

Letters to the Editor

Association Between Premenstrual Syndrome and Depression

Sir: We read with great interest the article by Roca and colleagues¹ focusing on the follow-up of women with a previous diagnosis of premenstrual syndrome (PMS). Roca and colleagues demonstrated that PMS seems to be a stable diagnosis over time (5- to 12-year follow-up) by confirming previous diagnosis using 2 prospective cycles of daily ratings (visual analogue scale) and a retrospective evaluation (DSM-IV criteria for premenstrual dysphoric disorder [PMDD]). Despite the fact that only 7 (26%) of 27 former PMS patients and 11 (52%) of 21 controls completed 2 cycles of daily ratings, the revalidation of the PMS diagnosis was remarkable, and all PMS patients met DSM-IV criteria for PMDD. Thus, the stability of the diagnosis seen over time appears to strengthen the validity of PMDD as a distinct syndrome.

The authors also reported a nonsignificant higher incidence of depressive disorders among PMS patients (N = 27) compared with controls (N = 21) in this small clinic-based study. Several authors^{2,3} have also addressed the question of the relationship between depression and severe PMS (lifetime and/or current comorbidity), given the existing overlap of symptoms (e.g., mood swings, lack of energy, and irritability). Previous large community-based studies, on the other hand, have systematically pointed out the significant association between premenstrual symptoms and a lifetime occurrence of psychiatric disorders, as shown in a 10-year prospective epidemiologic cohort study of 218 young adults in Zurich, Switzerland,⁴ and, more recently, in a community-based cohort study of 4000 women from the Harvard Study of Moods and Cycles.⁵

Moreover, it has been postulated that women with premenstrual depressive symptoms may constitute a subgroup with a particular vulnerability to depression during periods of intense hormonal fluctuations, such as the postpartum period or the transition to the menopause.⁶ Thus, to better understand the possible association between depressive episodes and PMS, it would be helpful to know the percentage of PMS patients and controls in the study by Roca and colleagues who developed postpartum blues and/or postpartum depression.

In addition, taking into account the study design, Roca and colleagues had to exclude PMS subjects and controls who were menopausal at follow-up. Those women may have experienced depressive symptoms during the menopausal transition. Similarly, PMS patients and controls with menstrual irregularity also had to be excluded. Considering that a significant percentage of patients suffering from PMS and reporting menstrual irregularity were probably becoming perimenopausal (mean age = 47.1 ± 5.7 years), this could constitute a new opportunity to investigate the extent to which the transition to the menopause would strengthen the association between depression and reproductive-associated psychiatric disturbance.

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Dr. Roca and Colleagues Reply

Sir: We appreciate the thoughtful and astute questions posed by Drs. Soares and Cohen. They correctly raise the possibility that women who display susceptibility to mood disturbance during the menstrual cycle might be vulnerable to depression during other periods of reproductive endocrine change. Although one of the patients (and none of the controls) had a history of postpartum depression, the Structured Clinical Interview for DSM-IV did not enable us to determine retrospectively the occurrence of postpartum blues. While the role of gonadal steroids in postpartum blues, a fairly ubiquitous phenomenon, has not been determined, we have recently shown that euthymic women with a history of postpartum depression will experience depression in association with gonadal steroid manipulations that are without effect in women lacking a history of postpartum depression,¹ thus reinforcing the relevance of the first question raised by Drs. Soares and Cohen.

Similarly, although we were unable, for obvious reasons, to confirm the diagnosis of premenstrual syndrome (PMS) in women who no longer were menstruating, it is possible that the perimenopause might represent a period of increased vulnerability to depression in those with a history of PMS. At follow-up, 9 women with histories of PMS were postmenopausal and 4 were probably perimenopausal (based, albeit imperfectly, on age and recent-onset menstrual cycle irregularity). Of the 9, 3 were currently symptomatic and were being treated with antidepressants, and 2 were asymptomatic but on treatment

with an antidepressant. The 4 remaining subjects were asymptomatic and on no psychotropic medication treatment. Regrettably, the inaccuracy of retrospective estimates of the onset of perimenopause and depression precludes conclusion about the proximity of depression to the perimenopause. Additionally, none of the 4 currently perimenopausal subjects was symptomatic. We conclude, therefore, that this data set is inadequate to answer the important question of the role of the perimenopause in the onset of depression in those with demonstrated reproductive endocrine-related affective disorders.

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Is Antipsychotic Drug-Induced Weight Gain Associated With a Favorable Clinical Response?

Sir: I am writing to comment on Dr. Ganguli's recent article¹ on weight gain associated with antipsychotic drugs. The article stated that reports by Leadbetter et al.² and Lamberti et al.³ differed as to whether clozapine-induced weight gain correlated with clinical improvement among patients with schizophrenia. As a point of clarification, our findings were consistent with those of Leadbetter et al. We found a trend for Brief Psychiatric Rating Scale score changes to correlate inversely with amount of weight gained such that lower (improved) scores were associated with larger gains. Most recently, this issue was examined in a large group of patients with schizophrenia or related disorders receiving treatment with olanzapine, risperidone, or haloperidol.⁴ Analyzing data from a total of 2266 patients, weight gain was found to be associated with a favorable clinical response for each of the 3 drugs.

As noted by Dr. Ganguli, other investigators have not found an association between antipsychotic drug-induced weight gain and clinical improvement.^{5,6} While it remains unclear whether the association exists, the strength of the available evidence suggests that further study is needed. If an association between drug-induced weight gain and clinical improvement is established, it may provide a clue to the mechanisms underlying antipsychotic drug efficacy. Beyond the neuropharmacologic relevance of this issue, the clinical relevance of drug-induced weight gain is clear. Weight gain is a common side effect of antipsychotic medications. While not all patients will experience the side effect to a concerning degree, effective clinical strategies are needed for management of those who do.

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Dr. Ganguli Replies

Sir: I appreciate Dr. Lamberti's comments on my article.¹ He is correct in pointing out that, in his 1992 report, there was an inverse correlation between weight gain and decrease in the Brief Psychiatric Rating Scale score. However, the correlation was not statistically significant (Spearman $r = 0.31$, $df = 28$, $p < .1$). We were not aware of the second study cited by him, which was apparently an unpublished oral presentation. Without further peer-reviewed evidence, we would still contend that the relationship between weight gain and improvement in clinical state remains tentative.

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Polypharmacy of 2 Atypical Antipsychotics

Sir: I am writing to respond to the BRAINSTORMS article by Dr. Stephen Stahl in the July 1999 issue of the *Journal*.¹ I agree that polypharmacy should be avoided. I was a resident in the early 1970s, when even having a person on treatment with an antidepressant and diazepam was considered a serious therapeutic misadventure. In his article, Dr. Stahl stated that no justification exists for using 2 expensive atypical antipsychotics and that this mixture usually results from being trapped in a cross-titration between 2 atypical agents without an adequate trial of monotherapy. I describe a case of a patient who did receive adequate trials of clozapine and olanzapine but nevertheless did best on a mixture of the 2 drugs.

Case report. Ms. A, a 55-year-old woman with a 30-year history of schizoaffective disorder, had numerous admissions over the years for paranoia, delusions, agitation, and some mixed affective components. Finally in 1993, Ms. A's condition was stabilized with clozapine, 300 mg/day. She had tried most neuroleptics as well as lithium, carbamazepine, and divalproex sodium without success until she took clozapine. She was able to live independently in an apartment and was involved in the local mental health center's socialization program. Unfortunately, despite attempts to manipulate her clozapine dosage or

supplement clozapine with antidepressants or typical antipsychotics, Ms. A remained very sedated. Because she slept all night and much of the day, she did not bother anyone, but she would not attend the socialization program very often because she was sleeping.

The mental health center then tried to switch her to olanzapine. Over 3 months, clozapine was gradually decreased and olanzapine, 10 mg/day, was added. When clozapine was stopped, Ms. A's condition greatly deteriorated. She became delusional and agitated and was admitted to the hospital for threatening neighbors and family members. The olanzapine dose was raised to 25 mg/day without any diminution in symptoms. Divalproex, gabapentin, carbamazepine, haloperidol, and clonazepam were tried without any real success. Eventually, Ms. A calmed down enough for discharge back to her apartment on treatment with olanzapine and divalproex. This status lasted only 2 weeks before the paranoia became too great, leading again to agitation and threats. She called her daughter all night complaining about things that were happening or about to happen to her.

Ms. A was readmitted, and her behavior in the hospital was similar to that during the prior admission: paranoia, delusions, agitation, intrusiveness, and rage lasting 30 minutes were followed by her being cooperative and pleasant, only to re-cycle 30 minutes later. Her daughter mentioned that Ms. A was the best she had been in 30 years in late January, when she was taking clozapine and olanzapine. After a call to the mental health center, it was determined that she had been on clozapine, 100 mg/day, and olanzapine, 10 mg/day, at that time. This medication regimen was then instituted with the approval of Ms. A and her daughter, and Ms. A promptly improved. Within 4 days, she was calmer, pleasant, helping elderly patients in the unit, helping the nurses with meals, and not only slept well at night but was also awake and alert during the day. At follow-up 18 months later, Ms. A continued to do well. She went to day treatment regularly, drove neighbors to their doctors' appointments, and even had been allowed to baby-sit her granddaughter alone.

It is unclear why the combination of clozapine and olanzapine worked when numerous other combinations did not. Nevertheless, this patient definitely has had a return to an almost normal life. Fortunately, her daughter is very supportive and caring toward her mother. I spoke to the daughter recently, and she commented that she has not known her mother to be this functional in 30 years. One thing that this case shows is the need to listen to family members. Some of the old notions about monotherapy are not as important anymore; however, the best practice is still to maintain the patient on treatment with the lowest dosage of medication possible as well as the least number of medications.

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Dr. Stahl Replies

Sir: In response to my article on antipsychotic polypharmacy,¹ Dr. Rhoads reports serendipitous observations of a schizoaffective

patient who apparently did much better on treatment with a combination of clozapine and olanzapine than she did with either agent alone. A number of anecdotal observations like his are beginning to make their way into the medical literature, usually as case reports or uncontrolled case series. For example, both risperidone^{2,3} and loxapine⁴ have also been reported to have favorable effects in augmenting clozapine's efficacy in a small number of schizophrenic or schizoaffective patients. A recent report by Taylor et al.³ is the largest series to date (13 patients with only partial responses to clozapine monotherapy) and, although an open study, did use standardized rating scales to rate symptoms on nonclozapine monotherapy, clozapine monotherapy, and risperidone augmentation of clozapine. Their results suggest that 4 patients were much improved, 6 patients minimally improved, and 3 patients were unchanged when risperidone was added to clozapine.

Although it is gratifying to find the occasional patient who finally responds to 2 antipsychotics when monotherapies and other augmentation strategies, such as lamotrigine,⁵ have failed, it should be emphasized that there is no way to predict who might benefit from such an approach. Unfortunately, no controlled trials of antipsychotic augmentation by other antipsychotics have been conducted, even though the rate of use of 2 concomitant antipsychotics is between 10% and 60%.⁶⁻¹⁰ This lack of meaningful clinical guidelines for the use of 2 antipsychotics, plus the potentially huge costs of unlimited experimentation with 2 antipsychotic drugs in the hope of finding a clinically meaningful responder, must be borne in mind before this approach can be advocated.

As the costs of antipsychotic drug treatment skyrockets, there is increasing pressure from payers to restrict their use. For example, in California, the governor has recently convened a task force to control dramatically increasing prescription medication costs in the Medicaid (Medi-Cal) program, due predominantly to increasing costs of atypical antipsychotic drugs. The 2 most expensive drugs in the fee-for-service Medi-Cal program for 1999 were olanzapine at \$115,900,000 and risperidone at \$61,827,000 before any rebates.¹¹ The atypical antipsychotics were also the most expensive medications per claim, per pill, and per day, with olanzapine costing on average \$10.22 per day; risperidone, \$6.29 per day; clozapine, \$11.88 per day; and quetiapine, \$6.54 per day. Although the occasional patient may benefit from 2 such agents, approximately 25% of these patients are receiving 2 antipsychotics. Pressures to reduce escalating drug costs may soon lead to formulary restrictions unless prescribers are cautious about potentially very expensive and as yet unproven uses of these agents. Studies of the cost-effective use of 2 antipsychotics are long overdue. In the meantime, it might be best to administer these powerful and important therapeutic agents as treasured resources whose use will be soon curtailed unless they are prescribed prudently.

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Clarification of Anticholinergic Effects of Quetiapine

Sir: In Table 1 of the article by Kumar and Brecher,¹ the muscarinic receptor binding affinity shown for quetiapine is not supported by the pharmacologic and clinical properties of quetiapine and may mislead the readers regarding the anticholinergic effects of quetiapine. The reference used to support the affinity for the muscarinic receptor (rated as “+++,” or “moderate,” in Table 1) was taken from Pickar,² but this value has previously been refuted by Goldstein.³ It is again important to set the record straight, in particular because their article deals with elderly patients who are especially sensitive to the distressing adverse effects resulting from blockade of the muscarinic receptor.

With regard to anticholinergic properties, the following are true about quetiapine:

- Quetiapine has no appreciable affinity for muscarinic cholinergic receptors ($IC_{50} > 5000$ nM).^{4–8}
- Quetiapine demonstrates no muscarinic acetylcholine antagonist activity in a standard isolated tissue assay (guinea pig ileum) for anticholinergic activity (data on file, AstraZeneca Pharmaceuticals).
- Quetiapine demonstrates no muscarinic acetylcholine antagonist activity in a standard behavioral model (physostigmine-induced lethality in mice) for anticholinergic activity (data on file, AstraZeneca Pharmaceuticals).

It is clear from preclinical pharmacology findings that quetiapine would be predicted to have minimal anticholinergic effects in humans.

In clinical use, the incidence of anticholinergic effects is low. Any observed anticholinergic effects are most likely due to quetiapine's high affinity for the histamine H_1 receptor, since it is known that histamine blockade can cause some “anticholinergic-like” actions that can be manifest in clinical use.⁹ However, quetiapine is very well tolerated in special populations that are especially sensitive to anticholinergic effects, such as elderly patients with psychoses due to Parkinson's disease and Alzheimer's disease. Quetiapine's use as a first-line agent for these populations and for patients with schizophrenia is a testament to this characteristic.

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Side Effect Profile of Enteric-Coated Divalproex Sodium Versus Valproic Acid

Sir: Valproic acid and its derivatives are important agents in the treatment of patients with bipolar illness. This drug has been extensively researched in the treatment of epilepsy, where 2 of its common side effects have included gastrointestinal side effects and thrombocytopenia.^{1–4} Two representative derivatives are valproic acid and divalproex sodium (the enteric-coated derivative), the latter being more expensive but equally effective. However, in individual clinical cases, the side effect profile and tolerability of each of these derivatives also need to be taken into consideration. We present here a case report of a naturalistic A-B-A design, which included the replacement of divalproex by valproic acid that resulted in the occurrence of gastrointestinal symptoms and thrombocytopenia, while a switch back to divalproex resulted in the disappearance of these adverse effects.

Case report. Mr. A, a 45-year-old white, divorced, unemployed man diagnosed by DSM-IV with bipolar I illness, was admitted to a psychiatric hospital with depressed and irritable (mixed) mood state, suicidal intent, and increasing anxiety and agitation. He was started on buspirone, 10 mg t.i.d., and divalproex, 750 mg t.i.d. Thyroxine was continued at a daily dose of 50 μ g for hypothyroidism that had been diagnosed in the past. Four weeks later, Mr. A's divalproex treatment was switched to valproic acid, given twice daily at the same dose. This occurred when he was transferred to another facility, where unless divalproex is specifically requested by the physician, valproic acid is dispensed instead of divalproex. His platelet count the day before the change from divalproex to valproic acid was 151,000/ μ L (normal range, 130,000–400,000/ μ L). Four and 5 weeks later during routine checking of the complete blood count and differential for the appearance of leukopenia, his

platelet count decreased to 122,000/ μ L and 110,000/ μ L, respectively, while no thrombocytopenia-associated symptoms were noted. Such a decrease to below the normal level is not expected to occur spontaneously. These changes were also accompanied by nausea and emesis. These side effects led to a switch back to divalproex and discontinuation of the valproic acid treatment. A gradual increase of the platelet count was noted, up to 151,000/ μ L 2 weeks later. Symptoms of nausea and emesis also improved within 3 days of the switch. Valproate levels were examined along with the platelet count and were found to be within the therapeutic range.

Mr. A's medical conditions included mild obesity, hypothyroidism, and type 2 diabetes mellitus. The history of adverse effects of drug treatment included a history of rash from carbamazepine treatment. Mr. A is a nonsmoker and has a remote history of alcohol abuse, but has been abstinent for 5 years. The type 2 diabetes mellitus and hypothyroidism remained under control with diet and thyroxine treatment, respectively.

Our data concur with the findings of Zarate and colleagues,³ who reported fewer gastrointestinal side effects with divalproex compared with valproic acid. The literature for valproate suggests that gastrointestinal side effects occur in more than 20% of subjects taking this drug, whereas about 1% develop thrombocytopenia with low doses and more than 20% with higher doses.⁴ However, Tohen et al.⁵ reported no case of thrombocytopenia (platelet count < 100,000/ μ L) in a large sample of patients treated with valproate.

We are not aware of previous reports that the frequency of thrombocytopenia is decreased with divalproex versus valproic acid administration. Divalproex, compared with valproic acid, seems to be associated with a less rapid increase of peak plasma levels, reaching peak levels after 3 hours.¹ In contrast, peak plasma levels for valproic acid were observed 0.6 to 1.2 hours after its administration,^{4,6} and its rate of absorption was suggested to be more rapid as compared with divalproex.⁷

No consensus exists as to the mechanism underlying valproate-induced thrombocytopenia.² Interestingly, Gidal et al.² reported that valproate administration also alters some key physiologic functions of platelets. Thrombocytopenia was suggested to occur more frequently in those with high versus low plasma valproate levels.^{2,8,9} On the basis of data associated with a variety of side effects such as tremor and lethargy,⁴ thrombocytopenia may also be associated with a rapid increase in plasma levels. It might be that the less rapid increase of plasma levels with a more flattened curve over time may be relevant to the disappearance of thrombocytopenia in our subject after he was switched from valproic acid back to divalproex. The thrombocytopenia in the present report developed 4 weeks after the initiation of valproic acid. In general, blood dyscrasias are reported with this drug after 2 to 4 weeks of treatment.⁴ The thrombocytopenia with this drug is reported to be transient, that is, it disappears on reduction or discontinuation of the drug. In general, it is recommended to monitor for the appearance of thrombocytopenia if other drugs (e.g., carbamazepine) with potential for inducing a reduction in platelet count are added or as a part of preoperative procedures.^{2,4}

Since other causes, including spontaneous changes and autoimmune processes, may be associated with the thrombocytopenia as observed in our case, there is a need to compare the incidence of thrombocytopenia associated with valproic acid versus divalproex in larger databases. If there are differences in this regard, they may be important from several perspectives: patients' acceptance (side effects, tolerability, adherence to long-term treatment), costs (use of ancillary medications—histamine-2 blockers for gastrointestinal symptoms, laboratory costs of monitoring thrombocytopenia), and the risk-to-benefit ratios in prescribing these different formulations for certain patients.

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Correction

In the article "Mirtazapine Substitution in SSRI-Induced Sexual Dysfunction" by Alan J. Gelenberg, M.D., et al. (May 2000 issue, pp. 356–360), the order of authorship should have shown Cindy McGahuey, B.A., as the second author. The corrected byline is as follows: Alan J. Gelenberg, M.D.; Cindy McGahuey, B.A.; Cindi Laukes, M.A.; Ghadeer Okayli, M.D.; Francisco Moreno, M.D.; Lynda Zentner, R.N.; and Pedro Delgado, M.D.