjects, improving ADHD symptoms may be helpful in a number of ways.

Summary

Given the paucity of effective treatments for persons with autism, clinicians face special challenges whenever they encounter persons on the autistic spectrum who present with medical problems. This chapter presents a few interventions that may lessen this challenge and provide better care for this population of patients. A major obstacle includes the difficulty of obtaining an

accurate history. Verbal communication skills range from nonverbal on the severely autistic side of the spectrum, to those with precocious vocabularies at the Asperger's disorder end of the spectrum. Despite their impressive vocabularies, most of these patients still struggle with expressing internal states. This lack of a first-person description of internal states often obscures the clinical picture and can hinder accurate reporting of adverse events. Since many young people show difficulty expressing internal states, child and adolescent psychopharmacologists adhere to the adage "Start low and go slow." In treating persons of any age who carry a diagnosis of ASD, the prescribing clinician would be wise to start very low and go very slow, if possible.

Although studies can help guide treatment in youths with PDD and disruptive behaviors, the literature has neglected adults who continue to meet criteria for PDD and consistently or intermittently display aggressive, irritable, or disruptive behaviors. The clinician treating these issues in older persons on the PDD spectrum must rely on safety data from studies of these drugs in adults with other psychiatric disorders and presume that some measure of effectiveness of these drugs in dampening disruptive behaviors in children and adolescents will also apply to adults. Until well-controlled studies in the adults with PDD are done, extrapolating results from studies of youths with autism will be the best approach.

Clinical Pearls

- Common symptoms occur with pervasive developmental disorder (PDD): self-injurious behaviors, poor concentration, insomnia, sensory integration issues, and other comorbid psychiatric conditions. These deserve separate consideration and attention.
- Sensory integration issues include:

    - Hyposensory-social: does not respond to own name, ignores new persons, seeks rough-housing play
    - Hyposensory-nonsocial: stares at lights/objects; flaps arms, does not give attention to novel objects, mouths objects, ignores loud noises, smells objects, does not respond to pain, craves movement
    - Hypersensory-social: dislikes being held, is distressed during grooming, is averse to social touch, avoids eye contact, dislikes tickling
    - Hypersensory-nonsocial: is sensitive to loud noises, avoids textures, is sensitive to lights, is averse to water, avoids food taste/texture (Baranek, 2006)
- The astute clinician treating autistic patients should have a close relationship with a compounding pharmacist who can convert certain medications from pill form to solutions or suppositories.
- Mood and anxiety disorders and psychosis often go undiagnosed in the patient with autism.
- Clinicians must be aware that persons with autism frequently exhibit finicky eating patterns because of sensory integration issues or restrictive behavior. They are sensitive to tastes and textures of food.
- A person with autism may be “stuck” on eating foods of a certain color and stick to a “beige” diet. Such restricted diets can lead to dietary deficiencies.
- Even those autistic patients with impressive vocabularies might display great difficulty in expressing their feelings or internal states.

- Clinicians should remain aware that their patients with higher functioning autism probably interpret conversations in literal terms with concrete thinking.
- Insomnia is common and should be treated as a separate problem or as a component of a comorbid psychiatric disorder.
- Repetitive behaviors include whirling, flapping, pacing, head banging, rocking, and self-injury.
- Partial complex seizures and other seizures occur more frequently in individuals with autism spectrum disorder (ASD).
- Alcohol is the most common substance abused among those with autism. ADHD is common.
- Restrictive repetitive behaviors and interests (RRBIs) resemble obsessions and compulsions typical of obsessive compulsive disorder (OCD). These include: a preoccupation with stereotyped and restricted patterns of interest; inflexibility in adhering to routines and rituals; stereotyped and repetitive motor mannerisms; and persistent preoccupations with parts of objects.
- Stimulants are not as effective in ASDs as they are in attention-deficit disorder.
- Atypical antipsychotics improve disruptive behavior in patients with ASD.

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