Neuroleptic Malignant Syndrome and Low-Dose Olanzapine

TO THE EDITOR: Neuroleptic malignant syndrome is a rare yet potentially fatal adverse reaction generally associated with typical neuroleptics (1). Some case reports describe neuroleptic malignant syndrome associated with olanzapine, an atypical neuroleptic, at high doses or when combined with other neuroleptics (2–5). We report on a patient taking a low dose of olanzapine who developed neuroleptic malignant syndrome. Upon his recovery, neuroleptic malignant syndrome recurred after olanzapine was restarted.

Mr. A, an 86-year-old man with an 8-month history of dementia with paranoia, was successfully treated for several months with olanzapine, 5 mg/day, until signs of parkinsonism led to a dose decrease to 2.5 mg/day. Two months later, when the daytime temperature was 96°F, he came to the hospital with uncontrollable shaking, confusion, a temperature of 105.6°F, and significant cogwheel rigidity. Paramedics believed his apartment's temperature had exceeded 110°F. His admission and 2-hour blood pressures were notable for fluctuation: 110/72 mm Hg and 162/62 mm Hg, respectively. The results of laboratory tests included an aspartate aminotransferase level of 72 U/liter (normal=10–47), a creatinine kinase level of 1184 U/liter (normal=45–230), and a mildly elevated cardiac isoenzyme level of 39 U/liter (normal=0–6), with a relative index of 3.3 (normal=0–2.5). Mr. A was diagnosed with myocardial infarction, and olanzapine was suspended, given presumptive neuroleptic malignant syndrome.

By hospital day 5, Mr. A's tremors had resolved, his cogwheel rigidity had minimized, his alertness had improved, his temperature had returned to normal, his creatinine kinase level had decreased to 245 U/liter, and his aspartate aminotransferase level had returned to normal. That night, he was rechallenged with one dose of olanzapine, 2.5 mg. The next morning, he was shaking vigorously, his temperature was 100.6°F, and he was notably more rigid. Olanzapine was discontinued, and his temperature again returned to normal, his tremor disappeared, and his cogwheel rigidity decreased substantially. His creatinine kinase level returned to normal, and he was treated with quetiapine, 25 mg/day, for several days with no signs of neuroleptic malignant syndrome.

This case differs from prior reports of neuroleptic malignant syndrome with olanzapine in that the olanzapine dose was notably lower and olanzapine was not given with other dopamine-blocking agents. The rechallenge symptoms also strengthen the association. Dehydration is a possible risk factor for neuroleptic malignant syndrome, and the overheated apartment may have contributed to it (1). It is unlikely that the patient's symptoms can be attributed to heatstroke, which generally is seen with hypotension and limb flaccidity—not fluctuating blood pressure and rigidity (1). Furthermore, the myocardial infarction does not account for the increased skeletal muscle breakdown, rigidity, tremors, fever, or rechallenge exacerbation. Clinicians should be aware that neuroleptic malignant syndrome can occur with low doses of olanzapine and that extremes of heat may precipitate such cases.

References

1. Jeste DV, Naimark D: Medication-induced movement disorders, in Psychiatry, 1st ed. Edited by Tasman A, Kay J, Lieberman JA. Philadelphia, WB Saunders, 1997, pp 1334–1350
2. Philibert RA, Adam LA, Frank FM, Carney-Doebbeling C: Olanzapine usage associated with neuroleptic malignant syndrome. Psychosomatics 2001; 42:528–529
3. Hickey C, Stewart C, Lippmann S: Olanzapine and NMS (letter). Psychiatr Serv 1999; 50:836–837
4. Apple JE, Van Hauer G: Neuroleptic malignant syndrome associated with olanzapine therapy (letter). Psychosomatics 1999; 40:267–268
5. Stanfield SC, Privette T: Neuroleptic malignant syndrome associated with olanzapine therapy: a case report. J Emerg Med 2000; 19:355–357

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Medicaid Reimbursement for Light Therapy

TO THE EDITOR: Medicaid does not reimburse patients for light therapy. Dr. Wirz-Justice (1) has commented, "Light is now recommended as the treatment of choice for seasonal affective disorder. However, in spite of international recognition, only in Switzerland has the additional economic argument that light is cheaper than drugs attained government endorsement and mandatory reimbursement by medical insurance." The following case report strikingly illustrates the shortsightedness of that policy.

Ms. A, a 40-year-old Guatemalan woman living in a family shelter with four school-age children, never experienced clinical depression before moving to New York 15 years ago. Since then, she regularly experienced winter depression accompanied by hyperphagia, hypersomnia, and cravings for sweets. These bouts of depression led to her losing a nurse's aide job and being abandoned by her husband. Treatment with venlafaxine, 375 mg/day, and later fluoxetine, 40 mg/day, provided minimal benefit in winter, but there was dramatic improvement in spring and summer. When Ms. A was initially evaluated, she was depressed and ready to drop out of a medical technician training program. We loaned her a 10,000-lux light box, which she used 30 minutes each morning. Within 2 weeks, she improved markedly. Subsequently, she finished her training and began working as a medical technician and living independently.

This case illustrates three major points:

1. Although patients with seasonal affective disorder are rarely ill enough to require hospitalization, their illness can precipitate catastrophic life events. In this case, we believe that seasonal affective disorder led to the loss of the patient's job, her husband, and finally her home.

2. Seasonal affective disorder is underdiagnosed. Despite describing a classic history for seasonal affective disorder and attending several hospital-based psychiatric clinics, our patient was diagnosed with nonseasonal major depression and was treated with antidepressants rather than light therapy. This resulted in a poor response to treatment; it is generally

recognized that light therapy is a more effective treatment than medication for winter depression.

3. Medicaid's policy is clinically and economically wrong for not covering light therapy. A light box costs approximately $200 and will provide treatment for many years. Our patient could not afford the $200 and would not have received the treatment had we not loaned her our light box. New York State Medicaid did pay for her antidepressants—fluoxetine and venlafaxine—which gave minimal relief and cost Medicaid approximately $200 per month ($164 per month for fluoxetine, 40 mg/day, and $212 per month for venlafaxine, 375 mg/day). Thus, Medicaid spent approximately $200 a month to provide an inferior treatment when this same $200 could have provided a light box for a universally accepted preferred treatment modality that would have assisted our patient not just for 1 month but for many years. Medicaid needs to finally "see the light" by including light therapy in its treatment formulary.

Reference

1. Wirz-Justice A: Beginning to see the light. Arch Gen Psychiatry 1998; 55:861–862

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Glucose Dysregulation and Mirtazapine-Induced Weight Gain

TO THE EDITOR: Weight gain, a common side effect of psychotropic medications, may cause diabetes, hyperlipidemia, coronary heart disease, and hypertension (1, 2) and is an important factor in medication noncompliance (3).

Mirtazapine is an atypical antidepressant with noradrenergic and serotonergic activity that blocks alpha 2 autoreceptors and selectively antagonizes serotonin 5-HT_2 and 5-HT_3 receptors. It also blocks histaminergic (H_1) and muscarinic receptors (4). Weight gain associated with mirtazapine treatment has been reported (3, 4) and may be accounted for by its effects on 5-HT_{2c} and H_1 receptors. To our knowledge, this is the first report of glucose dysregulation secondary to mirtazapine-induced weight gain.

Ms. A was 32 years old and had a history of depression and substance abuse. Her episodes of depression induced her to abuse cocaine, marijuana, and alcohol periodically. She took carbamazepine for seizures. Her mother was diabetic. On her first hospital admission for depression, her weight was 70.5 kg (body mass index=26.7 kg/mm^2), a random glucose measurement was 148 mg/dl, and a urine screening was positive for cocaine. At her discharge, mirtazapine, 15 mg at bedtime, was added, and she was referred to an outpatient chemical dependence program. She missed appointments and continued abusing cocaine. Although her mood improved, she experienced headaches, increased appetite, sluggishness, and weight gain.

Ms. A developed blurry vision, fatigue, and nausea, and 5 months after her first admission she was readmitted with severe hyperglycemia (1042 mg/dl) that paralleled her weight gain (to 86.4 kg). Ketoacidosis and other complications were absent. Her hemoglobin A_{1c} level was 10.9%, and the result of testing for antiglutamic acid decarboxylase antibodies was negative. Her insulin, proinsulin, and C-peptide levels were not measured.

She continued taking carbamazepine, she started taking citalopram, and she discontinued mirtazapine therapy. Her glucose levels were controlled with insulin and a diabetic diet. After discharge, metformin was added, as she required less insulin; her mood was stable, and she abstained from cocaine. Her glucose levels were normal, and she gradually lost weight.

Ms. A then discontinued her medications, and 6 months after her second admission, she was readmitted because of cocaine abuse and depression. Her weight was 83.0 kg, and her glucose level was below 160 mg/dl. Carbamazepine, citalopram, and a diabetic diet were resumed. Her fasting glucose level was 119 mg/dl, her insulin level was 23 mU/ml, and her hemoglobin A_{1c} level was 5.9%. Six months later, her weight was 79.2 kg, and a random glucose measurement was 123 mg/dl.

Our patient gained 16 kg in 5 months, severely aggravating her premorbid hyperglycemia, suggesting that obesity was an important risk factor for her glucose dysregulation. Controlled studies should follow, and diabetic patients and those at high risk of developing diabetes should be closely monitored.

References

1. Luna B, Feinglos MN: Drug-induced hyperglycemia. JAMA 2001; 286:1945–1948
2. Aronne LJ: Epidemiology, morbidity, and treatment of overweight and obesity. J Clin Psychiatry 2001: 62(suppl 23):13–22
3. Fava M: Weight gain and antidepressants. J Clin Psychiatry 2000; 61(suppl 11):37–41
4. Fawcett J, Barkin RL: Review of the results from clinical studies on the efficacy, safety and tolerability of mirtazapine for the treatment of patients with major depression. J Affect Disord 1998; 51:267–285

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Psychoanalytic Prison

TO THE EDITOR: In his discussion of Franz Alexander in Images in Psychiatry, Judd Marmor, M.D. (1), wrote, "Alexander was a rare psychoanalytic pioneer who, despite a thorough grounding in classical Freudian theory, had the courage, vision, and flexibility to modify his thinking in the light of newer knowledge." This presumably indicates how stifling the intellectual orthodoxy associated with psychoanalysis was, at least at the time that Alexander practiced, rather than constituting faint praise for him.

Reference

1. Marmor J: Franz Alexander, 1891–1964. Am J Psychiatry 2002; 159:1305

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Dr. Marmor Replies

TO THE EDITOR: Dr. Bernadt's presumption is correct. It is difficult in today's more enlightened psychoanalytic atmosphere to realize how stifling and controlling the intellectual psychoanalytic orthodoxy was at the time Alexander began to pub-

lish his modifications. It would be a complete misconception to interpret what I wrote as indicating "faint praise" for him.

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Recovery Rates for Anorexia Nervosa

TO THE EDITOR: We applaud Hans-Christoph Steinhausen, M.D., Ph.D. (1), for his latest update summarizing the literature on the outcome of anorexia nervosa. This was a particularly daunting task given the tremendous heterogeneity across studies. Although several key design issues and limitations were highlighted, the issue of study groups was not as thoroughly addressed. Generalizability is always an important factor in interpreting clinical research. As matter of practice, the majority of the anorexia nervosa outcome studies were conducted by academic centers and specialty research centers (2, 3). It is well known that such groups tend to be more severely ill and have more comorbidity than patients treated in the community setting, factors that are likely to negatively affect outcome (1, 3).

While additional studies of the natural history and outcome of anorexia nervosa in community and ambulatory practices are essential, our clinical experience conservatively indicates that 50% of patients remit within 1–3 years and never require an inpatient level of care. Of the remaining 50% who require inpatient care, the review by Dr. Steinhausen (1) estimated that an additional 50%–70% will recover, depending on the duration of follow-up. Combining these observations suggests that for the overall spectrum of patients with anorexia nervosa, approximately 75%–85% will completely recover. If patients who experience significant improvement are included, the rate of positive outcome rises to over 90%. Thus, a 75%–90% rate of recovery is a more accurate estimate and does not represent as poor a prognosis as the review by Dr. Steinhausen conveys. This perspective regarding the magnitude of the rate of recovery across the full spectrum of the illness has important implications for patients, families, clinicians, payers, and policy makers for the general view of anorexia nervosa as a chronic versus remitting illness.

References

1. Steinhausen H-C: The outcome of anorexia nervosa in the 20th century. Am J Psychiatry 2002; 159:1284–1293
2. Strober M, Freeman R, Morrell W: The long-term course of severe anorexia nervosa in adolescents: survival analysis of recovery, relapse, and outcome predictors over 10–15 years in a prospective study. Int J Eat Disord 1997; 22:339–360
3. Pike KM: Long-term course of anorexia nervosa: response, relapse, remission, and recovery. Clin Psychol Rev 1998; 18:447–475

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Dr. Steinhausen Replies

TO THE EDITOR: In their letter, Dr. Johnson and his colleagues raise an important issue for discussion, namely, a potential selection bias in the published outcome studies on anorexia nervosa due to referral of the patients to specialized centers and the predominant inclusion of inpatients. However, by referring to their clinical experience, my discussants do not provide convincing arguments that this is necessarily the case.

My review covers a wide range of almost 50 years of internationally published outcome studies. In this period, anorexia nervosa has required specialized treatment so that referral to expert centers has been the rule rather than the exception. Inpatient treatment has been the predominant mode of intervention, and treatment policies favoring day clinics and ambulatory practices have appeared only in the recent past. Currently, it is unclear whether the latter interventions are restricted to less severe and subclinical cases only. Prospective cohort studies, both in a single center (1) and in international multicenter studies (2, 3), have reflected the seriousness of anorexia nervosa by showing that the patients spent 25%–30% of the entire follow-up period in either inpatient or outpatient treatment. A large proportion of these patients required repeated hospitalizations. One of the very rare community-based studies (4) showed that after 10 years, 27% of the patients still suffered from an eating disorder and more than one-third had other psychiatric disorders.

These empirical observations argue strongly against the high remittance rate of at least 50% within 1–3 years. Furthermore, the data in my review showed that, depending on duration of follow-up, not 50%–70% but rather 33%–73% of the patients recovered with only very limited period effects over the past 50 years. The inclusion of the improved cases would not result in an average of 90% but, rather, only 80%. However, this combination of data would imply a problematic underestimation of clinical problems that remain in improved cases, leaving aside other psychiatric disorders, additional psychosocial problems, and the need for further treatment. As stated in my review, anorexia nervosa did not lose its relatively poor prognosis in the 20th century.

References

1. Steinhausen HC, Seidel R, Winkler Metzke C: Evaluation of treatment and intermediate and long-term outcome of adolescent eating disorders. Psychol Med 2000; 30:1089–1098
2. Steinhausen HC, Boyadjieva S, Griogoroiu-Serbanescu M, Seidel R, Winkler-Metzke C: A transcultural outcome study of adolescent eating disorders. Acta Psychiatr Scand 2000; 101: 60–66
3. Steinhausen HC, Boyadjieva S, Griogoroiu-Serbanescu M, Neumärker KJ: The outcome of adolescent eating disorders: findings from an international collaborative study. Eur Child Adolesc Psychiatry (in press)
4. Råstam M, Gillberg C, Wentz E: Outcome of teenage-onset anorexia nervosa in a Swedish community sample. Eur Child Adoles Psychiatry (in press)

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A Reappraisal of Atypical Depression

TO THE EDITOR: Gordon Parker, M.D., Ph.D., D.Sc., F.R.A.N.Z.C.P., et al. (1) challenged "the DSM-IV definition of the atypical features specifier in major depressive disorder as a valid entity" (p. 1477). This challenge was based on their analysis, which suggested that the symptoms we refer to as vegetative atypical features—overeating, oversleeping, a leaden feeling, or rejection sensitivity—did not co-occur and were not associated with mood reactivity.

Their critique's rationale has two flaws. The first misconception has to do with latent class analysis. Latent class analysis can be considered a technique to unmix data or uncover taxonomies or nonarbitrary classes. Kendler et al. (2) (cited by Dr. Parker et al.), in an epidemiologically defined twin sample, performed a latent class analysis, identifying atypical depression as a distinct subgroup. Once latent classes are identified, Dillon and Goldstein (3) noted that "within a cluster, the items are independent" (uncorrelated). Dr. Parker and colleagues reported the expected low correlation of vegetative symptoms. Actually, when the entire group was examined, Dr. Parker et al. found three significant correlations (of a possible six): rejection with hypersomnia ($p=0.02$), weight gain with leaden paralysis ($p=0.03$), and another by inference ($r=0.12$, $df=158$, $p<0.07$). From the manner in which the data were presented on the third correlation, it is unclear which two symptoms had this correlation. Within the patient subset with reactive mood and one accessory symptom, there were no significant correlations. The anticipated occurred: a less homogeneous group exhibited significant correlations, and a cluster (homogeneous group) had uncorrelated symptoms. Angst et al. (4) reported a relevant analysis after the study by Dr. Parker and colleagues was accepted for publication. In a Zurich epidemiological sample, which, by definition, was heterogeneous, a high association between atypical depressive symptoms was found.

The second misconception in the article was the suggestion that correlation (symptom interdependence) and not predictive validity is the gold standard for validating a phenomenologically derived syndrome. Height and weight are correlated. Although this correlation exists for men and women, it does not help differentiate the sexes. Predictive validity in medicine has clear heuristic and practical syndrome relevance, especially predictions of treatment outcome.

Do data support the predictive validity of the atypical subgroup? In fact, the validation for the DSM-IV atypical depressive parenthetical modifier is unusually robust for psychiatry (2, 4–10). Our group at Columbia University (8) performed six independent trials in which patients with varying degrees of atypical depression had superior response to phenelzine over imipramine. In two trials, patients lacking atypical features did no better taking phenelzine than imipramine. Sotsky and Simmens (6) also noted that atypical features were associated with a poor imipramine response. Subsequently, Kendler et al. (2) and, independently, Sullivan et al. (7), in epidemiological samples involving thousands of patients, defined a cluster of depressed patients with hypersomnia and hyperphagia who were distinct from other subgroups of depressed patients. Kendler et al. (2) reported that atypical depression bred true.

Dr. Parker et al. also questioned the relevance of mood reactivity. They failed to note the independent analysis of the National Institute of Mental Health Treatment of Depression Collaborative Research Program data by Sotsky and Simmens (6). A syndrome definition that included mood reactivity coupled with vegetative atypical symptoms best identified a group with poor response to imipramine. However, without the mood reactivity context, predictions were much weaker.

Reconciling disparate findings is a recurrent problem in clinical research. It is likely that differences in group selection explain discrepancies between the study by Dr. Parker et al. and the findings of the Columbia group. Roughly 65% of our patients were chronically ill, with a duration of illness of approximately 20 years; all were outpatients. Dr. Parker et al. selected patients with major depressive disorder "present less than 24 months"; "69%…were outpatients" (p. 1473) (we assume that 31% were inpatients). It is unclear why Dr. Parker et al. chose to exclude patients who were ill more than 2 years since atypical depression is a chronic illness. The relevance of chronic depression has been noted (11, 12).

Dr. Parker et al. inaccurately suggested that we define "elephants" (atypicals) as "not giraffes" (melancholics); therefore, elephants are poorly described. Atypicals (elephants) are characterized without reference to melancholia. Patients with major depression who have reactive mood and atypical symptoms respond best to monoxamine oxidase inhibitors (MAOIs) (poorly to tricyclic antidepressants). Patients with otherwise identical symptoms (i.e., those with nonautonomous mood and no atypical symptoms), referred to as having simple mood-reactive depression, do equally well taking tricyclic antidepressants and MAOIs (8). In the most recent "iterative refinement," we (9) demonstrated that only chronically ill patients with vegetative atypical symptoms had a superior response to MAOIs.

We also wish to correct several erroneous assertions by Dr. Parker et al. In the study by Mannuzza et al. (13), 36% of the patients with social phobia met criteria for atypical depression, not two-thirds, as Dr. Parker et al. suggested. Joyce and Paykel (14) did not present new data supporting the efficacy of MAOIs in patients with anxious depression but referred to Columbia data (15) suggesting that MAOIs were particularly effective for anxious patients with atypical depression. However, the relevance of anxiety was no longer evident in the expanded study group, suggesting that a fortuitous, nonreproducible finding had been produced. In the Robinson et al. studies (e.g., 16), phenelzine was never shown to be superior to tricyclics for anxious depression. Dr. Parker et al. stated that we (17) indicated that selective serotonin reuptake inhibitors (SSRIs) are equivalent to MAOIs for atypical depression. However, we did not compare SSRIs and MAOIs.

References

1. Parker G, Roy K, Mitchell P, Wilhelm K, Malhi G, Hadzi-Pavlovic D: Atypical depression: a reappraisal. Am J Psychiatry 2002; 159:1470–1479
2. 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
3. Dillon WR, Goldstein M: Multivariate Analysis: Methods and Applications. New York, John Wiley and Sons, 1984
4. Angst J, Gamma A, Sellaro R, Zhang H, Merikangas K: Toward validation of atypical depression in the community: results of the Zurich Cohort Study. J Affect Disord 2002; 72:125–138
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. Sotsky SM, Simmens SJ: Pharmacotherapy response and diagnostic validity in atypical depression. J Affect Disord 1999; 54: 237–247

7. 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
8. 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 1993; 163(suppl 21):30–34
9. Stewart JW, McGrath PJ, Quitkin FM: Do age of onset and course of illness predict different treatment outcome among DSM-IV depressive disorders with atypical features? Neuropsychopharmacology 2002; 26:237–245
10. McGrath PJ, Stewart JW, Harrison WM, Ocepek-Welikson K, Rabkin JG, Nunes EN, Wager SG, Tricamo E, Quitkin FM, Klein DF: Predictive value of symptoms of atypical depression for differential drug treatment outcome. J Clin Psychopharmacol 1992; 12:197–202
11. Keller MB, Gelenberg AJ, Hirschfeld RM, Rush AJ, Thase ME, Kocsis JH, Markowitz JC, Fawcett JA, Koran LM, Klein DN, Russell JM, Kornstein SG, McCullough JP, Davis SM, Harrison WM: The treatment of chronic depression, part 2: a double-blind, randomized trial of sertraline and imipramine. J Clin Psychiatry 1998; 59:598–607
12. Kornstein SG, Schatzberg AF, Thase ME, Yonkers KA, McCullough JP, Keitner GI, Gelenberg AJ, Ryan CE, Hess AL, Harrison W, Davis SM, Keller MB: Gender differences in chronic major and double depression. J Affect Disord 2000; 60:1–11
13. Mannuzza S, Schneier FR, Chapman TF, Liebowitz MR, Klein DF, Fyer AJ: Generalized social phobia: reliability and validity. Arch Gen Psychiatry 1995; 52:230–237
14. Joyce PR, Paykel ES: Predictors of drug response in depression. Arch Gen Psychiatry 1989; 46:89–99
15. Liebowitz MR, Quitkin FM, Stewart JW, McGrath PJ, Harrison WM, Markowitz JS, Rabkin JG, Tricamo E, Goetz DM, Klein DF: Antidepressant specificity in atypical depression. Arch Gen Psychiatry 1988; 45:129–137
16. Robinson DS, Nies A, Ravaris L, Ives JO, Bartlett D: Clinical pharmacology of phenelzine. Arch Gen Psychiatry 1978; 35:629–635
17. 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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Dr. Parker and Colleagues Reply

TO THE EDITOR: We appreciate the opportunity to reply to each point made by Dr. Quitkin and his colleagues. Our overview did note the latent class analysis study by Kendler et al. (1996) but without comment as to whether it supported atypical depression as an entity or not. Those authors noted the intrinsic limitations of latent class analysis ("It cannot prove that such discrete classes exist") and that their identified classes might "reflect only differing points on a single underlying continuum of severity." Dr. Quitkin et al. are correct that items will be independent within classes in latent class analysis. This could be expected to hold in the atypical latent class defined by DSM-IV criteria, provided these reflect all key items from the original studies. If DSM-IV criteria, however, define something closer to a syndrome, then independence is not to be expected. More pertinently, we found independence (very low associations) both in the subjects with atypical depression and in the entire group, indicating that not much would be accounted for by any latent variable.

Dr. Quitkin et al. argue that our "second misconception" lies in our suggestion that symptom interdependence is the gold standard for validation of a phenomenological syndrome. We made no "gold standard" reference but, as noted, interpreted lack of interdependence of accessory features and low internal consistency as arguing "against a syndromal construct" (p. 1476), later postulating differential determinants of its heterogeneous constituents.

In the Zurich study by Angst et al. (2002), adjusted odds ratios were reported rather than correlation coefficients, preventing judgment about comparative associations. Our results appear similar to those from another recent U.S. study (1), in which mood reactivity correlated trivially (i.e., coefficients of <0.10) with all accessory features. Like us, those authors challenged mood reactivity as an essential component of atypical depression. We would not be surprised by any study identifying mood reactivity as a predictor of a poorer tricyclic antidepressant response when studies of true tricyclic antidepressant responders indicate superior responses for those with melancholic depression (in which a nonreactive mood is held as a key feature). Ipso facto, those with nonmelancholic depression (and a more reactive mood) should show a poorer tricyclic antidepressant response.

Our study group was one of convenience. Findings similar to ours (including the implication of panic anxiety and social phobia) in the recent independent Providence study (1)—in which relevant subjects had a mean episode duration of 349 weeks—argue against episode duration as a distorter. However, despite such empirical support as the statement by Dr. Quitkin et al. that "atypical depression is a chronic illness," there is a conceptual paradox if mood reactivity is a mandatory feature when the DSM-IV (p. 385) states that "mood may become euthymic (not sad) even for extended periods of time if the external circumstances remain favorable." We suspect that chronicity more refers to (and emerges from) predisposing personality and anxiety trait features than any superimposed depressive states.

We concede and regret the errors in interpreting or reporting the studies by Mannuzza et al. (1995) and McGrath et al. (2000). However, we neither stated that Joyce and Paykel (1989) presented new data nor interpreted the Robinson et al. studies (e.g., 1978) as demonstrating that phenelzine is superior to tricyclic antidepressants for anxious depression.

It is important for Dr. Quitkin and colleagues to address the main thrust of our article. Following our argument (2) for a spectrum model (linking the personality and phenotypical picture) for modeling the nonmelancholic depressive disorders, Dr. Quitkin et al. (3) nominated atypical depression as a paradigm example, stimulating our study. Our results favored interpersonal rejection sensitivity as a primary feature, with that personality style perhaps disposing to or being otherwise associated with certain expressions of anxiety (social phobia and panic disorder). If the roots of atypical depression are planted more firmly in a personality-weighted anxiety base, it is unlikely to be a primary depressive entity.

References

1. Posternak MA, Zimmerman M: Partial validation of the atypical features subtype of major depressive disorder. Arch Gen Psychiatry 2002; 59:70–76
2. Parker G: Classifying depression: should paradigms lost be regained? Am J Psychiatry 2000; 157:1195–1203
3. Quitkin FM, Stewart JW, McGrath PJ, Klein DF: Classifying depression (letter). Am J Psychiatry 2001; 158:1332–1333; reply, 158:1334

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Viennese Anti-Semitism

Paul C. Horton, M.D. (1), is certainly entitled to his opinion of Louis Breger's revisionist and tendentious biography of Freud. One cannot, however, fail to be astounded by his skepticism about the nature and extent of Austrian and, specifically, Viennese anti-Semitism during Freud's lifetime (and, in fact, beyond). He seems to be blissfully unaware of the career of the notorious Karl Lueger, repeatedly elected mayor of Vienna largely on the basis of his anti-Semitic platform. He seems further to ignore the rapturous reception given to Hitler by the Viennese populace at the time of the 1938 *Anschluss,* not to mention the humiliation and worse suffered by Viennese Jews, many of whom were forced by the police to scrub sidewalks with toothbrushes before they were carted off to the death camps. Perhaps he knows nothing of the current Austrian politician Jorg Haider, whose political success was based in no small measure on his justification of certain of Hitler's policies.

If indeed Dr. Horton is unaware of all this, if indeed he truly finds it "hard to imagine anti-Semitism as having had legs in a country in which Jews had become so powerful" (p. 512), he ought to read a bit of the history of the period. One is tempted to say to him, paraphrasing Wittgenstein, "Of that about which one knows nothing it is best to remain silent."

Reference

1. Horton PC: Book review, L Breger: Freud: Darkness in the Midst of Vision. Am J Psychiatry 2002; 159:511–512

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