Pharmacoepidemiology: Recent Findings and Challenges for Child and Adolescent Psychopharmacology

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Pharmacoepidemiology is the study of drugs in large populations and typically applies descriptive and analytic epidemiologic methods to the study of the utilization, effectiveness, and safety of marketed medications. As a scientific field, pharmacoepidemiology has been advancing gradually since the 1980s with the rise of powerful computerized data management, statistical analysis, and population-based clinical questions.[1] Still, its role in assessing the benefits and risks of drug therapy for the treatment of mental disorders is minor. Neither is it prominent in the training, research activities, and clinical practice of U.S. psychiatrists and their counterparts in primary care.

Despite its relatively low profile, pharmacoepidemiology has particular value in the study of psychiatric drug therapy in an era of rapidly expanded drug use and widespread combination therapies, most of which are off-label and have insufficient evidence of effectiveness and safety in community-based populations.[2] This column offers a brief review of anticonvulsants as mood stabilizers (ATC-MS) in community-based treatment of children and adolescents, discusses off-label issues and the growth of concomitant psychotherapeutic drug therapy, and makes several recommendations for researchers and clinicians to consider in addressing these problems.

Anticonvulsants as Mood Stabilizers

The term *mood stabilizer anticonvulsant* is poorly defined and is adapted from the adult use of selected anticonvulsants to control symptoms related to aggressive behavior, poor impulse control, and symptoms of bipolar disorder.[3] Although for convenience this term is used, the reader should remember that it refers to treatment for an imprecise clinical description, rather than to an evidence-based diagnostic entity. The rapidly expanded use of anticonvulsants as mood stabilizers for youth started in the 1990s.[4] More recently, Hunkeler et al.[5] analyzed 10-year data (1994–2003) from approximately a half million health maintenance organization (HMO)–treated youth aged 5 to 17 years and showed that anticonvulsant use increased across this later time period. When the HMO-treated youth with seizure diagnoses were excluded, 47% of the anticonvulsant users in 2003 had a depression diagnosis and 48% had a bipolar diagnosis, compared with 10% and 5%, respectively, in 1995.[5] This study confirmed the anecdotal impression of the growing off-label use of these drugs for psychiatric and behavioral symptoms in children and adolescents.

The increased use of anticonvulsants is not likely to be explained by an increase in the prevalence or incidence of seizure disorders.[6,7] To confirm this hypothesis, we examined a mid-Atlantic state Medicaid population less than 18 years old with continuous enrollment throughout the study year and assessed the relative proportions of youth with diagnoses of mental disorders and seizure disorder among youth with a dispensed ATC-MS (carbamazepine, divalproex, and gabapentin) during the study year 2000.[8] The analysis confirmed that the vast majority of the dispensings to youth with a recorded ICD-9 diagnosis are allocated to youths with diagnoses of mental and behavioral conditions (81%) compared with those with a seizure diagnosis (19%). To consider why it is critical to know if the indications for use are off-label (as is the case for ATC-MS) for psychiatric or behavioral conditions, efficacy findings from clinical trials will be reviewed.

Clinical trial findings on oxcarbazepine[9] and topiramate[10] do not support anticonvulsant use in children and adolescents for mood stabilization. The lack of efficacy stands in contrast to the steadily increasing off-label usage of anticonvulsant mood stabilizers that comes from large pharmacoepidemiologic analyses as described above. In another youth trial, Wagner and colleagues[11] were unable to complete a randomized, double-blind study of divalproex for bipolar disorder because dropouts from the open pretrial phase were so extensive (23/40 = 57.5%). Thus, data from trials and pharmacoepidemiology are at odds: drugs that have not been shown to work under ideal conditions are, nevertheless, increasingly being used in community treatment.

In addition to negative efficacy findings from double-blind, placebo-controlled studies, decisions to use ATC-MS should take safety concerns into account. Adverse events related to ATC-MS are well established due to their extensive use in youth as antiepileptic medications. Adolescent females treated with divalproex, the most commonly used anticonvulsant, are at risk for polycystic ovaries,[12] and offspring of females treated with divalproex are at risk for major malformations.[13] Hepatotoxicity was initially emphasized as a problem for the immature liver enzyme system but later was found to be a risk in older children as well.[14] This risk has been clearly demonstrated by Dreifuss et al.,[15] Bryant and Dreifuss,[14] and Scheffner et al.[16] who described numerous cases of fatal liver toxicities with combinations of divalproex and other drugs. Since ATC-MS are rarely used as monotherapy, there is a sizably increased likelihood of risk with concomitant use of liver-metabolizing psychotropics.

Drug safety is particularly a concern for youths when drugs are prescribed off-label—reflecting the fact that the U.S. Food and Drug Administration has not approved labeling for a particular indication or in a particular age group. Off-label use of drugs is highest in children[17] and for drugs used for psychiatric disorders.[18] In recent years, off-label concerns have increased because concomitant treatment of youth has become so common.[19] Of concern is the degree of concomitant use associated with increased adverse drug events.[20,21] Larger scale pharmacoepidemiological studies provide additional examples of this pattern.[22,23]

This year, we examined concomitant treatment using a random sample (N = 472) from a large Medicaid dataset of foster care youth.[24] Concomitant drug therapy was found in 79% with 2 or more concomitant drugs and 49% with 3 or more concomitant drugs among psychotropic-medicated youth during a 1-month period in which precise dates of overlap clarified concomitant use. Outpatient diagnoses were also obtained in relation to concomitant treatment. The leading diagnoses were attention-deficit/hyperactivity disorder (ADHD), depression, and anxiety/adjustment disorder, and the use of anticonvulsants differed little among the 3 diagnostic groups. Thus, when concomitant therapy becomes common, a loss of specificity of drugs for major diagnoses becomes evident[24] and symptom suppression becomes the focus. For example, there may be a stimulant for ADHD, an atypical antipsychotic for aggressive behavior, and an ATC-MS for bipolar features. A discussion of underlying factors that might explain the growth of symptom-specific treatment is beyond the scope of this column, but DSM categorization has been implicated.[25]

To address the conundrum posed by the disparity between increasing off-label usage and negative or lack of robust efficacy data, a revised research agenda, such

as that precipitated by Best Pharmaceuticals for Children legislation,[26] should be funded to permit off-label pediatric usage to be assessed. In addition, national reporting of data on the drug utilization patterns of community populations should be regularly available. Finally, independent safety assessment of marketed medications needs the infrastructure for the design and analysis of studies that will enhance scientific judgments of safety.[27]

As epidemiologic methods develop to study cohorts longitudinally, an opportunity presents itself to evaluate outcomes in more rigorous ways to assure ourselves that medications for mental health conditions in youth are indeed safe, effective, and tolerable. At the least, data should show us reduced hospitalizations, fewer school suspensions, and absence of medical health adversities (e.g., absence of endocrine dysfunction in young women treated with divalproex), along with data on improved social, educational, and vocational functioning for those with successful persistence of treatment for conditions regarded as chronic.

Implications for Practitioners

In this brief review of psychotherapeutic drug use for children and adolescents, readers are asked to: (1) support the public financing of additional research on off-label psychiatric drug therapy, including legislation to reauthorize the Best Pharmaceuticals for Children Act; (2) support independent safety assessment of marketed medications and an improved infrastructure for the design and analysis of studies that will enhance scientific judgments of safety; (3) support national annual reporting of pediatric medication use; and (4) support the development of methods and fund prospective cohort studies to assess outcome in community-based treatment populations.

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