17 How to Make Effective Evaluation of Psychotropic Drug Effects in People with Developmental Disabilities and Self-Injurious Behavior

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Introduction

The purpose of this chapter is to give clinicians, especially behavior analysts, guidelines for evaluating the literature and making effective clinical decisions about the use of psychotropic medication for treatment of people with developmental disabilities (DD) who also have serious self-injurious behavior (SIB). We review only the literature relevant to the topic at hand. There are several conflicting reviews of the broader literature on psychotropic drugs and intellectual disabilities, from different countries, that are of varying quality and exhaustiveness. Different countries may not have the same practice guidelines for their use. We will restrict our discussion mostly to use in the USA, where the prevalence of behavioral intervention is common in the treatment of SIB and where most states already have guidelines for behavioral and pharmacological intervention in DD and a history of laws governing their use (see Valdovinos, Schroeder, & Kim, 2003 for review). Much of our discussion may also be applicable to other settings in other countries as well.

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Significance and Background

SIB refers to acts directed toward one's self that may result in tissue damage (see Rojahn, Schroeder, & Hoch, 2008; Schroeder, Oster-Granite, & Thompson, 2002; Schroeder, Loupe, & Tessel, 2008 for comprehensive reviews of both the human and the animal literature). It occurs most frequently among persons who have severe or profound intellectual developmental disabilities (IDD) and/or autism. It is a cardinal symptom of over 15 genetically linked syndromes (e.g., Lesch-Nyhan Syndrome) which involves a genetic disorder of purine metabolism (Lesch & Nyhan, 1964). Prevalence estimates of SIB among people with IDD range widely from 2 to 90 %, depending on a variety of variables and the population sampled, but they average from 10 to 25 % (Rojahn & Esbensen, 2002). Thus, people with severe or profound DD, who live in residential facilities and who have serious often life-threatening SIB in the USA, number at least 35,000. The total prevalence, including milder forms of SIB among higher functioning people, is unknown, but it is likely much higher (over 600,000+ in the USA).

SIB is a devastating chronic condition for which there is no known cure. A Consensus Development Conference by the National

D.D. Reed et al. (eds.), *Handbook of Crisis Intervention and Developmental Disabilities*, Issues in Clinical Child Psychology, DOI 10.1007/978-1-4614-6531-7_17,

Institute of Child Health and Human Development (National Institute of Health, 1991) on destructive behavior estimated that the annual cost of services to people with DD who injure themselves or harm others or damage property in the USA exceeds $3.5 billion dollars per year. Thus, destructive behavior is a significant problem, often leading to life-threatening crises among families and other caregivers. Thus far, few preventative efforts have been made. There is good agreement on the behavioral and environmental risk factors related to its occurrence, but not on its genetic and neurobiological bases.

There have been at least ten different hypotheses as to the etiology of SIB over the past 30 years (Rojahn et al., 2008). About half of them are based upon the premise that much of SIB is learned, since behavioral intervention procedures can change it in many cases. Only about 10 % of studies in this area, however, have experimented with generalization and maintenance of their interventions (Kahng, Iwata, & Lewin, 2002).

Unfortunately, most of these behavioral changes achieved do not generalize well and are not maintained in the long term without surveillance and continued intervention. Early studies (Schroeder et al., 1982; Schroeder, Schroeder, Smith, & Dalldorf, 1978), in which we followed up 208 individuals with SIB after behavioral and/or psychopharmacological interventions, showed that while approximately 20 % remitted spontaneously without treatment, 94 % improved while on behavioral and/or psychopharmacological programs, but 2 years after the program ended, all of the chronic severe cases (24) had relapsed. An even poorer outcome was described in a recent 20-year follow-up of a large total population study of SIB in the United Kingdom (UK) by Taylor, Oliver, and Murphy (2011). They found that 84 % of their cases continued their SIB topography and severity. Although these individuals had moved from institutions into the community, they were receiving even more anticonvulsant and psychotropic medications and were accessing fewer daily activities than previously. The authors advocated a stronger emphasis on early identification and intervention for SIB, as we also have (Mayo et al., 2012; Schroeder & Courtemanche, 2012).

Psychopharmacological interventions for SIB, especially those guided by neurobiological animal and human research on modulators of dopamine, serotonin, and opioid peptide hormones, have shown some success in managing subsets of the SIB population who have disorders in these neurotransmitter systems, but there remains a large number of individuals for whom results are mixed or negative. These treatment failures have led researchers to take a closer and more experimental look at the gene-brain-behavior (GBB) antecedents of SIB, which affect the probability of development and occurrence of SIB in all of its forms and functions (see Chap. 12 of this volume).

A 1999 NIHCD conference on SIB spurred considerable research in the past 10 years on the multiple causes and effects of this likely polygenic disorder. SIB is likely not a single disorder with one primary deficit. It is multiply caused and multiply affected. It is manifested in at least 38 different topographies (Rojahn, 1994) at selected locations on the surface of the body, although the most frequent ones are headbanging with a body part, headbanging with objects, self-biting, self-scratching, self-pinching, and hairpulling. It overlaps heavily, although not completely, with the occurrence of aggression and stereotyped behavior (Rojahn et al., 2008). Three biobehavioral animal and human models reflect GBB risk factors for SIB: (1) disruption of the endorphin system and HPA axis (Sandman, Hetrick, Taylor, & Chicz-Demet, 1997; Sandman, Touchette, Marion, & Chicz-Demet, 2008), (2) elevated brain serotonin and its effects on the HPA axis (Chen et al., 2010; Tiefenbacher, Novak, Lutz, & Meyer, 2005), and (3) dopamine depletion and related elevation of serotonin in the basal ganglia (Lewis & Kim, 2009). This chapter will focus on these three models in evaluating psychotropic drug effects because they have the most SIB-related genetic and neurobiological research published on them to date. We recognize that many of these SIB models are interrelated (Schroeder et al., 2008).

Common Methodological Problems

Designing and carrying out a credible clinical trial of psychotropic and behavioral intervention is a complex matter requiring consideration of many issues. It is very difficult to address them all well in a clinical trial. We will divide them into theoretical issues, design and analysis issues, common design problems in DD populations, common pharmacological issues, common side effects issues, common behavioral issues, consumer satisfaction issues, and political and funding issues.

Theoretical Issues

One's theoretical approach to the use of psychotropic drugs is likely to affect the choice of drug, the method of evaluation, the measures to be used, and the conclusions as to its effects. To many behaviorists, "drug" is a word with negative connotations for ineffective treatment, while to many psychiatrists and biomedical professionals, it is a major treatment for severe behavior disorders in DD, like SIB. Psychiatrists are trained to prescribe medications using DSM IV-TR diagnoses. A national survey by Rush and Frances (2000) revealed that most physicians are not trained to, nor do they readily use such DSM diagnoses for people with DD. Most of them infer some diagnosis from psychopathological symptoms apparently similar to those in the non-DD population.

Most physicians and psychologists in this survey by Rush and Frances (2000) responded that they only used drugs after behavioral programs had failed to be effective. This practice, however, does not appear to be the case everywhere, for example, in the UK (Unwin & Deb, 2008). In the USA, one author (SRS) has even recently done reviews for the Department of Justice, where the consulting psychiatrist came to the facility monthly to review cases and to adjust doses without even seeing the clients. This practice is clearly unethical and illegal.

There are now several psychometric instruments validated for people with DD which take a dimensional approach to psychopathology, but these instruments do not correlate well with DSM categories (see Chap. 8 of this volume). While several of these instruments are sensitive to drug effects, the bottom line is that severe behavior problems like SIB, aggression, and stereotypy of persons with DD are not well studied or placed into context in relation to current DSM diagnoses. Unfortunately, aggression and SIB have been the main reasons for their use. Very few drug studies have been aimed also at changes in symptoms of schizophrenia or depression among people with DD. Usually people with DD have been excluded from such studies.

Most psychiatrists who specialize in the population with DD tend to use the rationale underlying the genetic and neural substrates of the symptoms they are targeting with a certain medication. Many other physicians, who may have little training in DD or psychopharmacology, however, still use the trial-and-error method. Behaviorists also should inform themselves about the basic neuropsychopharmacology underlying behavior problems such as SIB so as to be able to contribute to the interdisciplinary team when making decisions about drugs (see Chap. 12). We have listed some basic papers and textbooks, where appropriate, throughout this chapter that may be helpful to them.

Although the rate of use of psychotropic drugs has decreased over the years from 1970 to 2000, it remains substantial (Valdovinos et al., 2003), and it is likely to continue. A recent survey from a national registry of over 5,181 children and adolescents with autism (Rosenberg et al. (2010) showed that 35 % of these children and adolescents received at least one psychotropic medication. We need to work as an interdisciplinary team with our colleagues in other disciplines (Zarcone, Napolitano, & Valdovinos, 2008) to keep the use of drugs to the minimum necessary.

Another theoretical issue is the research methodology for efficacy of a drug. According to McCannell and Duff (1995), the clinical development and evaluation of a drug by the Food and

Drug Administration (FDA) usually involves four phases: *Phase I,* i.e., testing of the basic pharmacokinetics, pharmacodynamics, and toxicology of the drug in a small number of normal male volunteers in a controlled setting, like a hospital clinical drug metabolism research unit; *Phase II*, i.e., testing larger numbers of patient volunteers selected for the disease under investigation in a hospital, using an open design; and *Phase III,* i.e., testing a broader selection of outpatients in a double-blind, placebo-controlled trial. Randomized assignment to groups or treatments is highly desired in Phase III trials because that is the only way to assure freedom from bias due to placebo effects. Such randomized controlled trials (RCTs) are considered the gold standard by many researchers and clinicians (Higgins & Green, 2006), but there are several pros and cons to such trials, as we will discuss below; *Phase IV* trials are testing with open studies for surveillance in large broader populations with fewer and less restrictive inclusion or exclusion criteria than Phase III trials. Phase IV trials also test the breadth of applicability and the adverse reactions to drugs after long-term use. These are the types of trials most commonly used for clinical decision making discussed in this chapter. Each of the above four phases yields complementary valuable information in the evaluation of a drug. All are necessary, as has been recognized in a widely cited proposed framework for categorizing five levels of evidence of efficacy of an intervention by Nathan and Gorman (2003). Direct drug comparisons are also warranted in large clinical trials to inform the evidence base regarding efficacy and side effects (Tamminga, 2011).

Design and Analysis Issues

We recently published a detailed position paper on designs and analyses of psychotropic and behavioral interventions in DD (Courtemanche, Schroeder, & Sheldon, 2011), which can be used as a companion to this chapter. We will summarize the main points relevant to the evaluation of Phase IV open and single-blind clinical drug and behavioral trials. It is unlikely that most clinicians would attempt a Phase III randomized double-blind placebo-controlled trial in their practice. These are very time-consuming, labor-intensive, and expensive. Nevertheless, clinicians' awareness of the research in this area and of the accepted criteria for a drug's efficacy is important in matching appropriate drugs in the right dose range for the right client, given that there is a wide variation of behavior phenotypes in a relatively small percentage of the DD population engaging in severe SIB.

The modern era of psychopharmacology for people with DD dates back to a classic review by Sprague and Werry (1971), although its history goes back to the early 1800s. Sprague and Werry (1971) recommended six methodological criteria for drug studies: (1) double-blind, (2) placebo control, (3) random assignment to treatment groups or to the order of treatments, (4) multiple standardized doses, (5) standardized evaluations, and (6) appropriate statistical analyses. These remain the major criteria today for group studies.

Interestingly, Sprague and Werry (1971) also noted the advent of behavior modification techniques, and they recommended their potential utility in evaluating drug and behavior effects. Ironically, their criteria excluded most single-subject behavioral research designs, as we show below. It is possible to test a large group of cases using a single-subject design and then to aggregate them into a group for statistical analysis (e.g., Hellings et al., 2006; Sandman et al., 1993; Thompson, Hackenberg, Cerutti, Baker, & Axtell, 1994), but these designs are the exception more than the rule. They are very expensive, labor-intensive, and may often be limited to smaller numbers of study participants than larger parallel-dose group-designed studies.

It is useful to independently compare the Sprague and Werry (1971) criteria for psychopharmacological trials and behavioral intervention trials, as we do below:

1. *Double-blind conditions* in drug trials require that the caregivers, participants, and prescribing and evaluating team be unaware of the drug condition until after the trial is over. In most behavior intervention studies, this criterion is

nearly impossible. Single-blind conditions may be achieved if videos are taken and coded by blinded coders not informed of the purpose and the treatment conditions in the study.

2. *Placebo conditions* in drug studies are recommended when possible. Because of ethical concerns, such procedures must be reviewed and approved regularly by a human rights committee. Some clinical facilities ban placebos as a matter of policy. In medical centers and outpatient clinics, placebos are more likely to be approved, but with the restriction that treatment not be withheld from a person who needs it. This situation can often be avoided by using wait-list groups in a crossover design in which all participants eventually receive treatment or if participants receive the "next best" treatment (O'Leary & Borkovec, 1978). These restrictions, however, often result in excluding crisis cases from a trial, the very people who need treatment the most. In behavioral intervention studies, a similar dilemma exists. Scahill et al. (2009) have suggested that placebo conditions can be avoided if the treatment has been proven effective previously in similar cases.
3. *Random assignment* in group-designed studies can rarely be done in either single-subject drug or behavior intervention trials used in a clinical setting, especially with crisis cases. Sometimes, order of treatments can be randomized or counterbalanced. In clinical drug trials, a baseline washout condition, then a placebo condition, if circumstances permit, and then a careful titration are usually done. The general rule with drug dosing is "Start low and go slow." In the case of clinical tapering off a drug or changing to another drug, it usually is done by add-on of the new drug in small steps, then cautious tapering, clinically, of the other drug. Abrupt changes are likely to increase side effects or serious relapse in behavior problems. Such a procedure usually precludes double-blind conditions. In most cases of behavioral interventions, double-blind conditions are inappropriate since success of the procedure usually depends on teaching clients and caregivers to change their behavior. Single-blind conditions for coding of behavior observations are sometimes possible, however, and are recommended.
4. *Multiple standardized doses* are useful for Phase III clinical trials using group designs to discover the average effective dose range, but they are rarely used in Phase IV open trials. Even in Phase III trials, a preliminary titration under open conditions often is done to find an individual's optimal dose range for the problem, and then this dose is used in a subsequent double-blind trial. In most behavioral intervention studies, different doses of the behavioral intervention are rarely used (Schroeder, Lewis & Lipton, 1983). We are only familiar with one group study comparing different doses of methylphenidate in combination with different doses of a behavioral intervention for typically developing children with ADHD (Fabiano, Aman, McCracken, McDougle & Vitiello, 2007).
   While desirable, it is unlikely that these dose-ranging, drug-behavior interaction studies will be done with crisis cases in DD. Napolitano et al. (1995) were able to find nine drug-behavior action studies using single-subject and group designs, five of which used multiple standardized drug doses, but none of which used multiple doses of behavioral intervention. In fact, in most of these drug studies, the therapist held behavioral interventions constant during the drug trial to avoid confounding their effects. A recent study by Aman et al. (2009) appears to be a true drug-behavior interaction study in children with autism using risperidone and a parent-training program. This appears to be one of the few published controlled studies of this type in a population with DD since the study by Campbell et al. (1978), which studied the effects of haloperidol alone and in combination with a Lovaas-type intervention program for children with autism.
5. *Standardized evaluations* with drug-sensitive psychometric instruments, validated with the DD population, are now available for use since the advent of the Aberrant Behavior Checklist (ABC) (Aman, Singh, Stewart, & Field, 1985). Used in over 300 studies, this 58-item rating scale has proven validity for assessment of drug

effects. Unfortunately, only 3 of the 58 items address the problem of SIB. The Behavior Problem Inventory (BPI-01) (Rojahn, Matson, Lott, Esbensen, & Smalls, 2001) is a 49-item scale that rates both the frequency and severity of SIB, aggression, and stereotypy. It has also proven valid in over 30 studies. Rojahn et al. (2012) have recently published norms across the entire age range based on a large sample from five countries. They also have developed a short form (BPI-S) with 30 items, which is briefer but well validated against the BPI-01. It should prove very useful for clinical purposes in assessing SIB and its overlap with aggression and stereotyped behavior. Other instruments aimed specifically at assessing SIB include the Self-Injurious Behavior Trauma Scale (SIT) (Iwata, Pace, Kissel, Nau, & Farber, 1990), which may also be useful for clinical purposes of rating intensity of SIB crisis cases. Behavioral studies rely on direct observations, clear operational definitions, and quantitative measures of frequency, duration, and their derivative measures. Usually, these are customized for the individual being treated, although some standard procedures have proven very useful. Analogue Functional Analysis (FA) (Iwata, Dorsey, Slifer, Bauman, & Richman, 1982) is such a procedure. A recent derivative of FA adapted for clinical drug trials by Johnson et al. (2007) is the Standard Observation Analogue Procedure (SOAP). These methods are useful in making comparisons across studies more possible. Some human rights committees, however, object to exposing an individual with SIB to further self-injury during these FA assessments. Safeguards, such as rules for halting the assessment due to potential tissues damage, should be instated. Our experience is that parents usually do not object to such procedures once the purpose and importance are explained. It is more likely that service providers will object in order to protect themselves against liability. In such a case, informant questionnaires, such as Questions About Behavior Function (QABF) (Vollmer & Matson, 1995), may be helpful. Consider, however, that questionnaires often do not provide the same conclusions as traditional FA.

6. *Appropriate statistical analyses* are relevant to larger group-designed studies and, in some cases, to smaller individual clinical trials. Single-subject statistics usually require copious trials per treatment (100+) and are therefore of limited use in crisis cases. Single-subject designs usually eschew statistics. The rationale for this practice has been explained in many papers (e.g., Birnbrauer, Peterson, & Solnick, 1974) and textbooks, (e.g., Barlow, Nock, & Hersen, 2008; Johnston & Pennypacker, 2009; Sidman, 1960). Single-subject trials receive their strength and internal validity from repeated measurements of each treatment, and they get their external validity (generalizability) from repeated replication. FA analysis is a good example; it has yielded valid information in over 450 studies (Kahng et al., 2002). Another example is that in drug studies for treating SIB, naltrexone has proven effective for subsets of SIB cases in 27 of 48 studies, most of which were single-subject but controlled, clinical trials (Symons, Thompson, & Rodriguez, 2004). This result lends to naltrexone's external validity as a potential candidate for use with SIB, although it is currently rarely used by psychiatrists in the USA.

In summary, Phase III clinical trials are an important step in demonstrating efficacy, but they are not the only step. Some have advocated only Phase III studies as evidence of efficacy (Higgins & Green, 2006). The psychopharmacology literature in DD contains mostly open clinical trials. For instance, Cheng-Shannon, McGough, Pataki, and McCracken (2004) reviewed 176 studies of atypical antipsychotics from 1974 to 2003 for all indications among children and adolescents with and without DD, aged 5–28 years, and found 15 double-blind controlled trials, 58 open-label trials, 18 retrospective chart reviews, and 85 case-series reports. While open studies are useful for reporting new drugs whose efficacy may justify more study with in-depth intensive Phase III trials, such as for SIB, where there are ethical concerns related to use of a placebo, or for reporting unusual or idiosyncratic adverse effects, or

drug-drug interactions, they tend to overestimate the effectiveness of a drug. At the same time, Phase III trials are not always useful in clinical decision making in a given case of SIB because they use narrow inclusion and exclusion criteria, which eliminate outlier cases (e.g., participants with multiple diagnoses, seizures, or mild cases). Doing so might increase the likelihood of demonstrating a larger effect, but such a sample also may actually fail to represent a large proportion of the population of interest.

Tunis, Stryer, and Clancy (2003) have argued for Practical Clinical Trials (PCTs), which would include a broader selection of participants more representative of the population under study and conducted in manner more closely aligned with clinical practice, as in the case of Phase IV trials. Few of these studies have been funded by the NIH or promoted by the FDA as yet for individuals with DD. Only two psychotropic drugs, risperidone and aripiprazole, have even been approved by the FDA for use in the DD population. This approval is restricted to aggression in children aged 6 years or older with autism. There is little evidence, however, that SIB, aggression, or stereotyped behavior in autism is any different from other forms of DD. Most physicians, working with the DD population, prescribe psychotropic medications "off-label." This is deemed a legitimate use of such drugs if there is a clear rationale for using them in a given case (Mayhew, 2005; Unwin & Deb, 2010; Ventola, 2009), and it applies to all branches of medicine, including neonatology.

Common Validity Problems in Clinical Trials with DD Populations

A book on design and statistical analysis of clinical drug trials, with both group and single-subject designs, which we have found very helpful, is by Chassan (1976), who was employed in the Intramural Program at NIMH at the time. He identified several threats to the validity of clinical drug trials that we have also found to be the case in the DD population over the last 45 years. Most of these are appropriate for research studies and not to clinical trials per se, but they help to explain potential biases in some research studies.

Lack of adequate sample size is often the bane of clinical group drug studies in DD. In order to have sufficient statistical power to detect a reliably significant effect, a sufficient number of participants of sufficient homogeneity, using instruments with sufficient sensitivity and specificity, are all required. Often it is difficult to recruit enough participants within a single clinic or facility. In such a case, multisite studies have been employed, involving many sites such as the studies by the Research Units for Pediatric Psychopharmacology (RUPP). As one might suspect, this strategy involves additional administrative, logistic, and statistical problems, in that all sites need to conduct the trials using the same inclusion/exclusion criteria in the same way, the same procedures, the same training on the same instruments, and the same reliability checks for procedural drift. If these criteria are not followed, the study may fail to find an effect of the drug. This was one of several criticisms of a recent widely cited large negative multisite study of risperidone and haloperidol among adults with DD in the UK (Tyrer et al., 2008). Trying to prove the null hypothesis from this study was problematic (Scahill, Aman, McCracken, McDougle & Vitiello, 2008; Scahill et al., 2009).

Single-subject trials do not have sample-size problems in interpreting their results, because they rely mostly on large visually apparent effects. Unfortunately, large unambiguous visually apparent effects are not always the result, and larger multimodal assessments from a variety of sources (e.g., parents, teachers, caregivers) are required to make a confident clinical decision about the drug's clinically significant effect. Interdisciplinary teams are central to this process.

Extreme heterogeneity of participants is common in this population of persons with DD and SIB, aggression, and stereotypy. Individuals with SIB often have genetic behavioral phenotypes, neurological impairments, physical handicaps, and behavioral difficulties, as well as impaired cognition, communication, and social skills that may affect the statistical and clinical outcome of a study. In ordinary clinical trials, however, this is the variability we must live with. It challenges us to be aware of these sources of variability and to

strive for more robust drug and behavioral treatments.

Participant attrition is another serious problem. Because of their many difficulties, individuals with SIB are often ill and unable to participate in programmed activities. In larger group drug studies, the dropout rate may be high.

Idiosyncratic all-or-none response is another problem for drug studies. Often such variability in response may be due to the way a person metabolizes a drug. If the route of administration is oral, the drug is absorbed by the gut and processed first by the liver. A large proportion of the drug may simply be excreted in the urine (i.e., first-pass effect) until it reaches a sufficient level to enter the blood stream. At this point, the next few elevations in dose may result in an unexpectedly large psychotropic effect or negative side effects like sedation or lethargy. The knowledge of the pharmacokinetics of the drug is very important in titrating it appropriately.

Lack of specificity of drug effects is a common complaint of critics, especially behavioral critics, of drug trials. Some of this criticism apparently comes from a lack of awareness of how psychotropic drugs in general work in the body. Their action is only relatively selective at best. They usually have multiple effects on interconnected neural target sites. It is often believed, for instance, that serotonin reuptake inhibitors should be restricted to treating affective disorders, yet they often also affect aggressive behaviors among certain cases. Antipsychotic drugs allegedly should be restricted to treating schizophrenia, yet they also often affect aggression, stereotyped behavior, and/or SIB. All of these drugs are prescribed for people with mental illness, based upon their symptomatology. These same symptoms overlap considerably with the behavioral symptoms observed in the DD population, although their expression may differ somewhat. By the same token, there is considerable overlap in symptomatology of affective disorders and schizophrenia among people with mental illness (Van Praag et al., 1990). Thus, the sensitivity and specificity of their symptomatology are also limited. By contrast, most behavioral descriptions of aberrant behavior are highly specific, often to a certain setting, stimulus, and consequence. Generalization and maintenance of behavioral treatments in other settings is often the main problem.

These specificity and sensitivity issues require some give-and-take by the interdisciplinary team. Often the psychiatrist, needing to make a decision about raising or lowering the dose of a drug, will look at all of the behaviorist's graphs of observations of SIB and ask, "Well, is he or she improving or not?" By the same token, the behaviorist will say, "Why are you relying on the Clinical Global Impressions Scale (Guy, 1976) as a valid measure, since it is only your clinical impression?" Meanwhile, the psychometrically oriented clinician will say, "You need to use my rating scale of the parents,' teachers,' and/or caregivers' impressions." Each of these is a different sample estimate of the behavior in question, and each is valuable. None alone is usually sufficient to make an effective consensus clinical decision about the efficacy of a drug treatment for a particular individual.

Ethics of placebo groups or wait lists is another issue that needs to be addressed, especially for crisis cases, such as severe SIB. As mentioned before, these people are often excluded from Phase III clinical trials and treated individually in open Phase IV trials. The use of wait-list and placebo groups with such cases is problematic. Nevertheless, the need to neutralize false expectations about an intervention is still important. Participants and their caregivers are often stressed and desperate for a treatment that will work (Lloyd & Hastings, 2008). Drug studies in this population usually have shown a large placebo effect. Therefore, baseline conditions, comparison of dose effects, and brief treatment reversals under controlled conditions are important whenever possible. Also, single-blinding of observers who code the behaviors may be helpful.

Difficulty in maintaining blinded conditions is another problem in drug and in behavioral studies. If either treatment has a large, immediate effect or serious side effects, it will be apparent (Barlow et al., 2008). If there is little effect, the longer the placebo condition is in effect, the more it will become clear that the treatment is

either working or not working. This outcome has been found several times in recent drug studies in the DD population (McAdam, Zarcone, Hellings, Napolitano, & Schroeder, 2002; Rickels, Lipman, Fisher, Park, & Uhlenhuth, 1970; Vitiello et al., 2005).

Common Pharmacological Issues

Dose Response. Achieving the optimal dose of a medication is one the most important factors in a successful psychopharmacological trial. All psychotropic drugs have side effects that usually increase with higher doses. A typical dose-ranging procedure is to titrate the dosage up slowly until a therapeutic window is found. This dose needs to be checked periodically, to see whether it is still effective. For most psychotropic drugs for SIB, it takes 2–6 weeks to reach steady state. The exception is stimulant drugs for hyperactivity, which are rarely used for individuals with SIB. During the acute phase of a clinical trial (e.g., the first 6 months), this checking should occur monthly or quarterly. After the patient has adjusted to the dose, psychiatrist visits should occur at least every 6 months. If side effects become unacceptable, the drug should be titrated down in small doses as appropriate. No client should be on a psychotropic drug longer than necessary. Even if the drug remains effective, many states have guidelines that call for annual drug holidays when the drug is not used for a short period of time. These dose-ranging trials are important because some individuals respond and some do not. Thus far, it is very difficult to predict who will be a responder. Also, a small number of clients may adversely respond to a medication, e.g., behavioral worsening. In this case, the drug trial is stopped immediately and the adverse response is recorded. In some cases, the drug may be retried later, perhaps in combination with another drug, and it might demonstrate efficacy. Most of these dosing procedures are rather straight forward, but surveys have shown that they often are not followed in practice (Unwin & Deb, 2008). Greater understanding of pharmacodynamics, how drug metabolizing genes affect efficacy and side effects, shows promise for a more evidence-based selection of a drug and dosing in an individual patient.

In our experience, the optimal dosage of many psychotropic drugs is lower for people with DD than in the non-DD population. There is no consensus guideline for optimal dose ranges, however, in the DD population. For instance, a recently proposed guideline for the use of atypical antipsychotics in DD (De Leon, Greenlee, Sabaawi, & Singh, 2009) recommends upper dose limits twice as high as we have found effective. In some cases (e.g., risperidone), it is even much higher than recommended doses by the pharmaceutical company marketing the drug.

The most comprehensive resource guide for psychopharmacology in DD available has been the *International Consensus Handbook on Psychotropic Medications and Developmental Disabilities* (Reiss & Aman, 1998), which covers each class of medication in terms of main effects, side effects, drug-drug interactions, and clinical indications. Consensus involved 113 expert members from several countries. Unfortunately, it is over 15 years out of date, and many of the more controlled studies have been published since then. Nevertheless, it still contains much useful information. It would be helpful to have an updated edition of this handbook or a comparable up-to-date authoritative information source.

Behavioral interventions should not be changed while a drug change has occurred, to avoid confounding the treatment effect. The general rule in clinical practice is to change only one treatment, drug or behavioral, at a time. This means that most dose titrations may to take several weeks, depending on the pharmacokinetics and pharmacodynamics of a given drug. Caregivers should be informed of this issue. However, in extremely serious and health-threatening cases, it may be clinically necessary and justified to make drug and behavioral changes simultaneously.

Drug-Drug Interactions. The best single resource to find drug-drug interactions for different drugs used for SIB is still Reiss and Aman (1998). Drug-drug interactions should be avoided and

monitored carefully when more than one drug at a time is used.

Many individuals with SIB have multiple disorders. Only a minority of individuals requiring psychotropic medication treatment respond adequately to one drug, especially if their behavioral problems have been severe enough to result in placement in a residential treatment or in a state hospital. This applies also to the population without developmental disabilities. In addition, a drug combination may achieve better outcomes with fewer side effects. Individuals require drug combinations selected based on their presentation and DSM IV-TR comorbid diagnosis if one can be honed in on. For example, individuals with severe hyperactivity, impulsivity, aggression, and SIB may require low doses of risperidone together with low-dose atomoxetine. Likewise, individuals presenting with bipolar-like illness, aggression, and SIB may benefit from a combination of low-dose antipsychotic, divalproex and gabapentin (Hellings, 1999).

Common drug interactions in individuals with seizures and DD result from induction of liver enzymes to more rapidly metabolize drugs, as occurs with phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and zonisamide. Another class of drugs commonly producing inhibition of cytochrome enzymes that metabolize many psychotropics is the SSRIs. Paroxetine, fluoxetine, and sertraline inhibit cytochrome P4502D6, which metabolizes many psychoactive medications as well as non-psychotropics. Paroxetine, for example, can increase the effective dose of an antipsychotic to more than tenfold of that prescribed. Drugs used in combination, if metabolized by the same CYP enzymes, will increase the effective doses of each other. For example, divalproex increases the effective dose of the tricyclic antidepressant amitriptyline by 30 %. Lithium toxicity may result if other drugs acting on the kidney are added for hypertension, including ACE inhibitors and diuretics, such as hydrochlorothiazide and furosemide.

Drugs Frequently Used for SIB and Their Side Effects. Every psychotropic drug may have positive and negative side effects, as do most behavior interventions (Williams & Saunders, 1997). In the literature on drugs for SIB in the population with DD, this is also true, although the most attention has been given to the negative side effects of drugs (Matson, 1998; Matson & Neal, 2009). Few studies have reported positive side effects. For example, some studies have reported increased attention and learning (Sandman et al., 1993), cooperation (Symons et al., 2004), and improved sleep (Thompson et al., 1994) in response to naltrexone and improved sleep and no decline in attention and cognition in response to a low dose of risperidone (Aman et al., 2008; Yoo et al., 2003). Williams and Saunders (1997) have provided a thorough critical review of the many tests and procedures, both cognitive and behavioral, which have been used. It is a good resource guide for the behavior analyst on these issues.

We have provided a detailed review of the psychopharmacological research in Chap. 4 of our recent book on SIB (Rojahn et al., 2008), which is a comprehensive review of the epidemiology; assessment; treatment, both behavioral and pharmacological; and the prevention of SIB, which we have not repeated but only updated in Table 17.1. We report optimum daily doses for adults found in the best-controlled drug studies. Most of these drugs are prescribed for a variety of neuropsychiatric conditions or for aggression, in which SIB may be a secondary target. While there is considerable overlap among these symptoms and SIB (Rojahn et al.), there may also be very different neural substrates for them (Schroeder et al., 2008). Thus, they should not be treated as if based upon the same underlying rationales. Only two drugs have been studied extensively, in which the rationale for SIB was the primary target (i.e., naltrexone and clozapine).

Table 17.1 also reports only side effects that were found in 3 % or more of cases in the drug studies reviewed by Rojahn et al. (2008). There is a much longer list of less common side effects that can usually be averted by lowering the drug dose. Some are very rare side effects (e.g., agranulocytosis), which may occur in less than 1 % of people receiving clozapine or carbamazepine, but which can be fatal if the white cell count is not monitored frequently with blood tests. In such cases, the drug is lowered or stopped if the white cell count continues to drop.

Table 17.1 Optimum effective adult daily dose ranges and adverse side effects of psychotropic medications used most for people with SIB and DD

Drug class	Name		Daily	Side
	Generic	Brand	Dose (mg)	Effects
Atypical anti-psychotics	Clozapine	Clozaril	200–300	1,2,3,4,11
	Risperidone	Risperdal	0.5–4	2,3,4,6,8,11
	Olanzapine	Zyprexa	6–16	2,3,
	Quetiapine	Seroquel	75–600	1,2,3
	Aripiprazole	Abilify	10–15	2,3,12 13
Serotonin uptake inhibitors	Clomipramine	Anafranil	100–250	1,2,3,7,10,14
Selective serotonin	Fluoxetine	Prozac	20–80	10,12,13,14,15
Reuptake inhibitors	Sertraline	Zoloft	50–200	10,12,13,14,15
	Paroxetine	Paxil	20–50	1,2,10,12,13,14,15
	Fluvoxamine	Luvox	50–300	2,10,12,13,14,15
Mood stabilizers	Valproic Acid	Divalproex (DVP)	750–3,000	2,3,9,16
		Depakote (tablet)	Same	
		Depakene (liquid)	Same	
	Carbamazepine	Tegretol	200–1,200	3,9,14
	Gabapentin	Neurontin	900–3,600	3,9,12,14,17
	Lamotrigine	Lamictal	100–500	3.9.14
	Topiramate	Topamax	50–400	3,9,12,14,17
	Tiagabine	Gabitril	12–56	3,9,14,17
	Lithium carbonate	Eskalith	600–1,800	1,2,3,11,13,16,17
	Lithium citrate	Cibalith-S	Same	
Narcotic analgesics	Naltrexone	Naltrexone	50–200	10,11,13,14,15
	Naloxone			
Atypical anxiolytics	Buspirone	Buspar	200–450	12,14,15
Beta-adrenergic blocker	Propanolol	Inderal	80–120	1,3,15,17

1-cardiovascular, 2-weight gain, 3-fatigue/sedation, 4-EPS/akathisia, 5-dystonia, 6-tardive dyskinesia, 7-seizures, 8-hyperprolactinemia, 9-elevated live enzymes, 10-bowel control, 11-enuresis, 12-nausea, 13-headache, 14-agitation, 15-sleep disturbance, 16-tremor, 17-impaired cognition. Sources: Reiss and Aman (1998), Cheng-Shannon et al. (2004), and Hellings (1999)

Drug history is important because behavioral interventions and clinical drug trials with SIB cases often turn out negative and sometimes worsen the behavior. There may be adverse drug reactions (ADRs) or drug-drug interactions that should not be repeated. It is important to have a detailed history of these trials so as not to put SIB clients through the same negative trials. Our experience has been that this circumstance is most likely to occur when there is staff turnover or the physician prescribing the drug changes. Burnout rate of service personnel providing services to SIB cases is high (Noone & Hastings, 2011) because the work is so stressful (Hastings, 2002). *Drug metabolism* is also a key factor in prescribing the dosage and the drug regimen (e.g., times of day, rules for drug monitoring blood levels, washout periods when changing to another drug, avoiding drug-drug interactions). For instance, the peak pharmacokinetic effect for a stimulant, like methylphenidate, may be 15–90 min after administration, and it may clear the system within 4 h after withdrawal, while the pharmacokinetic curves of an antipsychotic may be very different (it may take 2–6 weeks for the peak effective dose to reach steady state). The clearance of some antipsychotics may be on the order of weeks, with small doses remaining in the blood for up to a year or more (Gualtieri, Schroeder, Hicks, & Quade, 1986).

Pharmacodynamic effects, like drug tolerance, may result in loss of therapeutic effects and in the raising of the dose to achieve them again. This is a slippery slope that often is responsible for the overdoses one sees in pharmacy records of some

facilities. Thus, drug monitoring for risk of extrapyramidal movement disorders after chronic antipsychotics should continue much longer than for other drugs.

Drug monitoring needs to be done for all psychotropic drugs as well as annual reviews for drug holidays. Many states have such guidelines in place. Valdovinos et al. (2003) have reviewed these state guidelines and various drug- and side effects-monitoring systems available and their relative utility. De Leon et al. (2009) have recently published a useful set of practical guidelines for administration and monitoring of atypical antipsychotics, the most frequently used psychotropic medication for people with DD and aggression and SIB. Careful drug monitoring is usually the job of the pharmacist, caregivers, and the prescribing physician with the help of the interdisciplinary team.

Pharmacogenetics (i.e., genetic influences on the efficacy and adverse effects of drugs) is a relatively new development in the DD literature on drugs, but it is growing in importance. A good example is a recent paper by Sleister and Valdovinos (2011) demonstrating that several gene polymorphisms or variants may be related to weight gain resulting from the use of atypical antipsychotic drugs. Pharmacogenetics may eventually be able to predict who is likely, and who is not likely, to show important side effects of psychotropic medications.

Common Behavioral Issues

Weeden, Ehrhardt, and Poling (2010) give a good primer for the behavior analyst on psychopharmacological treatments for people with autism that are also relevant for people with SIB. We also have treated these topics in a recent position paper (Courtemanche et al., 2011). We will only summarize the main relevant points below.

Types of Measures

The types of measures most used are psychometric rating scales and checklists and direct observations. Preference should be given to properly standardized measures for the DD population under study. Matson's *Handbook on Assessing the Persons with Intellectual Disabilities* (2007) is a good guide for the full range of available instruments. Most behavior analysts are familiar with using direct observation measures, so we will not review those specialized for SIB here. Instead, the reader is referred to our book on SIB (Rojahn et al., 2008).

Monitoring Drug-Behavior Interactions. Monitoring drug-behavior interactions is important. Behavior pharmacology is the fundamental field of the study of such interactions as *rate dependency* (Branch, 1984). This phenomenon also can occur in drug studies on SIB. For instance, if the SIB rate of a crisis case is very high, any drug he/she receives is likely to lower the SIB. The use of PRNs (i.e., prescribed as needed) is likely based upon this rationale. On the other hand, the habitual use of PRNs is likely to result in habituation to their effect. Some guidelines prohibit the use of PRNs because they could be used excessively. Similarly, if the SIB rate is very low, any drug administered suffers the risk of increasing it. In our studies (e.g., Hellings et al., 2006; Zarcone et al., 2001), the dose response curves of people who were receiving risperidone for SIB varied greatly. Similarly, increased appetite resulting from receiving atypical antipsychotics may be a motivating operation (MO) for increased SIB.

Analogue Functional Analysis. It is also another method for examining drug-behavior interactions in the DD population. Several studies have shown that the functions of the aberrant behavior may change as a result of receiving medications (Crosland et al., 2003; Dicesare, McAdam, Toner, & Varell, 2005; Valdovinos, Nelson, Kuhle, & Dierks, 2009; Zarcone et al., 2004).

Monitoring Compliance with Drug Regimens. Compliance with drug regimens is another critical behavioral issue. In residential facilities, this problem may not be as prevalent, because

of ICF-MR (Intermediate Care Facility for the Mentally Retarded) regulations. In outpatient programs, however, drug compliance in some cases has been as low as 50 % (Rasaratnam, Crouch, & Regan, 2004). Such a compliance failure may result in an adverse effect of a usually effective drug for SIB, many of which depend upon strict compliance over an extended period of time to achieve steady state. To counter noncompliance, bubble packaging of capsules or monitoring the amount of elixir form of the drug consumed at clinic follow-up visits can help to detect noncompliance.

Reactivity of Evaluators of the Drug's Effect. The ratings of parents, teachers, and caregivers often differ, and these ratings correlate poorly with behavior observers' data in drug studies of SIB (Schroeder, Rojahn, & Reese, 1997). This result is not surprising since each is a sample based upon their respective roles, experience, and interests in achieving outcomes, which also may differ markedly. Parents and teachers may also have very different observations of a drug effect. At some molar level, however, they should agree (Valdovinos et al., 2002), and differences should be reconciled. Singh et al. (2002) have shown that training staff on how to integrate behavioral and pharmacological treatments can improve them. Aman, Bensen, Farmer, Hall, and Malone (2007) have produced Project MED, which is a series of eight brief training manuals, in English and Spanish, on the major psychotropic drugs used in DD, written in simple language for consumers and caregivers, which we have found very helpful. Consensus development by an interdisciplinary team is key to a successful outcome.

Consumer Satisfaction. Social validity study was invented by behaviorists (Kazdin, 1977; Wolf, 1978), to assess the acceptability of treatments by caregivers and consumers that might affect their long-term maintenance and generalization. Poling and LaSage (1995) called for social validity studies in psychotropic drug studies, especially for individuals with DD. Because people with SIB often have impaired ability to consent or assent to procedures, caregiver acceptability measures by people who know the client well are most frequently used (e.g., Aman & Wolford, 1995; McAdam et al., 2002; Tierney et al., 2007).

Consumer measures of satisfaction in drug studies of SIB have been difficult, although we have often observed positive and negative behavioral side effects (e.g., reduced stress and signs of pain, more smiling and cooperation with parents and caregivers, symptom substitution). More research in this area should be done. For instance, Courtemanche, Schroeder, Sheldon, Sherman, and Fowler (2012) demonstrated a method for coding videos of signs of pain and distress among chronic SIB cases. Symons, Harper, McGrath, Breau, and Bodfish (2009) have shown how a rating scale for noncommunicating persons can be used similarly for this purpose.

Political and Funding Issues

Most drug studies approved by the FDA are large group RCT studies that may cost hundreds of thousands of dollars to conduct. The main funding mechanism is the National Institute of Mental Health, which has the same bias toward large RCT studies. These practices make it difficult to win the funds necessary for research on large-scale PCTs, which may also involve single-subject designs of the type used by behavior analysts. Less than 10 % of all clinical trials approved or funded by the FDA are PCTs (Getz & Sisson, 2003). Less than 2 % of all NIH funding was allocated to research on all DD topics. Psychopharmacology studies of SIB are only a small fraction of that 2 %. Yet these people are some of the most overmedicated groups in our society.

The other major funders of drug research for people with DD are the pharmaceutical companies, who need to make enough profit. For a drug to be brought to market to enable further drugs to be developed, the average cost is $2,000,000,000. Researchers who receive pharmaceutical-company money are expected to disclose all of their potential conflicts of interest when publishing their research. It is impor-

tant for the clinician to check these footnotes in published papers because conflicts of interest may affect the outcomes and interpretations of such studies. Indeed, some investigators refuse to accept pharmaceutical company funding for this reason.

Research on naltrexone and SIB is a good example of drug company politics. Recently, there has been a dearth of research on naltrexone for SIB in the past decade, while over 50 studies were published from 1980 to 2000. Why? The answer likely has little to do with its effectiveness. It is more likely the case that the patent on the drug has expired and it is now sold more cheaply as a generic drug. Also, the company that originally developed the drug for treatment of alcohol abuse was bought by another pharmaceutical company, that now produces naltrexone, but has no interest in cooperating with investigators to submit an Investigative New Drug (IND) application permit to the FDA for treating SIB. An IND is necessary to conduct a research study on an off-label use of a drug. Thus, future research funding for naltrexone and SIB remains unlikely.

Summary and Conclusions

Since the Sprague and Werry (1971) review, much research effort has been expended on psychopharmacology in DD. We have tried to focus on drugs for persons with DD and SIB and to share some of our personal experiences and opinions gathered over these past four decades. We feel that we have learned much about what is necessary to conduct and analyze an effective clinical drug and behavioral trial. We have outlined these issues briefly in this chapter. For the clinician, performing an effective clinical trial for an individual case is a complex process, with the clinical arts as well as the sciences at its base. In clinical drug trials, one often hears the aphorism, "KISS. Keep it simple, stupid!" Unfortunately, it's not simple.

Acknowledgements NIH grants Nos. HD 060500, HD02528, HD 026927.

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