

# Letters to the Editor

## WATCHERS: Recognizing Generalized Anxiety Disorder

**Sir:** The recent article by Davidson et al.<sup>1</sup> raises awareness of generalized anxiety disorder (GAD), one of the most commonly diagnosed psychiatric illnesses in the United States, with an estimated life prevalence of 5.1%. To improve recognition of GAD, I have introduced the mnemonic WATCHERS, which describes the core symptoms of this condition as given in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.<sup>2</sup>

The first 2 letters signify the **W**orry and **A**nxiety about events or activities that are difficult to control and that impair functioning for at least 6 months. The remaining letters reflect the 6 symptoms of which at least 3 must be present to diagnose this common condition: **T**ension in muscles, **C**oncentration difficulty, **H**yperarousal (or irritability), **E**nergy loss, **R**estlessness, and **S**leep disturbance. It is hoped that increased recognition of GAD will lead to better management of these patients with improvement in well-being and quality of life.

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## Gold Versus Silver: The Issue of Functional Versus Symptomatic Recovery in Depression

**Sir:** The BRAINSTORMS article in the April 1999 issue of the *Journal* by Dr. Stahl<sup>1</sup> emphasizes an important yet frequently neglected aspect of clinical psychiatry, i.e., undertreatment of mood disorders. Like most of his articles, this is a no-nonsense piece highlighting the psychopharmacologic angle, especially from a clinician's viewpoint. However, the following points are to be considered while appreciating his arguments:

First, the term *recovery* may be divided into at least 2 categories, i.e., symptomatic and functional. Symptomatic recovery, sometimes equated with response to treatment, consists of improvement in psychopathology as assessed through commonly used rating scales such as the Hamilton Rating Scale for Depression. Functional recovery, on the other hand, represents true recovery and well-being of the patient, which are not properly assessed through conventional rating scales.

Next, the assumption that psychopharmacologic interventions can bring sustained resolution of symptoms in depressive disorders has not been fully substantiated. On the other hand, there is an increasing body of research to support the view that depression might be responsible for permanent changes in personality,<sup>2,3</sup> residual features, psychosocial dysfunction, and disability that may persist long after successful completion of pharmacotherapy.<sup>4,5</sup> Combined pharmacotherapy and psychosocial intervention strategies may be more effective than either modality alone, especially if administered at a proper treatment stage.

Finally, in the current context, Rush<sup>6</sup> made a similar statement in one of his editorials concerning the need for differentiating partial recovery from complete remission in mood disorders. He has compared partial recovery in depression to lowered blood pressure (as opposed to normotension) in hypertension or partial control of blood sugar (as opposed to full control) in diabetes mellitus.

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### Dr. Stahl Replies

**Sir:** Dr. Pradhan provides thoughtful input regarding the appropriate threshold of treatment response to target for patients with affective and anxiety disorders. By reminding us that scoring low on a rating scale is not the same thing as being “well,” his comments underscore the need for clinicians to have different outcome targets (i.e., true recovery and well-being) than clinical investigators, whose studies target 50% or greater reduction of symptoms.<sup>1</sup> After all, who would accept a 50% reduction of infectious organisms for an antibiotic or a 50% reduction of tumor cells in malignancies as appropriate outcome targets in these areas of medicine?

Dr. Pradhan also adds the important perspective to my article<sup>1</sup> that psychotherapy combined with pharmacotherapy may

be the ultimate route to a complete recovery from depression, given the psychosocial "damage" that this illness can cause in terms of personality, interpersonal dysfunction, vocational disability, and even increased liability to relapse and nonresponse to future antidepressant treatment. This idea is especially timely, since interesting new studies<sup>2,3</sup> have now appeared subsequent to the publication of my article that show for the first time that psychotherapy can indeed be synergistic with antidepressant treatments, a point well known to practicing clinicians, but only recently being proved in controlled trials.

The point of all this discussion is that clinicians need to "raise the bar" for our expectations of treatment outcomes and not "settle for silver when we can go for gold" for our patients with affective and anxiety disorders. We are currently in an exciting era when the use of antidepressants, psychotherapy, combinations of antidepressants, or combinations of antidepressants and psychotherapy in a sequential pattern are capable of extinguishing symptoms of depression and thus delivering not only symptomatic relief, but also functional recovery in a large proportion of depressed patients.

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### SIADH With Multiple Antidepressants in a Geriatric Patient

**Sir:** The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a known side effect of psychopharmacotherapy, having been reported with nearly all psychotropic drugs.<sup>1</sup> The mechanism of drug-induced SIADH is thought to be mediated serotonergically, but the mechanism is not known for certain at this time.<sup>2</sup> It is often difficult to predict which patients will develop this complication, although certain risk factors are known, such as age  $\geq$  65 years, concomitant diuretic use, and smoking.<sup>3,4</sup> The following case illustrates a propensity toward SIADH in a single patient.

**Case report.** Ms. A, a 70-year-old white woman, was admitted to our inpatient service for electroconvulsive therapy (ECT) for recurrent severe major depressive disorder with psychotic features (DSM-IV criteria). At the time of admission, she was being treated with mirtazapine, 15 mg daily; risperidone, 3 mg daily; and trazodone, 100 mg at bedtime. Serum sodium concentration at the time of admission was 126 mmol/L (all samples drawn at 6:00 a.m.). Ms. A's urine and serum osmolality, as well as urine sodium concentration, was consistent with

SIADH. Her psychotropic medications were rapidly tapered in preparation for the ECT. Within 4 or 5 days, her sodium concentration returned to the 132- to 134-mmol/L range, where it remained throughout the duration of ECT.

Ms. A responded well to ECT, and after her ninth treatment, she was started on venlafaxine (immediate-release form), 37.5 mg b.i.d., which was increased to 75 mg b.i.d. after 2 days. Two days later, her serum sodium concentration dropped to 131 mmol/L and further decreased to 125 mmol/L after 2 more days. Venlafaxine was immediately discontinued, fluid restriction was instituted, and her sodium concentration promptly returned to 135 mmol/L. Of note, at no time during the hospitalization was there evidence of increased fluid intake by Ms. A.

A trial of bupropion (immediate-release form), 75 mg b.i.d., was then initiated in the hope of avoiding the serotonin system. After 4 days of therapy, Ms. A's sodium concentration remained within normal limits, and she was discharged to our Geriatric Psychiatry Day Hospital. Two weeks after discharge, her serum sodium concentration was 137 mmol/L and she was doing well.

A review of Ms. A's chart from her previous admission 6 months prior to this one revealed that her admission sodium concentration, while she was being treated with desipramine, was 126 mmol/L, which rapidly corrected upon cessation of desipramine treatment. No other laboratory data are available for Ms. A.

There are a number of interesting points to this case. Firstly, it is one of the few reported cases of venlafaxine-induced SIADH.<sup>5-8</sup> Secondly, it highlights the fact that not only do idiosyncratic interactions exist between a particular agent and a particular patient leading to SIADH, but certain individuals may be particularly predisposed to the development of SIADH while on treatment with a variety of agents. This patient had documented SIADH on treatment with mirtazapine and risperidone, developed rapid onset of hyponatremia on venlafaxine treatment, and had documented hyponatremia on desipramine treatment that reversed rapidly upon cessation of desipramine. Further study of patients predisposed to the development of SIADH may help us understand the mechanism of medication-induced SIADH. This case also serves to remind clinicians that in assessing a mental status change after the initiation of a new psychotropic treatment, SIADH must be on the differential diagnosis, particularly in patients with known risk factors for the development of SIADH.

The final intriguing aspect of this case is the possibility that bupropion may be an agent that has less of a propensity to induce SIADH than other antidepressants. As mentioned above, some evidence suggests that antidepressant-induced SIADH is mediated through the serotonergic system. Bupropion is thought to have exclusive activity in the dopaminergic system and to completely avoid serotonin.<sup>9</sup> Further research is necessary to investigate whether or not this is a unique property of bupropion that can be used to clinical advantage.

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### Free Drug Fraction Versus Free Drug Concentration

**Sir:** In their article on pharmacokinetic considerations in the elderly, DeVane and Pollock<sup>1</sup> present a wealth of valuable information for the clinician. However, a small point needs clarification. The authors state—as do many textbooks and articles on this subject—that an increase in plasma binding proteins in the elderly “can lead to a diminished free concentration of basic drugs” (italics mine). This notion is also repeated in Table 1 in their article. In fact, however, changes in plasma binding proteins (such as  $\alpha$ -acid glycoprotein) have no lasting effect on the free concentration of a drug, which is the absolute amount of the drug available to affect target sites and cause clinical effects. Rather, increases or decreases in binding proteins alter the free fraction of drug, i.e., the proportion that is not bound to protein.

Alterations in free fraction change how we interpret the therapeutic and toxic ranges for the agent in question, but do not materially affect the actual amount of the drug available to act on target organs.<sup>2,3</sup> In practice, this means that an elderly patient with elevated  $\alpha$ -acid glycoprotein levels would show increased total (free plus protein-bound) drug concentration, decreased free fraction of the drug, and an unchanged free drug concentration. It would be a mistake, in such a case, to reduce the dose of the agent simply on the basis of an elevated total drug concentration; rather, the toxic range for the drug would need to be adjusted upward.<sup>2,4</sup> All this stems from the fact that the free concentration of a drug is dependent solely on the dosing rate and the intrinsic clearance of the agent. For confused clinicians, the article by Greenblatt et al.<sup>2</sup> provides some helpful diagrams on this point.

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### Drs. DeVane and Pollock Reply

**Sir:** We thank Dr. Pies for his thoughtful comments and agree that the free, non-protein-bound concentration of drugs in plasma is more closely correlated with drug effect than total concentration. In addition, for many drugs and situations, including drug-drug interactions that result in displacement of drugs from plasma protein binding sites, the increase in free drug concentration is transient. An exception to this generalization would be a drug with a high hepatic intrinsic clearance whose plasma protein binding is nonrestrictive for elimination and that is administered intravenously.<sup>1</sup> Few drugs are characterized in this manner. For many drugs therapeutically useful in psychiatry, a change in drug binding to plasma proteins results in an altered free fraction that is offset by a change in total drug clearance by the liver, resulting ultimately in an altered total drug concentration in plasma but a free drug concentration similar to that which existed before a change in binding. We intended to simplify this often confusing point in our summary of the effects of aging on the disposition of antidepressants,<sup>2</sup> and we regret any unintentional implication that aging results in a sustained change in free drug concentration. We have previously emphasized the importance of free drug concentration monitoring<sup>3,4</sup>; unfortunately, the techniques to do this are not widely available.

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### Zolpidem-Related Delirium: A Case Report

**Sir:** Zolpidem is a nonbenzodiazepine hypnotic that is used in the treatment of short-term insomnia. Although zolpidem is generally safe and well tolerated, a number of cases of perceptual disturbances and psychosis have been described.<sup>1,2</sup> At least 2 cases of probable zolpidem-related delirium have been reported.<sup>3,4</sup> We report a case of delirium that developed in a patient with low-grade fever after zolpidem was added to her psychotropic medications.

**Case report.** Ms. A, a 26-year-old woman, was treated at a psychiatric inpatient unit for psychotic depression. She had no formal thought disorder, showed no perceptual disturbances, and was cognitively intact. Ten days into the hospitalization, while stabilized on fluoxetine, 20 mg p.o. q.a.m.; risperidone, 3

mg p.o. b.i.d.; and benztropine, 1 mg p.o. b.i.d., Ms. A developed flu-like symptoms with a sore throat, watery eyes, malaise, and a temperature of 99.2°F (37.3°C). A mild increase in muscle tone had been detected after the initiation of risperidone that did not resolve after benztropine was added. Three days after the onset of the viral syndrome, she requested zolpidem for sleep and received a 10-mg dose. Thirty minutes after ingestion, Ms. A was found agitated and confused, rambling about wanting to go to the beach. Her speech was disorganized, and she had visual hallucinations. Her gait was described as "ataxic," and no signs of meningeal irritation were noted. Her temperature was 99.2°F (37.3°C), her pulse 114 b.p.m., and her blood pressure 116/78 mm Hg. When she was evaluated the next morning, her delirium had cleared. Only some lethargy remained for most of the day. Her white blood cell count was 6.2, her creatinine kinase level was 54 U/L (range, 41–117 U/L), and her mild muscular rigidity remained unchanged.

This case serves as a reminder that delirium is often due to multiple etiologies. Although the potential for benzodiazepine hypnotics such as triazolam to cause delirium is well recognized, even fairly benign agents such as zolpidem can contribute to the development of delirium in susceptible individuals. Fever alone can cause delirium, and a case of delirium resulting from risperidone use was described in an elderly woman.<sup>5</sup> Our patient, however, had had a low-grade fever for several days, and she had been treated with risperidone for 2 weeks. Moreover, the patient became delirious 30 minutes after zolpidem was given, consistent with its pharmacokinetic properties. This time course speaks against an acute drug-drug interaction involving the cytochrome P450 system. However, the use of fluoxetine could, through some pharmacodynamic interaction, have led to a predisposing brain state that created "fertile soil" for a later reaction to zolpidem. Cases with prolonged zolpidem-associated hallucinations in patients taking selective serotonin reuptake inhibitors have been described,<sup>6</sup> even though no significant pharmacodynamic or kinetic interaction was found in a formal study.<sup>7</sup> We considered neuroleptic malignant syndrome, since this patient could have been at higher risk for a neuroleptic malignant syndrome-like or serotonin syndrome-like reaction prior to receiving zolpidem.

It is notable that this case involved a woman, as have the majority of reported cases of zolpidem-related mental status changes. As Markowitz and Brewerton<sup>2</sup> point out in their report, young women achieve an almost 50% higher plasma zolpidem level compared with men with a given dose.

In these days of short inpatient stays and aggressive polypharmacy, many patients are treated with more than one agent. Medications that are safe in healthy individuals and routine settings should be used cautiously in ill patients receiving multiple medications. The nonbenzodiazepine hypnotic zolpidem is no exception to this rule, and the lowest effective dose should be used. Special note should be taken with women, who might require a lower dose of zolpidem than men.

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#### Bupropion-Tranlycypromine Combination for Treatment-Refractory Depression

**Sir:** We report the safe and successful use of combined bupropion and tranlycypromine in a case of treatment-refractory depression.

**Case report.** Ms. A, a 27-year-old woman with chronic major depression (DSM-III-R criteria), was treated in 1990 at age 17 with imipramine up to 150 mg/day. In March 1994, after a suicide attempt by imipramine overdose, paroxetine, 20 mg/day, replaced imipramine. On paroxetine, 30 mg/day, and amitriptyline, 50 mg q.h.s., she experienced only mild improvement at 6 months. By 1995, Ms. A was taking paroxetine, 30 mg/day; nortriptyline, 35 mg/day; and temazepam, 15 mg q.h.s. (with a plasma nortriptyline level of 71 ng/mL). Despite the addition of brief trials of methylphenidate, 5 mg b.i.d., her mood remained depressed.

In August 1995, bupropion was initiated with the gradual withdrawal of nortriptyline and paroxetine. Trazodone, 25 mg q.h.s., replaced temazepam. By October 1995, Ms. A was taking bupropion, 150 mg b.i.d.; trazodone, 100 mg q.h.s.; and lorazepam, 0.5 mg t.i.d., with only a partial response. A trial of adjunctive liothyronine (T<sub>3</sub>), 25–75 µg/day, failed to yield sustained improvement, and her dysphoria, fatigue, and insomnia instead worsened. Tranlycypromine was added and upon titration to 50 mg/day, Ms. A reported a gradual return to euthymia with resolution of her long-standing depressive symptoms.

Bupropion was tapered and discontinued in March 1996, but within 2 weeks, Ms. A noted a return of depressive symptoms. Bupropion was therefore restarted with good results. On one occasion, Ms. A developed symptomatic hypertension after eating cheese, but it was managed with nifedipine at home. Other than this episode, she was normotensive at all checkups. By the summer of 1996, T<sub>3</sub>, trazodone, and lorazepam were withdrawn. She remained on a regimen of tranlycypromine, 60 mg/day (40 mg in the morning and 20 mg at noon), and bupropion sustained release (SR), 150 mg b.i.d., with sustained euthymia. Transient and mild periods of stress-related dysphoria or insomnia were manageable with low-dose lorazepam. In November 1997, tranlycypromine was withdrawn in order for Ms. A to undergo a surgical procedure. During the 2 weeks off tranlycypromine treatment, she experienced an acute worsening of mood symptoms that quickly resolved with its reintroduction. Two years later, she remains on tranlycypromine, 60 mg/day, and bupropion SR, 150 mg b.i.d., without relapse of depression. She continues to keep nifedipine in the event of a hypertensive crisis, but aside from her 1 episode associated with ingestion of cheese 3 years ago, she has had no further blood pressure elevations over the course of her treatment.

Ms. A's case is remarkable for chronic depression unresponsive to treatment with a selective serotonin reuptake inhibitor and tricyclic antidepressants, as well as adjunctive methylphenidate and T<sub>3</sub>. The addition of tranylcypromine to bupropion finally resulted in a sustained remission of her depression. Depressive symptoms returned whenever either antidepressant was withdrawn over the course of treatment, thereby emphasizing the apparent necessity of both antidepressants for treatment response. Ms. A's poor response to multiple antidepressant trials, including both a tricyclic and tranylcypromine alone, classifies her depression at Stage IV resistance as defined by Thase and Rush.<sup>1</sup> The treatment of choice for Stage IV resistant depression is electroconvulsive therapy (ECT).<sup>1</sup> ECT was not administered to Ms. A, owing to her desire to continue employment and outpatient management of her depression.

While no controlled double-blind studies support the use of combination antidepressant therapy in treatment-resistant depression,<sup>2</sup> this practice is supported by anecdotal evidence and general clinical opinion. Ms. A's case adds to this body of evidence and suggests that combination antidepressant therapy deserves greater study in refractory depression. Although the combination of bupropion and a monoamine oxidase inhibitor is not usually recommended due to the risk of hypertensive crisis,<sup>3</sup> the cautious administration of tranylcypromine and bupropion together may be a safe and effective strategy in some cases of treatment-resistant depression.

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### Inappropriate Masturbation and Schizophrenia

**Sir:** Inappropriate masturbation and sexual preoccupation in schizophrenia can have disastrous consequences for a patient. We report a case of treatment-resistant schizophrenia in which inappropriate masturbation presented legal and housing problems for the patient and did not resolve with treatment of his psychosis. Behavioral redirection was of no avail, so we resorted to oral medroxyprogesterone acetate (MPA) in an attempt to decrease the incidence of masturbation.

**Case report.** Mr. A is a 42-year-old white man diagnosed with paranoid schizophrenia and alcohol/cocaine abuse (in remission). He was transferred to an inpatient ward from jail, where he was sent after a neighbor complained about his urinating off the porch of his board and care home. The police discovered that Mr. A was a sex offender and had not registered his current address. He had a history of inappropriate masturbation and sexual advances toward females, which led to his conviction after he exposed his genitalia to a minor.

During his recent jail stay, clozapine, which he had been taking for 1 year, was discontinued and he became grossly psychotic to the point of near-mutism and lying in his own feces. On admission to the hospital, his clozapine was resumed, and, even though his psychotic symptoms lessened, he continued to masturbate openly in the ward several times per week. Although he was receiving clozapine, 750 mg/day; divalproex sodium, 2500 mg/day (blood level = 108 µg/mL); and trazodone, 100 mg/day, his behavior did not change, and he often reported "seeing" nude women dance around his bed in the morning, which he acknowledged were not "real."

It was at this time that we considered beginning MPA. Preliminary laboratory values revealed that Mr. A's plasma testosterone (418 ng/dL), luteinizing hormone (6.4 mIU/mL), and follicle-stimulating hormone (4.3 mIU/mL) levels were all within normal limits. After giving consent, Mr. A began oral MPA, 30 mg/day. Over the course of the following week, his "visions" of frolicking nude women dissipated and his masturbation decreased to the point of nonexistence. Additionally, he no longer wore his masturbation "attire," which comprised sweat pants, a hat, and dark sunglasses. His mood remained euthymic throughout this period, and his testosterone level after 1 week of MPA treatment was 285 ng/dL. He was accepted into a community housing project.

Antiandrogenic agents such as MPA are often used to reduce sexual drive and improve sexual conduct in individuals such as Mr. A. MPA inhibits luteinizing hormone and follicle-stimulating hormone, preventing the release of testosterone from the testes and thus decreasing libido and sexual arousal.<sup>1</sup> Yet MPA, unlike some antiandrogens, has not been reported to cause feminization.<sup>2</sup> Additionally, MPA administration can decrease the frequency of erotic fantasies without altering plasma testosterone, luteinizing hormone, or follicle-stimulating hormone levels, suggesting the possibility of a direct central nervous system effect.<sup>1</sup> This potential dissociation between MPA's efficacy and testosterone is particularly important in a psychiatric setting because low testosterone levels can lead to depression.<sup>3</sup>

After starting MPA, Mr. A reported a decline in the frequency of his psychotic sexual fantasies, and although his testosterone level decreased, it remained within the normal range. Patients successfully treated with MPA for troubling fantasies have been shown to experience no adverse effect on penile response.<sup>1</sup> The preservation of sexual function allows for continued appropriate sexual activity while decreasing problematic sexual behavior—a combination that makes the use of MPA in such a setting more consistent with a medical treatment than a punitive measure.

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