Herbal Diuretics and Lithium Toxicity

TO THE EDITOR: Herbal products are readily available for purchase over the counter and often are not viewed by patients as medications. Since many herbs have pharmacological effects, significant side effects and interactions with medications are possible yet poorly understood. We report a case of life-threatening lithium toxicity associated with the use of herbal diuretics.

Ms. A was a 26-year-old single white woman with diagnoses of bipolar disorder and alcohol dependence; the latter was in early full remission. For 5 months she had been stable while taking 900 mg b.i.d. of lithium, 2 mg b.i.d. of risperidone, 20 mg b.i.d. of propranolol, 0.5 mg b.i.d. of lorazepam, 100 mg/day of sertraline, and 25 mg b.i.d. of hydroxyzine. Her lithium level on this drug regimen was 1.1 mmol/liter.

Ms. A came to the emergency room complaining of "dizziness," "grogginess," and loose stools over the several days since she had begun taking an over-the-counter medication (containing chlorpheniramine, pseudoephedrine, and acetaminophen) for sinus problems. She had stopped taking this medication 2 days before her emergency room visit because of these symptoms. She reported using no other nonprescribed medications, alcohol, or drugs. Her vital signs and the results of a physical examination were normal. She left the emergency room before an ECG was performed or any laboratory work was completed because of anxiety.

Ms. A was seen the next day for a scheduled psychiatric clinic visit and again reported feeling "groggy" but better since she had stopped taking the sinus medication. She was alert and oriented and had no tremor. Again she reported no use of any medications other than those previously mentioned. Two days later, Ms. A returned to the emergency room with complaints of nausea, diarrhea, an unsteady gait, tremor, and drowsiness. At this visit she reported that she had been taking an over-the-counter preparation of herbal diuretics for the past 2–3 weeks for weight loss. She was drowsy but oriented and had a coarse tremor, an unsteady gait, and nystagmus. She was admitted to the coronary care unit with a lithium level of 4.5 mmol/liter.

The preparation used by the patient contained the following ingredients: vitamin B_6, potassium, *Equisetum hyemale,* parsley, paprika, uva ursi, ovate buchu, corn silk, juniper, and bromelain. *Equisetum,* parsley, uva ursi, ovate buchu, corn silk, and juniper have diuretic properties (1, 2). Although some of these ingredients can be toxic, we know of no case reports documenting adverse effects nor any literature describing the mechanism of action of such herbal diuretics.

It seems likely that the herbal diuretics were responsible for the patient's lithium toxicity. She had been stable with the same psychotropic medication regimen during the event, and the time course involved makes it unlikely that the over-the-counter sinus medication played a significant role. As there were several herbal diuretics in the preparation used and the mechanism of action of each is unknown, it is impossible to determine which herb or combination of herbs caused the lithium toxicity. This case illustrates the potential for interactions of herbal products with medications and underscores the need for physicians to ask patients directly about any use of herbs.

References

1. PDR for Herbal Medicines, 2nd ed. Montvale, NJ, Medical Economics, 2000
2. Simpson D: Buchu: South Africa's amazing herbal remedy. Scott Med J 1998; 43:189–191

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Biperiden for Excessive Sweating From Clozapine

TO THE EDITOR: Although clozapine remains the gold standard for use with treatment-resistant psychosis, its use is complicated by numerous side effects that limit its acceptability. We report a case of excessive sweating caused by clozapine use that was reversed by biperiden therapy.

Mr. A was a 31-year-old white man with a 13-year history of schizophrenia. His distressing delusions and hallucinations were resistant to treatment with adequate trials of typical antipsychotics, risperidone, and olanzapine. Clozapine treatment produced a robust response but was accompanied by continuous generalized sweating. During sequential trials of chlorpromazine, clozapine, and olanzapine, the sweating occurred only during clozapine treatment.

The inconvenience of changing saturated clothes and linens nightly led Mr. A to request clozapine discontinuation, despite his acknowledgment of frequent suicide attempts during treatment with all other antipsychotics. Dose reductions led to a worsening of his symptoms but did not diminish the sweating. Trials of propranolol, up to 240 mg/day, followed by clonidine, 1.2 mg/day, resulted in no significant reduction in the sweating. Biperiden, titrated to 6 mg/day, resulted in the prompt cessation of generalized sweating without exacerbation of other anticholinergic side effects. Sialorrhea was also eliminated with biperiden therapy.

Excessive sweating occurred in 6% of 842 patients receiving clozapine in clinical trials (PDR), but its cause is puzzling given clozapine's reported antagonism of α_1 and muscarinic receptors. We initially hypothesized that excessive sweating was due to clozapine's effect on circulating norepinephrine (1), but neither propranolol nor clonidine reversed the condition.

Studies have provided evidence that clozapine is a partial agonist at the M_1, M_2, and M_3 subtypes of the muscarinic receptor (2) and a full agonist at the M_4 receptor (3). Muscarinic receptor subtypes are heterogeneously expressed in the autonomic nervous system. Exocrine glands express M_1 and M_3 receptors (4). Talsaclidine, an M_1 agonist, consistently produced hypersalivation in human volunteers and led to generalized muscarinic symptoms, including sweating, at higher doses (5). Sweating and sialorrhea caused by clozapine treatment were eliminated by treatment with biperiden, which possesses relative selectivity for the M_1 receptor (6). This case supports the view that some of clozapine's side effects are due

to its partial agonist effects at subtypes of the muscarinic receptor.

References

1. Pickar D, Owen RR, Litman RE, Konicki PE, Gutierrez R, Rapaport MH: Clinical and biologic response to clozapine in patients with schizophrenia: crossover comparison with fluphenazine. Arch Gen Psychiatry 1992; 49:345–353
2. Olianas MC, Maullu C, Onali P: Mixed agonist-antagonist properties of clozapine at different human cloned muscarinic receptor subtypes expressed in Chinese hamster ovary cells. Neuropsychopharmacology 1999; 20:263–270
3. Zorn SH, Jones SB, Ward KM, Liston DR: Clozapine is a potent and selective muscarinic M4 receptor agonist. Eur J Pharmacol 1994; 269:R1–R2
4. Caulfield MP: Muscarinic receptors: characterization, coupling and function. Pharmacol Ther 1993; 58:319–379
5. Adamus WS, Leonard JP, Troger W: Phase I clinical trials with WAL 2014, a new muscarinic agonist for the treatment of Alzheimer's disease. Life Sci 1995; 56:883–890
6. Bolden C, Cusack B, Richelson E: Antagonism by antimuscarinic and neuroleptic compounds at the five cloned human muscarinic cholinergic receptors expressed in Chinese hamster ovary cells. J Pharmacol Exp Ther 1992; 260:576–580

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Flushing in a Menopausal Woman Taking Venlafaxine

TO THE EDITOR: Many primary care physicians are prescribing venlafaxine for the treatment of mood and anxiety disorders in menopausal women. Since venlafaxine has been demonstrated to be effective in the management of hot flashes in cancer survivors (1, 2), primary care clinicians may select this agent for treating depressed menopausal women with vasomotor symptoms. We describe the apparent return of hot flashes in a depressed menopausal woman treated with venlafaxine.

Ms. A was a 52-year-old single white woman with a depressed mood associated with decreased sleep, increased crying, increased emotional sensitivity, poor concentration, decreased interests, ruminative thoughts, guilt feelings, and hopelessness. She reported no suicidal ideation or psychosis. She had had a prior major depressive episode characterized by similar symptoms. At that time, she was treated with sertraline at an unknown dose. One week after the initiation of sertraline therapy, Ms. A reported the unusual experience of "being unable to move her arms or legs" and feeling "in a fog" for 1 hour. She subsequently stopped taking the medication and did not return for psychiatric treatment.

Her gynecological history was remarkable for a total abdominal hysterectomy and a bilateral salpingo-oophorectomy for the management of severe pelvic pain due to uterine fibroid tumors and endometriosis. Immediately after her gynecological surgery, Ms. A briefly experienced marked vasomotor symptoms, particularly hot flashes, until treatment with conjugated estrogens, 0.625 mg/day, took effect. She remained asymptomatic while taking this dose of conjugated estrogens for 8 years.

After we confirmed her current major depression and gave comprehensive patient education about the medication's side effects, Ms. A agreed to a trial of extended-release venlafaxine. After 2 weeks of venlafaxine, 75 mg/day, she described transient nausea, dry mouth, and a return of "hot flashes." After 5 weeks of therapy, the hot flashes continued on a daily basis and were rated at a moderate severity level. Ms. A noticed a reduction in frequency (to every 2–3 days) and severity (mild to moderate) after 7 weeks of taking venlafaxine, 75 mg/day. At that time, her venlafaxine dose was increased to 150 mg/day in order to enhance the antidepressant response. Ms. A described approximately 5 days of daily hot flashes while taking the higher venlafaxine dose. The frequency and severity of the hot flashes subsequently were reduced to every 2–3 days and mild to moderate severity.

The patient's experience may represent the known flushing side effect observed with selective serotonin reuptake inhibitors, since venlafaxine is known to have minimal effect on noradrenergic activity. At higher doses, venlafaxine has been shown to block the reuptake of both serotonin and norepinephrine (3). This is important to consider because central noradrenergic activity has been implicated in the etiology of menopausal hot flashes (4). Therefore, it is possible that at higher doses of venlafaxine, when noradrenergic activity increases, true hot flashes may be exacerbated in vulnerable populations.

We think that this clinical finding is interesting given that research suggests that low-dose venlafaxine is effective in the management of hot flashes in cancer survivors (1, 2). We encourage clinicians to consider the possible effect of an enhanced flushing response or a return of hot flashes when treating menopausal women with venlafaxine.

References

1. Loprinzi CL, Pisansky TM, Fonseca R, Sloan JA, Zahasky KM, Quella SK, Novotny PJ, Rummans TA, Dumeski DA, Perez EA: Pilot evaluation of venlafaxine hydrochloride for the therapy of hot flashes in cancer survivors. J Clin Oncol 1998; 16:2377–2381
2. Quella SK, Loprinzi CL, Sloan J, Novotny P, Perez EA, Burch PA, Antolak SJ Jr, Pisansky TM: Pilot evaluation of venlafaxine for the treatment of hot flashes in men undergoing androgen ablation therapy for prostate cancer. J Urol 1999; 162:98–102
3. Harvey AT, Rudolph FL, Preskorn SH: Evidence of the dual mechanisms of action of venlafaxine. Arch Gen Psychiatry 2000; 57:503–509
4. Freedman RR: Biochemical, metabolic, and vascular mechanisms in menopausal hot flashes. Fertil Steril 1998; 70:332–337

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Zolpidem Abuse

TO THE EDITOR: Zolpidem is a commonly prescribed short-acting nonbenzodiazepine hypnotic that potentiates γ-aminobutyric acid, an inhibitory neurotransmitter, by binding to benzodiazepine type 1 (BZ_1) receptors. Zolpidem was thought to have low abuse potential (1); however, there are several case reports documenting zolpidem abuse and withdrawal (2–4). Successful zolpidem detoxification with a benzodiazepine has been reported (2). To our knowledge, this is the first case report of a patient who continued to have zolpi-

dem withdrawal symptoms despite treatment with a benzodiazepine.

Ms. A was a 67-year-old Causasian woman who came to a detoxification unit for zolpidem abuse/dependence. She was previously treated for depression, anxiety, and insomnia, as well as alcohol, barbiturate, and benzodiazepine dependence. Ms. A had been treated for insomnia with oral zolpidem, 10 mg at bedtime, but she said she had increased her dose without the knowledge of her physicians, using up to 100 mg/day (20 mg five times a day) for the last 1.5 years. She alternated this use with various benzodiazepines obtained from multiple physicians when zolpidem was unobtainable.

Ms. A came in for treatment with severe generalized tremor, psychomotor agitation, facial flushing, and anxiety, despite taking 300 mg of chlordiazepoxide in divided doses in the first 24 hours of detoxification. She had persistent symptoms despite treatment with benzodiazepines; a tapering dose of zolpidem was initiated in addition to the tapering dose of chlordiazepoxide. After taking 15 mg of zolpidem, her symptoms completely subsided within 30 minutes. Ms. A took zolpidem, 45 mg over 24 hours in divided doses; it was tapered along with chlordiazepoxide over 5 days.

This case demonstrates the risk for abuse/dependence from chronic use of zolpidem in high doses. Although effective for short-term use in suggested doses, it should be used with caution, especially in patients with a history of substance abuse. Since zolpidem acts on the BZ_1 receptor site (1), a benzodiazepine should control its withdrawal symptoms. This patient, however, continued to experience severe withdrawal, despite taking significant doses of chlordiazepoxide. It is possible that she may have also been abusing benzodiazepines and the dose of chlordiazepoxide was too low, but the dramatic resolution of withdrawal symptoms with the first dose of zolpidem makes this case remarkable. This issue requires further study.

References

1. Darcourt G, Pringuey D, Salliere D, Lavoisy J: The safety and tolerability of zolpidem: an update. J Psychopharmacol 1999; 13: 81–93
2. Ravishankar A, Carnwath T: Zolpidem tolerance and dependence: two case reports. J Psychopharmacol 1998; 12:103–104
3. Cavallaro R, Regazzetti MG, Covelli G, Smeraldi E: Tolerance and withdrawal with zolpidem (letter). Lancet 1993; 342:374–375
4. Gericke CA, Ludolph AC: Chronic abuse of zolpidem (letter). JAMA 1994; 272:1721–1722

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Repeated Self-Mutilation and ECT

TO THE EDITOR: In their Clinical Case Conference, Cheryl A. Green, M.D., et al. (1) described a homeless patient with bipolar disorder who had committed two very serious acts of self-mutilation: a near-amputation of his right arm and, 15 years later, an attempted self-enucleation of his right eye. In the intervening years, he had been hospitalized multiple times; several admissions had lasted longer than 10 months; his average length of stay had been approximately 4 months. His medications included one or more mood stabilizers, a neuroleptic, and a benzodiazepine. It appears that this patient, despite his very severe illness and prolonged hospitalizations, was never given ECT.

Readers may be interested in my recent case report (2) regarding a 35-year-old veteran with a 10-year history of repeated self-mutilation and 27 hospitalizations who was successfully treated with maintenance ECT. The patient bears some similarities to the man described by Dr. Green et al.

Mr. A had been given multiple courses of neuroleptics, antidepressants, and mood stabilizers, but he continued to manifest command auditory hallucinations, various religious delusions, and sporadic depressive symptoms. He continued to throw himself down stairs (once requiring plastic surgery for a severe head wound), pulled out his fingernails with his teeth, and attempted to catch a chain saw with his bare hands, severely injuring his right hand. He was then given a year-long trial of clozapine at therapeutic plasma levels—again without success. By then he had accumulated over 2,200 hospital days.

On referral to our hospital, he was given 10 bilateral ECTs at a suprathreshold charge, but on return to his primary hospital, he relapsed into serious self-mutilative behaviors within 1 month. On return, he was again given 10 bilateral ECTs. Haloperidol decanoate, 100 mg/month, was initiated, as well as fluvoxamine, 200 mg at bedtime (both medications had been given previously). Arrangements were then made for him to be transferred to our facility every 2 weeks for maintenance ECT. The interval between the maintenance treatments was gradually lengthened over the next 21 months, during which time he has experienced only one instance of minor self-injurious behavior. He is able to hold a steady job and reside in a board-and-care home with only minimal supervision. In marked contrast to the previous 10 years, he has required no emergency hospitalization.

The role of maintenance ECT in the management of such patients requires further study, but in this case it appears to be both life saving and highly economical.

References

1. Green CA, Knysz W III, Tsuang MT: A homeless person with bipolar disorder and a history of serious self-mutilation. Am J Psychiatry 2000; 157:1392–1397
2. Dean CE: Severe self-injurious behavior associated with treatment-resistant schizophrenia: treatment with maintenance electroconvulsive therapy. J ECT 2000; 16:302–308

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Questions About Reasons for Living

TO THE EDITOR: There is currently considerable uncertainty about which forms of psychosocial and physical treatment are most effective for patients who deliberately harm themselves (1). A study by Kevin M. Mallone, M.D., et al. (2) ascribed "reasons for living" as a protective factor against suicidal acts in subjects with major depression and proposed that eliciting and increasing awareness of reasons for living in depressed patients merit further study as a suicide-prevention strategy. We welcome this original line of enquiry and endorse the authors' recommendations for replication of their findings but contend that their conclusions may be prema-

ture and largely be the result of erroneous interpretation of the direction of causality and the inappropriate use of statistical tests.

The conclusions drawn by the authors appear to rest on three main findings. First, suicide attempters reported significantly greater subjective depression, hopelessness, and suicidal ideation than nonattempters. The significance of this difference was tested by use of the t test, which assumes that the data are normally distributed. However, in the authors' Table 1, it is readily apparent that for the measures of hopelessness and suicidal ideation, the standard deviation multiplied by two is greater than the mean. This indicates that the mean is unlikely to be the center of the distribution, and for data that do not follow a normal distribution, appropriate nonparametric tests ought to be used (3).

Second, the depressed patients who had not attempted suicide scored significantly higher on items from the Reasons for Living Inventory than the attempters. Moreover, the total score on the Reasons for Living Inventory was significantly inversely correlated with scores for hopelessness, suicidal ideation, and subjective depression that were evaluated separately or as a composite measure of "clinical suicidality." Third, objective measures of severity of depression and quantification of life events did not differentiate suicide attempters from nonattempters.

These findings seem to have led the authors to conclude that the nonattempters had a more optimistic mind set because they perceived (or had) more reasons to live or because inner restraints precluded suicide as an option. Although this conclusion appears intuitively appealing, the inverse correlation between reasons for living and clinical measures of suicidality could be equally due to the greater severity of subjectively perceived depression and hopelessness in attempters, resulting in the enumeration of fewer reasons to live and greater suicidal intent. Which of these explanations best fits the data awaits further clarification of the direction of causality, which may be possible with multivariate rather than univariate statistical analysis or a prospective study.

References

1. Hawton K, Townsend E, Arensman E, Gunnell D, Hazell P, House A, van Heeringen K: Psychosocial versus pharmacological treatments for deliberate self harm. Cochrane Database Syst Rev 2000; CD001764
2. Malone KM, Oquendo MA, Haas GL, Ellis SP, Li S, Mann JJ: Protective factors against suicidal acts in major depression: reasons for living. Am J Psychiatry 2000; 157:1084–1088
3. Altman DG, Bland JM: Detecting skewness from summary information. Br Med J 1996; 313:1200

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Dr. Malone and Colleagues Reply

TO THE EDITOR: We welcome the opportunity to address briefly the interesting issues raised by Dr. Mammen and colleagues in response to our article. We disagree with the suggestion by Dr. Mammen et al. that our conclusions are the result of inappropriate statistical tests. We are aware that in statistical analyses involving small groups it is important when employing a two-sample t test that the data are normally distributed. For larger groups, however, it is not so critical, because of the central-limit theorem. With our data, for example, the group sizes were large enough and the distributions were sufficiently nonpathological that the two-sample t test worked well. We confirmed this by using the "double-bootstrap method" to carry out an extremely accurate version of the t test (1). This calculation demonstrated that the ordinary two-sample t test works sufficiently well with these data to be considered an appropriate statistical test. Moreover, using a nonparametric test, as Dr. Mammen et al. suggest, yielded the same result, as use of the Wilcoxon rank sum test resulted in p=0.01 and p= 0.005 for hopelessness and suicidal ideation, respectively.

We agree that the results of clinical association studies are frequently open to more than one interpretation and require replication, as we suggested. Our cross-sectional finding, that a greater score on the Reasons for Living Inventory may protect against the emergence of suicidal behavior during depression, is being tested in a prospective longitudinal study in which multivariate statistical analyses will be used. We look forward to completing and reporting on our findings in due course. In the meantime, we encourage researchers to consider developing clinical treatments to possibly enhance reasons for living during depression that may then be tested to see if they protect against the emergence of suicidal behavior.

Reference

1. Hall P: The Bootstrap and Edgeworth Expansion. New York, Springer-Verlag, 1992

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Classifying Depression

TO THE EDITOR: In his article (1), Gordon Parker, M.D., Ph.D., D.Sc., F.R.A.N.Z.C.P., suggested that the "approach to pursuing potential nonmelancholic subgroupings" is to clinically identify "meaningful syndromes" (p. 1199) with "substantive treatment-specific implications" (p. 1201). We agree with these guidelines, but the failure to include atypical depression as a nonmelancholic subtype is a shortcoming. Atypical depression is included in DSM-IV (296.2) as a parenthetical modifier of major depressive disorder. Atypical depression has been studied in a variety of contexts; a literature review suggests this work fulfills many of Dr. Parker's criteria and indicates its clinical utility.

Psychopharmacological dissection has been used to identify clinically meaningful subtypes among moderately ill, depressed patients (2). In a series of studies (3–7), patients with nonautonomous mood disorder received imipramine, phenelzine, or placebo. On the basis of this work, depressive subtypes were identified: a subgroup with atypical depression (overeating and oversleeping) that was characterized by poor response to tricyclic antidepressants (65 of 147, 44%) and good response to monoamine oxidase inhibitors (MAOIs) (118 of 165, 72%) and a second group with simple mood-reactive depression (mild typical) that was characterized by a

good response to both tricyclic antidepressants and MAOIs. In both groups, response to placebo was approximately 25%.

By use of items from the Hamilton Depression Rating Scale, a measure of endogeneity (melancholia) was constructed. This analysis implied that melancholic symptoms did not seem to be a precondition for imipramine benefit in this group, which suggests that mild typical depression might differ from severe typical depression (melancholia). Clearly, this distinction is not as well supported as that of atypical depression versus other depressions. The prospective identification of a group with a superior response to MAOIs (versus tricyclic antidepressants) supports a unique pathophysiology and a distinct subtype (8).

A prospective epidemiological study by Kendler et al. (9), using latent class analysis, identified mild typical, atypical, and severe typical depression as categorically distinct subtypes. Subjects with atypical depression were characterized by overeating and oversleeping and a high concordance in monozygotic but not dizygotic twin pairs. The syndrome appeared stable over time. Sullivan et al. (10) independently reproduced this typology and noted, "Particularly interesting…was the identification of depressive classes defined principally by the atypicality of the symptoms."

In another context, the concept of atypical depression helped clarify an obscure outcome in a study contrasting imipramine treatment and two types of psychotherapy (11). The effect of imipramine on subjects with nonatypical depression produced a much brighter signal than psychotherapy when patients with atypical depression were separately analyzed. As anticipated, the response of atypically depressed subjects to imipramine did not surpass their response to placebo.

Although no treatment has been shown equal to that of MAOIs, imipramine, and some second-generation drugs, it is important to identify patients with an atypical depressive subtype (12). Subjects with atypical depression who fail to respond to one or two trials with newer antidepressants should receive a trial with an MAOI. These studies meet Dr. Parker's concerns and amplify his conclusions. Patient types identified by two distinct approaches, latent class analysis and psychopharmacologic dissection, had strikingly similar phenomenology (8–10). The use of MAOIs, especially in subjects with atypical depression who have failed to respond to other treatments, is not as widely appreciated as it should be.

References

1. Parker G: Classifying depression: should paradigms lost be regained? Am J Psychiatry 2000; 157:1195–1203
2. Klein DF: The pharmacological validation of diagnoses, in The Validity of Psychiatric Diagnoses. Edited by Robins LN, Barret JE. New York, Raven Press, 1989, pp 203–217
3. Quitkin FM, Stewart JW, McGrath PJ, Liebowitz MR, Harrison WM, Tricamo E, Klein DF, Rabkin JG, Markowitz JS, Wager SG: Phenelzine versus imipramine in the treatment of probable atypical depression: defining syndrome boundaries of selective MAOI responders. Am J Psychiatry 1988; 145:306–311
4. Quitkin FM, McGrath PJ, Stewart JW, Harrison W, Wager SG, Nunes E, Rabkin JG, Tricamo E, Markowitz J, Klein DF: Phenelzine and imipramine in mood reactive depressives: further delineation of the syndrome of atypical depression. Arch Gen Psychiatry 1989; 46:787–793
5. Quitkin FM, McGrath PJ, Stewart JW, Harrison W, Tricamo E, Wager SG, Ocepek-Welikson K, Nunes E, Rabkin JG, Klein DF: Atypical depression, panic attacks, and response to imipramine and phenelzine: a replication. Arch Gen Psychiatry 1990; 47: 935–941
6. Quitkin FM, Harrison W, Stewart JW, McGrath PJ, Tricamo E, Ocepek-Welikson K, Rabkin JG, Wager SG, Nunes E, Klein DF: Response to phenelzine and imipramine in placebo nonresponders with atypical depression: a new application of the crossover design. Arch Gen Psychiatry 1991; 48:319–323
7. Quitkin FM, Stewart JW, McGrath PJ, Tricamo E, Rabkin JG, Ocepek-Welikson K, Nunes E, Harrison W, Klein DF: Columbia atypical depression: a subgroup of depressives with better response to MAOI than to tricyclic antidepressants or placebo. Br J Psychiatry Suppl 1993; 21:30–34
8. Quitkin FM, Stewart JW, McGrath PJ, Nunes EV, Klein DF: The identification and validation of distinct depressive syndromes in a population-based sample of female twins (letter). Arch Gen Psychiatry 1997; 54:970–972
9. Kendler KS, Eaves LJ, Walters EE, Neale MC, Heath AC, Kessler RC: The identification and validation of distinct depressive syndromes in a population-based sample of female twins. Arch Gen Psychiatry 1996; 53:391–399
10. Sullivan PF, Kessler RC, Kendler KS: Latent class analysis of lifetime depressive symptoms in the National Comorbidity Survey. Am J Psychiatry 1998; 155:1398–1406
11. Stewart JW, Garfinkel R, Nunes EV, Donovan S, Klein DF: Atypical features and treatment response in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Clin Psychopharmacol 1998; 18:429–434
12. McGrath PJ, Stewart JW, Janal MN, Petkova E, Quitkin FM, Klein DF: A placebo-controlled study of fluoxetine versus imipramine in the acute treatment of atypical depression. Am J Psychiatry 2000; 157:344–350

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TO THE EDITOR: Dr. Parker reported that bipolar depression is melancholic. Bipolar I and II may be distinct disorders (1, 2). The prevalence of melancholic features may be low in bipolar II outpatients with depression (3), a common (30%–50% of depressed outpatients) and often atypical depression (4, 5). Bipolar II depression in outpatients may be different from the bipolar I depression, primarily in inpatients, studied by Dr. Parker.

Sixty-four consecutive outpatients with unipolar disorders (major depressive disorder or dysthymic disorder) and 97 consecutive outpatients with bipolar II disorder who were seen for treatment of a major depressive episode in a private practice were interviewed at intake with the Structured Clinical Interview for DSM-IV Axis I Disorders—Clinician Version (6). Because the modal duration of hypomania is 1–3 days (7), the 4-day minimum duration of hypomania found in DSM-IV was not a criterion. "At least some days" of hypomania were required in the bipolar outpatients (5). Most bipolar II subjects had experienced 2–3 days of hypomania, and all had had more than one episode of hypomania. Family members or close friends supplemented clinical information. After complete description of study to the subjects, written informed consent was obtained.

Melancholic features were present in 20 of the bipolar II subjects (20.6%) and in 16 of the unipolar subjects (25.0%) (χ^2=0.42, df=1, p=0.51, two-tailed). Atypical features were present in 44 of the bipolar II subjects (45.4%) and in 11 of the

unipolar subjects (17.2%) (χ^2=13.60, df=1, p=0.0002, two-tailed). These findings are in line with those from previous reports (4, 7–10). Outpatient bipolar II depression seems more atypical, not more melancholic, than unipolar depression. Bipolar I and II depressions may have different clinical pictures in different settings.

References

1. Benazzi F: A comparison of the age of onset of bipolar I and bipolar II outpatients. J Affect Disord 1999; 54:249–253
2. Coryell W: Bipolar II disorder: the importance of hypomania, in Bipolar Disorders: Clinical Course and Outcome. Edited by Goldberg JF, Harrow M. Washington, DC, American Psychiatric Press, 1999, pp 219–236
3. Benazzi F: Bipolar II depression with melancholic features. Ann Clin Psychiatry 2000; 12:29–33
4. Benazzi F: Prevalence and clinical features of atypical depression in depressed outpatients: a 467-case study. Psychiatry Res 1999; 86:259–265
5. Akiskal HS: Mood disorders: clinical features, in Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 7th ed. Edited by Sadock BJ, Sadock VA. Philadelphia, Lippincott Williams & Wilkins, 2000, pp 1338–1377
6. First MB, Spitzer RL, Gibbon M, Williams JBW: Structured Clinical Interview for DSM-IV Axis I Disorders—Clinician Version (SCID-CV). Washington, DC, American Psychiatric Press, 1997
7. Akiskal HS: The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. J Clin Psychopharmacol 1996; 16(suppl 1):4S–14S
8. Himmelhoch JM: The paradox of anxiety syndromes comorbid with the bipolar illnesses, in Bipolar Disorders: Clinical Course and Outcome. Edited by Goldberg JF, Harrow M. Washington, DC, American Psychiatric Press, 1999, pp 237–258
9. Perugi G, Akiskal HS, Lattanzi L, Cecconi D, Mastrocinque C, Patronelli A, Vignoli S, Bemi E: The high prevalence of "soft" bipolar (II) features in atypical depression. Compr Psychiatry 1998; 39:63–71
10. Baldessarini R: A plea for integrity of the bipolar disorder concept. Bipolar Disord 2000; 2:3–7

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Dr. Parker Replies

TO THE EDITOR: I agree strongly with Dr. Quitkin and colleagues that atypical depression can well be conceptualized according to our spectrum model of the nonmelancholic disorders. In seeking to articulate the model in the article, I restricted examples to the two most consistently identified disorders (i.e., "anxious depression" and "irritable/hostile depression") but suggested that other expressions must be presumed. In our current research, we included other personality styles (e.g., obsessional, introverted, impulsive) to examine the extent to which a meaningful definition of the nonmelancholic disorders involves respecting a temperament style diathesis. Atypical depression is a useful candidate as its (DSM-IV) criteria include "a long-standing pattern of extreme sensitivity to perceived interpersonal rejection," as well as a set of "atypical" depressive features.

The Columbia group's initial observations and their validation efforts are another excellent example of the importance of building on clinical observation to identify intrinsic depressive types instead of using the homogenizing approach of modeling depression on a dimensional paradigm. In addition to undertaking further phenomenological and validation studies, the world might nevertheless appreciate their deriving a better name for this interesting syndrome.

Dr. Benazzi reports me somewhat incorrectly, as I actually stated that "those with bipolar disorder have been reported to be distinctly more likely to have melancholic and psychotic expressions of depression when in a depressed phase" (p. 1199) and referenced both Goodwin and Jamison (1) and one of our own studies (2) in support. The latter compared 83 bipolar and 904 unipolar patients on respective rates for (current) psychotic depression (N=16, 19.3%, versus N=90, 10.0%, respectively) and for DSM-III-R-defined melancholic depression (N=57, 68.7%, versus N=334, 36.9%). Thus, only 10 of our bipolar patients (12.0%), compared to 480 of our unipolar patients (53.1%), might have been presumed to have nonmelancholic depression.

I commented on Dr. Benazzi's study group elsewhere (3). None of his subjects were receiving medication (which calls into question the illness severity of his group), the minimum duration criterion for hypomania in DSM-IV was not respected, and melancholic status was not formalized by use of DSM-IV or another criteria set. Instead, his prevalence data are in regard to unspecified melancholic "features"; the previously mentioned factors limit their interpretation.

Researchers (and clinicians) have long been concerned about the problematic diagnosis and differential diagnosis of bipolar II disorder. As bipolar I and II may or may not be independent conditions, there are advantages to conducting research studies with consideration of the disorders both in combination and separately.

Although patients with bipolar disorder appear highly likely to develop psychotic and melancholic expressions of depression, as with any generalization, there are exceptions. Thus, while I managed the treatment of a patient with bipolar disorder across many episodes of classic melancholic depression, she once appeared with a distinctly different clinical picture—a more reactive depressive disorder that appeared in response to her husband's desertion. Although we concede that there may be exceptions, the possibility that bipolar depression is highly likely to be of the melancholic type allows an indirect approach to defining the nature of melancholia in more refined study groups.

References

1. Goodwin FK, Jamison KR: Manic-Depressive Illness. New York, Oxford University Press, 1990
2. Parker G, Roy K, Wilhelm K, Mitchell D, Hadzi-Pavlovic D: The nature of bipolar depression: implications for the definition of melancholia. J Affect Disord 2000; 59:217–224
3. Parker G: Response to Dr Benazzi. J Affect Disord (in press)

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Late-Onset Schizophrenia-Like Psychosis

TO THE EDITOR: At the risk of being isolationist, I want to take issue with the international consensus on late- and very-late-onset "schizophrenia-like psychosis" (1). I see no heuristic advantage and potentially great therapeutic harm in labeling patients with such illnesses schizophrenic, no matter the prefix or suffix. Conceptually, I thought the international consensus was that schizophrenia is likely a developmental disorder

resulting from an interaction between a genetic predisposition and adverse gestational, labor and delivery, or perhaps neonatal effects on the developing nervous system. Furthermore, this initial lesion expresses itself in childhood with neuromotor, cognitive, and emotional deficits and in late adolescence and young adulthood as a nonaffective psychosis, most likely with negative symptoms and a variable but generally poor long-term course (2). How are we to reconcile this concept with the schizophrenia that develops after 40 or 60 years of age? If we cannot, why call the late-onset psychosis "schizophrenia"? What is wrong with Kraepelin's term "paraphrenia"?

In the recent article on this topic, the consensus group summarized information about these late-onset psychoses: they are more likely to occur in women and to be associated with mood disturbances and with positive rather than negative features (particularly visual hallucinations in elderly subjects) and less likely to be familial for schizophrenia and more likely to be familial for mood disorders. Subjects with these disorders are also more likely to commit suicide. This pattern does not seem to fit the standard set 31 years ago by Robins and Guze (3) for establishing the diagnostic validity of disorders of unknown etiology. Why isn't the late-onset illness a form of mood disorder and the very-late-onset illness part of a heterogeneous group of illnesses that includes delirium, dementia, depression, and the like?

More important, what useful clinical purpose does it serve to call these patients "schizophrenic"? Too many patients are already needlessly exposed to antipsychotics and their risks. Words affect thinking. A patient labeled "schizophrenic" is more likely to receive an antipsychotic and less likely to receive an antidepressant, a mood stabilizer, or ECT than a patient labeled as having an atypical mood disorder or paraphrenia. There used to be an international consensus that illness results from an imbalance in four body humors. Consensus without conceptual logic or clinical utility is meaningless and dangerous.

References

1. Howard R, Rabins PV, Seeman MV, Jeste DV, International Late-Onset Schizophrenia Group: Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. Am J Psychiatry 2000; 157:172–178
2. Susser ES, Brown AS, Gorman JM (eds): Prenatal Exposures in Schizophrenia. Washington, DC, American Psychiatric Press, 1999
3. Robins E, Guze SB: Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry 1970; 126:983–987

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Dr. Howard and Colleagues Reply

TO THE EDITOR: We thank Dr. Taylor for raising several interesting questions about the consensus statement by the International Late-Onset Schizophrenia Group. Such issues have for many years intrigued those who see patients develop psychotic symptoms for the first time in later life. Schizophrenia is, indeed, currently conceptualized as a neurodevelopmental disorder, with onset in late adolescence and young adulthood, but our consensus group concluded that the research evidence base supports the existence of a minority group of patients who show all the features of schizophrenia, except that their illness onset is delayed into middle age. Such a psychosis, with onset after age 40, has been called late-onset schizophrenia since the 1940s (1). The evidence we reviewed does not support Dr. Taylor's suggestion that these patients have a misdiagnosed atypical affective disorder.

The group with onset after age 60 has historically provoked more controversy. It is worth noting that Kraepelin did not coin the term "paraphrenia" to denote a later age at onset; he believed that such patients differ most from those with dementia praecox by their lack of affective flattening and personality deterioration (2). The term "late paraphrenia" never gained acceptance outside European psychiatry and was itself a source of ambiguity and dispute. Indeed, its originators intended that the patients it described be considered to have schizophrenia with an onset delayed into late life (3). This was not the view of the consensus group, as is reflected in the suggested name "schizophrenia-like psychosis."

We agree with Dr. Taylor that psychotic symptoms are seen in elderly people with depression, delirium, and dementia. However, all such patients do not belong in the same category with the now well-recognized group of individuals who develop a schizophrenia-like illness after the age of 60 but do not have a cognitive or mood disorder or acute confusion. Dr. Taylor suggests that by diagnosing a person with schizophrenia we increase the chances of his or her being treated with antipsychotics. We do not believe that a diagnosis of schizophrenia necessitates a need for antipsychotic use. These drugs are appropriately labeled "antipsychotic," not "antischizophrenic." Indeed, schizophrenia patients constitute only a small minority of the elderly individuals who receive antipsychotic drugs.

We accept that cutoffs for age at onset will always be arbitrary and that our choice of terminology was on the basis of what little we know about what Kraepelin called "the darkest area of psychiatry" (2). Our hope is to stimulate further study and debate regarding such patients.

References

1. Bleuler M: Die spatschizophrenen Krankheitsbilder. Fortschr Neurol Psychiatr 1943; 15:259–290
2. Kraepelin E: Dementia Praecox and Paraphrenia (1919). Translated by Barclay RM; edited by Robertson GM. New York, Robert E Krieger, 1971
3. Kay DWK, Roth M: Environmental and hereditary factors in the schizophrenias of old age ("late paraphrenia") and their bearing on the general problem of causation in schizophrenia. J Ment Sci 1961; 107:649–686

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Aggression, Serotonin, and Seasonality

TO THE EDITOR: Barbara Stanley, Ph.D., and colleagues (1) reported decreased concentrations of 5-hydroxyindoleacetic acid (5-HIAA) in CSF in a cohort of aggressive and nonaggressive patients without the "potential confound" of suicidal behavior. However, the authors did not acknowledge the important potential confound of seasonal variation in both

serotonin function and aggressive behavior. Significant seasonal variation in CSF 5-HIAA concentrations in healthy humans has been reported (2). A review of studies demonstrating significant seasonal variation in a variety of measures of serotonin function in humans has been published elsewhere (3). This fluctuation may underlie the seasonal variation seen in a number of psychiatric disorders and phenomena, including suicide. Notably, the prevalence of human aggression has been shown to vary significantly across seasons (4, 5).

Therefore, given that the role of seasonality in this study was not analyzed by the authors, their conclusions about possible links between CSF 5-HIAA concentrations and aggression may be premature. Seasonal differences in time of lumbar punctures could explain any group differences the authors found. A seasonal analysis could be accomplished by performing a two-way analysis of variance by using the presence of aggression and season as independent variables. Another approach would be to use season or even photoperiod as covariates in an analysis of covariance. Arguably, ample evidence now mandates that seasonality be controlled in all studies of serotonin function.

References

1. Stanley B, Molcho A, Stanley M, Winchel R, Gameroff MJ, Parsons B, Mann JJ: Association of aggressive behavior with altered serotonergic function in patients who are not suicidal. Am J Psychiatry 2000; 157:609–614
2. Brewerton TD, Berrettini WH, Nurnburger JI Jr, Linnoila M: Analysis of seasonal fluctuations of CSF monoamine metabolites and neuropeptides in normal controls: findings with 5HIAA and HVA. Psychiatry Res 1988; 23:257–265
3. Brewerton TD: Seasonal variation of serotonin function in humans: research and clinical implications. Ann Clin Psychiatry 1989; 1:153–164
4. Michael RP, Zumpe D: Sexual violence in the United States and the role of season. Am J Psychiatry 1983; 140:883–886
5. Michael RP, Zumpe D: An annual rhythm in the battering of women. Am J Psychiatry 1986; 143:637–640

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Dr. Stanley Replies

TO THE EDITOR: Dr. Brewerton raises an interesting point regarding a potential confound of seasonal variation in serotonin function and aggressive behavior. He suggests that our findings of lower CSF 5-HIAA concentrations in aggressive individuals may be accounted for by seasonal fluctuation. This seems unlikely. Our measure of aggression was a lifetime history of aggressive behavior, not a single incident that occurred at a specific time of the year. It was an accumulation of behaviors across seasons and over many years. Thus, our aggression measure was not seasonal.

Furthermore, although there is evidence of seasonality in aggression, the findings are not straightforward. Murder does not show a seasonal change (Michael and Zumpe, 1983); the rates of occurrence for rape (Michael and Zumpe, 1983) and the battering of women (Michael and Zumpe, 1986) are higher in the summer. When all forms of suicide are considered, seasonal variation is not always found (1). However, violent suicides are at their peak in the spring (1).

According to Brewerton et al. (1988), CSF 5-HIAA concentrations are at their highest during the summer. When this finding is coupled with the increased rates of battering and rape found during the summer, the results are contrary to the inverse correlation we, as well as others (2, 3), have found between CSF 5-HIAA concentrations and aggression. Dr. Brewerton's point would be more convincing if CSF 5-HIAA levels were lower, rather than higher, in the summer. Nevertheless, Dr. Brewerton's point is well taken, and it seems worthwhile to remember to consider the effect of seasonality on both biological and behavioral measures.

References

1. Pretti A, Miotto P: Seasonality in suicides: the influence of suicide method, gender and age on suicide distribution in Italy. Psychiatry Res 1998; 81:219–231
2. Brown GL, Goodwin FK, Ballenger JC, Goyer PF, Major LF: Aggression in humans correlates with cerebrospinal fluid amine metabolites. Psychiatry Res 1979; 1:131–139
3. Brown GL, Ebert MH, Goyer PF, Jimmerson DC, Klein WJ, Bunney WE, Goodwin FK: Aggression, suicide, and serotonin: relationships to CSF amine metabolites. Am J Psychiatry 1982; 139: 741–746

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Risperidone, Tardive Dyskinesia, and the Elderly

TO THE EDITOR: Dilip V. Jeste, M.D., et al. (1) provided good evidence for the use of risperidone to reduce psychotic symptoms and to prevent and treat tardive dyskinesia in elderly patients with moderate to severe dementia. However, there are problems with their methods, most notably with their analysis of the patients who did not complete the study. They state that of the 330 patients enrolled in an open-label trial of risperidone, 133 (40.3%) completed the 12-month trial. Few reasons were given for patients dropping out, except that nine patients stopped taking risperidone because of extrapyramidal symptoms. The remaining 188 (57.0%) remained unaccounted for at the end of the study.

It is unclear if they dropped out from the study because of other toxic side effects, withdrawal of consent, worsening cognitive impairment, or intercurrent physical illness or if they simply were not deemed to need risperidone any more. The mortality rate of such an elderly group (mean age=82.5 years) with advanced dementia could have been predicted to be high but was not stated by the authors. Hence, the low risk of tardive dyskinesia is presented in isolation from the overall tolerability of risperidone, and a judgment cannot be made about its overall safety.

It is also unclear exactly how many patients the authors were able to follow up in order to assess the presence of tardive dyskinesia. One must assume that all 255 patients who did not initially have tardive dyskinesia must have been assessed for it because the authors did not explicitly state how many did not participate. Therefore, at the 1-year follow-up, the authors concluded that six patients developed emergent tardive dyskinesia during the study and gave an incidence rate of 2.6% of the patients treated for a year. However, only a minority actually received treatment for this long.

Alternatively, the incidence of tardive dyskinesia could be calculated in the 133 patients receiving risperidone at the end of the study. It would not be possible to give an exact rate of

tardive dyskinesia on the basis of these figures, as the relative completion rates of those with and without tardive dyskinesia at the beginning of the study were not provided. However, the number would be in excess of 4.5%. Such a distinction is important, as the length of antipsychotic treatment is associated with the development of tardive dyskinesia in the first few years of treatment (2).

References

1. Jeste DV, Okamoto A, Napolitano J, Kane JM, Martinez RA: Low incidence of persistent tardive dyskinesia in elderly patients with dementia treated with risperidone. Am J Psychiatry 2000; 157:1150–1155
2. Woerner MG, Alvir JM, Saltz BL, Lieberman JA, Kane JM: Prospective study of tardive dyskinesia in the elderly: rates and risk factors. Am J Psychiatry 1998; 155:1521–1528

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Dr. Jeste and Colleagues Reply

TO THE EDITOR: We thank Dr. Chaplin for his thoughtful comments on our article. We reported the results of an open-label study in which 330 institutionalized patients with moderate to severe dementia (mean age=82.5 years), complicated by psychosis or severe agitation, were treated with risperidone for up to 1 year. With a mean dose of 1 mg/day, the 1-year cumulative incidence of persistent tardive dyskinesia, calculated by use of Kaplan-Meier survival analysis (1), was 2.6%—considerably lower than that expected with conventional neuroleptics in an elderly group with dementia.

Dr. Chaplin raises questions about the dropout rate and the use of statistical analysis. Of the 330 patients who entered the study, 133 (40.3%) completed the 1-year investigation, whereas 197 (59.7%) discontinued treatment prematurely. The reasons for discontinuation (with percentages of the total group) were as follows: adverse events (N=87, 26.4%), voluntary discontinuation or administrative reasons (N=77, 23.3%), inadequate response (N=15, 4.5%), or intercurrent illness or abnormal laboratory results (N=18, 5.5%). The types of adverse events ranged from rigidity, agitation, and depression to cellulitis, pneumonia, and, in 8.8% of the patients (N=29), death. Given the advanced age of the subjects and the severity of their cognitive impairment, it is not surprising that a substantial proportion of these institutionalized patients experienced adverse events, whether related to the study medication or not. Because of the design of the investigation, our report did not provide good evidence to address causal associations of any of these events with risperidone therapy.

Survival analysis is a standard statistical technique employed in prospective longitudinal studies for the cumulative incidence of conditions such as tardive dyskinesia (2–4; Woerner et al., 1998). In long-term follow-up investigations, subjects may drop out at different time points. The Kaplan-Meier method (1) is one of the most commonly used techniques that allows use of "at least this long" information on all of the subjects who entered the study to prepare unbiased survival curve estimates. Survival analysis takes the "survival" times for a group of subjects and generates a survival curve, which shows the proportion of members who survive or remain "alive" over time (5). In this study, "survival" referred to the likelihood of a patient's surviving without developing tardive dyskinesia.

References

1. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Statistical Assoc 1958; 53:457–481
2. Kane JM, Woerner M, Lieberman J: Tardive dyskinesia: prevalence, incidence, and risk factors. J Clin Psychopharmacol 1988; 8(4 suppl):52S–56S
3. Jeste DV, Caligiuri MP, Paulsen JS, Heaton RK, Lacro JP, Harris MJ, Bailey A, Fell RL, McAdams LA: Risk of tardive dyskinesia in older patients: a prospective longitudinal study of 266 outpatients. Arch Gen Psychiatry 1995; 52:756–765
4. Jeste DV, Lacro JP, Bailey A, Rockwell E, Harris MJ, Caligiuri MP: Lower incidence of tardive dyskinesia with risperidone compared with haloperidol in older patients. J Am Geriatr Soc 1999; 47:716–719
5. Lawless JF: Statistical Models and Methods for Lifetime Data. New York, John Wiley & Sons, 1982

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Lithium Discontinuation: Uncovering Latent Bipolar Disorder?

TO THE EDITOR: Michael Bauer, M.D., Ph.D., et al. (1) added to the compelling evidence that the supplementation of antidepressant treatment with lithium can enhance response in many treatment-resistant subjects with depression (2). Among patients with major depression and no evidence of bipolar disorder or suicidality who responded poorly to antidepressants for 1 month, 41 of 75 (54.7%) recovered with open-label lithium treatment added for 8–10 weeks. Of 30 who were followed up, one withdrew consent, and 29 were randomly assigned to continue lithium therapy (N=14) or to switch to placebo (N=15); antidepressant treatment continued up to 4 months. After lithium discontinuation, seven of the 15 placebo patients (46.7%) again became ill: five of the seven (71.4%) were depressed, and two (28.6%) were manic; one (6.7%) of the 15 placebo patients committed suicide. Therefore, two of 30 previously depressed unipolar patients (6.7%) (two of 15 patients taking placebo, 13.3%) were rediagnosed as bipolar. These responses all emerged within 4 months (mean=4 weeks) after they stopped taking lithium.

Relatively rapid lithium discontinuation (1–7 days) led to a 47% risk of an early return of affective illness. Such a high early risk of depression and mania is found in many studies of major affective disorders after lithium discontinuation (3). Some of the differences between subjects treated with lithium and placebo in study outcomes—particularly after rapid discontinuation of lithium—may include responses related to treatment withdrawal (3). The development of mania soon after the discontinuation of lithium in previously nonbipolar depressed subjects is not widely documented, although the emergence of spontaneous or antidepressant-associated mania, hypomania, or mixed states after recurrent depression is well known (4, 5).

Switching to mania or hypomania has been reported in 70 of 559 subjects within approximately 5.5 years (2.28/100 pa-

tient-years) (4). However, in the study by Dr. Bauer and colleagues, the rate of switching was 70 times greater (two of 15 patients per 0.0833 year, 160/100 patient-years) in depressed patients who were unresponsive to antidepressants and who stopped taking lithium while taking antidepressants. These rediagnosed patients may have had latent bipolar disorder with an apparently unipolar course and experienced unprotected exposure to antidepressants before they stopped taking lithium. In general, subjects with depression who have been unresponsive to antidepressant therapy may have a disproportionate risk of potential bipolarity. Moreover, many of the one-third to one-half of treatment-resistant depressed subjects who respond to lithium augmentation of antidepressants (2) may derive from this latent-bipolar subgroup.

Evidently, lithium discontinuation can be dangerous for patients with unrecognized bipolar disorder, perhaps particularly among those who have been unresponsive to antidepressant treatment. We encourage 1) vigorous exploration of past and family histories of potential bipolarity in depressed subjects who are resistant to antidepressant treatment, 2) gradual tapering of lithium, and 3) special attention soon after rapid discontinuation (3). The work by Dr. Bauer and colleagues also raises questions of how to interpret differences in drug/placebo results involving drug discontinuation, since the findings may not simply represent comparisons of treatment versus no treatment, as is often assumed (3).

References

1. Bauer M, Bschor T, Kunz D, Berghöfer A, Ströhl A, Müller-Oerlinghausen: Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. Am J Psychiatry 2000; 157:1429–1435
2. Bauer M, Döpfmer S: Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. J Clin Psychopharmacol 1999: 19:427–434
3. Baldessarini RJ, Tondo L: Recurrence risk in bipolar manic-depressive disorders after discontinuing lithium maintenance treatment: an overview. Clin Drug Investigation 1998; 15:337–351
4. Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Keller M, Warshaw M, Clayton P, Goodwin F: Switching from "unipolar" to bipolar II: an 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch Gen Psychiatry 1995; 52:114–123
5. Kukopulos A, Reginaldi D, Laddomada P, Floris G, Serra G, Tondo L: Course of the manic-depressive cycle and changes caused by treatments. Neuropsychopharmakologie 1980; 13: 156–167

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Dr. Bauer and Colleagues Reply

TO THE EDITOR: We appreciate the comments by Dr. Faedda and colleagues suggesting that rapid lithium discontinuation may uncover latent bipolar disorder in patients unresponsive to antidepressant treatment and that these patients may represent a separate group with a disproportionately high risk of bipolarity. Such interpretation, however, should be made with some caution.

Dr. Faedda et al. base their interpretation on two points. First, the rate of switching to mania in our study seemed higher than that found by Akiskal et al. (1995). However, the number of subjects in our placebo group (N=15) was too small to estimate reliably a switching rate, and it is difficult to directly contrast findings from the 11-year, long-term study by Akiskal et al. with findings from our short-term study of acute and continuation treatment. Second, Dr. Faedda et al. feel that the increased risk of rapid recurrence, particular of mania, after lithium discontinuation played a role in our results. This is possible; nevertheless, what may be more important is that each subject was taking antidepressants—mostly tricyclics—throughout our study, including the period after lithium discontinuation. A switching rate of 13.3% in patients taking antidepressants does not seem unusually high. There have been numerous reports that, on average, tricyclic antidepressants induce switching in 9% of the patients treated for depression (1) and, in some studies, even up to 25% (2). With respect to the suggestion that unipolar patients who are unresponsive to antidepressants may represent a particular group with a disproportionately high risk of switching, we are not aware of any report in the literature to support this supposition.

The possible effect of lithium discontinuation is more difficult to evaluate. The risk of rapid recurrence after lithium discontinuation is controversial (3) and may depend on patient selection. In addition, the studies reporting an increased risk are all long term, generally extending for years (4), and the observation may not be applicable to our study, in which subjects were treated with lithium for only 8–10 weeks.

We agree that it is wise in practice to look for indications of bipolarity in individual subjects and in the family histories of patients who receive lithium augmentation and to taper lithium gradually (5). Finally, we agree that the two unipolar subjects who switched to mania after lithium augmentation and discontinuation during the double-blind phase of our study, in fact, suffered from a pseudounipolar illness (bipolar disorder with a unipolar course). Of these two patients, one had already experienced three depressive episodes before the index episode, and the other had a family history of major depressive disorder. This observation would be in agreement with the finding of Angst et al. (6), who reported that patients with three or more unipolar depressive episodes are especially prone to a diagnostic change from unipolar to bipolar disorder.

References

1. Wehr TA, Goodwin FK: Can antidepressants cause mania and worsen the course of affective illness? Am J Psychiatry 1987; 144:1403–1411
2. van Scheyen JC, van Kammen DP: Clomipramine-induced mania in unipolar depression. Arch Gen Psychiatry 1979; 36:560–565
3. Schou M: Has the time come to abandon prophylactic lithium treatment? a review for clinicians. Pharmacopsychiatry 1998; 31:210–215
4. Suppes T, Baldessarini RJ, Faedda GL, Tohen M: Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen Psychiatry 1991; 48:1082–1088
5. Baldessarini RJ, Tondo L, Floris G, Rudas N: Reduced morbidity after gradual discontinuation of lithium treatment for bipolar I and II disorders: a replication study. Am J Psychiatry 1997; 154: 551–553

6. Angst J, Felder W, Frey R, Stassen HH: The course of affective disorders, I: change of diagnosis of monopolar, unipolar, and bipolar illness. Arch Psychiatr Nervenkr 1978; 226:57–64

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Genetic Architecture of Temperament

TO THE EDITOR: With great interest we read the article by Jeffrey H. Herbst, Ph.D., and colleagues (1), who, in a sample of up to 587 elderly Baltimore community residents, failed to find support for the previously described associations of a 48-base-pair repeat in the dopamine D_4 receptor gene (DRD4) with the personality trait of novelty seeking and of the 5-HTTLPR polymorphism of the serotonin transporter gene with harm avoidance. Although in this study on DRD4, as in most previous ones, the sample seemed to cover a broad range of trait values, a prior report on the same cohort (2) compared 188 individuals selected from the extremes of the novelty-seeking distribution. Although the authors were unaware of the actual degree of overlap in their samples, it is reassuring to see that both strategies, when applied to the same cohort, may well lead to identical results.

Dr. Herbst and co-workers discussed the ambiguous factor structure of Cloninger's Temperament and Character Inventory as a possible source of negative findings. Given the less than 4% contribution of the DRD4 polymorphism to the overall variance in the novelty-seeking trait, as described in the original studies, blurred factor structure could indeed mask an existing but considerably weak genetic association even in sizable samples. We can partly confirm the results of the authors' factor analysis with data obtained from the 4,753 participants of the Northern Finland 1966 Birth Cohort Study who fulfilled the temperament items from the Temperament and Character Inventory at age 31. Novelty seeking has been found to be associated with the DRD4 polymorphism in 190 subjects from this large, unselected cohort from the general population (3) who scored in the extreme range. Similar to the results in Table 3 of the article by Dr. Herbst et al., all of the items from the four subscales for harm avoidance loaded strongly (0.75–0.79) on a single factor in a promax-rotated principal-components analysis that forced four factors to be extracted from the 11 subscales that measured novelty seeking (subscales 1–4), harm avoidance (subscales 1–4), reward dependence (subscales 1, 3, and 4), and persistence (formerly reward dependence subscale 2). Subscale 1 for novelty seeking loaded negatively on the same factor I (–0.47). Of the four novelty seeking subscale loadings greater than 0.66 in their analysis, two each were confined to one of two separate factors (IV and V). The loadings of the novelty seeking subscales were more homogeneously distributed in our sample (novelty seeking subscales 2–4 loaded on a common factor with loadings of 0.61–0.80); this may have allowed detection of a DRD4 association in our sample but not in theirs. Less dispersion than in their analysis was also seen in major loadings for reward dependence, which fell on two separate factors (reward dependence subscales 3 and 4: loadings=0.72 and 0.76; reward dependence subscale 1: loading=0.81; persistence loaded at 0.63 on the same factor). However, we agree that according to its most stringent phenotypic structure, harm avoidance should offer an easier target than novelty seeking for the identification of the genetic factors behind temperament measures.

References

1. Herbst JH, Zonderman AB, McCrae RR, Costa PT Jr: Do the dimensions of the Temperament and Character Inventory map a simple genetic architecture? evidence from molecular genetics and factor analysis. Am J Psychiatry 2000; 157:1285–1290
2. Vandenbergh DJ, Zonderman AB, Wang J, Uhl GR, Costa PT Jr: No association between novelty seeking and dopamine D4 receptor (D4DR) exon III seven repeat alleles in Baltimore Longitudinal Study of Aging participants. Mol Psychiatry 1997; 2: 417–419
3. Ekelund J, Lichtermann D, Järvelin M-R, Peltonen L: Association between novelty seeking and the type 4 dopamine receptor gene in a large Finnish cohort sample. Am J Psychiatry 1999; 156:1453–1455

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Dr. Herbst and Colleagues Reply

TO THE EDITOR: In our article, we tested the psychobiological model of temperament and character of Cloninger et al. (1) on both molecular genetic and phenotypic levels. Our molecular genetic analyses offered no support for the model. There were no significant associations between polymorphisms in D4DR and the personality trait of novelty seeking, nor were there associations between 5-HTTLPR and harm avoidance. At the phenotypic level, a factor analysis of the 25 subscales of the Temperament and Character Inventory did not reveal the hypothesized seven-factor structure. In particular, the subscales of novelty seeking defined two separate factors.

In their comment on our article, Dr. Lichtermann and colleagues report the results of a factor analysis conducted in their Finnish sample (Ekelund et al., 1999). Like us, they found a clear harm avoidance factor, but they also found a relatively clear novelty seeking factor. They suggest that this "may have allowed detection of a DRD4 association in our sample but not in theirs."

This is unlikely to be the explanation. The structure that Dr. Lichtermann and colleagues describe resulted from a different analysis than the one we reported. They extracted four factors from the 12 temperament subscales of the Temperament and Character Inventory, whereas we extracted seven factors from all 25 subscales of the same inventory. When we restricted our analysis to four factors from the 12 temperament subscales, we, too, observed a single factor defined by the novelty seeking subscales. The phenotypic structure of the Temperament and Character Inventory appears to be similar in the U.S. and Finnish samples when analyzed in the same manner.

However, we did not observe the same genotypic associations. Although our smaller sample made it impossible to duplicate the analyses Dr. Lichtermann et al. reported, we did examine the distribution of alleles in groups with high and

low levels of novelty seeking by using a median split and groups found at the extremes, which were defined both as those scoring in the upper and lower 27% and as those scoring more than one standard deviation from the mean. No significant associations were found.

However, we believe the most important point has been missed by Dr. Lichtermann and colleagues. The significant associations they reported in their article (Ekelund et al., 1999) were in the wrong direction and did not support the temperament and character model. Their original hypothesis was that long alleles of D4DR would be associated with novelty seeking, whereas in their study they found that short alleles were more frequent among individuals with high novelty seeking levels—a finding with no obvious biological rationale. Neither their study nor ours supports the temperament and character model.

Reference

1. Cloninger C, Svrakic D, Przybeck TR: A psychobiological model of temperament and character. Arch Gen Psychiatry 1993; 50: 975–990

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Yohimbine for Anxiety Disorders

TO THE EDITOR: We read the article by Floyd R. Sallee, M.D., Ph.D., et al. (1) with great interest. The authors used the growth hormone response to the α_2-adrenergic antagonist yohimbine as a measure of presynaptic norepinephrine activity in a study comparing anxious children with comparison subjects. There are, however, methodological problems inherent in the use of growth hormone as a measure of norepinephrine activity, largely because the release of growth hormone from the pituitary is inhibited by cortisol (2). The authors appeared to measure a single baseline blood sample for each subject for the estimation of cortisol content and reported that there was no significant difference in baseline cortisol levels between comparison children (mean=6.5 g/ml, SD=2.8) and children with anxiety disorders (mean=9.1 g/ml, SD=8.4). Measuring single blood samples of cortisol is often unreliable, and integrated measures of cortisol output are preferred (3). In view of the effect of cortisol on growth hormone release, we believe it would be prudent for these authors to examine a robust measure of cortisol as a covariate of growth hormone response. We further suggest that all studies in which neurotransmitter function is inferred from pituitary hormone measures must measure corticosteroids as a potentially confounding covariate.

References

1. Sallee FR, Sethuraman G, Sine L, Liu H: Yohimbine challenge in children with anxiety disorders. Am J Psychiatry 2000; 157: 1236–1242
2. Watson S, Porter RJ, Young AH: Effect of hydrocortisone on the pituitary response to growth hormone releasing hormone. Psychopharmacology 2000, at http://dx.doi.org/10.1007/s002130000491
3. Kirschbaum C, Hellhammer DH: Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology 1994; 19:313–333

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Dr. Sallee and Colleagues Reply

TO THE EDITOR: The letter of Drs. Watson and Young relates to two methodological issues: the use of multiple baselines to more accurately measure baseline levels of neurohormones (e.g., cortisol) and the use of cortisol concentrations in particular as a covariate in the analysis of growth hormone release.

To clarify, we measured cortisol at two time points before administration of yohimbine. In effect, we had two baseline values for cortisol and growth hormone but chose the value at 30 minutes before administration as the reference baseline. The statistical validity of using one value as the baseline instead of averaging a number of values lies in the fact that an estimate based on averages from the same subjects decreases the within-subject correlation coefficient. This affects the repeated measures analysis of variance that is derived from the premise that within-subjects correlation is greater than between-subjects correlation.

The mean cortisol concentration at –30 minutes was 9.1 μg/ml (SD=8.4) for the anxious subjects and 6.5 μg/ml (SD=2.8) for the comparison subjects and was reported as such in the baseline results of the article. The cortisol levels at time 0 (immediately before administration of yohimbine) were 8.0 μg/ml (SD=6.7) for the anxious subjects and 6.8 μg/ml (SD=3.2) for the comparison subjects. The average of the two baseline values for all subjects yielded a baseline of 8.5 μg/ml (SD=7.4) for the anxious subjects and 6.7 μg/ml (SD=2.4) for the comparison subjects. The two groups did not differ on either baseline cortisol measure.

As Drs. Watson and Young suggest, we measured the correlations between cortisol and growth hormone concentrations at –30, 0, 60, 90, and 120 min; the correlation coefficients (ρ) were, respectively, –0.04, –0.21, 0.45, 0.37, and –0.20 for the anxious group and 0.50, 0.14, –0.70, –0.50, and –0.30 for the comparison group. The correlation values are modest; none approach statistical significance. Thus, the use of cortisol as a covariate does not appear to enhance the model.

To reiterate, this was a small study. Our hypotheses were formed to evaluate the effect of yohimbine on hormonal output, including cortisol and growth hormone. We agree that under most circumstances corticosteroids have the potential for interaction with growth hormone output from the pituitary but apparently not under the conditions or the population addressed by this study.

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The Letter to the Editor (Am J Psychiatry 2001; 158:970–971) by Edward Teitelman, M.D., should have had as its title "Off-Label Uses of Modafinil." The letter with the correct title appears below.

Off-Label Uses of Modafinil

TO THE EDITOR: Modafinil, a wakefulness-promoting oral agent, is approved for the treatment of the excessive daytime sleepiness associated with narcolepsy. It is thought to work by means of the hypocretin-orexin system in the hypothalamus (1). A class IV drug, it is only minimally stimulating in the traditional manner. These facts suggested that it might be useful in treating the excessive daytime sleepiness often seen as a side effect of the neuroleptic treatment of psychosis or depression and in closed-head brain injury (dementia due to head trauma). In both cases the somnolence can be severely disabling and the use of traditional psychostimulants is cumbersome and may be risky or impractical.

I report the successful open-label clinical use of modafinil in 10 outpatients with closed-head brain injury and excessive daytime sleepiness and in two patients with somnolence due to sedating psychiatric drugs. In these instances, it either replaced a schedule II agent or was used as the initial treatment for excessive daytime sleepiness.

The patients ranged in age from 42 to 72 years. All were outpatients whose excessive daytime sleepiness limited their activity and quality of life. The patients were informed that the drug had been approved for other uses, but it seemed to have benefits that might serve their needs. They were informed of possible side effects, including overstimulation. In these individuals, modafinil was well tolerated at doses of 100–400 mg taken once every morning; effectiveness lasted all day and resulted in an apparently normal nighttime sleep. With proper titration, excessive daytime sleepiness was markedly decreased in nine patients and moderately decreased in three; all changes were felt to be beneficial by the patients.

At prescribed doses, there was increased wakefulness and feelings of normality. Some patients noticed a greater sense of attention and other cognitive benefits. The results have often been rapid (within 1–2 hours of taking modafinil) and dramatic and have frequently led to a sense of relief and increased well-being. It is not clear if there is a direct effect on affect or if the patients simply responded to their increased quality of life and function—or both.

To date, my patients have used modafinil between 5 and 13 months, and there has been no evidence of tolerance or decreased effectiveness and no apparent adverse interactions with concurrent medications. Side effects, when present, have usually been mild and transient, primarily complaints of stimulation or gastrointestinal upset. It should be noted, however, that outside of this group, two middle-aged brain-injured women with multiple other complications and medications could not tolerate modafinil. This was due to strong feelings of emotional instability brought on soon after taking the first dose of 100 mg. Both reported similar reactions to many other medications and felt they were generally hypersensitive to drugs. No further trials were made at a lower dose.

Modafinil appears to be useful in the treatment of excessive daytime sleepiness associated with closed-head brain injury and with sedating psychiatric drugs, facilitating rehabilitation and enhancing quality of life. However, adequately controlled clinical trials will be needed to fully determine the role of modafinil in the treatment of excessive daytime sleepiness associated with these and other medical conditions apart from narcolepsy.

Reference

1. Sigel J: Narcolepsy. Sci Am 2000; 282:77–81

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The author is currently a consultant to Cephalon, Inc., maker of ProVigil (brand name of modafinil). Compensation has been limited to attendance at the Cephalon regional consultants' meeting, Feb. 11–13, 2000.

Reprints are not available; however, Letters to the Editor can be downloaded at http://ajp.psychiatryonline.org.