2. Meyer JM, Koro CE: The effects of antipsychotic therapy on serum lipids: a comprehensive review. Schizophr Res 2004; 70:1–17
3. Mollet J, Boivin J: Bias and confounding in pharmacoepidemiology, in Pharmacoepidemiology, 3rd ed. Edited by Strom BL. Chichester, UK, John Wiley & Sons, 2000, pp 765–784
4. McMahon AD: Approaches to combat with confounding by indication in observational studies of intended drug effects. Pharmacoepidemiol Drug Saf 2003; 12:551–558
5. Porta M, Hartzema AG, Tilson HH: The contribution of pharmacoepidemiology to the study of drug uses and effects, in Pharmacoepidemiology: An Introduction, 3rd ed. Edited by Hartzema AG, Porta M, Wilson HH. Cincinnati, Harvey Whitney Books, 1998, pp 1–28
6. Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman B, McEvoy JP, Cooper TB, Chakos M, Lieberman JA: Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. Am J Psychiatry 2003; 160:290–296
7. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209–1223
8. Kingsbury SJ, Fayek M, Trufasiu D, Zada J, Simpson GM: The apparent effects of ziprasidone on plasma lipids and glucose. J Clin Psychiatry 2001; 62:347–349

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## Dr. Olfson and Colleagues Reply

TO THE EDITOR: Drs. Rico-Villademoros and Calandre suggest that in our case control study confounding by indication may have attenuated associations of olanzapine with hyperlipidemia and exaggerated associations of risperidone and ziprasidone with hyperlipidemia. While we can not exclude this possibility, the assessment of pretreatment risk of hyperlipidemia among patients who receive these antipsychotic medications remains a challenge in clinical practice. In this context, we believe that by matching comparison subjects to individuals on age, sex, race, psychiatric diagnosis, and time period, we have created comparable groups in terms of underlying pretreatment risk for hyperlipidemia.

The two randomized controlled trials cited by Drs. Rico-Villademoros and Calandre were not adequately powered to detect differences among antipsychotic medications in the development of hyperlipidemia. In the study by Lindenmeyer et al., all of the cholesterol increases remained within the normal clinical range (1). In the CATIE trial, the five study groups (olanzapine, quetiapine, risperidone, perphenazine, and ziprasidone) did not significantly differ from one another in the proportion started on a cholestatin (2).

The study reported by Kingsbury et al. provided preliminary evidence of a reduction in serum cholesterol following switch from olanzapine, risperidone, or a first-generation antipsychotic to ziprasidone (3). However, without an untreated comparison group, it remains unclear the extent to which this decrease was mediated by withdrawal of the previous medication or by initiation of ziprasidone. Comparison of untreated patients and ziprasidone-treated patients is an important feature of our case control study.

We agree that observational research is vulnerable to problems that flow from differences between patient groups in pretreatment risk factors for the disease outcome (e.g., hyperlipidemia) and that randomized controlled trials offer an unrivaled check against such bias. In the absence of adequately powered randomized controlled trials, however, carefully conducted observational research may help physicians in their evaluation of the risks of hyperlipidemia.

### References

1. Lindenmayer JP, Czobor P, Voavka J, Citrome L, Sheitman B, McEvoy JP, Cooper TM, Chakos M, Lieberman JA: Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. Am J Psychiatry 2003; 160:290–296
2. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209–1223
3. Kingsbury SJ, Fayek M, Trufasiu D, Zada J, Simpson GM: The apparent effects of ziprasidone on plasma lipids and glucose. J Clin Psychiatry 2001; 62:347–349

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## Effects of Topiramate

TO THE EDITOR: Drew H. Barzman, M.D., and Melissa P. DelBello, M.D., published a case report in the August 2006 edition of *The American Journal of Psychiatry* titled "Topiramate for Co-Occurring Bipolar Disorder and Disruptive Behavior Disorders" (1). This case report suggests that topiramate is "helpful" in the treatment of bipolar disorder and that topiramate monotherapy may be "effective in treating disruptive behavior disorders independent of its therapeutic effect for mania that is possibly related to its efficacy in decreasing impulsivity in binge eating disorder, borderline personality disorder, and pathological gambling in adults" (1, p. 1452). The authors make a broad scientific claim regarding the benefits of topiramate. They suggest a link in efficacy for this anticonvulsant/anti-migraine agent based on observed diagnostic classification, but do not address the possibility that disorders that are related by phenotypic expression may be unrelated genotypically or mechanistically. We are concerned that the authors present information suggesting effectiveness of topiramate without offering balanced commentary regarding the significant side-effects of topiramate, including word-finding difficulty, impaired concentration, depression, confusion, encephalopathy, and memory interference (2, 3). These and other problems with topiramate were recently highlighted elsewhere (4).

Finally, we find little basis for the authors, suggestion that the actions of topiramate, a gamma-aminobutyric acidergic (GABAergic) drug, has beneficial effects independent of any possible antimanic effects. The statement that topiramate monotherapy may be similarly efficacious in treating disruptive disorders in children, gambling in adults, binge eating, and borderline personality disorder suggests a mechanism of action for topiramate that is not supported by current research.


### References

1. Barzman DH, DelBello MP: Topiramate for co-occurring bipolar disorder and disruptive behavior disorders (letter). Am J Psychiatry 2006; 163:1451–1452
2. Abramowicz M (ed): The Medical Letter: On Drugs and Therapeutics, 14th ed. New York, The Medical Letter, Inc., 2001, pp 38–39
3. Janssen LP: Risperdal, in PDR 60th Edition 2006 Physicians Desk Reference (PDR), 60th ed. Edited by Montvale ML, New Jersey, Thompson PDR, 2006, pp 1658–1664
4. Aarsen FK, van den Akker ELT, Drop SLS, Catsman-Berrevoets CE: Effect of topiramate on cognition in obese children. Neurology 2006; 67:1307–1308



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## Drs. Barzman and DelBello Reply

TO THE EDITOR: Although the underlying biology of binge eating disorder, borderline personality disorder, pathological gambling, and disruptive behavior disorders remains largely unknown, our clinical observations, along with randomized controlled data, have shown that topiramate is effective for treating these psychiatric disorders, which are phenomenologically linked by impulse dyscontrol (1–4). Furthermore, following our case report (5), there have been two open-label studies confirming our preliminary finding that topiramate is effective for the treatment of disruptive and impulsive behavior in children and adolescents with psychiatric illnesses (6–7). Additionally, in contrast to the statement by Drs. Kruszewski and Klotz, a review of the literature reveals that the aforementioned disorders may be genotypically related. For example, the G allele of the 5H-T2A receptor gene (1438A/G polymorphism) is associated with both binge eating and borderline personality disorder (8). More strikingly, a specific gene, GABRA2, has been associated with conduct disorder and adult alcohol dependence (9). Finally, topiramate is a novel broad-spectrum anticonvulsant that inhibits glutamate activity at a subtype of glutamate receptors and augments the effects of GABA receptor subtypes ($GABA_A$) (10). Therefore, contrary to the assertion by Drs. Kruszewski and Klotz, topiramate may be effective for impulse control disorders through its effect on glutamate as well as other receptors (11).

We agree that it is important to consider both efficacy and tolerability when prescribing any medication. However, topiramate is generally well tolerated in children and adolescents. In fact, data suggest that topiramate may be better tolerated in children and adolescents than in adults (12); for example, only 14% of 56 children and adolescents experienced paresthesia, and 14% experienced somnolence in a recent double-blind placebo controlled trial of topiramate for pediatric mania (13).


### References

1. McElroy SL, Arnold LM, Shapira NA, Keck PE, Rosenthal NR, Karim MR, Kamin M, Hudson JI: Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. Am J Psychiatry 2003; 160:255–261
2. Johnson BA, Ait-Daoud N, Akhtar FZ, Ma JZ: Oral topiramate reduces the consequences of drinking and improves the quality of life of alcohol-dependent individuals: a randomized controlled trial. Arch Gen Psychiatry 2004; 61:905–912
3. Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache JD, Lawson K, Javors MA, Ma JZ: Oral topiramate for treatment of alcohol dependence: a randomized controlled trial. Lancet 2003; 361:1677–1685
4. Dannon PN, Lowengrub K, Gonopolski Y, Musin E, Kotler M: Topiramate versus fluvoxamine in the treatment of pathological gambling: a randomized, blind-rater comparison study. Clin Neuropharmacol 2005; 28:6–10
5. Barzman DH, DelBello MP: Topiramate for co-occurring bipolar disorder and disruptive behavior disorders (letters). Am J Psychiatry 2006; 163:1451–1452
6. Song DH, Shin WC, Ha EH, Shin YJ, Kim JY, Kim YK: Short-term effects of topiramate on externalizing behaviors in youths with or without mental retardation. American Academy of Child and Adolescent Psychiatry, 53rd Annual Meeting, San Diego, 2006
7. Dolengevich SH, Rodriguez SB, Conejo GA, San Sebastian CJ: Efficacy of topiramate in children and adolescent with problems in impulse control: preliminary results. Actas Esp Psiquiatr 2006; 34:280–282
8. Nishiguchi N, Matsushita S, Suzuki K, Murayama M, Shirakawa O, Higuchi S: Association between 5HT2A receptor gene promoter region polymorphism and eating disorders in Japanese patients. Biol Psychiatry 2001; 50:123–128
9. Dick DM, Bierut L, Hinrichs A, Fox L, Bucholz KK, Kramer J, Kuperman S, Hesselbrock V, Shuckit M, Almasy L, Tischfield J, Porjesz B, Begleiter H, Nurnberger J Jr, Xuei X, Edenberg HJ, Foroud T: The role of GABRA2 in risk for conduct disorder and alcohol and drug dependence. Behav Genet 2006; 36:577–590
10. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE: An overview of the preclinical aspects of topiramate pharmacology, pharmacokinetics and mechanism of action. Epilepsia 2000; 41(suppl1):S3–S9
11. Johnson BA: Recent advances in the development of treatments of alcohol and cocaine dependence: focus on topiramate and other modulators of GABA or glutamate function. CNS Drugs 2005; 19:873–896
12. Winner P, Pearlman EM, Linder SL, Jordan DM, Fisher AC, Hulihan J, Topiramate Pediatric Migraine Study Investigtors: Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. Headache 2005; 45:1304–1312
13. DelBello MP, Findling RL, Kushner S, Wang D, Olson WH, Capece JA, Fazzio L, Rosenthal NR: A pilot controlled trial of topiramate