Possible Bipolar Nature of Irritability in Major Depressive Disorder

Sir: Perlis et al.[1] found that irritability was present in 40% of outpatients with major depressive disorder (MDD). The finding mirrors DSM-IV-TR,[2] which lists irritability not only as a core symptom of mania and hypomania, but also as a common symptom of MDD. Kraepelin[3] classified irritability as a manic (excitement) symptom. The bipolar nature of irritability in MDD can have an important impact on treatment of MDD. Although a study[4] on MDD with irritability showed that fluoxetine was effective in reducing irritability, clinical observations suggest adding mood-stabilizing agents to antidepressants in MDD with irritability because antidepressants alone may worsen irritability.[5–9]

To test the bipolar nature of irritability, I scanned a large database of patients who presented to our practice from June 1999 to January 2005. As the present analyses were not planned when data were recorded, an interviewer's bias is unlikely. Detailed study methods are reported elsewhere.[10–12] The present sample includes 379 consecutive bipolar II disorder (BPII) and 271 consecutive MDD outpatients who were assessed when they presented to a private practice for treatment of a major depressive episode (MDE) before starting psychopharmacologic treatment. Patients were interviewed by a senior clinical and research psychiatrist using the Structured Clinical Interview for DSM-IV,[13] the Hypomania Interview Guide[14] to assess hypomanic symptoms in the MDE, and the Family History Screen[15] for assessing bipolar (type I and II) family history in probands' first-degree relatives.

In the BPII sample, the mean (SD) age was 41.3 (13.0) years, 67.2% were women, the mean (SD) Global Assessment of Functioning (GAF) score was 50.3 (9.2), the mean (SD) age at onset of first MDE was 22.6 (10.5) years, and 45.2% had a family history of bipolar disorder. In the MDD sample, the mean age was 46.6 (14.6) years, 61.6% were women, the mean GAF score was 50.7 (9.6), the mean age at onset of first MDE was 31.7 (13.7) years, and 16.0% had a family history of bipolar disorder. Irritability was present in 60.6% of BPII patients, compared with 37.9% of MDD patients ($\chi^2 = 34.6$, df = 1, p = .0000) (a figure close to that reported by Perlis et al.[1]).

An important external validator of diagnosis of bipolar disorder is bipolar family history.[16] My logistic regression analysis of irritability versus family history of bipolar disorder found an odds ratio (OR) of 2.1 (95% CI = 1.4 to 3.2, p = .000); when the analysis was controlled for the confounding effect of BPII, the OR was 1.7 (95% CI = 1.1 to 2.6, p = .007). Difference in age at onset between bipolar disorders and depressive disorders is also an important diagnostic validator.[17] My logistic regression analysis of irritability versus onset age found an OR of 0.7 (95% CI = 0.6 to 0.8, p = .000); when the analysis was controlled for the confounding effect of BPII, the OR was 0.8 (95% CI = 0.7 to 0.9, p = .006). We also tested whether MDD with irritability, as distinguished from MDD without irritability, shared demographic and family history characteristics with bipolar disorder. Family history of bipolar disorder and onset age were the validators. Logistic regression analysis of MDD with irritability versus family history of bipolar disorder found an OR of 3.2 (95% CI = 1.5 to 7.1, p = .003). Logistic regression analysis of MDD with irritability versus onset age found an OR of 0.7 (95% CI = 0.6 to 0.9, p = .010).

These results seem to support the bipolar nature of irritability. This does not mean that irritability is always bipolar (no symptom is 100% specific in psychiatry), but that it is more likely than not to be bipolar. Treatment implications can be important, as the bipolar nature of irritability could require mood-stabilizing agents with antidepressants for the treatment of MDD with irritability, as suggested by clinical observations.[5–9] Controlled studies are required to confirm the findings of the study reported here.

Dr. Benazzi reports no financial or other relationship relevant to the subject of this letter.

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Dr. Perlis and Colleagues Reply

Sir: In his letter, Dr. Benazzi provides an important addition to his previous work,[1–3] as well as our own,[4,5] suggesting that many bipolar subjects experience substantial irritability during depressive episodes. We would, however, emphasize 2 additional aspects of these studies.

First, to refer to the "bipolar nature of irritability" is to neglect the observation, in his study cohort and our own, that roughly 40% of major depressive disorder (MDD) subjects also experienced irritability. Given the greater prevalence of MDD compared to bipolar disorder, it follows that, among patients with an irritable depressive episode, the majority will have MDD. In much the same way, family studies suggest that first-degree family members of bipolar subjects may be more likely to suffer from MDD than bipolar disorder.[6]

Second, while the risks of antidepressant monotherapy in bipolar subjects are well documented[7–9] (but see also Amsterdam et al.[10]), we are aware of only 2 studies that specifically examined the effects of antidepressant treatment of irritable MDD (in particular, MDD with anger attacks); those studies reported a good response to fluoxetine, sertraline, or imipramine, with no evidence of manic switch or precipitation of anger attacks.[11,12] The hypothesis that these individuals would also benefit from mood stabilizer treatment, as Dr. Benazzi suggests, is intriguing but simply has not been studied.

The concept of a bipolar spectrum[13] has greatly enriched the mood disorder literature and continues to generate testable hypotheses. Certainly, a spectrum model accounts well for the overlap in clinical phenomenology between irritable MDD and bipolar disorder noted by Dr. Benazzi in his letter. However, with apologies to Dr. Freud, and despite the clarion call of a host of continuing medical education programs touting underdiagnosis of bipolar disorder, sometimes MDD—even with irritability—is just MDD.

Dr. Perlis has received honoraria, research support, or consulting fees from Eli Lilly, Bristol-Myers Squibb, AstraZeneca, GlaxoSmithKline, and Pfizer. Dr. Fava has received research grant support and honoraria from Aspect Medical Systems, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Johnson & Johnson, Novartis, Organon, Pharmavite, Pfizer, Roche, Sanofi-Synthelabo, Solvay, and Wyeth; has received honoraria only from Bayer AG, Janssen, Lundbeck, Knoll Pharmaceuticals, and Somerset Pharmaceuticals; has received honoraria and company shares from Compellis; and has received research grant support only from Abbott, Lorex, and Lichtwer Pharma GmbH. Dr. Rush has received grant/research support from the National Institute of Mental Health and the Stanley Foundation; has been a consultant/advisor for Bristol-Myers Squibb, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Merck, Organon (Akzo), and the Urban Institute; and has been on the speakers bureau for Cyberonics, Eli Lilly, and Forest.

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Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes: Response to Consensus Statement

Sir: We had made the following points in an earlier letter[1] published in *Diabetes Care*, in which the Consensus Conference report was initially published.[2] In the same spirit that the report was reproduced in *The Journal of Clinical Psychiatry*, it would be useful to reprint our letter, with minor modifications as suggested by the reviewers, in this journal, as it is read more widely by psychiatrists than is *Diabetes Care*.

The following letter, with minor modifications, is the same as that which appeared in Diabetes Care *2004;27:2087–2088:*

The report from the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes consensus panel[3] contains valuable advice for the appropriate and prudent monitoring of patients who are at risk for type 2 diabetes mellitus. The recommendations made are similar to those from a prior consensus conference[4] and, if they are followed, will benefit our vulnerable patients by the early identification and treatment of metabolic disorders. However, the report probably overreaches available evidence when suggesting that clinicians should consider prescribing one antipsychotic over another with the aim of avoiding diabetes.[1]

Quantifiable risk differences among the second-generation antipsychotics regarding an association with diabetes have been inconsistent in large published pharmacoepidemiologic studies.[5,6] This remains puzzling because clear differences exist in liability for weight gain (and consequently dyslipidemias). Taking a conservative stance, the U.S. Food and Drug Administration has required the manufacturers of the second-generation antipsychotics to include a new warning about hyperglycemia and diabetes in the product labeling for all drugs in that class.[7] Risk for type 2 diabetes mellitus attributable to antipsychotics

may be quite small compared with established risk factors such as family history and advancing age. Recent attempts to quantify attributable risk of prescribing clozapine, risperidone, olanzapine, or quetiapine compared to prescribing first-generation antipsychotics revealed attributable risk percentages of 2.03%, 0.05%, 0.63%, and 0.80%, respectively.[8] From the evidence, choosing a second-generation antipsychotic medication does not, in and of itself, have significant practical predictive value for treatment-emergent diabetes compared to established risk factors.

Moreover, the report did not adequately address the complex issues regarding antipsychotic efficacy. Although the Consensus Conference report acknowledged the primacy of appropriate treatment, for example with clozapine having unique benefits for treatment-refractory patients and those at significant risk for suicidal behavior, other antipsychotics may also have a favorable efficacy profile among treatment-resistant patients in specific treatment domains such as cognitive dysfunction (favoring risperidone and olanzapine).[9] In addition, interindividual differences in response may be large, leading to patients' receiving several sequential medication trials over the years to find the optimal regimen for that individual.

As clinicians and researchers in a state-operated psychiatric center, where the average patient has failed a number of medication trials, we find obtaining an adequate antipsychotic medication response to be a major challenge. When such a response is achieved, a major focus is to manage somatic problems should they emerge. Efficacy is the prime mover for treatment decisions.[10] A switch from a beneficial antipsychotic regimen is usually the last resort after other management approaches have not been successful. Taken out of context, the Consensus Conference report might lead the inexperienced practitioner to switch medications prematurely and thus expose the patient to the risk of deterioration in his or her symptoms and, ultimately, relapse.

This letter, with minor modifications, is the same as that which appeared in Diabetes Care *2004;27:2087–2088 (©2004 by the American Diabetes Association). The* Journal *has agreed to publish this letter, as it agreed to dual publication of the article, because it is a topic of great concern to clinical psychiatrists.*

Dr. Citrome has been a consultant for Abbott, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, and Pfizer; has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Janssen, Eli Lilly, Pfizer, and RepliGen; has received honoraria from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Novartis, and Pfizer; has been on speakers or advisory boards for Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Novartis, and Pfizer; and is a stock shareholder in Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, and Pfizer. Dr. Volavka has received grant/research support from GlaxoSmithKline and Forest and has received honoraria from AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, and Eli Lilly.

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Antipsychotic-Induced Sexual Dysfunction and the Strength of the Evidence

Sir: Olfson and colleagues[1] conclude from a cross-sectional study in 139 outpatients with schizophrenia that sexual dysfunction is common in men who are treated with olanzapine, risperidone, quetiapine, or haloperidol and is associated with diminished quality of life and decreased occurrence of romantic relationships.

Their results concerning rates of sexual dysfunction are somewhat surprising both because of the high rates encountered with olanzapine (54.1%) and quetiapine (50%) and because of the lack of differences in impact on sexual functioning among the antipsychotics under study. We agree with the study limitations mentioned by the authors: causality based solely on patients' attribution, lack of baseline assessment of sexual functioning, and lack of power. In addition, a survival bias could partially explain the lack of differences in impact on sexual function. Patients suffering from sexual dysfunction seem to be at greater risk of stopping their medications.[2] Therefore, this survival bias could have favored those antipsychotics accounting for the most troublesome cases of sexual dysfunction (i.e., those cases leading to drug discontinuation and thus not captured by a cross-sectional study).

The authors also state that their results broadly resemble findings from earlier reports.[3–6] However, all those earlier reports were observational and included 2 cross-sectional studies,[3,4] a retrospective study,[5] and a prospective monitoring program,[6] all of which are subject to similar limitations and provide a low level of evidence.[7] In contrast, 2 recent 6-week, open-label, randomized clinical trials have shown more consistent results on the impact of atypical antipsychotics on sexual functioning.[8,9] Sexual dysfunction was reported by 12% of olanzapine-treated patients as compared with 52% of risperidone-treated patients ($p = .004$) in a partially reported randomized trial[8] and by 16% of subjects in the quetiapine group and 50% of subjects in the risperidone group ($p = .006$) in a second trial.[9] Similarly, at 6 months, the risk of loss of libido and impotence/sexual dysfunction was significantly less in the olanzapine group compared with risperidone or haloperidol treatment groups and comparable to that found with quetiapine in a large prospective observational study.[10]

A causal link usually cannot be established from a cross-sectional study, and therefore the findings of Olfson and colleagues[1] on the impact of sexual dysfunction on quality of life and relationships should also be seen with caution. The causal relationship could be the reverse: the main clinical predictor of sexual dysfunction in a large cross-sectional survey of people attending general practitioners[11] was poor physical functioning as measured using the physical subscale score of the Medical Outcomes Study 12-Item Short Form Health Survey (SF-12). Certainly, sexual dysfunction could have an impact on quality of life[12,13]; however, its impact on the quality of life of patients with schizophrenia seems to be much smaller than the impact of other clinical and psychosocial factors.[13]

Sexual dysfunction is an important side effect of antipsychotics. Nevertheless, information on this topic is scanty and largely based on studies providing a low level of evidence. There are multiple unmet research needs for this area, including validation in this population of well-established assessment tools such as Changes in Sexual Functioning Questionnaire,[14] long-term randomized clinical trials to study the effect of antipsychotics on sexual functioning, and further study of the impact of sexual dysfunction on compliance with antipsychotic treatment, quality of life, marital relationships, and illness recurrence. The work of Olfson and colleagues provides some interesting clues, but the evidence they report is not enough to support their firm conclusion.

The authors have received no financial support for this letter. Dr. Rico-Villademoros is an employee of a contract research organization that works or has worked for the manufacturers of the drugs mentioned in this letter. Dr. Calandre reports no financial or other relationship relevant to the subject of this letter.

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Dr. Olfson and Colleagues Reply

Sir: Drs. Rico-Villademoros and Calandre raise important concerns about the limited strength of evidence linking specific antipsychotic medications to sexual dysfunction. We share these concerns and join their call for long-term prospective randomized controlled trials that compare the development of sexual dysfunction in patients treated with various antipsychotic medications. Our study describes the prevalence of sexual dysfunction in schizophrenia and does not seek to establish a cause-effect relationship with individual antipsychotic medications.

Sexual dysfunction is highly prevalent in the general population[1] and is especially common among adults with schizophrenia and other severe mental illnesses.[2] Our study indicates that sexual dysfunction occurs in roughly one third to one half of a community sample of male patients with chronic schizophrenia treated with haloperidol, olanzapine, risperidone, or quetiapine. The study[3,4] cited by Drs. Rico-Villademoros and Calandre, which reported comparatively low rates of sexual dysfunction in patients treated with olanzapine (12%) or quetiapine (16%), differs in several respects from our report. Perhaps most importantly, the study by Knegtering et al. involved young men and women during their first episode of psychosis. It also focused exclusively on sexual dysfunction that patients attributed to their antipsychotic medications. Finally, it was a 6-week study, and as Dr. Rico-Villademoros and colleagues have noted elsewhere, antipsychotic-associated adverse sexual effects "mainly occur in the long term."[5]

Sexual dysfunction is often highly distressing. In the study by Ritsner and colleagues[6] cited by Drs. Rico-Villademoros and Calandre in their letter, sexual dysfunction was strongly and inversely correlated with quality of life ratings in patients with schizophrenia ($r = -0.28$, $p < .001$). Contrary to the assertion made by Drs. Rico-Villademoros and Calandre, Ritsner and colleagues did not examine the relative strength of associations of sexual dysfunction and other clinical and psychosocial factors with quality of life ratings.

Issues of sexuality, including sexual side effects, are rarely addressed in the routine community of treatment of schizophrenia.[4] We agree with Drs. Rico-Villademoros and Calandre that several factors, including clinical and psychosocial factors, commonly have a substantial impact on quality of life in schizophrenia. However, this in no way lessens the importance of sexual dysfunction or of clinical efforts to assess and treat sexual dysfunction in patients with schizophrenia.

Dr. Olfson has been a consultant for McNeil, has received grant/research support from Eli Lilly and Bristol-Myers Squibb, and has participated in speakers or advisory boards for Janssen, Eli Lilly, and Bristol-Myers Squibb. Dr. Carson is an employee of Otsuka Pharmaceutical Co., Ltd. Dr. Tafesse is an employee of Bristol-Myers Squibb. Dr. Uttaro reports no financial or other relationship relevant to the subject of this letter.

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It Looks Like "Bradyphylaxis" to Me

Sir: I call to your attention that the combining form *tachy-* means swift or rapid and that *tachyphylaxis* has been defined as a "rapidly decreasing response to a drug or physiologically active agent after administration of a few doses."[1(p1656)]

That led me to question the use of the term *tachyphylaxis* by Solomon et al., in their recent article, to describe "recurrences of major depression despite maintenance pharmacotherapy,"[2(p283)] especially since the median time to recurrence was 31 weeks—hardly "tachy." Admittedly, *poop-out* leaves something to be desired as a way of communicating among professionals, but rather than distorting the meaning of *tachyphylaxis*, perhaps *bradyphylaxis* would be the better term. Ferrier[3] made the same point a few years ago, but no one seemed to be listening.

A final quibble—Solomon et al. refer to "unipolar major depressive disorder" in the title of their article. Are we dealing with a bit of redundancy, or is there such an entity as non-unipolar major depressive disorder lurking somewhere in the weeds?

Dr. Jefferson reports no financial or other relationship relevant to the subject of this letter.

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Dr. Solomon Replies

Sir: I thank Dr. Jefferson for his interest in our work,[1] which described recurrences of major depression despite full doses of maintenance medication. We observed such recurrences in 25% of the cases in which study subjects were maintained on their antidepressant therapy after successful treatment for an episode of major depression. The morbidity and impairment associated with these recurrences can be devastating.

On the basis of the following, I maintain that *tachyphylaxis*, which literally means "rapid protection," is the proper term to describe recurrences of major depression despite maintenance pharmacotherapy. Goodman & Gilman's pharmacology textbook defines *tachyphylaxis* as a phenomenon in which patients' exposure to agents such as adrenergic agonists "causes a progressive diminution in their capacity to respond to such agents."[2(p141)] Another pharmacology textbook defines *tachyphylaxis* as a process characterized by "gradually diminished responses to repeated administration" of drugs,[3(p111)] and yet another pharmacology textbook states that the term *tachyphylaxis* "describes the loss of response in an organ (e.g., smooth muscle) after repeated exposure to an agonist."[4(p22)] *Mosby's Medical, Nursing, & Allied Health Dictionary* defines *tachyphylaxis* as "a phenomenon in which the repeated administration of some drugs results in a marked decrease in effectiveness."[5(p1676)] Absent from all of these definitions is the idea that the loss of response is rapid, contrary to the sources cited by Dr. Jefferson. Furthermore, Price et al., writing specifically about the treatment of depression, state that the concept of tachyphylaxis "refers to the loss of an initial response to treatment despite maintenance of the drug at the initially effective dosage. Tachyphylaxis usually occurs after several months of treatment. . . ."[6(p196)] This is precisely the manner in which we used the word.

A review of the recent medical literature reveals that tachyphylaxis has been studied in a multitude of medical specialties, including anesthesia, cardiology, dermatology, endocrinology, gastroenterology, neurology, oncology, ophthalmology, otolaryngology, pulmonology, and urology. More to the point, tachyphylaxis has been evaluated over a wide range of time periods, spanning minutes,[7] hours,[8] days,[9] 6 weeks,[10] 8 weeks,[11] 12 weeks,[12] 6 months,[13] 12 months,[14–16] 16 months,[17] 18 months,[18] 2 years,[19] 3 years,[20] 4 years,[21,22] 5 years,[23] 8 years,[24] and 10 years.[25] There are many other studies to cite in which tachyphylaxis has been evaluated for a time period lasting for at least 1 year. Consistent with the sources cited by Dr. Jefferson, it may well be that at one time *tachyphylaxis* did indeed mean rapid loss of response to a drug. However, over time, the rapid aspect of the definition has disappeared, perhaps in part due to the difficulty in deciding where "tachy" ends and "brady" begins.

In the current nosology of DSM-IV, Dr. Jefferson is correct that the phrase *unipolar major depressive disorder* in the title of the article is redundant. DSM-IV recognizes episodes of "major depression," which can occur in either major depressive disorder or bipolar disorder.[26] However, the Collaborative Depression Study is based on Research Diagnostic Criteria,[27] the leading system of psychiatric nosology in 1978, when the Collaborative Depression Study began enrolling subjects. (Research Diagnostic Criteria served as the progenitor to DSM-III.) Research Diagnostic Criteria do not employ the phrase *major depression*; instead, they describe episodes of "major depressive disorder." The subtypes of major depressive disorder include unipolar major depressive disorder and bipolar major depressive disorder.

Dr. Solomon reports no financial or other relationship relevant to the subject of this letter.

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