Correspondence

Managing Depression in Outpatients

To the Editor: An important point in Whooley and Simon's review article on managing depression in outpatients (Dec. 28 issue)[1] that needs greater emphasis is the differential diagnosis of depressive and bipolar disorders. Although most patients will truthfully admit to having had a manic episode if they are asked directly, few patients, in my experience, volunteer this information. A history of hypomania is not volunteered simply because having had periods of feeling very upbeat, having lots of energy, accomplishing a great deal, and needing less sleep than usual is unlikely to be viewed as evidence of illness. And yet bipolar II disorder is quite common, with a prevalence estimated at 1 in 200 or higher.[2,3]

I strongly recommend that every patient being evaluated for depression be asked two simple questions: "What are you like when you are well?" And "Have there ever been periods in your life when you seemed not to need much sleep, you got a lot of things done, and you were really energetic and upbeat?" Alternatively, the Mood Disorder Questionnaire is a simple, valid, and reliable instrument.[4]

Why look for bipolar II disorder? First, it is an inherently life-threatening condition. Patients with the disorder are more likely to attempt suicide than are patients with a depressive disorder or bipolar I disorder, and they are more likely to abuse substances.[3] Second, it is a condition we can easily, if inadvertently, exacerbate. Whereas neglecting to treat unipolar depression prolongs unnecessary suffering, mistreating bipolar depression with antidepressant monotherapy is dangerous: it increases the risk of mania, hypomania, and cycle acceleration.[5]

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To the Editor: Whooley and Simon conclude that for cases of mild depression, *Hypericum perforatum* (St. John's wort), an herbal remedy marketed as a dietary supplement, appears to be as effective as low-dose tricyclic antidepressants, and that "side effects are infrequent." The use of St. John's wort has increased sharply in the United States[1] and in Europe.[2] Given the tendency to regard remedial herbal extracts as harmless, it is essential to be aware of the potential interactions between hypericum and various drugs. At least eight reported cases have suggested that hypericum extracts are potent inducers of hepatic enzymes. These reports are supported by strong evidence that hypericum activates hepatic cytochrome P-450, roughly doubling its metabolic activity.[2] More specifically, hypericum may alter serum concentrations of commonly used drugs, such as warfarin, digoxin,[3] and theophylline.[4] The concomitant use of hypericum in patients being treated with serotonin-reuptake–inhibiting antidepressants (e.g., paroxetine and sertraline) has been reported to result in symptoms characteristic of the serotonin syndrome, a potentially life-threatening condition caused by excess cerebral serotonin.[5] Thus, it is necessary to be aware of potential interactions with hypericum and to recognize the importance of reporting such interactions when they occur.

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1. Gaster B, Holroyd J. St John's wort for depression: a systematic review. Arch Intern Med 2000;160:152-6.
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INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication (subject to editing and abridgment) provided they do not contain material that has been submitted or published elsewhere. Please note the following: •Your letter must be typewritten and triple-spaced. •Its text, not including references, must not exceed 250 words if it is in reference to a recent *Journal* article, or 400 words in all other cases (please provide a word count). •It must have no more than five references and one figure or table. •It must not be signed by any more than three authors. •Letters referring to a recent *Journal* article must be received within four weeks of its publication. •Please include your full address, telephone number, fax number, and e-mail address. •You may send us your letter by standard mail, fax, or e-mail.

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To the Editor: Drs. Whooley and Simon state that "beta-blockers do not cause depression" and cite a study by Gerstman and colleagues.[1] Although beta-blockers may not significantly increase the incidence of depression in the general population, the study by Gerstman et al. does not answer the question of whether beta-blockers increase its incidence among patients with previous episodes of major depression, or whether these drugs should be discontinued if depression develops. We are concerned that some physicians may assume that beta-blockers have been proved safe for patients with previous or ongoing major depression.

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1. Gerstman BB, Jolson HM, Bauer M, Cho P, Livingston JM, Platt R. The incidence of depression in new users of beta-blockers and selected antihypertensives. J Clin Epidemiol 1996;49:809-15.

To the Editor: I would like to call your attention to a mistake in the review by Whooley and Simon. Table 4 on page 1946 lists the antidepressant doxepin (Sinequan) as approved by the Food and Drug Administration (FDA) for alcoholism as well as for depression. In fact, one of the FDA-approved indications for doxepin is "depression and/or anxiety associated with alcoholism" — not alcoholism itself. Readers should not think that doxepin is an effective treatment for alcoholism itself.

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To the Editor: Whooley and Simon's review article on depression made me depressed. Considering depression entirely within a medical model, as one might consider, say, nephritis, sets a low standard of care. Often the most useful thing physicians can offer to a depressed patient is their caring interest. This is best indicated not only by talking and counseling, but especially by listening to the patient. In every case of depression, it is necessary to at least broach the question of what is troubling the patient. Any subsequent therapy or referral is much more likely to be successful in the context of a doctor–patient relationship in which the doctor listens to the patient.

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To the Editor: Whooley and Simon's review did not focus on depression in patients with coexisting chronic physical illness. It may be difficult to diagnose depression in patients with symptoms of chronic illness, such as fatigue or anorexia. In such cases, the cognitive symptoms of depression, such as anhedonia, hopelessness, and a wish to die, gain relative importance in the diagnostic process. Medical staff may view depression as an expected reaction to chronic illness, which may account for the low rates of detection of depression in patients with chronic illness.[1] Randomized, controlled trials have demonstrated that antidepressant medications are effective in patients with many types of chronic illnesses.[2] Most physically ill patients do not tolerate the side effects of tricyclic antidepressants, so the selective serotonin-reuptake inhibitors or other, newer antidepressants should be considered the first-line drugs for such patients.[3] Drug interactions may be of less concern if citalopram or venlafaxine is used to treat depressed patients taking multiple medications.

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1. Perez-Stable EJ, Miranda J, Munoz RF, Ying YW. Depression in medical outpatients: underrecognition and misdiagnosis. Arch Intern Med 1990; 150:1083-8.
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To the Editor: The experiences of women are noticeably absent from Whooley and Simon's review. The higher suicide rate among men is emphasized, but the incidence of depression is twice as high in women as in men,[1] and although men commit more suicides, women make more suicide attempts. Clinicians need guidance on how to advise women who take antidepressants and want to become pregnant, on the safety ratings for antidepressants during pregnancy, and on the postpartum depression that follows 10 to 15 percent[2] of all pregnancies.

Childhood sexual abuse is a powerful predictor of depression, particularly for women.[3] Physicians treating outpatients with depression must ask about such painful past experiences. By neglecting to ask, physicians reinforce the secrecy, shame, and isolation frequently associated with such victimization.[4]

A broader issue illustrated by this article is the way in which women's experiences, both as patients and providers, become invisible if a sex-neutral approach is taken. Female primary care physicians see more female patients than do their male counterparts[5] and thus see far more women with depression.

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1. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8-19.

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The authors reply:

To the Editor: We thank Dr. Carnes et al. for their comments regarding the higher incidence of depression in women, the use of antidepressant medications during pregnancy, the prevalence of postpartum depression, and the relation between childhood sexual abuse and the risk of depression. We regret that space constraints made discussion of these and other important issues beyond the scope of our paper, but we can refer readers to comprehensive reviews of these topics.[1,2]

We agree with Dr. Paley that patients should be asked about a history of mania (elevated mood, increased energy, and impulsivity) whenever a diagnosis of major depression is being considered. This history taking is especially important before one prescribes antidepressant medications, which can precipitate manic episodes in patients with bipolar disorders.

Dr. Gross highlights the potential side effects and drug interactions of *H. perforatum* (St. John's wort). We agree that herbal remedies should never be perceived as risk-free. Recent evidence does suggest that St. John's wort may lower the concentrations of certain drugs, such as warfarin, digoxin, theophylline, cyclosporine, oral contraceptives, and human immunodeficiency virus type 1 protease inhibitors.[3] In addition, at least five cases of symptoms consistent with the serotonin syndrome have been reported in elderly patients taking *H. perforatum* with serotonin-reuptake inhibitors (e.g., sertraline and nefazodone).[4]

Drs. Greisman and Greisman express concern that our statement regarding beta-blockers may cause some providers to assume that beta-blockers have been proved safe for patients with a history of depression. Since there is no clear evidence that beta-blockers are unsafe in patients with a history of depression,[5] we believe it is important not to withhold these medications from any patients who might otherwise benefit from therapy (especially those with heart disease). If depression occurs after the patient starts taking a beta-blocker, it is reasonable to explore potential causality by stopping the drug. However, unless discontinuation clearly alleviates depressive symptoms, concern about the potential contribution of the beta-blocker to depression should not prevent patients from taking it again.

We thank Dr. Gorelick for pointing out that doxepin is approved by the FDA for "depression and/or anxiety associated with alcoholism" and not for alcoholism itself.

We agree with Dr. Blum about the importance of health care providers' offering depressed patients their listening ears and caring interest. Such interventions can be particularly useful as the initial treatment for patients with mild depression and as adjunct therapy for patients with more severe depression.

As Dr. Swenson points out, the detection and treatment of depression are of particular importance in patients with chronic physical illness because depression worsens the prognosis associated with such medical illnesses as cardiovascular disease. We agree that selective serotonin-reuptake inhibitors may be better tolerated than tricyclic antidepressants in many patients and that some serotonin-reuptake inhibitors may slow the metabolism of other medications, but we would not specifically endorse citalopram or venlafaxine as preferred options.

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1. Weissman MM, Olfson M. Depression in women: implications for health care research. Science 1995;269:799-801.
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Fine Particulate Air Pollution and Mortality in 20 U.S. Cities

To the Editor: Samet et al. (Dec. 14 issue)[1] provide compelling, additional evidence of the link between outdoor air pollution — respirable particulate matter less than 10 μm in aerodynamic diameter (PM_{10}), in particular — and mortality. One perplexing finding, however, is the observed associations between outdoor ozone levels and mortality. These were marginally significant and positive during the summer but significant and negative during the winter. The authors suggest that the associations in the summer may reflect the higher levels of ozone during these months, but they fail to address the significance of the negative associations in the winter.

In a recent study, we showed that outdoor ozone levels are not associated with actual exposures to ozone but are strongly associated with exposures to fine particulate matter ($PM_{2.5}$), a correlated component of PM_{10} that has been widely implicated in epidemiologic studies as the size fraction responsible for adverse effects on health.[2] During the summer, we found that outdoor ozone levels were significantly and positively correlated with both outdoor levels of and personal exposures to $PM_{2.5}$. During the winter, outdoor ozone levels were also strongly associated with outdoor levels of and personal exposures to $PM_{2.5}$, but in a negative direction. These results suggest that the results with respect to ozone and mortality reported by Samet et al. are attributable to the fact that ambient ozone is a surrogate for $PM_{2.5}$ and that the observed associations between ozone levels and mortality, both positive and negative, reflect the effect of exposures to $PM_{2.5}$.

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1. Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. N Engl J Med 2000;343:1742-9.
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The authors reply:

To the Editor: Sarnat and colleagues speculate about our finding of a negative association between ozone levels and mortality during the coldest months. We note that in the seasonal analyses, we considered ozone levels alone and did not control for levels of PM_{10} particulate matter. We did perform analyses for the full year that simultaneously included both ozone and PM_{10}; these analyses showed that the estimate of the effect of ozone was not changed by inclusion of PM_{10} in the statistical model. Similar analyses were not carried out for the coldest months alone because of the limited data available for this three-month interval. As we expand our data base, we will be able to test the hypothesis offered by Sarnat and colleagues.

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Chromosomal Abnormalities in Chronic Lymphocytic Leukemia

To the Editor: Döhner and colleagues (Dec. 28 issue)[1] report that in a study of chromosomal abnormalities in patients with chronic lymphocytic leukemia, patients with 17p deletions had a poor prognosis, with a median survival time of 32 months. Of the 325 patients enrolled in the study, 77 (24 percent) had received prior chemotherapy. Although prior chemotherapy is not reported as a prognostic factor in this study, it is the standard of care for patients with advanced disease. Therefore, the high percentage of previously treated patients may have had a confounding effect on this important analysis. Can the authors state how many patients with 17p deletions had received prior treatment and perhaps repeat their analysis with the data for the previously treated patients censored?

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1. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000;343:1910-6.

The authors reply:

To the Editor: Dr. Garcia-Manero raises the important point of the relation between prior chemotherapy and chromosomal aberrations in patients with chronic lymphocytic leukemia. When we analyzed the data for the 77 previously treated patients and the 248 previously untreated patients separately, we found the following differences in the proportions of patients with specific chromosomal aberrations: 13q deletion, 57 percent of previously untreated patients versus 48 percent of previously treated patients; 11q deletion, 14 percent versus 32 percent; 12q trisomy, 17 percent versus 14 percent; and 17p deletion, 5 percent versus 13 percent; 17 percent of the previously untreated patients had a normal karyotype, as compared with 21 percent of the previously treated patients. These results indicate that previously treated patients are more likely to have high-risk chromosomal aberrations (11q and 17p deletions) than are patients without previous treatment. These findings are in line with the more rapid progression of disease, reflected by a shorter time from diagnosis to initial treatment, in the groups with high-risk aberrations.[1]

The limitations of our study sample, particularly with respect to differences in the time at which treatment was initiated and variations in therapy, are obvious. However, the 325 consecutive patients at a single institution (University Hospital in Heidelberg, Germany) constituted a representative population of patients with chronic lymphocytic leukemia. We believe that a separate analysis of previously untreated patients would only introduce a bias toward the selection of patients with benign disease.

The incidence and prognostic importance of chromosomal aberrations in chronic lymphocytic leukemia are being studied prospectively by our group in connection with multicenter treatment trials. Preliminary results show that the rates of high-risk aberrations are similar among previously untreated patients. Even among patients at the earliest stage of chronic lymphocytic leukemia (Binet stage A) in the CLL1 trial of the German CLL Study Group, the incidences of 11q and 17p deletions were 8 percent and 6 percent, respectively.[2] Moreover, the sequential analysis of chromosomal aberrations over time has shown that a clonal evolution in chronic lymphocytic leukemia occurs in 16 percent of patients, with 17p deletions being the most common additional aberration.[3] The occurrence of additional aberrations can be observed in the absence of intercurrent treatment.

All the patients in our study were seen at University Hospital in Heidelberg, Germany. By the time we submitted the manuscript, our entire research group, including all the investigators involved in the study, had moved to University Hospital in Ulm, Germany.

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1. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000;343:1910-6.
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Herbal Medications in the *Physicians' Desk Reference*

To the Editor: The foreword to the 2001 edition of the *Physicians' Desk Reference* (PDR) states, "Each full-length entry provides you with an exact copy of the product's FDA [Food and Drug Administration]-approved labeling."[1] The foreword goes on to say, "For products which do not have official package circulars, the publisher has emphasized the necessity of describing such products comprehensively." However, herbal medications with no FDA approval are now being listed in the PDR. For example, page 2843 of the 2001 edition of the PDR includes "Calm Colon" capsules, states that "Calm Colon is indicated for irritable bowel syndrome," and lists the composition of the supplement, noting that "each Calm Colon capsule contains 500 mg of a 5:1 aqueous extract [of 20] herbs." Some of these herbs have been associated with serious toxicity.[2-6] The PDR should review its policies and should not list potentially toxic herbal medications with no proven efficacy.

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A spokesperson for the *Physicians' Desk Reference* replies:

To the Editor: We concur with Dr. Lawyer that entries on products such as "Calm Colon" are inappropriate in the PDR. It is against our policy to include such entries, and we are taking measures to prevent similar oversights in the future.

We have attempted to address the recent proliferation of unapproved dietary supplements with the publication of two new volumes, the *PDR for Herbal Medicines* and the *PDR for Nutritional Supplements*. These references supply physicians with detailed information on the actions and pharmacology of specific herbs and supplements, including their potential for toxicity and the circumstances in which they are contraindicated. Both books present unbiased clinical findings drawn from the scientific literature and discuss which purported benefits have been verified and which are unfounded.

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