Catatonia or No Catatonia: Still Beyond Lorazepam/Amobarbital

TO THE EDITOR: Max Fink, M.D., and Michael Alan Taylor, M.D., have put forward a strong case in favor of making catatonia a separate category in subsequent editions of the DSM. However, their assertion that the diagnosis of catatonia should be made by observing the patient's response to the administration of lorazepam/amobarbital seems to be an oversimplification of the issue. It is correct that catatonic features have been shown to respond to the administration of these compounds. However, the assumption that "[t]he diagnosis may be confirmed by symptomatic improvement after the acute administration of a challenge dose of lorazepam or amobarbital" (1, p. 1875) seems to be an overgeneralization. Response to these agents by no means provides a definitive diagnosis of catatonia, and there is no evidence to support the use of these tests as confirmatory. Catatonic features are not specific to any one condition and can be observed in a variety of conditions. Some of these conditions might respond to lorazepam or amobarbital; for example, conversion disorders such as conversion mutism are associated with features that do resemble catatonia and do respond to the amobarbital assisted interview. In summary, it may be prudent to avoid the use of response to lorazepam/amobarbital as a confirmatory test for the presence of catatonia.

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Dr. Balhara reports no competing interests.

Drs. Fink and Taylor Reply

TO THE EDITOR: Catatonia is a syndrome defined by two or more persistent clinical signs cited in catatonia rating scales (1, 2). It is commonly identified in patients with depressive illness, manic-depression, and psychotic disorder. It is frequently seen in patients with seizure disorder, frontal circuitry brain disease, and in toxic metabolic states (1). Dr. Balhara objects to the suggestion that the rapid relief of catatonia by the intravenous administration of lorazepam or amobarbital verifies the diagnosis in subjects who meet the clinical criteria. He recognizes that catatonic features are not specific to a single condition and cites elective mutism as an example of a condition that does not meet the criteria for catatonia and yet responds to amobarbital assisted interviews.

In 1930, barbiturates were replaced by benzodiazepines for reasons of safety. In recent trials among patients who meet rating scale criteria for catatonia, more than 80% of patients had a rapid reduction in symptoms with an intravenous lorazepam challenge (1, 2). Such a response to lorazepam typically results in a lorazepam treatment trial, followed by electroconvulsive therapy if substantial relief is not maintained. Adhering to this algorithm achieves remission of catatonia in almost all patients.

Dr. Balhara notes that conversion disorders like mutism "are associated with features that do resemble catatonia and do respond to amobarbital assisted interview" as a negation of the lorazepam challenge test as verification of the diagnosis. In his example, however, the patient with elective mutism and "associated features [of catatonia]" would meet the diagnostic criteria for catatonia, and the relief afforded by amobarbital would verify the diagnosis and encourage the prescription of effective treatments of the syndrome.

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Confounding by Indication and the Risk of Hyperlipidemia in Observational Studies of Antipsychotics

TO THE EDITOR: Using an elegant case-control design, Mark Olfson, M.D., M.P.H., et al. have reported a somewhat weak but significant association between treatment with clozapine, risperidone, olanzapine, quetiapine, or ziprasidone, and the risk of developing hyperlipidemia (1). The authors stated that the strength of the association for olanzapine was smaller than previously reported. We agree with them that a possible explanation for this discrepancy is that physicians might be aware of the metabolic risks of olanzapine and thus be reluctant to prescribe it to those patients at high risk of developing hyperlipidemia. However, we think that this effect, known as confounding by indication, also could have biased the results against risperidone and especially ziprasidone. Since these two drugs appear to be associated with a lower risk of hyperlipidemia (2), it is possible that physicians might be prone to prescribe them to patients with a higher risk for hyperlipidemia.

Confounding by indication is probably the most important confounder when evaluating treatment effects in observational studies (3). Although there are several methods for dealing with confounding by indication (4), randomization is the best way to avoid it (5). Randomized controlled trials appear to indicate that neither risperidone (6, 7) nor ziprasidone (7, 8) is associated with an increased risk of hyperlipidemia. While two of these studies were short-term (6, 8), the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (7) was long-term and therefore more suitable for evaluating drug effects on plasma lipids. In the CATIE study, after adjusting for the duration of treatment, olanzapine was associated with greater increases in total cholesterol and triglycerides, while risperidone produced almost no changes, and ziprasidone was associated with improvement in these metabolic variables (7).

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Dr. Rico-Villademoros has worked as a freelance consultant for AstraZeneca and Pfizer. Dr. Calandre reports no competing interests.

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.

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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).