Letters to the Editor

Underdiagnosis of Bipolar II Disorders in the Community

Sir: I have read the important article by Hirschfeld et al.,[1] which states that the Mood Disorder Questionnaire (MDQ) screening tool found a 3.4% community prevalence of bipolar I and II disorders. The authors stress that this figure is much higher than the figures previously found in large community studies, figures that are also reported in DSM-IV. The authors also rightly state that the MDQ may underestimate the prevalence of bipolar spectrum disorders. Adding together the prevalence of each bipolar disorder classified in DSM-IV results in a bipolar disorders (spectrum) prevalence of up to 3.1%, which is similar to that found by Hirschfeld et al.[1] using the MDQ.

This comparison suggests that the MDQ may not represent a marked improvement over the structured interviewing assessments done in previous community studies reported in DSM-IV. One must remember, however, that the MDQ is a screening tool (not a diagnostic interview), and it requires much less time to administer (with similar prevalence results) compared with structured interviews. Still, compared with the Structured Clinical Interview for DSM-IV (SCID) diagnoses, the MDQ had low sensitivity (0.28) and high specificity (0.97) in the community, meaning that 7 in 10 true bipolar individuals were missed.[2] In screening, high sensitivity (few false negatives) is more important than specificity,[3] because it can reduce the high underdiagnosis of bipolar disorders when administration of the screening instrument is followed by a clinical interview.[4] Many community studies have reported a higher prevalence of bipolar disorders,[5–7] and the last community study by Angst et al.[5] (of which I am a coauthor) found a prevalence of bipolar II and minor bipolar disorders of up to 11%, similar to that of depressive disorders. The narrow DSM-IV criteria underestimate bipolar prevalence, according to the American Psychiatric Association.[8] Semistructured interviews (based on diagnostic criteria) done by skilled clinicians had much higher reliability and validity compared with structured interviews by nonclinician interviewers (DSM-IV figures are based on studies using the latter type of interviews).[4,9–11]

However, the MDQ does have advantages compared with structured interviews such as the SCID: lack of skip-out instruction in questions about mood change (requiring switching to a nonbipolar disorder if the answer is negative), lack of priority of mood change (in DSM-IV, mood change must always be present for bipolar diagnosis), and many questions assessing overactivity. Overactivity showed the same priority as, or higher priority than, mood change for the diagnosis of bipolar disorders.[12–17] MDQ criteria have the limitation of requiring moderate/severe impairment to diagnose bipolar disorders ("marked impairment" in DSM-IV marks the unclear boundary between mania and hypomania). Because hypomania often causes improved functioning,[18–21] the MDQ highly underdiagnoses bipolar II and minor bipolar disorders. High prevalence of bipolar II was found by clinicians using semistructured interviews, which probed more for overactivity than for mood change and did not require impairment for bipolar II diagnosis.[5,16,18,22–24]

Structured interviews and self-assessed questionnaires cannot take the place of skillful clinical evaluation for bipolar II diagnosis.[4,9–11,16,18] Only the latter kind of interviews could estimate community prevalence of bipolar spectrum disorders without too much underdiagnosing.

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

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Charles Bonnet Syndrome With Visual Hallucinations of Childhood Experience: Successful Treatment of 1 Patient With Risperidone

Sir: Charles Bonnet syndrome (CBS) is characterized by the occurrence of scenic visual hallucinations in elderly patients suffering from an ophthalmologic disorder in the absence of any psychiatric illness. The exact etiology of CBS remains unknown, although it has been associated with lesions at different levels of the visual system or in areas not related to the visual system. The present case report describes the response of a woman with CBS to treatment with risperidone.

Case report. Ms. A, a 57-year-old woman, had a personal history of depression and diabetes mellitus. She was diagnosed with major depressive disorder (DSM-IV criteria) at age 50. After 2 years of treatment with amoxapine, 50 mg daily, her symptoms remitted and the treatment was discontinued. Her blood glucose level was maintained in a reasonable range by regular insulin injections. There was no family history of psychiatric disorder.

Ms. A was admitted to our hospital with a diagnosis of diabetic retinopathy and cataract. She had undergone a surgical operation for cataract, but her visual acuity had not improved. A week after the operation, she experienced visual hallucinations, which she described later as being scenes from her childhood. The psychiatric examination performed after the episode of hallucination showed that she was fully oriented, and her Mini-Mental State Examination score[1] was within the normal range. She displayed no symptoms of depression, and the Hamilton Rating Scale for Depression score[2] indicated that she was not depressive at the time of examination. Electroencephalogram and magnetic resonance imaging revealed no abnormalities. The psychiatric symptoms that Ms. A displayed at the time of examination matched the diagnostic criteria for CBS described by Gold and Rabins[3]: (a) visual hallucinations, which are formed, complex, persistent (repetitive), and stereotyped; (b) fully or partially retained insight; (c) absence of primary or secondary delusions; and (d) absence of hallucination in other modalities.

After the CBS diagnosis was established, we initiated treatment with risperidone, 1 mg daily. After 1 week, the number of episodes of hallucination was markedly reduced. Two weeks later, Ms. A had no visual hallucinations, and she remained free of psychiatric symptoms with risperidone treatment for another 3 months. No significant side effects to treatment with risperidone were described.

It is important to notice that in this case, the patient's visual hallucinations were based on actual life experiences from her childhood. Geoffrey and Ronald[4] reported that the relationship between CBS visual hallucinations and the patient's memory remains unclear, and that in 62 of 64 CBS cases the patients could see no relationship between their hallucinations and past experience. Teunisse et al.[5] reported that in 46 of 60 CBS cases, the patients could detect no recollection of personal past experience in their visual hallucinations and only 1 patient could recognize a clear recollection of her dead husband.

In the present case of CBS, the outcome of treatment with risperidone was excellent. Until now, an effective treatment of CBS has not been described. Several case reports have described the effect of using carbamazepine,[6,7] valproate,[8] melprone,[9] or haloperidol[10] in the therapy of this syndrome. Thorpe[11] mentioned treatment with low doses of risperidone in psychotic disorders and CBS. This drug was also reported to be effective in visual hallucinations during disturbance of consciousness such as delirium.[12,13]

In conclusion, our report presents a case of CBS with visual hallucinations related to actual life experiences from childhood that was successfully treated with an atypical neuroleptic, risperidone. Further studies are needed to confirm the effectiveness of risperidone in CBS.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Polypharmacy in Schizophrenia: A Fuzzy Concept

Sir: It is easy to criticize the practice of "polypharmacy" for schizophrenia, on theoretical grounds, on evidence-based grounds, and on economic grounds.[1] Unfortunately, the term *polypharmacy* suffers from conceptual fuzziness and from ambiguity and imprecision in its definition. Clearly, not all polypharmacy is the same. It is imperative to understand what exactly we mean by "polypharmacy," or if there even is such a thing as "monotherapy." Otherwise, we come to wrong conclusions about the merits or dangers of polypharmacy.

Most often, polypharmacy in the treatment of schizophrenia is used to mean antipsychotic polypharmacy—the use of 2 antipsychotics. The limitations and methodological issues of this practice are fairly well understood.[2] In other instances, however, it is used to mean adding *any* second psychotropic to increase the efficacy of the antipsychotic. It can also mean that a second psychotropic is added to combat side effects from the primary treatment. Last, it can mean using other psychotropics for the treatment of comorbid psychiatric conditions. Thus, in its broadest sense, polypharmacy is defined by simply counting the number of psychotropics without regard to class or intent. Differences between regimens are obfuscated if the intent is ignored. Surely, a patient with schizophrenia receiving bupropion for smoking cessation added to his antipsychotic is to be viewed differently than the patient receiving bupropion for residual negative symptoms or subsyndromal depressive symptoms.

Conceptually, the issue is further complicated in that many monotherapies are in fact intrinsically polypharmacy: essentially all antipsychotics combine several pharmacodynamic actions in one molecule. Clozapine is a good case in point, acting upon at least 6 classes of receptors in brain. At the receptor level, monotherapy is a myth, polypharmacy the rule.

These theoretical considerations have real-life implications. Since we will never have adequate trial-based evidence for all combinations that we use clinically, evidence-based medicine can be used to argue against combining medications: lack of scientific proof for the efficacy of a particular combination is taken to mean that the regimen is irrational. By extension, the number of medications that can be prescribed is administratively proscribed, which is particularly true in times of limited resources. While, undoubtedly, medications can often be simplified, complex regimens are sometimes necessary, justified, and helpful. A thoughtful clinical approach does not throw out the baby with the bath water. Future studies of polypharmacy must acknowledge this conceptual confusion and at a minimum clearly state what is being studied: what class of medication is added and for what purpose (enhanced efficacy, prophylaxis, or side effects). Pending data from controlled studies, careful empirical trials with individual patients remain the best approach for optimizing treatment response.[3]

Dr. Freudenreich has received grant/research support from Pfizer. Dr. Goff has served as a consultant for Eli Lilly, Pfizer, Janssen, AstraZeneca, and Bristol-Myers; has received grant/research support from Eli Lilly and Janssen; and has received honoraria from Eli Lilly, Pfizer, Janssen, and Bristol-Myers.

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Dr. Stahl Replies

Sir: Polypharmacy in schizophrenia can indeed be a fuzzy concept as Freudenreich and Goff point out. It can range from the thoughtful concomitant use of 2 therapeutically synergistic agents, such as adding divalproex to an atypical antipsychotic to hasten and boost antipsychotic actions,[1] to the empiric, possibly irrational, and definitely highly expensive use of 2 fundamentally similar agents at the same time, such as adding full doses of 1 atypical antipsychotic to another.[2–7] When I have written critically about polypharmacy in schizophrenia,[2–6] it has been in reference to atypical-atypical antipsychotic polypharmacy and the concern that expanding without limits certain high-cost practices that have little evidence to support them is now adding significantly to cost-cutting pressures in financially desperate states that are providing treatment for indigent patients with schizophrenia. When pharmacy budgets come under fire, such as they are in California[7] and many other states at the present time, the challenge is to curtail only high-cost/low-evidence practices, but the trend is to cut any high-cost practice. In the treatment of schizophrenia, budget cutbacks are already beginning to lead to restricted access of indigent patients to atypical antipsychotics that have some of the highest costs but also some of the best evidence for therapeutic value.

The loss of best-practice options for our patients with schizophrenia is not a fuzzy concept at all, but one that should increase our resolve to provide the best treatments available for this devastating illness. The point is whether we are willing to accept some restrictions on high-cost practices whose benefits are still not well documented in return for the ability to have open access to the best therapies, regardless of cost. Practitioners should not be forced into never trying innovative drug combinations for schizophrenia, yet might usefully keep in mind that prescribing within systems with limited resources may increasingly require prudence when electing options that have a great deal of cost but not yet a great deal of evidence to support their use, including making sure that the best-documented practices have been exhausted prior to electing even more expensive options.

Fortunately, Freudenreich and Goff have thoughtfully reviewed the evidence for both the risks and the benefits of adding

Table 1. Baseline[a] Demographic and Clinical Characteristics of 107 Patients Receiving Second-Generation Antipsychotics

Characteristic	Clozapine (N = 10)	Olanzapine (N = 55)	Quetiapine (N = 8)	Risperidone (N = 34)
Sex, % male	90	65	50	72
Race, %				
White	67	59	50	55
Black	33	28	37.5	41.5
Other	0	13	12.5	3.5
Age, mean ± SD, y	36.9 ± 4.7	44.0 ± 16.0	43.0 ± 15.8	43.3 ± 12.4
Antipsychotic dose, mean ± SD, mg/d	587.5 ± 248.1	20.9 ± 6.7	587.5 ± 247.5	6.3 ± 3.7
Weight, mean ± SD, lb	182.9 ± 39.1	178.4 ± 43.2	168.6 ± 49.1	173.5 ± 34.3
Total cholesterol, mean ± SD, mg/dL	175.3 ± 33.4	189.5 ± 41.6	195.9 ± 22.7	174.4 ± 32.3
Triglycerides, mean ± SD, mg/dL[b]	136.0 ± 44.7	173.5 ± 90.0	105.0 ± 23.2	127.0 ± 43.7
Blood glucose, mean ± SD, mg/dL	93.0 ± 11.4	90.0 ± 14.3	88.6 ± 11.2	99.0 ± 34.7

[a]Baseline = within 3 months prior to starting second-generation antipsychotic.
[b]$F = 3.47$, $df = 3$, $p = .0203$.

2 atypical antipsychotic agents together and have also proposed a way forward to investigate the usefulness of this approach.[8] In the meantime, perhaps we ought to prioritize the value of evidence over pharmacy costs when we make decisions about resource allocation, and continue to strive to keep the best therapies available for our patients while encouraging innovative applications of new evidence as it becomes available.

Dr. Stahl has received grant/research support and honoraria from and served as a consultant to and on the speakers board for AstraZeneca, Bristol-Myers, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Lundbeck, Organon, Parke-Davis, Pfizer, Pharmacia, Sanofi-Synthelabo, Solvay, Watson, and Wyeth; has received grant/research support and honoraria from and served as a consultant for Asahi, Bayer, Boehringer-Ingelheim, Cypress Bioscience, Pierre Fabre, and Yamanouchi; and has received honoraria from and served as a consultant for Abbott, Aventis, Lorex, Neurocrine, Novartis, Roche, Sanao, Searle, Sumitomo, and Takeda Abbott.

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Six-Month Review of Weight and Metabolic Parameters in Patients Receiving Clozapine, Risperidone, Olanzapine, or Quetiapine

Sir: Recently, due to the expanded use of the second-generation antipsychotics (SGAs), many reports of weight gain and metabolic abnormalities of treatment have emerged. These adverse effects of antipsychotic treatment may lead to morbidities such as cardiovascular disease, cancer, osteoarthritis, type 2 diabetes, and early death. Very few long-term comparative studies of the metabolic consequences of antipsychotic treatment are available. Furthermore, little is known about weight gain and metabolic changes associated with long-term treatment with quetiapine.

Method. This retrospective study identified all patients with a DSM-IV diagnosis of schizophrenia who were prescribed clozapine, risperidone, olanzapine, or quetiapine in a state inpatient mental health facility in Maryland between June 1997 and June 1998. Along with demographic and medication information, baseline and 6-month weights, blood glucose, total cholesterol, triglycerides, and blood pressure results were collected for all of the patients. Laboratory data were collected prior to morning meals, in a fasting condition, and no patients were undergoing a weight reduction program. All patients had been treated with conventional antipsychotics or risperidone prior to this current trial. Approximately 35% of all patients were receiving mood stabilizers prior to the antipsychotic treatment and continued throughout the period of study. Pearson chi-square tests and analyses of variance (ANOVAs) and covariance (ANCOVAs) were used to examine differences among drug groups.

Results. One hundred seven chronic inpatients with schizophrenia were treated with SGA medications during the study period (olanzapine N = 55, risperidone N = 34, clozapine N = 10, and quetiapine N = 8). Baseline demographic and clinical information is listed in Table 1. Results are expressed as mean ± SD. Weight gain was associated with all of the SGAs during the 6-month period (clozapine 15.5 ± 17.2 lb [7.0 ± 7.7 kg], olanzapine 7.8 ± 12.6 lb [3.5 ± 5.7 kg], quetiapine 8.3 ± 32.0 lb [3.7 ± 14.4 kg], risperidone 6.7 ± 13.9 lb [3.0 ± 6.3 kg]). For each of the SGAs, there were patients who experienced weight loss during treatment; however, gains of over 35 lb (16 kg) were noted in at least 1 patient in all of the SGA groups. Total cholesterol levels rose (by 20%) with clozapine (endpoint: 210.3 ± 21.3 mg/dL), yet were essentially unchanged with

the other SGAs (olanzapine 187.0 ± 33.4 mg/dL, quetiapine 197.4 ± 46.7 mg/dL, risperidone 179.0 ± 33.9 mg/dL) ($F = 2.44$, $p = .071$, ANCOVA). Triglyceride levels increased by 40% in patients treated with clozapine (endpoint: 189.1 ± 58.1 mg/dL), 6% in patients treated with olanzapine (endpoint: 182.5 ± 98.7 mg/dL), 48% in patients treated with quetiapine (endpoint: 155.3 ± 139.7 mg/dL), and 15% in patients treated with risperidone (endpoint: 147.0 ± 54.2 mg/dL). However, after we controlled for baseline differences in triglycerides, the endpoint values did not represent significant differences in the amount of change among groups ($F = 0.49$, $p = .69$, ANCOVA). Blood glucose levels increased by 16% with clozapine (endpoint: 107.8 ± 32.3 mg/dL) and by 4% with olanzapine (endpoint: 93.3 ± 21.2 mg/dL). Blood glucose levels were found to decrease in the quetiapine (endpoint: 84.4 ± 11.4 mg/dL) and risperidone (endpoint: 90.9 ± 15.8 mg/dL) groups.

Discussion. Clozapine was associated with the greatest increases in weight, lipid levels, and blood glucose levels. This is not surprising, as clozapine is known to be associated with these metabolic changes.[1] Clozapine and olanzapine have also been implicated in most cases of new-onset type 2 diabetes.[2] The blood glucose level changes in this study also demonstrate the propensity of these 2 medications to cause glucose dysregulation. The most interesting finding is the association between the SGAs and elevated triglyceride levels. Triglyceride levels have been reported to be increased in numerous studies involving clozapine and olanzapine.[3] Baseline triglyceride levels for those prescribed olanzapine in this study were significantly higher than in patients prescribed the other SGAs, which may explain lower changes than would be expected with olanzapine. Although the sample size was fairly small, patients prescribed quetiapine experienced a 48% increase in triglyceride levels. Increase in triglyceride levels with quetiapine has only been rarely reported, as 1 article describes hypertriglyceridemia in 2 patients taking quetiapine.[4]

Presently, there is a lack of consensus on the issue of metabolic monitoring during SGA treatment. The concern, however, for severe adverse metabolic outcomes necessitates some investigation in this area. Clinicians should be aware of the potential risk for elevated triglycerides with SGA treatment, and proper monitoring should be undertaken.

Dr. Kelly has received grant/research support from AstraZeneca, Janssen, and Zenith Goldline and has received honoraria from AstraZeneca and Janssen. Dr. Love has been a consultant for Janssen and has received honoraria from and been a speakers/advisory board member for Janssen, AstraZeneca, Pfizer, and Bristol-Myers Squibb. Dr. Conley has been a consultant for AstraZeneca, Aventis, Eli Lilly, Janssen, and Zenith Goldline; has received grant/research support from AstraZeneca, Janssen, Zenith Goldline, Novartis, and Stanley; and has been a speakers/advisory board member for Eli Lilly, Janssen, Zenith Goldline, AstraZeneca, and Bristol-Myers Squibb. Drs. Kreyenbuhl and Van-Duong report no financial affiliation or other relationship relevant to the subject matter of this letter.

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