5 Measuring the Effects of Medication for Individuals with Autism

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Abstract

Psychotropic medication is often prescribed for individuals with autism spectrum disorders (ASD) for a variety of behavioral concerns. These concerns can include problem behaviors such as aggression, self-injury, or property destruction, as well as repetitive and compulsive behavior. Other concerns such as impulsivity, inattentiveness, and mood disturbances may also be targeted by psychotropic medication. Unfortunately, medical providers often have to rely on caregivers to report changes in behavioral outcomes rather than gathering the information directly from the person taking the medication. Thus, the goal of this chapter is to help guide clinicians and educators to work collaboratively with medical providers to assist in measuring the effects of medications on the behavior targeted. In addition, information on collateral effects of the medication on other behaviors as well as side effects of medication can be monitored. Information on the drug development process, physiological measures that can be used to assess therapeutic outcomes, and tools for clinicians and families to use to measure medication effects are also described. Finally, guidelines for enhancing collaboration between patients, families, educators, and providers on treatment plan development are emphasized.

Psychotropic medications are used extensively in individuals with autism spectrum disorders (ASD) and other disabilities. For some, these medications are prescribed for behavioral concerns such as problem behavior like aggression, self-injury, or repetitive behavior and for others they are prescribed for concerns such as impulsivity, anxiety, and/or ritualistic behavior. Langworthy-Lam, Aman, and Van Bourgondien (2002) surveyed members of the Autism Society of North Carolina to determine to frequency of medication use by members. Of the 1538 families who responded, 45.7% of individuals with ASD were taking psychotropic medication. Of that group, antidepressants were the most commonly prescribed (21.7%), then antipsychotics (16.8%), followed by stimulants (13.9%). This study relied on parents volunteering to participate and thus, to get a more objective measure, Mandell et al. (2008) reviewed 60,641 national Medicaid claims and found that 57% of children with ASD were prescribed at least one psychotropic medication. Houghton, Ong, and Bolognani (2017) found that 64% of children with ASD enrolled in commercial insurance programs and 69% of children

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enrolled in Medicaid programs were prescribed psychotropic medication, indicating a growing trend in the use of psychotropic medication even within the past 10 years.

Studies have identified that the age that medication is being prescribed for children with ASD is getting younger and younger. For example, Mandell et al. (2008) found that 18% of children 0–2 years of age and 32% of children 3–5 years were prescribed medication. Finally, polypharmacy was also common in that 20% of the children studied by Mandell et al. were prescribed three or more medications. Individuals with ASD and intellectual disabilities (ID) are at even greater risk for polypharmacy (Straetmans, van Schrojenstein Lantman-de, Schellevis, & Dinant, 2007).

Although it is not always clear what behaviors are targeted for medication, there is evidence that children with ASD are more likely to have comorbid psychiatric disorders than their peers with ID only (LoVullo & Matson, 2009) or their neurotypical peers (Stortz, Lake, Cobigo, Ouellette-Kuntz, & Lunsky, 2014). Houghton et al. (2017) found that individuals aged 3–50 years with ASD who had a psychiatric comorbid condition were more likely to be prescribed medication, with attention-deficit hyperactivity disorder and anxiety disorder being the most common conditions. Other psychiatric conditions commonly associated with ASD include bipolar disorder and depression. The authors also found that a large proportion of people with ASD without a comorbid psychiatric condition were also prescribed medication (i.e., 31% for commercial insurers, and 33% for those on Medicaid).

Characteristics most commonly associated with medication use for individuals with ASD include greater age, more severe autism symptoms, more severe intellectual disability, and more restrictive housing arrangements (Langworthy-Lam et al., 2002). This was particularly true for individuals taking antipsychotic medication. Interestingly, these authors also found that antidepressants were more likely to be prescribed for females with autism, individuals who were white, and those who had a higher paternal education level. Houghton et al. (2017) also found that medication was more likely to be prescribed for older children, with the highest likelihood being just before adulthood.

Given that there are limited guidelines for prescribing medication for children with ASD and/or ID, it's important to consider how a provider determines when medication is needed and when it's not. Much of a provider's prescription practices develop through experience and training history, and based on patient response or caregiver's opinion of their response to the medication. As clinicians and educators working with children with ASD, what is our role? How can we help inform prescription practices for our patients and students, and how do we navigate the complicated system of effective collaboration with other clinicians, providers, and the child's parents?

5.1 Medication Development and Prescription Guidelines

The first step in developing a new medication is to conduct a series of clinical trials which initially involve preclinical testing with nonhumans for safety and toxicity. This is followed by a series of phase trials that involve testing for safety in human volunteers without the targeted behavioral or medical issue, and then doing a series of larger scale trials with adults with the disorder. Once the medication is reviewed and approved by the US Food and Drug Administration (FDA), additional clinical trials with children and other vulnerable populations, such as individuals with ASD, can be conducted (e.g., Aman et al., 2004; Handen, Johnson, & Lubetsky, 2000; McCracken et al., 2002; McDougle et al., 2005). To find a list of current clinical trials available for individuals with autism, the website clinicaltrials.gov is sponsored by government agencies such as the National Institute of Health and can identify medication trials (and other behavioral or medical intervention studies) currently being conducted.

The gold standard for evaluating medication is to conduct a randomized clinical trial (RCT;

Sprague & Werry, 1971). This has several key characteristics including the following: (1) it is double blind and placebo controlled so neither the participant nor the prescriber know when the person is taking active medication versus a placebo; (2) all other interventions are kept constant with no change in behavioral interventions or placement; (3) well-validated instruments are used to evaluate the efficacy of the medication; and (4) participants are randomly assigned to study conditions. Napolitano and her colleagues (1999) suggested that RCTs with participants with disabilities also include evaluations to determine the social validity of the intervention being assessed (to determine if there was a clinically significant change in the behavior), and the level of client satisfaction. The authors also suggested that the separate and combined effects of medication and behavioral interventions should be evaluated by conducting RCTs using multiple sites or centers (e.g., Aman et al., 2009; Handen et al., 2015; Scahill et al., 2012).

While many clinical trials include Sprague and Werry's (1971) guidelines and use random assignment to a placebo or medication test group (sometimes referred to as a two-arm study), alternative clinical trial designs may also be considered. One design is the crossover design in which all study participants receive the active treatment (medication) and placebo (e.g., Zarcone et al., 2001), sometimes using multiple, or escalating doses. One concern with using a crossover design (sometimes referred to as a case crossover design) is that there can be carryover between phases; thus washout periods between placebo and medication phases are often recommended to control for these effects (Mills et al., 2009). Another concern is that these trials tend to take longer, even though more information can be obtained from each study participant, because all participants can serve not only as their own control but as a group control as well (e.g., Arnold et al., 2006; Hollander et al., 2005; Zarcone et al., 2001).

Given that it is often difficult to conduct clinical trials with the experimental rigor required of a RCT, the idea of evaluating the clinical effectiveness of an intervention (medication or otherwise) under more naturalistic conditions is called a practical clinical trial (PCT). An RCT is characterized by evaluating whether the intervention works under ideal circumstances of a very selective group of people under controlled conditions. A PCT evaluates whether the intervention works best under practical conditions with a more diverse, heterogeneous group of individuals using less controlled conditions (Brass, 2010). While a PCT is often less costly and the outcomes more variable, the results are possibly more generalizable to the larger clinical group.

Once a medication is approved by the FDA based on their safety trials, it can be prescribed immediately. Unfortunately, because clinical trials have often not yet been conducted with children or individuals with disabilities, nearly all psychotropic medications for that population are prescribed "off label" (i.e., not fully tested or approved by the FDA). Several medications have been approved for use in children such as Prozac (fluoxetine), Zoloft (sertraline), and other selective serotonin reuptake inhibitors (SSRIs) for the treatment of obsessive compulsive disorder. Many stimulants and other medications have been approved for the treatment of attention-deficit/hyperactivity disorder in children and adolescents as well. But it is very rare for the FDA to approve psychotropic medications in children with ASD or other developmental disabilities. Currently, there are only two medications approved for use in the treatment of irritability in children and adults with autism, Risperdal (risperidone) and Abilify (aripiprazole). The reason that "irritability" was specifically targeted for approval was based on the initial clinical trials that primarily relied on the Aberrant Behavior Checklist Irritability Subscale (Aman, Singh, Stewart, & Field, 1985) as the primary outcome measures. The ABC is often used as a measure for clinical trials and the Irritability Subscale includes several items that address problem behavior including "injures self on purpose," "aggressive to other children and adults (verbally and physically)," and "temper tantrums/outbursts" in addition to "irritable and whiny." So

while both of these medications are used for the treatment of a variety of problem behaviors including aggression, property destruction, and self-injury (Pandina, Bossie, Youssef, Zhu, & Dunbar, 2007), the FDA chose to identify irritability as the primary target (see more in the section Outcome Measures, below).

In addition to reviewing the literature on case studies and RCTs, providers also have practice parameters and clinical guidelines provided by groups such as the American Academy of Child and Adolescent Psychiatry (AACAP) to guide medication selection. The most recent guidelines by the AACAP for children and adolescents with ASD provide a broad range of recommendations for conducting diagnostic assessments, and using evidence-based behavioral and educational treatments but there is also a detailed list of the medications that have undergone clinical trials with individuals with ASD (Volkmar et al., 2014). The authors also recommended that pharmacotherapy should be offered to children with ASD only when there is a specific target symptom or comorbid condition that the medication would target. In addition, the review provides a list of commonly used instruments for measuring different aspects of behavior related to autism. Most of these rating scales are completed by parents to indicate their child's behavioral response to their medication as primary measure of treatment efficacy (e.g., Arnold et al., 2000; Marcus et al., 2009). Rarely are direct observation data used to evaluate the effects of the medication across time.

5.2 Outcome Measures

There are a variety of ways that medical providers determine whether there has been a positive or negative effect in behavior due to the medication. These can vary from asking the caregivers their opinion as to whether the medication is working to reviewing graphs of the frequency of the target behavior. In addition, there are also physiological measures that may be used to determine whether a medication is working optimally or not. Below is a description of some of these measures.

5.2.1 Therapeutic Drug Monitoring

Some medications can have the amount of active medication measured via levels in the patient's blood. This level can provide an indication of whether the medication is being absorbed adequately and is within a specific therapeutic range. Therapeutic drug monitoring can be helpful to determine if medication is at the recommended plasma level. While this can be a good guideline for dosing, without concurrent behavioral data, the information may not be very meaningful and should not be the primary measure of efficacy. Although therapeutic levels are becoming more common, there are still many medications for whom these data are not yet available or for whom levels have not been standardized. For example, valproic acid is often used for agitation and mood stabilization in individuals with autism (Hellings et al., 2005) and a blood level near 100 is considered to be within the therapeutic range and within safety standards (Allen, Hirschfeld, Wozniak, Baker, & Bowden, 2006). But the efficacy of the medication is not necessarily synonymous with a medication being within a therapeutic range. It is also unclear whether metabolic issues (or how quickly the medication is metabolized) can affect therapeutic blood levels.

Recent research in pharmacogenetics, or the study of the genetic differences in drug metabolism that affects an individual's response to medication, is now being used more often to not only evaluate the therapeutic effects but also adverse side effects of medications (Klotz, 2007; Smith, Sharp, Manzardo, & Butler, 2015). A person's sensitivity to certain genetic polymorphisms in the medication can have a significant effect on how a medication is metabolized. Fortunately, there are a relatively small number of enzymes that are used to metabolize psychotropic medications. For individuals whose genotype for a particular enzyme is typical, in that they have functional copies of the gene on both chromosomes, they are considered "normal metabolizers." For those that are identified as "fast metabolizers," there may be the presence of extra copies of the gene for that enzyme. "Slow

metabolizers" carry mutations in one or both copies of the gene for the enzyme that may reduce or even eliminate the function or expression of the enzyme (Meyer, 2000). As a result, the individual who is a slow metabolizer may experience an "overdose" by a normal dose of medication because they cannot metabolize the medication quickly enough. In addition to determining whether one is a fast or slow metabolizer, it may be possible to identify gene polymorphisms that are associated with specific side effects or adverse drug reactions. For example, Sleister and Valdovinos (2011) demonstrated that several gene polymorphisms or variants may be related to weight gain resulting from the use of atypical antipsychotic drugs.

The study of pharmacogenetics may eventually lead to the identification of who might show side effects or be the best responders to psychotropic medications (Schroeder, Hellings, & Courtemanche, 2013). Pharmacogenetics has become a growing part of the precision medicine or personalized medicine approach which is a developing trend in health care that takes into account the differences in individual genes, environments, and lifestyles to determine medication (and other treatment) efficacy (US Food and Drug Administration, 2017).

5.2.2 Side Effects or Adverse Drug Reactions

Although there are not a lot of data to support this view, several authors have suggested that compared to psychiatric patients without ID, patients with ID may be more sensitive to adverse drug reactions and side effects and may be treatment effects with lower doses of medication (Arnold, 1993; Kalachnik, 1999). Sometimes side effects can be measured physiologically (e.g., labs, blood pressure, electrocardiogram, or EKG) or using therapeutic blood levels as described above. In addition, general behavioral observations can be made and changes from an individual's "baseline" can be noted, including changes in irritability or other dimensions of mood, sleep (increased or decreased), changes in appetite, and extrapyramidal symptoms.

There are several rating scales that have been developed to measure medication side effects in individuals with disabilities including individuals with ASD. These scales can be comprehensive (e.g., the Matson Evaluation of the Drug Side Effects; Matson et al., 1998), medication specific (e.g., the Stimulant Drug Side Effects Scale; Barkley, McMurray, Edelbrock, & Robbins, 1990), or side effect specific like the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976) or the Dyskinesia Identification System Condensed User Scale (DISCUS; Kalachnik & Sprague, 1993). Kalachnik (1999) and Matson and Mahan (2010) provide an excellent review of commonly used rating scales and measures for individuals with ID.

Kalachnik (1999) also provides a clarification in the formal terminology used in relation to side effects that may lead to confusion during patient care. Specifically, *side effects* are the unintended effects of a medication (or other "agent") that occur at normal doses like a hand tremor in a person taking lithium. *Adverse drug reactions* (ADRs) or "adverse reactions" or "adverse effects" are more uncharacteristic or unexpected reactions to drugs. Specifically, they can vary from allergic reactions to toxic reactions and can occur due to the effect of a single medication or a drug-drug interaction. Finally, there are *adverse drug events* in which an injury occurs that is related to the medication. According to the FDA, a serious adverse event is considered anything that is fatal, life threatening, and permanently or significantly disabling; requires hospitalizations or prolongs it; causes a congenital anomaly or birth defects; or requires intervention to prevent permanent impairment (FDA, 2016). Examples include serious breathing issues requiring an emergency room intervention, a seizure, or development of a blood disorder.

5.3 Behavioral Measures

5.3.1 Rating Scales/Indirect Assessments

Rating scales are a common method for measuring treatment effects, and are used in both clinical trials and treatment settings (Matson & Neal, 2009). There is no single or "best" assessment for measuring changes in *core* symptoms of ASD, just as there are no medications currently approved to directly treat the *core* symptoms of ASD. There are, however, several interviews, rating scales, and questionnaires available to measure changes in the frequency and severity of *related* symptoms targeted in pharmacological treatment in ASD. Completed by caregivers or treatment providers working directly with the child, these measures can be helpful in estimating treatment effects.

5.3.1.1 Aberrant Behavior Checklist (ABC)

The ABC is a standardized rating scale used to measure treatment effects, including psychotropic medication, for people with ID; it is widely used in medication trials and clinical settings (Aman et al., 1985). It was originally developed for adult patients in residential setting with the intended purpose of evaluating treatments in like settings, but is now used in home, community, and residential settings. The 58-item rating scale is organized into 5 subscales: irritability, agitation, and crying (15 items); lethargy/social withdrawal (16 items); stereotypic behavior (7 items); hyperactivity/noncompliance (16 items); and inappropriate speech (4 items). All items are scored on a 4-point scale (0 = not a problem to 3 = severe problem). Individual subscale items are scored and summarized to give an overall subscale score; a total score is not calculated. The assessment is designed to be completed by a person who knows the individual well, such as a parent, teacher, case worker, or therapist within 10–15 min (Farmer & Aman, 2017). It has been extensively evaluated in the experimental literature and is considered one of the most valid and reliable rating scales for this population (Aman, 2012b; Aman, Burrow, & Wolford, 1995; Kaat, Lecavalier, & Aman, 2014; Karabekiroglu & Aman, 2008; Marshburn & Aman, 1992). It is available in 40 languages and has been used in over 325 empirical evaluations (Aman, 2012a). The ABC was used as an outcome measure in the original clinical trials of risperidone in children with autism, which contributed to the FDA approval of the drug for treatment of irritability and later approval of aripiprazole for severe behavior problems for people with ASD.

5.3.2 Nisonger Child Behavior Rating Form (NCBRF)

The NCBRF (Aman, Tassé, Rojahn, & Hammer, 1996) is an adapted version of the Child Behavior Rating Form (CBRF; Edelbrock, 1985). The purpose of adapting the CBRF was to create a rating scale that was brief (i.e., completed in fewer than 10 min), could be reliably completed by parents and teachers, valid for use among child within a broad age range of presentations, and appropriate for the assessment of a variety of symptoms including stereotypy and self-injury. It is intended for use with children aged 3–16 years old, to assess behavior during the past month, and includes items that address both the child's strengths and challenges (Hastings, Brown, Mount, & Cormack, 2001).

There are two versions of the scale: parent and teacher. Both versions contain two subsections: social competence (10 items) which is rated on a 4-point scale (0 = not true to 3 = always true) and problem behaviors (60 items across 6 subscales: conduct problem, insecure/anxious, hyperactivity, self-isolated/ritualistic, overly sensitive, self-injurious/stereotypy) which are rated for both frequency and severity on a 4-point scale (0: does not occur/not severe to 3: occurred a lot/severe problem) (Aman et al., 1996; Tasse, Aman, Hammer, & Rojhan, 1996). Psychometric elevations of the scale have shown high levels of construct validity (Lecavalier, Aman, Hammer, Stocia, & Mathews, 2004; Rojahn et al., 2010). It has been used to

determine the efficacy of risperidone (e.g., Aman, Alvarez et al., 2002; Biederman et al., 2006; Findling et al., 2004; Reyes, Croonenberghs, Augustyns, & Eerdekens, 2006; Shea et al., 2004; Snyder et al., 2002; Turgay, Binder, Snyder, & Fisman, 2002) and quetiapine (e.g., Findling et al., 2006, 2007) in children with ID.

5.3.3 Clinical Global Impressions Scale (CGI)

The CGI was initially developed for use in federally funded clinical trials to assess global functioning throughout medication treatment in patients across all psychiatric disorders (Guy, 1976). It is organized into two subscales: severity (CGI-S) and improvement (CGI-I). Severity is rated by a single item on a 7-point scale (1 = normal to 7 = extremely ill). Improvement is assessed by comparing the patient's overall condition to his/her condition 1 week prior to initiating treatment and again scored on a 7-point scale (1 = very much improved to 7 = very much worse). The assessment should be administered by a trained professional, someone who is very familiar with the condition and the individual (Busner & Targum, 2007). It is the most widely used measure of medication effects in individual with ID, but has been criticized for its lack of specificity at the individual behavior level and vague descriptions of level of severity and degree of change (Zarcone, Napolitano, & Valdovinos, 2008). Another consideration is that there is no universal system for interpreting the scores or changes in scores across time; interpretation of the meaningfulness or magnitude of change relies on clinical judgment alone (Busner & Targum, 2007).

For medication studies with individuals with ASD and ID, the CGI has been used to evaluate the effects of risperidone (e.g., Aman, Alvarez, et al., 2002; Buitelaar, van der Gaag, Cohen-Kettenis, & Melman, 2001; RUPP Autism Network, 2002; Shea et al., 2004; Snyder et al., 2002; Van Bellinghen & De Troch, 2001), aripiprazole (e.g., Marcus et al., 2009; Owen et al., 2009), and citalopram (e.g., King et al., 2009).

5.3.4 Children's Psychiatric Rating Scale (CRPS)

The CPRS was originally designed as a 63-item scale for federally funded research programs as a general, broad-ranging rating scale for the evaluation of symptoms and behaviors related to childhood psychopathology in clinical medication trials (Guy, 1976). It was not designed to be used as a diagnostic tool but rather a way to quantify the severity of presenting symptoms and is therefore useful in measuring treatment effects in therapeutic settings as well as clinical trials. There are two parts of the scale. First, the clinician rates both observed and reported behaviors. Second, the clinician rates an overall impression based on data from multiple sources including teacher reports, school records, etc. A rating from 0 to 9 is scored, based on the severity of the problems reported and observed (Robinson, 2013).

Overall and Pfefferbaum (1984) abbreviated the scale to a subset of 14 items specific to individuals with ASD (CBRF-14). The ASD-specific subscale includes a direct assessment of the patient's behaviors and symptoms during the visit or from a videotaped observation of the child and might therefore be considered more of a direct measure than an indirect rating scale. Initial evaluations of the psychometric properties of the CPRF-14 have found the scale to be valid and reliable for measuring treatment effects in individuals with ASD (Overall & Campbell, 1988). Examples of the CPRF/CPRF-14 used in the psychotropic medication literature include measurement of the effects of risperidone (Gagliano et al., 2004; Nicolson, Awad, & Sloman, 1998), clomipramine and desipramine (antidepressants; Gordon, State, & Nelson, 1993), and haloperidol (Anderson et al., 1989) with individuals with ASD.

5.3.5 Yale-Brown Obsessive Compulsive Scale (Y-BOCS)

The Y-BOCS is a well-known clinical measure used to evaluate the severity of symptoms of obsessive-compulsive disorder (OCD; Goodman et al., 1989). The scale contains two distinct

sections: Symptom Checklist and Severity Scale. The Symptom Checklist is used to evaluate 54 obsessions and compulsions for two criteria: current (i.e., occurred within a week of assessment) and past (i.e., occurred in the past but is no longer occurring). The Severity Scale contains 10 items, rated on a 5-point Likert scale, that further assess the items indicated as a current obsession or compulsion on the Symptom Checklist. As clinical judgment is incorporated into the scoring of the Y-BOCS, administration is usually provided by a trained clinician.

The Y- BOCS was revised and a second edition is available (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006). Revisions include updated items and scoring for the Severity Scale, adding consideration of avoidance behaviors to the Severity Scale items, and modified content and format of the Symptom Checklist. The Y-BOCS-II has shown to have strong internal consistency, test–retest and interrater reliability, and construct validity (Storch et al., 2010). For children aged 8–17 years old, the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Scahill et al., Scahill et al., 1997) is administered to both parent and child. This version of the measure allows for clinical judgment regarding additional items such as insight, avoidance, and overvalued sense of responsibility. Among youth with ASD, the CY-BOCS has shown good internal consistency, good-to-excellent interrater reliability, and satisfactory convergent and divergent validity (Wu et al., 2014). Versions of the Y-BOCS have been used to evaluate the effects of several medications with individuals with ASD including memantine (Hage et al., 2016), risperidone (McDougle et al., 1997), levetiracetam (Wasserman et al., 2006), citalopram (King et al., 2009), fluoxetine (Hollander et al., 2005; Hollander et al., 2012), and fluvoxamine (Buchsbaum et al., 2001; McDougle et al., 1996).

5.3.6 Direct Observation Measures

Direct observation is another method of assessment that can be particularly useful in the evaluation of the effects of psychotropic medications, for both targeted behavioral effects and those that may be unintended (Schroeder et al., 2013; Zarcone et al., 2008). Direct observations require the careful definition of the targets to be observed and the development of measurement systems to track their occurrence (Zarcone et al., 2008). Because direct observations yield quantitative data, the information that they provide reflects the actual occurrence of behavior and is inherently more objective than information that may be gleaned from sources that rely on opinion or on memory of past events, such as rating scales or other indirect assessments (Alter, Conroy, Mancil, & Haydon, 2008).

Although studies examining the effects of psychotropic medications for individuals with disabilities have relied primarily on the use of rating scales and biological measures (Matson & Neal, 2009; Schroeder et al., 2013; Unwin & Deb, 2011), research has demonstrated the value of direct observation as a primary method of data collection for determining not just changes in the occurrence of target behaviors following the introduction of a medication but also the changes that may occur in motivating operations and behavioral function (e.g., Carlson, Pokrzywinski, Uran, & Valdovinos, 2012; Valdovinos, Henninger-McMahon, Schieber, Beard, & Haas, 2016). These findings support the assertion that direct observation can be a valuable tool in both research and clinical settings.

There are a variety of techniques that can be employed to measure behavior that is observed using direct observation (Matson & Neal, 2009). Typically these data collection methods focus on gathering information on the frequency or duration of a behavior and can include methods such as event recording, duration and latency recording, time sampling, and interval recording. Although a detailed description of each of these methods is beyond the scope of this chapter, a variety of resources are available that outline how each method can be used, the associated benefits and challenges, and the ways that data collected via these methods can be evaluated for the purposes of decision-making (see Johnston, Pennypacker, & Green, 2010; Ledford, Lane, & Gast, 2018).

Regardless of the specific techniques used to measure behavior during direct observations, there are important logistical issues that must be considered, namely what specific target behaviors

to observe, when and where to observe, and how to observe (Ledford et al., 2018). This is true for both research and clinical settings.

When determining the specific target behaviors to observe and measure, it is beneficial for considerations to be made to assess both the intended effects of the medication and the potential unexpected effects (Zarcone et al., 2008). Measurement of the intended effects is necessary to evaluate whether or not the medication is working in the way it was intended; however, measurement of other behaviors can also provide valuable information that may help in the overall evaluation of the medication. Although medications for individuals with autism and IDD are typically prescribed to address specific problem behaviors (e.g., aggression, self-injury), observational data can also provide information about the effects that medications may have on a variety of related behavior (Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008). For instance, research has incorporated direct observation to examine effects of medication on on-task behavior in classroom settings (e.g., Sibley, Kuriyan, Evans, Waxmonsky, & Smith, 2014), academic skills (e.g., Ballinger, Varley, & Nolen, 1984; Benedetto-Nasho & Tannock, 1999), and prosocial behaviors, such as sportsmanship (e.g., LaRue et al., 2008). For each behavior, be it a behavior specifically targeted by the medication, or one that may be unexpectedly affected, it is important that careful definitions be created to ensure that the behaviors are both observable and measurable (see Ledford et al., 2018).

Once the target behaviors have been identified and defined, decisions must then be made regarding when and where to observe and collect data (Cooper, Heron, & Heward, 2007). The location and timing for direct observations will often be based upon the specifics of the target behavior, namely what is already known about the occurrence of the behavior and when direct observation and data collection are likely to yield information that will be useful for evaluation (Ledford et al., 2018). When direct observations are being conducted to assess the effects of medications, however, additional factors related to the specific medications themselves should also be taken into consideration. For example, the pharmacokinetics of a medication, which loosely refers to the time it takes for medications to be absorbed into the body or excreted from the body, will impact the ways in which medications may be expected to impact behavior at differing points in time (Singh, Singh, Lancioni, & Adkins, 2010). As a result, it will be important that timings of direct observations be scheduled to ensure that medications are assessed at various levels of concentration, and particularly when they have reached therapeutic, steady-state levels. This will increase the likelihood that the full effects of the medications, both intended and adverse, can be determined. Because this is information that is typically outside of the scope of training and practice for many clinicians, close collaboration with prescribers will be necessary to ensure that data collection represents the true effects of a medication.

Often the observation techniques that are selected for a particular study or clinical evaluation are specifically identified to adequately capture the target behaviors in the specific research or clinical setting; however, standard procedures, such as those employed during analogue functional analyses (FAs; Iwata, Dorsey, Slifer, Bauman, & Richman, 1994), have been shown to be beneficial for determining the impact of psychotropic medications on behavior in a manner that allows for comparison across studies (Schroeder et al., 2013). FAs involve the systematic manipulation of specific variables in the environment, allowing for the assessment of potential functional relations between those variables and the target behaviors (Iwata et al., 1994). Although FAs were not intended to be tools for the evaluation of treatment effects (Johnson et al., 2007), it has been recommended that FAs be conducted prior to medication evaluations (Danvo, Tervo, Meyers, & Symons, 2012; Thompson, Zarcone, & Symons, 2004) and any time that there is a change to the medication regimen (Valdovinos, Nelson, Kuhle, & Dierks, 2009; Valdovinos et al., 2016). Although they can be difficult to implement, due to the time and training that are required (Danvo et al., 2012), several studies have indicated that FAs can provide important information about both rates of behavior and behavioral function. When FAs are conducted

at key points in time, data can allow for comparisons and hypotheses to be made about the effects of medications and medication changes (Schroeder et al., 2013; Valdovinos et al., 2009, 2016; Zarcone et al., 2008). The inclusion of an assessment procedure that can capture information about the amount of the behavior that occurs, in addition to information about behavioral function, is particularly beneficial for the development of function-based behavioral interventions that may need to be adapted over time as changes are made to medication regimens. Although research has indicated that behavioral function tends to be fairly static over time (Kearney, 2008), additional studies have suggested that changes to medication regimens have correlated with changes in the functions of target behaviors (Valdovinos et al., 2009, 2016).

Although there are several advantages of the use of direct observation for the evaluation of psychotropic medication effects, there are also several limitations that should be noted. First, data collection that is required to document observed behavior can be complex and time intensive. Individuals responsible for data collection are often frontline staff and/or caregivers, who may have limited training related to data collection and who may also have a multitude of additional responsibilities (Madsen, Peck, & Valdovinos, 2016). This is problematic, as each of these factors may increase the likelihood that behavior analysts may have to expend a large amount of time to provide initial and ongoing training and support, yet there remains a high risk that data may still be inaccurate or incomplete (Madsen et al., 2016). Second, it can be difficult to collect data that accurately and thoroughly reflect the occurrence of the target behaviors, particularly if the target behaviors occur at a low frequency or if they are covert (Madsen et al., 2016; Zarcone et al., 2008). This is also true of behaviors for which there may be ethical issues with observation, such as private behavior (e.g., sexual behavior, hygiene-related behavior) or very dangerous behavior (e.g., setting fires, severe SIB).

There are a variety of methods for assessing the effects of psychotropic medications for individuals with ASD. Each of these methods contributes valuable information to the medication management process, yet none are without their limitations. It may be the most advantageous approach to use both indirect and direct observation methods to evaluate the true effects of a medication based on the context, target behavior, and resources available.

5.4 Collaborating with Providers

Volkmar et al. (2014) and the AACAP recommend that clinicians maintain an active role in the long-term treatment planning and support for the family and the individual. The goal of ongoing and long-term collaboration for behavioral, education, and psychopharmacological interventions is particularly important for adolescents with ASD. While there are guidelines for prescription practice, there doesn't exist clear guidelines for how parents or other providers work in an interdisciplinary way to evaluate medication effects.

Schall (2002) provided a good guide for parents as consumers to help them monitor the effects of medication on their child's behavior. She provided a series of questions or concerns that parents might ask or consider before starting a medication with their child. Many of these concerns are probably shared by educators and clinicians providing care for the child as well. These issues include asking why the medical provider recommended a particular medication, what behavior(s) it is expected to change, how long it will take before effects will be observed, what are the possible adverse side effects, and what to do if they observe these side effects.

These questions will help parents make more informed decisions regarding the efficacy of the medication, but they also allow educators, in home support staff, and other clinicians to gather critical information parents need to be informed in the decision-making process (Tsai, 2000). For example, if a medication is being given for "mood stabilization," what does that translate to in terms of observable behavior (e.g., positive or negative affect, a decrease in crying)? Or would they expect changes in the frequency of problem behavior such as aggression or SIB? Asking questions during the medication management appointment can help guide the family and those providing care

to the individual to ensure that they are looking for behavioral changes that match what the prescribing provider is targeting with the medication.

5.5 Summary

De Kuiper and Hoekstra (de Kuijper & Hoekstra, 2017) recently evaluated the reasons that physicians gave for discontinuing long-term use of antipsychotic medication. They reviewed the medical and pharmaceutical records of 3299 adults with disabilities receiving services in the Netherlands. The authors found that of the 30% of individuals prescribed antipsychotic medication, 51% of the time the physicians were willing to discontinue their prescription if the person lived in an environment that provided ongoing care and support. In other words, the individual had other treatment options that could preclude the use of medication. Physicians also cited either the ongoing presence of problem behavior or a recent increase in problem behavior as a likely reason that they would not discontinue medication. Interestingly, reasons given for not discontinuing antipsychotic medication also included the presence of ASD, previous unsuccessful attempts to discontinue medication, or lack of consent from legal guardians as reasons to discontinue the medication. While these decisions were primarily made based on information from the caregivers and/or changes in problem behavior, for some individuals, simply having a diagnosis of ASD may have biased the physicians towards keeping an individual on a medication when otherwise they might consider discontinuing it. This implies that having a diagnosis of ASD may be a risk marker for being more likely to receive a prescription for psychotropic medication. While it is clear that medications are an important form of intervention for individuals with ASD and many have been demonstrated to be effective, with the extensive use of medication comes a number of risks. We hope that this review will provide clinicians, educators, and families with resources to be informed and empowered when evaluating the effects of medication so that their effects can be objectively evaluated.

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