Risks From Antipsychotic Medications in Children and Adolescents

To the Editor: In their cohort study, Dr Correll and colleagues[1] reported that first-time use of antipsychotic medications in children was associated with weight gain and adverse effects on serum lipids. Although we do not question the basic findings of the study, we are concerned that selection biases related to baseline weight and race/ethnicity may have influenced the results of this nonrandomized study.

Selection bias is suggested by the body composition data, with 13 of 41 patients (32%) treated with aripiprazole already obese (≥95th body mass index [BMI] percentile) at baseline compared with 4 of 45 patients (9%) treated with olanzapine, with no overlap in BMI percentile range between these cohorts (aripiprazole, 59.2-78.9; vs olanzapine, 40.0-60.0). Genetic or environmental differences contributing to higher baseline adiposity might facilitate adverse medication effects and affect study outcomes.

Race/ethnicity can influence cardiometabolic risk and previous studies have documented racial differences in antipsychotic-induced metabolic effects in adults.[2,3] The study by Correll et al had unequal racial/ethnic distributions across the nonrandomized treatments (eg, 18% of Asian participants vs 63% of Hispanic participants were prescribed risperidone), limiting opportunities to evaluate treatment effects across racial/ethnic groups.

Christina Mangurian, MD
christina.mangurian@ucsf.edu
Department of Psychiatry
Elena Fuentes-Afflick, MD, MPH
Department of Pediatrics
University of California, San Francisco
John W. Newcomer, MD
Department of Psychiatry
Washington University School of Medicine
St Louis, Missouri

Financial Disclosures: Dr Mangurian reported receiving research grant support from the National Alliance for Research on Schizophrenia and Depression; receiving pharmaceutical-company co-sponsored fellowships (American Psychiatric Association/Bristol-Myers Squibb Fellowship in Public Psychiatry, the American Psychiatric Institute for Research and Education [APIRE]/Janssen Scholarship, and the APIRE/Lilly Research Fellowship); and being a research mentor for the APIRE/Janssen Scholarship Program. Dr Newcomer reported receiving research grant support from the National Institute of Mental Health, the National Alliance for Research on Schizophrenia and Depression, the Sidney R. Baer Jr. Foundation, Janssen, Bristol-Myers Squibb, Wyeth, and Pfizer; serving as a consultant to AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Pfizer, Solvay, Otsuka, Wyeth, Forest, Sanofi, Lundbeck, Tikvah, and Vanda; being a member of data and safety monitoring boards for Organon, Schering Plough, Dainippon Sumitomo, and Vivus; being a consultant to litigation involving antipyschotic medication patents and adverse event risk; and receiving royalties from Compact Clinicals/Jones and Bartlett Publishing for a metabolic screening form. Dr Fuentes-Afflick reported no financial disclosures.

1. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302(16):1765-1773.
2. Ader M, Garvey WT, Phillips LS, et al. Ethnic heterogeneity in glucoregulatory function during treatment with atypical antipsychotics in patients with schizophrenia. *J Psychiatr Res*. 2008;42(13):1076-1085.
3. Krakowski M, Czobor P, Citrome L. Weight gain, metabolic parameters, and the impact of race in aggressive inpatients randomized to double-blind clozapine, olanzapine or haloperidol. *Schizophr Res*. 2009;110(1-3):95-102.

To the Editor: The substantial weight gain, lipid elevations, and other metabolic abnormalities associated with 12 weeks of second-generation antipsychotic medication use among youth in the cohort study by Dr Correll and colleagues[1] was alarming. As discussed in the accompanying Editorial by Drs Varley and McClellan,[2] lower-risk alternatives should be considered before prescribing atypical antipsychotic medications in children, especially given cardiometabolic risks and unclear efficacy for certain psychiatric disorders. However, behavioral and psychotherapeutic alternatives were not mentioned.

Given that approximately 53% of the sample in the study by Correll et al had nonschizophrenia spectrum and nonbipolar syndromes, behavioral or cognitive behavioral therapies (CBTs) may be considered as first-line interventions. Atypical antipsychotic medications are increasingly being prescribed for childhood obsessive-compulsive disorder (OCD), tic disorders, eating disorders, and refractory anxiety disorders. We believe that before initiating treatments with a medication class accompanied by a mean weight gain of 4.4 to 8.5 kg over 12 weeks (and other metabolic abnormalities), other empirically supported therapies should be attempted.

Three well-designed and large multisite studies demonstrated the efficacy of CBT for pediatric depression, OCD, and anxiety.[3-5] In general, children randomized to psychotherapy achieved comparable or better response and remission outcomes in comparison with those receiving selective serotonin reuptake inhibitor (SSRI) monotherapy. Gains secondary to behavioral, cognitive, and familial changes were typically better maintained following treatment discontinuation relative to their psychopharmacological counterparts. Although the adverse event profile for SSRIs is gen-

GUIDELINES FOR LETTERS. Letters discussing a recent *JAMA* article will have the best chance of acceptance if they are received within 4 weeks of the article's publication date. Letters may have no more than 3 authors. They should not exceed 400 words of text and 5 references. Letters reporting original research should not exceed 600 words and 6 references. They may have no more than 5 authors. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters will be published at the discretion of the editors and are subject to editing and abridgment. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment is required for publication. Letters not meeting these specifications are generally not considered. Before submitting a Research Letter, please review the Instructions for Authors (http://jama.com/instructions). Letters should be submitted via the *JAMA* online submission and review system at http://manuscripts.jama.com (note: do not include "www" before the URL). For technical assistance, please contact jama-letters@jama-archives.org.

Letters Section Editor: Robert M. Golub, MD, Senior Editor.

erally mild in comparison with second-generation antipsychotic medications, adverse events secondary to CBT are rare. Cognitive behavorial therapy may actually protect against harm-related adverse effects (eg, suicidal ideation) in comparison with SSRIs.[4] Long-term SSRI use should be approached cautiously given the unknown effects of prolonged use on the developing central nervous system, and the findings in the study by Correll et al raise a significant concern about serious metabolic changes over a 3-month period.

Adam B. Lewin, PhD
alewin@health.usf.edu
Eric A. Storch, PhD
Henry D. Storch, MD
Rothman Center for Neuropsychiatry
University of South Florida College of Medicine
St Petersburg

Financial Disclosures: Dr E. Storch reported receiving grant support from Ortho-McNeil-Janssen and serving as a consultant for Jazz. Drs Lewin and H. Storch reported no financial disclosures.

1. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302(16):1765-1773.
2. Varley CK, McClellan J. Implications of marked weight gain associated with atypical antipsychotic medications in children and adolescents. *JAMA*. 2009;302(16):1811-1812.
3. Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med*. 2008;359(26):2753-2766.
4. March J, Silva S, Petrycki S, et al; Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292(7):807-820.
5. Pediatric OCD Treatment Study (POTS) Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. *JAMA*. 2004;292(16):1969-1976.

In Reply: Dr Mangurian and colleagues note the importance of racial/ethnic influences on metabolic outcomes in psychiatrically ill patients. Race/ethnicity has been associated with cardiometabolic risk status in the general population and in psychiatric patients,[1] including the control of risk factors.[2] However, in most randomized controlled trials, members of minority ethnic groups are underrepresented. We acknowledge that in this naturalistic cohort study the choice of specific antipsychotic medications was likely influenced, at least in part, by preexisting metabolic risk factors. Unfortunately, the number of children and adolescents who were antipsychotic-naive in our cohort study was not large enough to allow for meaningful subgroup analysis.

In response to Dr Lewin and colleagues, we believe that the effectiveness of nonpharmacologic treatment options for the management of nonpsychotic conditions in youth, particularly conditions associated with aggressive behaviors, has been insufficiently studied. A large proportion of the sharp increase in antipsychotic prescriptions for children and adolescents appears to be due to their use for treating aggression.[3] Current guidelines advocate nonpharmacologic treatments in these youth as the first step, with consideration of pharmacologic treatments for aggression only after psychosocial interventions have failed or after a specific medication trial targeting an underlying disorder.[4]

However, although this recommendation has considerable face validity in that a lower-risk intervention is used first, randomized trials evaluating sequential treatment with psychosocial and psychopharmacologic interventions are needed. There is also a need for large randomized studies comparing psychosocial interventions, medication treatment, and their combination, which has been successfully performed in youth with anxiety, depression, and OCD. Clinical decision making and the use of antipsychotic medications in the treatment of children and adolescents with severe and often debilitating psychiatric disorders requires appropriate evidence and consideration of benefit-to-risk ratio.

Christoph U. Correll, MD
ccorrell@lij.edu
John M. Kane, MD
Anil K. Malhotra, MD
The Zucker Hillside Hospital
Psychiatry Research
Glen Oaks, New York

Financial Disclosures: Dr Correll reported being a consultant or receiving honoraria from Actelion, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Hoffman-LaRoche, Intra-Cellular Therapeutics, Lundbeck, Medicure, OrthoMcNeill-Janssen, Otsuka, Organon, Pfizer, Schering-Plough, Solvay, Supernus, Takeda, Vanda, and Wyeth; and serving on the speakers bureau of AstraZeneca, Bristol-Myers Squibb/Otsuka, and Pfizer. Dr Kane reported being a consultant or receiving honoraria from Abbott, Astra-Zeneca, Bristol-Myers Squibb, Cephalon, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Intra-Cellular Therapeutics, Janssen Pharmaceutica, Johnson & Johnson, Lundbeck, NuPathe, Otsuka, Pfizer, PgXHealth, Proteus, Schering, Shire, Solvay, Targacept, Takeda, Vanda, and Wyeth; serving on the speakers bureau of AstraZeneca, Bristol-Myers Squibb/Otsuka, and Eli Lilly; and being a shareholder of MedAvante. Dr Malhotra reported being a consultant or receiving honoraria from Bristol-Myers Squibb, Otsuka, Pfizer, and Vanda; and serving on the speakers bureau of Bristol-Myers Squibb/Otsuka and Pfizer.

1. Johnson WD, Kroon JJ, Greenway FL, Bouchard C, Ryan D, Katzmarzyk PT. Prevalence of risk factors for metabolic syndrome in adolescents: National Health and Nutrition Examination Survey (NHANES), 2001-2006. *Arch Pediatr Adolesc Med*. 2009;163(4):371-377.
2. McWilliams JM, Meara E, Zaslavsky AM, Ayanian JZ. Differences in control of cardiovascular disease and diabetes by race, ethnicity, and education: U.S. trends from 1999 to 2006 and effects of medicare coverage. *Ann Intern Med*. 2009;150(8):505-515.
3. Olfson M, Blanco C, Liu L, Moreno C, Laje G. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry*. 2006;63(6):679-685.
4. Steiner H, Remsing L; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with oppositional defiant disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(1):126-141.

In Reply: We agree with Dr Lewin and colleagues that CBTs are often safe and effective alternatives or adjuncts to atypical antipsychotic medications for nonpsychotic psychiatric syndromes in children and adolescents. Cognitive behavioral therapies have demonstrated efficacy for pediatric depression, OCD, anxiety, and posttraumatic stress disorder.[1] Parent training programs are effective for children with behavioral problems.[2] Recent studies support the benefit of CBT-based therapies for pediatric bipolar disorder[3] and developmentally tailored behavioral interventions for autis-