Psychotropic Medications as Treatments for People with Autism Spectrum Disorder

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Alan Poling, Kristal Ehrhardt, and Anita Li

Introduction

To be diagnosed with autism spectrum disorder (ASD) according to the criteria described in the current version of the *Diagnostic and Statistical Manual of Mental Disorder* (*DSM-V*), a person must exhibit restricted, repetitive patterns of behavior and deficits in social communication and social interaction (American Psychiatric Association, 2013). The reported prevalence of ASD has increased over the last 30 years, probably due to increased public awareness of the condition and broadening of the diagnostic category (Elsabbagh et al., 2012). For example, the Center Disease Control (2016) indicates that 1 in 150 children was identified with ASD in 2000, but 1 in 68 was so identified 12 years later.

Many people diagnosed with ASD exhibit challenging behaviors that are not part of the defining features of the disorder, as well as the kinds of behavioral excesses and deficits required for the diagnosis (Huete, Schmidt, & Lopez-Arvizu, 2014; Matson & Nebel-Schwalm, 2007a). Moreover, some people diagnosed with ASD exhibit behaviors similar to those required to meet the diagnostic criteria for other disorders, including attention deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and intellectual disability (ID) (Charman et al., 2011; Lecavalier, Kaat, & Stratis, 2014; Matson & Nebel-Schwalm, 2007b). Helping people with ASD change their behavior in desired ways is an invaluable strategy for enhancing the quality of their lives, and professionals from many disciplines use the tools of their trade in attempts to do so. Psychotropic drugs, which are medications prescribed with the intent of improving mood, cognitive status, or overt behavior, are the behavior change tools of psychiatrists and other physicians. It is unsurprising that they frequently prescribe such drugs for people with ASD. This chapter provides a skeptical appraisal of this practice.

The Prevalence of Pharmacological Interventions

Several studies have examined the prevalence of psychotropic drug use in people with ASD. Findings differed across studies, with prevalence rates ranging from 19.5% (Witwer & Lecavalier, 2005) to 65% (Schubart, Camacho, & Leslie, 2014), but most found that approximately 40–50% of sampled individuals were receiving or had received at least one psychotropic medication (e.g., Aman, Lam, & Collier-Crespin, 2003; Croen, Najjar, Ray, Lotspeich, & Bernal,

A. Poling (✉) • K. Ehrhardt • A. Li
Western Michigan University,
Kalamazoo, MI 49008, USA
e-mail: alan.poling@wmich.edu

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2006; Goin-Kochel, Myers, & Mackintosh, 2007; Green et al., 2006; Gringras, 2000; Langworthy-Lam, Aman, & Van Bourgondien, 2002; Logan et al., 2015; Sheehan et al., 2015; Williams et al., 2012; Witwer & Lecavalier, 2005). Although most researchers examined only relatively young people with ASD, substantially higher prevalence rates have been reported in adults compared to children and adolescents (Park et al., 2016; Seltzer, Shattuck, Abbeduto, & Greenberg, 2004; Tsakanikos et al., 2006). Additionally, lower levels of social competence and adaptive behavior, like the presence of challenging behaviors, are associated with increased likelihood of pharmacological treatment (Myers & Johnson, 2007).

It is not unusual for people with ASD to simultaneously receive two or more medications intended to improve their behavior, a practice we will term polypharmacy. For example, in a study of 33,565 children with ASD conducted by Spencer et al. (2013), 35% of the individuals were prescribed two or more psychotropic medications simultaneously, while 30% of them were prescribed a single drug. Very similar results were reported by Schubart et al. (2014), who examined psychotropic drug use among Medicaid-enrolled children and adolescents with ASD in 41 states over a 4-year period. They "found that 65% of children with ASD were prescribed one or more psychotropics and approximately 30% were prescribed medications in more than one class with at least a 60-day overlap" (p. 634). As a third example, Mandell et al. (2008) used Medicaid claims to examine the psychotropic medications prescribed for 60,641 children with ASD. They found that 56% of them received at least one such medication and 20% received three or more (data for two or more drugs were not reported).

Clearly, the use of medications in an attempt to improve the behavior of people with ASD, and thereby benefit them, is widespread. An important, and obvious, question is "why is this so?" Matson and Konst (2015) provided a partial answer, which we expand in the next section.

Drug Treatment as Evidence-Based Practice

Professionals in medicine, psychology, and other helping disciplines agree that widespread adoption of evidence-based practice is the cornerstone of effective clinical treatment (e.g., APA Presidential Task Force on Evidence-Based Practice, 2006; Institute of Medicine, 2001; Montori & Guyatt, 2008). Although there is no consensus as to what, exactly, constitutes evidence-based practice, it is widely acknowledged that clinicians should select and administer treatments for a given problem based on three factors. Those factors are (a) their own training and expertise, (b) the characteristics and preferences of the client being treated, and (c) the scientific evidence supporting the effectiveness of various treatments for the problem at hand.

Pharmacology is a major part of medicine, and medical doctors from all specialties receive extensive training in selecting drugs to deal with diverse health issues, arranging appropriate doses of those drugs, monitoring their effects, and altering treatment as appropriate to achieve desired outcomes (e.g., by altering dosage or changing to another medication). Psychiatrists are specialists in the use of psychotropic drugs, but many other physicians also have the training and experience necessary to use drugs as tools for managing behavior. In so doing they are operating within the ethical and legal boundaries of their discipline and are offering what is often the only tenable treatment option given their training and the limited time they have to spend with individual clients. It is natural and appropriate for physicians who are asked to help in improving someone's behavior to prescribe psychotropic drugs, regardless of whether or not the clients are diagnosed with ASD. In so doing they are using tools that are both familiar and arguably the best at their disposal.

Although some people with ASD are old and competent enough to make legally binding decisions, in most cases treatments for people with ASD are sought and selected by their parents or legal guardians. There are five obvious reasons

for parents and guardians to view pharmacotherapy as a preferred option for dealing with behavioral challenges. One is that pharmaceutical companies have been hugely successful in convincing the public at large that most behavioral challenges are the result of underlying biochemical anomalies that respond favorably to drug treatments (Whitaker, 2010). A second, related reason is that viewing challenging problems as the result of an underlying neurochemical issue, rather than as learned behaviors, frees caregivers of the nagging fear that they are responsible, albeit unintentionally, for the occurrence of those behaviors. A third is that insurance companies, and Medicare, typically pay for pharmacological interventions, while other intervention strategies may not be covered. A fourth is that drug treatments are easy to administer, especially when compared to alternatives such as behavior-analytic interventions. A fifth is that a concerned individual looking for an effective treatment for any of a range of challenging can easily find endorsements for pharmacological interventions.

If, for example, a parent consults the National Autism Center's (2011) well-regarded book, *A Parent's Guide to Evidence-Based Practice and Autism*, she or he will learn that risperidone (Risperdal®) is an effective for treating "core symptoms [of ASD] (generally), maladaptive behavior, hyperactivity, irritability" (p. 54). In addition, methylphenidate (Ritalin®) is deemed an effective treatment for addressing the symptoms of "inattention and hyperactivity (but response rate may be lower in children with ASD)" (p. 53). Given these endorsements, and the other reasons for favoring drug treatments, it is perfectly reasonable for parents to support administering one of these drugs to their children.

Irritability: Creation and Treatment of a Make-Believe Disease

Even though risperidone is classified as an effective treatment for the core symptoms of ASD in *A Parent's Guide to Evidence-Based Practice* (National Autism Center, 2011), no medication is currently approved by the US Food and Drug Administration (FDA) for treating the defining behavioral features (i.e., "core symptoms") of autism, and, as discussed in the section entitled "Research Findings," there is no compelling evidence that any medication is effective in this regard.

Two drugs, risperidone (Risperdal®) and aripiprazole (Abilify®), are FDA approved for treating "irritability" in children and adolescents diagnosed with ASD (United States Food and Drug Administration, 2006, 2009). "Irritability" is a shorthand label for several forms of challenging behavior, including crying, self-injury, aggression directed toward others, and property destruction. The term is commonly used in articles evaluating drug effects in people with ASD but rarely used in other contexts. Its popularity in the drug literature stems from the widespread use of a particular behavior rating scale, the Aberrant Behavior Checklist (ABC; Aman, Singh, Stewart, & Field, 1985), to index drug effects.

The ABC is a 58-item symptom checklist that is completed by a caregiver. The instrument was first used with children and adults diagnosed with cognitive impairment (and then termed "mental retardation"), but it is now widely employed to study drug effects in people with ASD. Each item is scored on a four-point scale (0, not a problem; through 3, problem is severe in degree). The items are categorized into five subscales revealed through factor analysis: (1) *irritability, agitation, and crying* (commonly termed "irritability," 15 items), (2) *lethargy and social withdrawal* (16 items), (3) *stereotypic behavior* (7 items), (4) *hyperactivity and noncompliance* (16 items), and (5) *inappropriate speech* (4 items). Although the ABC is easy to use and is reported by its developer to be a reliable and valid behavior rating instrument (Aman, 2002), it is also a crude instrument that yields ordinal data and provides no detailed information about how a person with ASD is behaving. Moreover, it provides data that are based on raters' subjective opinions and memories and provides no information about contextual variables that affect behavior.

Perhaps the worst problem in using "irritability" to describe certain kinds of challenging

behaviors emitted by people with ASD is that one can all too easily reify the term and then assert that it *causes* the occurrence of the behaviors the label was initially used to describe. It appears, in fact, that FDA administrators did exactly this when they approved risperidone for treating people with ASD. Consider the full prescribing information for risperidone (Risperdal®), which includes the following statement:

> RISPERDAL® [risperidone] is indicated for the treatment of irritability associated with autistic disorder in children and adolescents aged 5–16 years, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods [see Clinical Studies (14.4)]. (downloaded from http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020272s056,020588s044,021346s033,021444s03lbl.pdf.

Note that risperidone is indicated for the treatment of "irritability associated with autistic disorder" and that "aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods" are specifically described as *symptoms* of that irritability. In fact, there is no evidence for the existence of "irritability," save for the behaviors described as symptoms of it (e.g., self-injury). Irritability is not a disease or a behavior disorder, and it is utter foolishness to contend that risperidone, or any other psychotropic drug, alleviates "irritability" in people with ASD, which in turn reduces their challenging behavior.

In most cases, challenging behaviors emitted by people with ASD are operant responses controlled by their consequences. For example, a review of 173 studies in which functional assessment techniques were used to isolate environmental variables related to the challenging behavior of people with ASD revealed that, in most participants, attention or escape from demands maintained the responses of interest (Matson et al., 2011). In such cases, operant conditioning, not an internal state of irritability, was responsible for the challenging behaviors. Although researchers and clinicians frequently discuss drug effects on "irritability" (e.g., Elbe & Lalani, 2012), doing so is at best misleading.

Behavioral Mechanisms of Drug Action

What psychotropic drugs actually do is to perturb neurochemical processes. These perturbations sometimes influence an individual's sensitivity to environmental events, and in such cases it is possible to specify the drug's behavioral mechanism of action. In contrast to neurochemical mechanisms of drug action, which relate to the effects of drugs in the brain, behavioral mechanisms of action refer to the stimulus functions of drugs in the context of operant and classical conditioning and to the effects of the drugs on the capacity of other stimuli to control behavior.

The stimulus properties of drugs involve their ability to serve as conditional stimuli, unconditional stimuli, discriminative stimuli, positive reinforcers (conditioned or unconditioned), and negative reinforcers (conditioned or unconditioned). Drugs also can serve as motivational operations, increasing or decreasing the reinforcing or punishing effects of certain other stimuli. In addition, they can alter sensitivity to particular dimensions of reinforcement (e.g., amount, probability, delay), influence sensory acuity (hence discrimination), and elicit responses incompatible with required operants. Finally, drugs and their effects can be described in statements (rules) that alter behavior through rule governance. These and other behavioral mechanisms of drug action are described elsewhere (Poling & Byrne, 2000).

Little is known regarding the relation between behavioral mechanisms of action and the beneficial (as well as adverse) effects of psychotropic medications in people with autism (Poling, Ehrhardt, Wood, & Bowerman, 2010), but some recent progress has occurred. To determine behavioral mechanisms of drug action, one must first identify the environmental variables which typically regulate the behavior in question. Functional analysis (and functional assessment in general) provides a tool for doing so and has been used in a few studies to examine the variables controlling challenging behavior and how risperidone interacts with those variables (Crosland et al., 2003; Valdovinos et al., 2002; Zarcone et al., 2004). Unfortunately, those studies failed to disclose a

characteristic behavioral mechanism of drug action for risperidone. In many participants, the environmental variables controlling destructive behavior could not be isolated. In some participants, however, the functions of the response class were apparent, and risperidone appeared to produce consequence-dependent effects, specifically, to weaken escape-maintained responding.

A more recent study that used analogue functional analysis and other methods to examine the effects of several drugs on the rate and function of problem behaviors exhibited by four children with ASD also revealed that atypical antipsychotics often reduce escape-maintained responding (Valdovinos, Nelson, Kuhle, & Dierks, 2009). In this study, rates of problem behaviors exhibited by two students decreased in the demand condition (where responding was escape-maintained), but not in other conditions, when risperidone or olanzapine was discontinued.

In another recent study, Danov, Tervo, Meyers, and Symons (2012) examined the effects of aripiprazole on the problem behaviors of four people with severe developmental disabilities, one of whom was diagnosed with ASD. Aripiprazole "had some apparent differential effects across behavioral function and behavioral topography for 3 of 4 participants" (p. 286), but not for the participant with ASD, whose behavior worsened in all conditions when the drug was administered. The reason for the difference in drug effects across participants is not clear, but the results of this and other studies suggest that, as others have argued (e.g., Schaal & Hackenberg, 1994; Thompson, Egli, Symons, & Delaney, 1994), functional analysis methodology may be useful in isolating behavioral mechanisms of drug action. Discerning such mechanisms may prove useful in consistently matching clients with ASD to effective pharmacological interventions, a task which is currently impossible.

ASD and Comorbidity: Dual Diagnosis

Although progress is being made in understanding how brain structure and function differ in people who are and who are not diagnosed with ASD, current knowledge is inadequate to provide a sound rationale for the use of pharmacotherapy (Bethea & Sikich, 2007; Buxbaum & Hof, 2013; Thompson, 2007). That is, there is no known disease process that is responsible for the behaviors that lead to a diagnosis of autism, or for co-occurring challenging behaviors, which can be corrected by administering a drug with a particular mechanism of action. At this point in time, the only valid justification for prescribing behavior-modifying drugs for people with ASD is sound empirical evidence that such drugs are effective. As Heute et al. (2014) point out, "psychopharmacological interventions may be used to treat [all behaviors indicative of] an entire suspected psychiatric disturbance, a specific behavior as a symptom of a psychiatric diagnosis, or a behavior occurring in the absence of a psychiatric diagnosis" (p. 735).

A drug would be used to treat a psychiatric disturbance in a person with ASD if that person was to be dually diagnosed, that is, properly identified as having both ASD and a recognized psychiatric condition (e.g., one identified in *DSM-V*), such as schizophrenia, a mood disorder, an anxiety disorder, or ADHD. As noted previously, many people with ASD also are concurrently diagnosed with ADHD, ODD, or ID (Charman et al., 2011; Lecavalier et al., 2014; Matson & Nebel-Schwalm, 2007b). Matson and Konst (2015) suggest that, while psychotropic drugs are generally overused to treat people with autism, "the use of pharmacological interventions is appropriate for some symptoms of co-occurring psychopathology such as anxiety, depressions, and schizophrenia" (p. 35). That may be true, but it is important to recognize that the behavioral characteristics that cause a person to be diagnosed with ASD also make it hard to diagnose comorbid conditions (Mason & Scior, 2004; Shaw, Bruce, Ouimet, Sharma, & Glaser, 2009), and studies reveal that drugs are commonly prescribed in an effort to reduce challenging behaviors (Bamidele & Hall, 2013; Canitano & Scandurra, 2011; Medeiros, Kozlowski, Beighley, Rojahn, & Matson, 2012; Tureck, Matson, Turygin, & Macmillan, 2013; West, Waldrop, & Brunssen, 2009). Unfortunately, these responses are rarely defined carefully or measured precisely,

and, as Matson and Konst contend, "...a very large segment of psychotropic drug use involves prescribing for extremely vague and/or ill-defined target behavior" (p. 35).

Limitations of Published Research

Researchers have been rightly critical of the quantity and quality of drug studies involving people with developmental disabilities, including ASD, for more than 40 years (e.g., Sprague & Werry, 1971; Gadow & Poling, 1988; Matson et al., 2000). The number of studies examining the effects of psychotropic drugs in people with ASD has increased greatly in recent years, and the quality of research in this area arguably has improved with time. For example, the number of studies of children with ASD that used a randomized between-group design with a placebo-control condition, which is typically (but not necessarily wisely) considered as the "gold standard" in clinical psychopharmacology, increased dramatically from 1981–1990 to 2001–2010 (Siegel & Beaulieu, 2012). Nevertheless, as regularly emphasized in reviews of the literature and other articles (e.g., Courtemanche, Schroeder, & Sheldon, 2011; Farmer, Thurm, & Grant, 2013; Matson & Hess, 2011; Mohiuddin & Ghaziuddin, 2013; Poling et al. 2010; Siegel & Beaulieu, 2012), many published studies are not methodologically strong, and several important research questions have not been adequately addressed. These limitations are understandable given the practical and ethical challenges that are an inevitable part of conducting drug research with a protected population, but they also seriously limit the conclusions supported by the current research base. Ten limitations of the research base are considered in this section. It should be noted that other limitations, such as failure to standardize drug dosages and studying heterogeneous and ill-defined samples of people with ASD, are also significant.

1. *There are no long-term studies of the value or adverse effects of drug treatments.* People with ASD often receive one or more psychotropic medication for years, even decades, but no studies have examined drug effects over such long periods. Given that psychotropic drugs are often prescribed for children with ASD, whose brains and bodies are rapidly developing, long-term studies are especially important. As others have noted (e.g., Anderson et al., 2007; Haddad & Sharma, 2007), almost nothing is known about the long-term side effects of antipsychotics in young people with ASD, even though these drugs are widely used and are known to produce several adverse effects. Relevant research is both badly needed and difficult to conduct.
2. *The possibility of gender differences in drug effects has been largely ignored.* Although there are differences in the behavior of males and females with ASD (Rivet & Matson, 2011), gender often influences drug effects (Poling et al. 2009), and the importance of examining possible gender differences is widely recognized in psychopharmacology (Volkow, 2005–2008), the usual practice in drug studies involving people with ASD is to include relatively few female participants and to aggregate data across females and males.
3. *The effects of psychotropic drugs in people past young adulthood remain to be determined.* Although ASD is nearly always a lifelong condition, people with ASD continue to emit challenging behaviors as they age (although the form of the behaviors often changes with time), and as drugs are frequently prescribed in response to those challenging behaviors, researchers have paid very little attention to drug effects in older people with ASD (see Dove et al., 2012). Most published studies involve children, and Dove et al. found only eight studies of medications that focused on 13- to 30-year-olds with ASD, four of fair quality and four of poor quality. Given the quantity and quality of the studies examining drug effects in adolescents and young adults with ASD, no compelling conclusions can be drawn concerning the value of pharmacotherapy in this

population. Even less can be concluded regarding the value of psychotropic drugs for older people with ASD, including those who are elderly, because relevant research is lacking. The absence of research examining the effects of pharmacotherapy in older people with ASD is vexing, given that data reported by Shimabukuro, Grosse, and Rice (2008) indicate that "individuals with an ASD are utilizing increasingly intense pharmacotherapy to control behavioral symptoms as they grow older" (p. 550).

4. *Very little is known about the effects of polypharmacy*. As noted, people with ASD often receive two or more psychotropic drugs simultaneously. There are very few data to provide empirical support for this practice. For instance, a recent review of polypharmacy involving risperidone or aripiprazole in combination with other drugs revealed that few relevant articles have appeared, and none of them provide compelling support for commonly used drug combinations (in press).
5. *Drug treatments are rarely compared to alternative treatments*. Other interventions, notably those characteristic of applied behavior analysis, have proven useful in reducing the kinds of challenging behaviors that are commonly treated with psychotropic drugs, but head-to-head comparisons of the two intervention modalities rarely, if ever, appear. For example, research shows that both risperidone and behavior-analytic interventions can be effective in reducing challenging behaviors, but a review indicates that no direct comparison of risperidone and a nondrug treatment has appeared (Weeden, Ehrhardt, & Poling, 2010a). Moreover, different research strategies are typically used to evaluate behavior-analytic and pharmacological interventions, which make it nearly impossible to compare findings across studies.
6. *The effects of combinations of psychotropic medication and non-pharmacological interventions are largely unknown.* People with ASD often are simultaneously exposed to both pharmacological and non-pharmacological interventions (which are often behavior-analytic) with the same intended outcome, typically the reduction of challenging behavior (Frazier, 2012). As Courtemanche, Schroeder, and Sheldon (2011) point out, very little is known about the effects of such combinations. They provide an excellent discussion of strategies for examining drug combinations and the importance of doing so.
7. *Measures of desired and side effects are often weak*. As Zarcone, Naolitano, and Valdovinos (2008) discuss, one of the most important issues in designing a drug study is determining which behaviors to measure and the best way to measure them. Checklists and rating scales, such as the ABC, are used to index beneficial changes in behavior in most studies that examine drug effects in people with ASD. Although they are widely accepted and easy to use, such assessments yield limited information and have been soundly criticized. For example, Huffman, Sutcliffe, Tanner, and Feldman (2011) found that the Clinical Global Impression (CGI) scale was the most commonly used general measure of drug effects in the 89 studies they evaluated (it was used in 23 of them), even though, as they note, "its shortcomings have been recognized in criticisms of the scale on semantic, logical, and statistical grounds and in recommendations for its improvements [references omitted]" (p. 63). Alternatives to the ABC and CGI for quantifying drug effects are sorely needed and summarized elsewhere (e.g., Gadow & Poling, 1988; Zarcone et al., 2008). Moreover, as Matson and Hess (2011) emphasize, side effects are rarely assessed adequately, even though such effects can be quite serious. They offer a number of useful suggestions for improving the measurement of side effects.
8. *Data analysis is often weak*. Three separate issues bear mention. One is that inferential statistics, in which group means (e.g., on the irritability subscale of the ABC) for a placebo and drug group (or condition) are compared, are widely used in an attempt to

determine whether drug treatment produced a beneficial change in behavior. Statistical significance is not the same as clinical significance, which must be assessed using a social validation procedure (Poling & Ehrhardt, 1999; Poling, Methot, & LeSage, 1995). A second is that the number of participants in many studies is relatively small, which compromises the power of statistical analyses. A third is that meaningless data are sometimes analyzed, as when researchers consider total ABC scores rather than subscale scores (e.g., Fung, Chahal, Libove, Bivas, & Hardan, 2012; Thompson, Zarcone, & Symons, 2004).

9. *The potential for bias to affect findings is high in many studies.* As Matson and Konst (2015) point out, many studies of the pharmacological treatment of people with ASD are funded by the companies that manufacture the drugs being evaluated. Such funding automatically raises the issue of researcher bias, both intentional and unintentional. Knowledge of the conditions to which individual participants are exposed is another source of potential bias, and it is conventionally controlled through the use of double-blind conditions, in which neither the participants in a study nor the researchers (or others) who evaluate them know whether particular participants are receiving drug or placebo when data are collected. These controls are absent in open-label drug trials, which should always be viewed with extreme skepticism, especially in view of data suggesting that placebo responses are especially strong in studies of participants with ASD (Sandler & Bodfish, 2000). Even when a placebo is given, it may be easy to tell whether or not a participant is receiving active medication, because such medication produces obvious changes in that participant's physiological status or behavior. In such cases, an active placebo, that is, a substance that produces some detectable effects similar to those of the medication of interest, but has no psychotropic action, should be used (Khan & Brown, 2015; Moncrieff, 2015). Unfortunately, studies of drug effects in participants with ASD that compare medication to an active placebo have not appeared.
10. *Predictors of positive responses to drugs have not been isolated.* Studies repeatedly show that there are important individual differences in how people with ASD respond to a given psychotropic drug, even when the dose for each is equivalent (or optimized) and the condition being treated appears to be comparable. For this reason, researchers should routinely distinguish "responders," who are people who respond favorably to a drug, from "nonresponders," who fail to benefit from the medication, and many (but by no means all) do so. When this is done, a significant proportion of patients inevitably proves to be nonresponders. For example, in a study of the effects of risperidone in adults that used scores on the Clinical Global Impression of Improvement scale to index drug effects, 8 of 14 participants who received risperidone were rated as responders, defined as people whose scores were "much improved" or "very much improved" when they received risperidone (McDougle et al., 1998). It stands to reason that the patients who responded favorably to risperidone differed in some important way or ways from patients who did not benefit. If empirical variables that reliably distinguish responders from nonresponders could be identified, then it would be possible to accurately match patients to effective treatments, which is the essence of sound clinical practice. Although researchers have searched for valid predictor variables at several levels of analysis and have made some progress, as in the studies (previously overviewed) suggesting that antipsychotic drugs weaken escape-maintained behavior, it is not presently possible to accurately predict individual responses to a given medication. Until this is accomplished, if ever, it is imperative that every treated individual's response to medication be carefully monitored, as discussed in the section entitled "Everyday Medication Monitoring."

Research Findings

Hundreds of studies have examined the effects of various drugs on the behavior of people with ASD. Although there are serious limitations to this body of research, as discussed in the foregoing section, "Limitations of Published Research," published findings support some conclusions, and dozens of scholarly reviews have summarized these findings. Table 25.1 lists 18 peer-reviewed reviews, all published in the past decade. Readers seeking informed summaries of the published literature are advised to consult these sources. Useful information is also available in book chapters and books not specifically devoted to the psychopharmacology of autism (e.g., Huete et al., 2014; Thompson, 2007) and in a good but somewhat outdated book concerned solely with the topic (Tsai, 2001). It is important to recognize, however, that authors differ from one another with respect to their general orientation toward pharmacological interventions, with some being more skeptical than others. Moreover, there is no consensus concerning the specific characteristics that enable a drug evaluation to yield creditable findings (Courtemanche et al., 2011; Higgins & Green, 2006); therefore, reviewers can legitimately differ with respect to the weight they assign to the findings of particular studies and the conclusions that they draw from them. Despite these considerations, the conclusions of most reviews are similar. Based on our reading of these reviews and most of the original articles upon which they are based, it is our opinion that the following conclusions are justified at this time.

A Wide Range of Medications Have Been Evaluated, Inadequately

In descending order of frequency, the drug classes most commonly prescribed for people with ASD appear to be antipsychotics, antidepressants, stimulants, and anticonvulsants (Bertelli, Rossi, Keller, & Lassi, 2016). Multiple drugs from each of these classes have been evaluated in one or more studies. In addition, drugs from many other classes, several with no recognized psychotropic applications, have also been examined. For example, a review by Bertelli et al. summarized the effects of the following drug classes (and individual drugs): antipsychotics (risperidone, palperidone, aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone, and asenapine), antidepressants (tricyclics, notably clomipramine, nortriptyline; serotonin-specific reuptake inhibitors, notably fluvoxamine, fluoxetine, sertraline, citalopram, escitalopram, venlafaxine, trazodone, and mirtazapine), anticonvulsants and mood stabilizers (valproic acid, topiramate, levetiracetam, and lamotrigine), central nervous system stimulants (methylphenidate and atomoxetine), other compounds (clonidine, guanfacine, naltrexone, and secretin), new frontier pharmacotherapy (cholinergic drugs, notably tacrine, rivastigmine, galantamine, donepezil, and mecamylamine; glutamatergic agents, notably *d*-cyclosterine, amantadine, memantine, acamprosate, arbaclofen, and bumetanide), melatonergic agents (melatonin and agomelatin), and oxytocin.

That list comprises 42 individual drugs. Published studies are inadequate to support compelling conclusions about the benefits or risks of the vast majority of them. Nonetheless, regardless of the drug evaluated or what it is prescribed to treat, most original investigations report a beneficial outcome in at least some patients, and many reviews echo these reports. For example, methylphenidate is often reported to be effective in treating "hyperactivity," although some reviewers view the supporting evidence as compelling (e.g., Huffman et al. 2011), while others view it as suggestive (e.g., Siegel & Beaulieu, 2012). Such disagreements make it clear that extant data are inadequate to provide adequate guidance for physicians who are contemplating the use of psychotropic medications to treat a person with ASD, even if they are familiar with the relevant studies and committed to the use of scientifically verified practices.

As Heute et al. (2014) point out, "...psychiatrists are challenged with basing their understanding of medication utility on a less than optimal body of research and more often on case study reports, and sometimes must refer to

Table 25.1 Summary of published reviews in the last 10 years (listed alphabetically)

Published reviews	Drug or drug classes	Demographic[a]	Target symptoms[b]
Aman et al. (2014)	Atomoxetine	Children (19 or younger)	Hyperactivity
Baribeau and Anagnostou (2013)	Multiple drug agents	Children and adults	Social communication
Broadstock, Doughty, and Eggleston (2007)	Multiple drug agents	Children and adults	Core symptoms of ASD
			Comorbid symptoms
Dove et al. (2012)	Multiple drug classes	Adolescent and young adults (13–30 years old)	Core symptoms of ASD
			Comorbid symptoms
Doyle and McDougle (2012)	SRIs	Child and adults	Core symptoms of ASD
	Antipsychotics		Comorbid symptoms
Elbe and Lalani (2012)	Antipsychotics	Children and adults	Irritability
	Misc. drug agents		
Fung et al. (2012)	Aripiprazole	Children (4–18 years old)	Sensory abnormalities
Ghanizadeh (2012)	Atomoxetine	Children and adults	ADHD symptoms
Krishnaswami et al. (2011)	Secretin	Children (12 or younger)	Core symptoms of ASD
McPheeters et al. (2011)	Multiple drug classes	Children (12 or younger)	Challenging and repetitive behaviors
Mohiuddin and Ghaziuddin (2013)	Multiple drug classes	Children and adults	Hyperactivity
			Irritability
			Aggression
Parikh, Kolevzon, and Hollander (2008)	Multiple drug agents	Children and adolescents	Aggression
			Self-injurious behaviors
Preti et al. (2014	Oxytocin	Children and adults	Emotion recognition
			Eye gaze
Reichow, Volkmar, and Bloch (2013)	Methylphenidate	Children	ADHD symptoms
	Atomoxetine		
	Clonidine		
Rossignol and Frye (2014)	Multiple drug agents approved for Alzheimer's disease	Children and adults	Core symptoms of ASD
			Comorbid symptoms
Roy, Roy, Deb, Unwin, and Roy (2015)	Naltrexone	Children	Core symptoms of ASD
			Comorbid symptoms
Siegel and Beaulieu (2012)	Alpha-2 agonists	Children (18 or younger)	Core symptoms of ASD
	Antipsychotics		Comorbid symptoms
West et al. (2009)	SSRIs	Children	Core symptoms of ASD
			Comorbid symptoms

[a]Demographics as reported by the authors in the review
[b]Target symptoms and/or areas as reported by the authors in the review

reported results and clinical trials of medications used in the general population for similar symptoms to guide their decisions" (p. 736). They assume, for example, that people with ASD can experience all of the psychiatric conditions (or behavior disorders) exhibited by other people and that the presence of ASD does not fundamentally alter how a person with a given psychiatric condition, such as depression of ADHD, responds to medication. Both assumptions are reasonable. But, as discussed previously, it is hard to diagnose comorbid psychiatric conditions in people with ASD, and medications are usually prescribed to reduce specific challenging behaviors in people with ASD, not to reduce established symptoms of recognized psychiatric conditions (e.g., *DSM-V*

criteria for specific disorders). Put simply, the rationale for prescribing most psychotropic drugs for people with ASD is weak, and the common practice of using polypharmacy to manage supposed coexisting psychiatric conditions in people with ASD is fraught with difficulty.

No Drug Significantly Improves the Core Symptoms of Autism

Although a few authors might disagree, most people who reviewed the relevant literature reached conclusions similar to the two that follow, as do we:

> In summary, despite their widespread use, there exist no medications that are specific to the core symptoms of autism. At best medications result only in modest symptomatic response. (Mohiuddin & Ghaziuddin, 2013, p. 652)
>
> [T]his review finds that there are no definitely effective or efficacious pharmacologic treatments for the core symptoms of autism. (Farmer et al., 2013, p. 310)

No medication that substantially reduces the core symptoms of ASD is currently available, but researchers continue to search for one. Like everyone concerned with the well-being of people with ASD, we hope they find it soon.

Antipsychotic Drugs Often Reduce Challenging Behaviors in Children and Adolescent

Although several antipsychotic drugs appear to reduce challenging behaviors, the evidence is best for risperidone, unsurprising because the drug has been approved for a decade for reducing such behaviors. As noted, many but not all children and adolescents treated with appropriate doses of risperidone show substantial reductions in challenging behaviors, such as self-injury, temper tantrums, and aggression directed toward property and other people. This outcome can be of great value to the treated individuals and those who love and care for them. There is also substantial evidence that aripiprazole, also approved for reducing challenging behavior, is often effective.

Antipsychotic drugs can produce a range of troublesome and potentially serious side effects, including sedation, weight gain, metabolic changes, and motor disturbances. Although antipsychotic drugs are often efficacious, we agree with McPheeters et al. (2011), who contend that "caution is warranted regarding their use in patients without severe impairments or risk of injury" (p. 1319).

Secretin Is Useless

Although secretin, which is a gastrointestinal peptide, was once a popular treatment for young people with ASD, several methodologically sound studies show beyond reasonable doubt that it is of no value whatsoever (Huffman et al., 2011; Krishnaswami, McPheeters, & Veenstra-Vaderweele, 2011).

Everyday Medication Monitoring

As noted, there are substantial differences in how what appear to be similar people with ASD respond to a particular psychotropic drug. Some are responders, others nonresponders, and, moreover and importantly, there are substantial individual differences in the form and severity of the side effects produced by a given drug and dose. Moreover, people with ASD, and especially children, may not be able to self-monitor and report the effects of medications to their physicians and other caregivers. Given these considerations, every person with ASD who receives a psychotropic medication should be carefully monitored to ensure that they are receiving significant benefit from it.

We have repeatedly argued (e.g., Poling, 1994; Poling & Ehrhardt, 1999; Poling, Laraway, Ehrhardt, Jennings, & Turner 2004; Poling, Methot, & LeSage, 1995; Weeden, Ehrhardt, & Poling, 2010b), and argue again, that accountable,

hence appropriate, pharmacotherapy requires that (a) treatment goals (i.e., the desired changes in target behaviors) are clear and in the participant's best interest, (b) treatment procedures (i.e., who does what to whom) are unambiguous and implemented with fidelity, and (c) treatment decisions (i.e., whether the intervention is continued, altered, or terminated) are made on the basis of actual changes in target behaviors and other relevant characteristics of the participant (e.g., evidence of significant side effects). In fact, caregivers who are committed to using evidence-based practice – and all of them should be so committed – have two essential obligations. One is to select interventions based on scientific evidence indicating that those interventions *are likely to be effective* in the patients that receive it. The other is to provide compelling evidence that the interventions *actually are effective* in the patients that receive them.

As Sprague and Werry (1971) emphasized many years ago, every prescription of a psychotropic medication is in essence an experiment in which the physician and other caregivers hypothesize that administering a specific drug will produce a desired change in one or more aspects of a client's behavior. They hope and expect that the hypothesis will be confirmed but must collect relevant data to validate their expectation. If they do not, patients may be exposed indefinitely to interventions that fail to help, and may even hurt, them.

Depending on the desired effects of the drug in question, in a particular situation, checklists, rating scales, interviews, and direct observations may be useful in quantifying drug effects. Good assessment procedures are easy to use, provide a meaningful index of the behaviors of clinical concern, and are acceptable to parents, other relevant caregivers, the prescribing physician, and (insofar as possible) the person with ASD. Several articles provide good coverage of issues relating to quantifying the behavioral effects of drugs in people with ASD in clinical research (e.g., Arnold et al., 2000; Courtemanche et al., 2011; McDougle et al., 2000; Matson & Nebel-Schwalm, 2007a; Zarcone et al., 2008), and the same general issues pertain to the everyday assessment of medication effects. It is beyond our purpose to discuss these issues, but four points are worth making. First, some people with ASD lack sufficient communication skills to participate in certain types of assessments. Second, people are inclined to see (and report) what they expect (and hope) to see, so the potential for observer bias affecting results is always a consideration.

Third, some of the strategies necessary to collect important data are invasive and will not be well tolerated by some people with ASD. For instance, when patients are prescribed an antipsychotic, like risperidone, their blood lipids and fasting blood glucose should be regularly monitored (Panagiotopoulos, Ronsley, Elbe, Davidson, & Smith, 2010) with blood collections. But, as Elbe and Lalani (2012) indicate, "for some children with autism spectrum disorder, attempts at blood collection can lead to severe behavioural outbursts and intervention may be required to complete appropriate monitoring" (Davit, Hundley, Bacic, & Hanson, 2011, p. 145). Rather than arranging such an intervention, caregivers may simply forego the monitoring.

Fourth, most physicians are not trained in behavioral assessment, and even those who are well trained do not have the time to collect relevant data. Therefore, if physicians' decisions regarding the behavioral effects of psychotropic medications are to be data based, other people must collect appropriate data. We have suggested that behavior analysts, by virtue of their training and professional functions, are in an especially good position to collect such data (Poling & Ehrhardt, 1999; Weeden et al., 2010b), but, regardless of who actually collects data, it is essential that all concerned parties decide before medication is prescribed what the drug is intended to do and how its effects will be measured and evaluated. Strategies for detecting possible untoward drug effects should also be selected at this time. Collecting multiple measures of drug effects in different situations, such as at home and at school, is typically desirable, because challenging behaviors are often situation specific. Having multiple individuals collect data also is desirable, because doing so reduces (but does not eliminate) the likelihood of observer bias confounding results.

The rigor with which drug effects can be assessed in different individuals with ASD varies substantially, depending on the situation and the caregivers involved. In our experience, it is common to have little or no formal assessment. That is, no data relevant to drug effects are collected, and the value of the intervention is assessed based on the global impressions of parents, teachers, or other caregivers. It is unsurprising that this is the case – most people are not committed to data-based decision-making and even those who are may find it difficult to collect appropriate information regarding drug effects. It is also unfortunate.

Consider the study by Zarcone et al. (2004), summarized previously. In that study, risperidone did not appear to reduce destructive behavior in 3 of 13 participants. Nonetheless, the parents of two of three of the persons with ASD who did not show a beneficial response to the drug during functional analysis sessions elected to continue their children on medication after the study ended. Zarcone et al. noted that "They [the parents] felt that although their children continued to engage in some destructive behavior, the intensity was reduced, and the medication was helpful in reducing behaviors that were not captured by the functional analysis, such as hyperactivity, perseverative, and obsessional behavior" (p. 319). This may be the case, but it is not clear whether risperidone actually improved aspects of the children's behavior not adequately captured by the researchers' assessments or whether the parents *believed* there were improvements where none really existed. This distinction is far from trivial because risperidone can produce a range of significant adverse effects. Therefore, people who do not receive real and direct benefit from risperidone should not receive it. The same is true of all other psychotropic medications.

Concluding Comment

For more than half a century, prescribing psychotropic drugs for people with developmental disabilities has been a common, and controversial, practice. It remains so today, although the focus has largely shifted from the effects of such drugs in people with ID to their effects in people with ASD. It is sadly ironic that many of the same concerns that were expressed years ago, as in reviews of the literature by Baumeister and Sevin (1990) and Matson et al. (2000), remain relevant today. Consider the following comment on the methodology of published studies involving people with ID (once termed "mental retardation"), which appeared more than three decades age:

> Thirty-nine articles (1970–1982) on drug effects in mentally retarded participants were evaluated on 14 methodological dimensions. Methodological shortcomings were evident in most, but not all, studies. The relative scarcity of methodologically sound studies has significant implications for clinicians, whose decisions concerning drug use with the mentally retarded should be data-based. (Poling, Picker, & Wallace 1983, p. 110)

As we have discussed, methodological limitations also characterize recent studies of the effects of psychotropic drugs in people with ASD. It is easy to bemoan the shortcomings of the research that has appeared, but it is hard to improve upon it because funding to support relevant studies is limited. Moreover, both practical and ethical considerations limit the kind of work that can be done. Evidence adequate to support strong conclusions concerning the value of many psychotropic drugs commonly prescribed for people with ASD will not appear soon, if ever. Nonetheless, such drugs are routinely prescribed. In the absence of such evidence, the known adverse effects of many medications, and the availability of safer and better-documented alternative treatments, a good case can be made that psychotropic medications are routinely overprescribed for people with ASD (Matson & Konst, 2015; Matson & Hess, 2011).

Early in this chapter, we discussed some of the reasons why psychotropic drugs are so often prescribed for people with ASD. The best reason, of course, is that some members of this population derive benefits from a drug treatment that no other intervention can provide. Prescribing medication is the primary tool that physicians have available to improve the mood, cognitive status, or overt behavior of people with ASD, and this tool is neither intrinsically good nor bad.

Appropriate drug treatment requires that the right people receive medication and that their medication regimen is managed to produce optimal benefit. When this occurs, a psychotropic medication can provide quick, effective, and cost-efficient benefits. Ensuring that it occurs consistently is a worthy goal for everyone who cares for people with ASD.

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