Clinical Psychopharmacology of Pediatric Mood Stabilizer and Antipsychotic Treatment, Part 1: Challenges and Developments

Christoph U. Correll, M.D.

Challenges

The field of clinical psychopharmacology has a long and productive history. Only recently, however, has the field begun to include children and adolescents on a larger scale. Reasons for this delay include concerns about safety and tolerability in this vulnerable population, diagnostic uncertainties, and the reluctance of the industry to embark on pediatric registration and labeling studies for diagnoses that traditionally have not been seen as predominant disorders of childhood and adolescence.

Child and adolescent psychiatrists have therefore had to base their prescribing mostly on data collected in adults. This practice is problematic, however, since children are not simply "small adults." Rather, youngsters are undergoing critical biological, psychological, and social changes that can affect the way they will take, absorb, distribute, excrete, and respond to medications. In addition, youth have an early disease onset that is frequently associated with poor outcomes. A few examples of differences between psychotropic medication effects in youngsters compared with adults include the greater likelihood of nonresponse to tricyclic antidepressants,[1] placebo response[2] and suicidality during antidepressant treatment,[3] and weight gain during antipsychotic treatment.[4]

In a recent "ASCP Corner" article,[5] several concerns regarding the use of anticonvulsants as mood stabilizers in the treatment of children and adolescents were highlighted. Reasons for criticism included the frequent and rising off-label use for aggressive behaviors, poor impulse control, and symptoms of bipolar disorder in pediatric populations; the increasing use of polypharmacy; and risk of adverse effects and drug-drug interactions, as well as the insufficient or even negative evidence base to support such off-label prescribing in psychiatrically ill youth. These concerns echo a growing general awareness of the need to close the gap between increasing psychotropic medication utilization in children and adolescents[6,7] and limited data to support the safety and efficacy of these agents in pediatric populations.

As a matter of fact, these issues pertain to pediatric pharmacology in general,[8] but are heightened in psychiatrically ill youth.[9] As a result, a pediatric psychopharmacology initiative was developed that includes members of the Food and Drug Administration (FDA), National Institute of Mental Health (NIMH), academia, and the pharmaceutical industry. A very important outcome of this collaboration of resources is the advent of a new phase in pediatric psychopharmacology, during which large-scale randomized controlled trials (RCTs) are being conducted that assess the safety and efficacy of major medication classes for conditions like schizophrenia and bipolar disorder, which have been traditionally seen as typical adulthood disorders. Importantly, the extension of the pediatric psychopharmacology database by large-scale, state-of-the-art RCTs occurs at a time of growing awareness that schizophrenia and bipolar disorder have their onset in childhood and adolescence in the majority of patients.[10,11]

Developments

In terms of evidence for the efficacy of mood stabilizers in pediatric bipolar disorder, several smaller-scale trials have shown efficacy of divalproex,[12,13] alone or in combination with quetiapine. On the other hand, recent trials with oxcarbazepine[14] and with topiramate[15] have not proven the efficacy of these mood stabilizers in youth. Lithium has been shown to have superiority in one small placebo-controlled study of 24 adolescents with bipolar disorder and substance abuse.[16] However, other RCTs in youth are missing. Data from a recently started, NIMH-funded Collaborative Lithium Trial (CoLT), which has a pharmacokinetic, acute stabilization, discontinuation, and restabilization phase and allows for comedications, will greatly enhance the existing database. Finally, a recently completed 18-month discontinuation study in bipolar youth[17] suggested, in parallel to adult data,[18] that for patients with rapid-cycling bipolar disorder stabilized on combined treatment with lithium and divalproex, neither of the 2 mood stabilizers is very effective to prevent relapse when given as monotherapy. This finding highlights the importance of studying the combination treatment approach that is frequently utilized in bipolar youth[19] including combinations of more than 2 mood stabilizers. In addition, controlled pediatric data are still sorely needed for the treatment of bipolar depression.

Regarding antipsychotic use in pediatric populations, risperidone has already been approved for the treatment of irritability associated with autism on the basis of several RCTs (e.g., references 20, 21, 22). For schizophrenia and bipolar disorder, however, few published RCTs are available. These include 2 studies showing efficacy of quetiapine for bipolar mania,[12,13] as well as 3 trials showing efficacy of clozapine for treatment-refractory early-onset schizophrenia compared with haloperidol,[23] olanzapine,[24] and "high"-dose olanzapine.[25] In addition, RCTs with all of the nonclozapine atypical antipsychotics in pediatric bipolar disorder and schizophrenia either are underway or have just been completed and will provide invaluable data regarding atypical antipsychotic efficacy and safety in this understudied population. Furthermore, the largest federally funded study to date, which compared olanzapine, risperidone, and molindone, a mid-potency first-generation antipsychotic, in 119 youngsters aged 8 to 17 years with early-onset schizophrenia,[26] has been completed recently, and data are expected to be available soon.

Conclusions

While these recent and ongoing developments are very encouraging, there will still be a considerable number of severely mentally ill youngsters in need of psychotropic treatments who do not fit neatly into DSM-IV diagnostic categories. Many of these youngsters will require so-called "off-label" prescriptions of antipsychotics and/or mood stabilizers, without available data from RCTs.

Although this state of affairs is clearly lamentable, it is not an indication that off-label prescribing is necessarily irresponsible or irrational. Pharmacoepidemiologic studies[5] can only inform the public and researchers about a gap in the knowledge base regarding commonly utilized prescribing practices. However, the absence of evidence for the efficacy and safety of a given treatment in a specific population does not translate directly into evidence of the absence of safety and efficacy in this population. Current diagnostic criteria do not capture well the emerging illness expressions that may differ from those in

adults because of the different illness phase and ongoing physical, psychological, and social changes that children and adolescents undergo.

In next month's "ASCP Corner," I will review and discuss methodological considerations that are important for the gathering of data that can bridge the gap between the clinical need to intervene in markedly disturbed or distressed youngsters and the lack of an evidence base to guide clinical practice in this population, particularly those that do not fit neatly into DSM-IV diagnostic criteria.

Dr. Correll is with The Zucker Hillside Hospital, Glen Oaks, and Albert Einstein College of Medicine, Bronx, N.Y. He has served as a consultant to AstraZeneca, Eli Lilly, Bristol-Myers Squibb, Vanda, Otsuka, Solvay, Supernus, Pfizer, and Intra-Cellular Therapeutics and on the speakers or advisory boards for AstraZeneca, Bristol-Myers Squibb, Otsuka, and Janssen.

References

1. Hazell P, O'Connell D, Heathcote D, et al. Tricyclic drugs for depression in children and adolescents. Cochrane Database Syst Rev 2002;(2):CD002317
2. Mayes TL, Tao R, Rintelmann JW, et al. Do children and adolescents have differential response rates in placebo-controlled trials of fluoxetine? CNS Spectr 2007;12:147–154
3. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA 200718;297:1683–1696
4. Safer DJ. A comparison of risperidone-induced weight gain across the age span. J Clin Psychopharmacol 2004;24:429–436
5. Zito JM, American Society of Clinical Psychopharmacology. Pharmacoepidemiology: recent findings and challenges for child and adolescent psychopharmacology. J Clin Psychiatry 2007;68:966–967
6. Zito JM, Safer DJ, DosReis S, et al. Psychotropic practice patterns for youth: a 10-year perspective. Arch Pediatr Adolesc Med 2003;157:17–25
7. Olfson M, Blanco C, Liu L, et al. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. Arch Gen Psychiatry. 2006;63:679–685
8. Roberts R, Rodriguez W, Murphy D, et al. Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. JAMA 2003;290:905–911
9. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med 2006;166:1021–1026
10. Perlis RH, Miyahara S, Marangell LB, et al. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biol Psychiatry 2004;55:875–881
11. Häfner H, an der Heiden W. The course of schizophrenia in the light of modern follow-up studies: the ABC and WHO studies. Eur Arch Psychiatry Clin Neurosci 1999;249(suppl 4):14
12. DelBello MP, Schwiers ML, Rosenberg HL, et al. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry 2002;41:1216–1223
13. DelBello MP, Kowatch RA, Adler CM, et al. A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. J Am Acad Child Adolesc Psychiatry 2006;45:305–313
14. Wagner KD, Kowatch R, Emslie GJ, et al. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. Am J Psychiatry 2006;163:1179–1186
15. DelBello MP, Findling RL, Kushner S, et al. A pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005;44:539–547
16. Geller B, Cooper TB, Sun K, et al. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J Am Acad Child Adolesc Psychiatry 1998;37:171–178
17. Findling RL, McNamara NK, Youngstrom EA, et al. Double-blind 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005;44:409–417
18. Calabrese JR, Shelton MD, Rapport DJ, et al. A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. Am J Psychiatry 2005;162:2152–2161
19. Bhangoo RK, Lowe CH, Myers FS, et al. Medication use in children and adolescents treated in the community for bipolar disorder. J Child Adolesc Psychopharmacol 2003;13:515–522
20. McCracken JT, McGough J, Shah B, et al. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. N Engl J Med 2002;347:314–321
21. McDougle CJ, Scahill L, Aman MG, et al. Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. Am J Psychiatry 2005;162:1142–1148
22. Aman MG, Arnold LE, McDougle CJ, et al. Acute and long-term safety and tolerability of risperidone in children with autism. J Child Adolesc Psychopharmacol 2005;15:869–884
23. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia: a double-blind clozapine-haloperidol comparison. Arch Gen Psychiatry 1996;53:1090–1097
24. Shaw P, Sporn A, Gogtay N, et al. Childhood-onset schizophrenia: a double-blind, randomized clozapine-olanzapine comparison. Arch Gen Psychiatry 2006;63:721–730
25. Kumra S, Kranzler H, Gerbino-Rosen G, et al. Clozapine and olanzapine in refractory early-onset schizophrenia: a 12-week randomized and double-blind comparison. Biol Psychiatry. In press
26. McClellan J, Sikich L, Findling RL, et al. The Treatment of Early-Onset Schizophrenia Spectrum Disorder (TEOSS): rationale, design, and methods. J Am Acad Child Adolesc Psychiatr. In press