Clinical Psychopharmacology of Pediatric Mood Stabilizer and Antipsychotic Treatment, Part 2: Methodological Considerations

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In last month's ASCP Corner, I discussed some of the challenges and recent developments regarding the available evidence base for the use of antipsychotics and mood stabilizers in children and adolescents.[1] In this month's column, I will focus on some of the pertinent clinical psychopharmacology trials design issues that are relevant to the collection of data in children and adolescents who are in need of antipsychotic or mood stabilizer treatment.

While it is clear that studying psychotropic medication effects in children and adolescents is crucial, it is also a difficult task. Difficulties arise from age-dependent differences in physical, psychological, and social development; illness expression and categorization; vulnerability to acute and long-term adverse effects; and ethical concerns about trials involving either an active comparator of unproven efficacy or placebo.[2]

On the other hand, studying psychotropic efficacy and safety in youngsters is also an opportunity. In addition to providing currently unavailable data on young patients in need of symptomatic and functional improvement, such studies can also inform treatment in adult populations. Many more youngsters are either treatment-naive or in the early illness phases, which enables us to study effects of medications at periods where the effect of previous medications or illness chronicity is minimized or absent. In addition, patients share the phenotype of early illness onset and are often enrolled in studies with parental consent despite being severely ill, which improves generalizability. Furthermore, the closer involvement of caregivers and school personnel provides the opportunity to gather data from multiple sources and may improve adherence through closer supervision, thereby reducing the "noise" introduced by covert nonadherence. All of these factors may improve the ability to identify predictors of psychiatric illness progression and recovery in pediatric samples.

Methodological Considerations

Several challenges need to be addressed in order to gather the most informative data when studying children and adolescents with mental disorders in need of mood stabilizer and antipsychotic treatment.

Clinical trials design. Independent of the age of the studied population, double-blind randomized controlled trials are considered the gold standard to assess the effect of a given drug in a group of patients. The narrow inclusion criteria and highly controlled nature of such trials ensure great internal validity, i.e., the ability to test a given hypothesis with few uncontrolled and confounding variables. However, the narrow inclusion criteria limit these studies to relatively small numbers of patients with 1 disease treated with 1 medication and to those who are willing and able to give informed consent for a placebo-controlled trial. Because of these characteristics, the external validity is reduced, i.e., the ability to generalize the findings to large groups of patients who have medical and psychiatric comorbidities, are treated with multiple medications, and are too severely ill to consent to research. Moreover, the focus of such trials that are usually short-term is mostly efficacy, i.e., the reduction of specific, disease-related symptoms.

In order to address the limitations of the important proof-of-principle studies, larger scale, so-called pragmatic trials are being proposed. These studies have much broader inclusion criteria and reduce the burden of assessments to patients and requirements for investigators. This allows for studying a greater number of patients who are treated in generalizable settings, thereby increasing the external validity of the findings. In addition, these studies are generally longer-term trials that target effectiveness, which is more closely linked to functional outcomes. However, since patient, setting, and comedication characteristics are much more varied than in efficacy trials, the number of patients required for such trials is usually quite large.

Different study designs are needed to more comprehensively assess safety and tolerability, particularly potentially serious adverse effects that occur either at a relatively rare rate or later in the treatment course (e.g., renal toxicity, diabetes mellitus, tardive dyskinesia, neuroleptic malignant syndrome, coronary heart disease event, death). These include larger-scale naturalistic studies and pharmacoepidemiologic and safety registry studies. The methods used in these types of studies have the advantage of collecting long-term data in large numbers of patients in generalizable settings. However, they are limited by the introduction of prescriber, recording, and reporting biases and are likely to miss "silent" adverse events (e.g., dyslipidemia, hyperglycemia, elevated blood pressure). Therefore, results from these studies are hypothesis-generating and require confirmation by more controlled studies.

Finally, large, simple trials that have more detailed information about patient and environmental variables than usually provided by pharmacoepidemiologic and safety registry studies are needed to identify high-risk groups and clinical as well as biological predictors of efficacy and adverse effects.

Influence of development on treatment targets. Due to ongoing brain maturation, the disease and symptom expression may differ in youth compared to adults. In pediatric bipolar disorder, for example—a condition that is being increasingly diagnosed and is a controversial topic of discussion[3]—patients frequently have ultra-rapid or ultradian cycling. This causes pediatric patients to miss the duration criterion for a mood episode required for DSM-IV bipolar I disorder.[4] Therefore, patients can only be diagnosed with bipolar disorder not otherwise specified (NOS)[5] even though they have the full number of required symptoms at the required level of severity. Furthermore, since pediatric patients are often in an early phase of their illness, other subsyndromal diagnoses, such as psychosis NOS or mood disorder NOS, may be the most appropriate classification. However, even though these conditions can be highly impairing, prescribing an antipsychotic or mood stabilizer for these youngsters would still be off-label, even if controlled trials have provided evidence for the efficacy of these agents for syndromal schizophrenia or bipolar I or II disorder as per DSM-IV.

Influence of development on treatment outcomes. Since children and adolescents are treated at different developmental stages, therapeutic and adverse event outcomes may need to be developmentally adjusted. This adjustment may involve using rating scales that target different symptoms than in adults. Moreover, due to differences in physical development across children and adolescents, sex-and/or age-adjusted outcome measures and thresholds for pathological values should

be utilized.[6] These include body mass index (BMI), waist circumference, blood pressure, and fasting lipid values.[6] In particular, weight gain over time needs to be adjusted for age-appropriateness by using BMI z-scores, which unfortunately are not being used widely, making it impossible to compare weight gain across studies with varying follow-up durations.[7]

Assessment methods. Both efficacy and adverse effects need to be assessed systematically, ideally with standardized measures that are being used across multiple studies.[8,9] Having an informant available can enhance the completeness and accuracy of the assessments, but scales may require adaptation of the language and/or anchors based on age and maturation.

Many scales are specifically designed to assess child or adolescent psychopathology. This enhances the internal validity of the assessments and trials; however, if rating instruments differ too much from those used in adults, useful comparisons across these 2 populations are compromised.

Furthermore, in order to inform clinical practice, the field should move toward reporting key adverse effects as a time-dependent measure, as is done routinely for efficacy measures. Thus, rather than simply reporting overall incidence rates of adverse effects that are present at any level and at any time during the trial, it is much more clinically relevant to report the severity at each assessment time, providing information about the level of impairment and the time course of the symptom. In addition to the display of change in continuous variables, meaningful and developmentally adjusted categorical variables need to be reported.

Clearly, long-term studies are needed[10] to document maintenance of the efficacy and lack of adverse effects that may develop after a lag time. Because these studies have not been done, it is unclear whether and to what degree lithium causes renal toxicity, valproate causes reproductive hormone disturbances, and hyperprolactinemia at levels observed with some antipsychotics is responsible for a delayed puberty, osteoporosis, or pituitary or breast tumors or what the direct and indirect effects of antipsychotics are on the development of diabetes.

Interventions. Children and adolescents have emerged as a high-risk group for many medication side effects, namely weight gain, metabolic abnormalities, hyperprolactinemia, sedation, extrapyramidal side effects, and withdrawal dyskinesia.[11] Therefore head-to-head studies of higher- versus lower-risk medications should be conducted to provide data for rational risk-benefit evaluations. Moreover, due to overall reduced response rates in many severely ill youngsters with early-onset illness and to the finding of frequently combined pharmacotherapy in routine clinical practice, combination and polypharmacy studies need to be performed. In this context, augmentation with nonpharmacologic interventions should also be evaluated. Finally, the field should not stop at measuring and comparing adverse effects. Rather, different pharmacologic and nonpharmacologic interventions to reduce key adverse effects need to be investigated. This is particularly pertinent for the often "silent" adverse effects on body composition, blood pressure, and glucose and lipid metabolism that have severe consequences for quality of life and longevity.

Subpopulations. Studies are needed that assess efficacy and adverse effects in subpopulations. These include patients from minority ethnicities, treatment-naive youths, or those in the early illness phase. Moreover, after the identification of high-risk subgroups for adverse therapeutic and side effect outcomes, these particularly vulnerable patients should be studied separately, trying to maximize therapeutic outcomes and/or to reduce or reverse significant adverse effects. Additionally, thought should be given to including control groups in the various types of studies, which—depending on the study design and focus—could involve healthy controls, unaffected siblings who share the same environment, psychiatrically ill control subjects, or patients refusing treatment.

Conclusions

The database for the efficacy and safety of antipsychotics and mood stabilizers in the treatment of severe mental disorders in children and adolescents is rapidly expanding.[1] Although clinicians have had to use most agents in these medication classes off-label in pediatric patients, this practice is quite likely going to change, at least for schizophrenia and bipolar disorder, in the near future. Still, many prescriptions are written for subsyndromal presentations and syndrome clusters, such as mood disorder and psychosis NOS, aggression, impulsivity, and agitation. Therefore, off-label prescribing will continue in the substantial group of youngsters who do not meet full DSM-IV criteria for a disorder for which psychotropics are indicated, but who are nevertheless severely disturbed and unable to function sufficiently well.

Future studies are required that evaluate the efficacy and safety of antipsychotics and mood stabilizers also for these less well-defined presentations and that follow patients long-term to determine the outcome of treated and untreated individuals. Furthermore, drug safety and tolerability should be studied systematically, taking into account the time course and severity of the disorder and the developmental stage of patients. Finally, clinical and biological markers of illness subtypes and predictors of therapeutic and adverse effect outcomes need to be studied in sufficiently large pediatric cohorts who are followed for sufficiently long periods of time.

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