

## Addition of Lamotrigine to Clozapine in Inpatients With Chronic Psychosis

**Sir:** Two studies have reported a substantial reduction of symptoms when the anticonvulsant drug lamotrigine was added to clozapine in patients with treatment-resistant schizophrenia.<sup>1,2</sup> We report on 6 inpatients with persistent and severe psychotic symptoms who were treated for 24 weeks with a combination of lamotrigine and clozapine.

**Method.** The study, which was conducted between December 2000 and August 2002, was approved by an independent medical ethics committee, and all patients gave informed consent. Four patients had a diagnosis of schizophrenia, and 2 patients had a diagnosis of schizoaffective disorder according to DSM-IV criteria. Their mean  $\pm$  SD age was  $47.2 \pm 7.8$  years. All had had therapeutic serum levels of clozapine for at least 6 months. Lamotrigine therapy was initiated at 12.5 mg/day and was titrated on the basis of tolerability and patients' symptoms, by no more than 25 mg/week. All other medication was kept as stable as possible. Symptoms were rated every 4 weeks by the Positive and Negative Syndrome Scale (PANSS)<sup>3</sup> during the 24-week trial.

**Results.** Three patients were withdrawn from the study: 1 was removed after 6 weeks because of abuse of cannabis followed by an immediate deterioration of psychotic symptoms; 1, after 8 weeks owing to an increase in agitation and verbal aggression; and 1, after 12 weeks owing to complaints about sedation.

Three patients completed the open clinical trial. Their mean  $\pm$  SD maximum dose of lamotrigine was  $116.7 \pm 20.4$  mg with a mean  $\pm$  SD serum lamotrigine level of  $1.80 \pm 0.56$  mg/L. Mean  $\pm$  SD serum levels of clozapine decreased nonsignificantly from  $409 \pm 38$   $\mu$ g/L at baseline to  $328 \pm 102$   $\mu$ g/L at endpoint ( $t = 1.6$ ,  $df = 2$ ,  $p = .26$ ).

None of the 6 patients showed more than a 20% reduction in PANSS total score at endpoint or at any point during the trial. The mean  $\pm$  SD PANSS total score decreased nonsignificantly in the last-observation-carried-forward analysis from  $82.5 \pm 13.6$  at baseline to  $81.7 \pm 13.7$  at endpoint ( $t = 0.28$ ,  $df = 5$ ,  $p = .79$ ) and in the completer analysis from  $83.0 \pm 11.5$  to  $77.0 \pm 5.0$  ( $t = 1.5$ ,  $df = 2$ ,  $p = .27$ ).

Adding lamotrigine was not effective in our group of patients. Our findings contradict the prompt and substantial improvements reported in the open studies by Dursun et al.<sup>1</sup> and Saba et al.<sup>2</sup> It is not plausible to argue that we were too cautious with regard to the maximum lamotrigine doses (100–125 mg/day) because the mean serum lamotrigine level in responding patients (0.88 mg/L) in the study by Saba et al.<sup>2</sup> was lower than that in our nonresponders (1.80 mg/L). However, it should be stated that small studies are prone to both type I and type II errors.

So far, there has been only 1 report of a double-blind, placebo-controlled trial in which lamotrigine was added to clozapine in treatment-resistant patients.<sup>4</sup> Tiihonen et al.,<sup>4</sup> like us, found no statistically significant change in PANSS total scores. However, they did report a statistically significant mean change of 1 point on the PANSS positive subscale. Although clinically this is a small effect, we agree with Tiihonen et al.<sup>4</sup> that this finding could mean that lamotrigine might be beneficial for a small but as yet unidentified subgroup of patients. Further research should focus on identification of this potential subgroup.

In conclusion, adding lamotrigine to clozapine does not seem to be an effective strategy for most patients with treatment-resistant psychosis. However, if lamotrigine is added to clozapine, the treatment should be administered only in a time-limited trial, and efficacy should be closely monitored.

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### REFERENCES

1. Dursun SM, McIntosh D, Milliken H. Clozapine plus lamotrigine in treatment-resistant schizophrenia [letter]. *Arch Gen Psychiatry* 1999; 56:950
2. Saba G, Dumortier G, Kalalou K, et al. Lamotrigine-clozapine combination in refractory schizophrenia: three cases [letter]. *J Neuropsychiatry Clin Neurosci* 2002;14:86
3. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261–276
4. Tiihonen J, Hallikainen T, Ryyänen O-P, et al. Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. *Biol Psychiatry* 2003;54:1241–1248

**Adolph H. Heck, M.D.**  
**Izaäk W. de Groot, M.Sc.**  
**Peter N. van Harten, Ph.D.**

Symfora Group, Centers for Mental Healthcare  
Amersfoort, the Netherlands

## Is There a Real Difference Between the First Onset of Efficacy for Atypical Antipsychotic Monotherapies in Acute Bipolar Mania?

**Sir:** Several points beyond those mentioned in Dr. Keck's recent article<sup>1</sup> are relevant to the appraisal of relative onset of efficacy of atypical antipsychotics for mania. What Figure 1 of Dr. Keck's article does demonstrate is that all of the atypicals tended to show faster onset of action versus placebo at the earliest timepoint at which efficacy was first measured. For the olanzapine trials, efficacy was not measured until after 7 days.<sup>2,3</sup> The aripiprazole trial first measured efficacy at 4 days, while the risperidone and ziprasidone trials first measured efficacy at 1 or 2 days. This limited comparison between trials gives the mistaken impression that important differences in onset of action may exist, when in fact these differences are probably an artifact of the clinical trial designs themselves.

Furthermore, the discussion of the onset of action of olanzapine is mostly in comparison to divalproex sodium,<sup>4</sup> whereas for the other atypicals the discussion focuses on comparisons with placebo. Clearly, this alternate comparison could show olanzapine in a more negative light since it is more difficult to show superiority versus an effective compound.

Other differences between the trials also exist. For example, the Schedule for Affective Disorders and Schizophrenia, Change Version (SADS-C), used in the ziprasidone trial,<sup>5</sup> is more sensitive to changes in positive symptoms and disordered thinking than is the Young Mania Rating Scale, which focuses specifically on manic symptoms.<sup>6</sup> But since positive symptoms and disordered thinking are known to improve earlier in treatment than manic symptoms, use of the SADS-C could lead to the impression of earlier onset of action.

Care is needed when comparing trials with similar objectives but different designs, time schedules, and assessments because the conclusions can be misleading for readers who are not familiar with the details of the trials. Unfortunately, time-of-onset data for atypicals in head-to-head comparisons in the treatment of mania are still not available.<sup>7</sup>

*Dr. Treuer and Mr. Basson are employees of Area Medical Center Vienna, Eli Lilly Regional Operations, Austria. Mr. Basson is a major stock shareholder in Eli Lilly and Company.*

#### REFERENCES

1. Keck PE Jr. The role of second-generation antipsychotic monotherapy in the rapid control of acute bipolar mania. *J Clin Psychiatry* 2005;66 (suppl 3):5-11
2. Tohen M, Sanger TM, McElroy SL, et al. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. *Am J Psychiatry* 1999;156:702-709
3. Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzapine HGGW Study Group. *Arch Gen Psychiatry* 2000;57: 841-849. Erratum: *Arch Gen Psychiatry* 2002;59:91
4. Tohen M, Ketter TA, Zarate CA, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry* 2003;160:1263-1271
5. Keck PE Jr, Versiani M, Potkin S, et al. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry* 2003;160:741-748
6. Thompson PA, Meltzer HY. Positive, negative, and disorganization factors from the Schedule for Affective Disorders and Schizophrenia and the Present State Examination: a three-factor solution. *Br J Psychiatry* 1993;163:344-351
7. Tohen M, Jacobs TG, Feldman PD. Onset of action of antipsychotics in the treatment of mania. *Bipolar Disord* 2000;2:261-268

**Tamas Treuer, M.D., Ph.D.**

**Bruce R. Basson, M.S.**

Area Medical Center Vienna  
Department of Neuroscience  
Central Eastern Europe & Middle East &  
Africa & Commonwealth of Independent States  
Eli Lilly Regional Operations GmbH  
Vienna, Austria

#### Dr. Keck Replies

**Sir:** Dr. Treuer and Mr. Basson make an important point of clarification regarding the onset of efficacy for atypical antipsychotics in patients with acute mania. Although the data from placebo-controlled trials indicate that there were significant mean reductions in measures of manic symptoms from placebo at day 2 in patients receiving ziprasidone, at day 3 in patients receiving risperidone (in 1 trial), and at day 4 in patients receiving aripiprazole, these data should not be construed to imply differences in onset of efficacy. They do indeed represent the timepoints at which improvement was first assessed following baseline evaluations prior to randomization in these trials. To my knowledge, there is only 1 head-to-head comparison trial of atypical antipsychotic monotherapies in patients with acute bipolar mania, a trial comparing risperidone and olanzapine.<sup>1</sup> In that trial, no significant differences in onset of efficacy were detected.

Dr. Treuer and Mr. Basson's comments regarding possible differences in sensitivity between rating scales used are also potentially relevant. However, the Mania Rating Scale is derived

from the Schedule for Affective Disorders and Schizophrenia, Change Version (SADS-C), and was the primary outcome measure in several of the trials they referred to, not the overall SADS-C.

I thank them for emphasizing these methodological differences in trial design.

*Dr. Keck is a consultant to or member of the scientific advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Eli Lilly, Ortho-McNeil, Pfizer, and Shire and is a principal or co-investigator on research studies sponsored by Abbott, the American Diabetes Association, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Elan, Eli Lilly, Janssen, Merck, the National Institute of Mental Health, the National Institute of Drug Abuse, Organon, Ortho-McNeil, Pfizer, the Stanley Medical Research Institute, and UCB Pharma.*

#### REFERENCE

1. Brown EB, Ahmed S, Schuh LM, et al. Olanzapine versus risperidone treatment of bipolar I disorder. In: *New Research Abstracts of the American Psychiatric Association Annual Meeting*; May 1-6, 2004; New York, NY:NR783

**Paul E. Keck, Jr., M.D.**

Department of Psychiatry  
University of Cincinnati College of Medicine  
Cincinnati, Ohio

#### Thyroid Dysfunction During Treatment With Atypical Antipsychotics

**Sir:** In their recent (January 2005) article,<sup>1</sup> Kelly and Conley report on a relatively underappreciated side effect of certain atypical antipsychotics. Although effects of certain psychotropics, such as lithium, on thyroid hormones have been extensively studied, the effects of atypical antipsychotics merit further attention. In patients with preexisting mental illness, drug-induced impairments in thyroid function may exacerbate their symptoms and significantly complicate their diagnosis and management.<sup>2</sup> Both hypothyroidism and hyperthyroidism can be associated with psychiatric manifestations, such as depression, anxiety, irritability, and even psychosis.

The double-blind study by Kelly and Conley<sup>1</sup> included 38 patients with schizophrenia. The results of that study indicate that mean total serum thyroxine (TT<sub>4</sub>) levels decrease significantly in quetiapine-treated patients, but not in fluphenazine- or risperidone-treated patients after 6 weeks. As the authors point out, the observation of effects on thyroid hormones with quetiapine is not new. Peuskens and Link,<sup>3</sup> Arvanitis and Miller,<sup>4</sup> and Small et al.<sup>5</sup> have reported similar findings.<sup>2-4</sup> Kelly and Conley<sup>1</sup> also report that thyroid-stimulating hormone (TSH) levels did not change significantly in any of the 3 treatment arms after 6 weeks, a time frame considered to be adequate for such effects to be observed. There were no clinical signs of overt hypothyroidism for any patient in the trial. The authors conclude that the change in TT<sub>4</sub> levels is probably not clinically significant and that routine monitoring of thyroid function in patients without a history of thyroid disease is not recommended.

Kelly and Conley acknowledge that additional studies are needed with larger samples to further address the significance of their findings. The results of a recently completed large international study<sup>6</sup> address this issue and may provide new insight into the effects of risperidone and quetiapine on thyroid function. This 6-week double-blind study excluded patients with

**Table 1. Change From Baseline in Thyroid Function in Patients Receiving Placebo, Risperidone, or Quetiapine<sup>a,b</sup>**

Thyroid Variable	Placebo (baseline N = 73, endpoint N = 35)	Risperidone (baseline N = 153, endpoint N = 101)	Quetiapine (baseline N = 153, endpoint N = 79)
TT <sub>4</sub> (µg/dL)			
Baseline	114.4 ± 25.8	111.5 ± 26.5	113.6 ± 25.8
Endpoint	115.0 ± 29.0	107.7 ± 27.5	85.1 ± 22.5
Change, mean ± SE	1.9 ± 3.5	-1.7 ± 2.3	-26.9 ± 2.4*†‡
TT <sub>3</sub> (ng/mL)			
Baseline	2.1 ± 0.5	2.1 ± 0.5	2.2 ± 0.6
Endpoint	2.3 ± 0.6	2.2 ± 0.6	1.9 ± 0.5
Change, mean ± SE	0.2 ± 0.1*	0.1 ± 0.04*	-0.2 ± 0.05*†‡
TSH (µIU/mL)			
Baseline	2.2 ± 2.5	1.8 ± 1.5	1.8 ± 1.2
Endpoint	2.2 ± 1.1	2.1 ± 1.5	2.2 ± 2.3
Change, mean ± SE	-0.1 ± 0.3	0.1 ± 0.2	0.4 ± 0.2*

<sup>a</sup>Between-group comparisons based on analysis of covariance model including treatment, center, and baseline as covariates. Baseline thyroid data were not available for 3 patients in the quetiapine group.

<sup>b</sup>Values shown as mean ± SD unless otherwise noted.

\*p ≤ .05 vs. baseline.

†p ≤ .001 vs. placebo.

‡p ≤ .001 vs. risperidone.

Abbreviations: TSH = thyroid-stimulating hormone, TT<sub>3</sub> = total serum triiodothyronine, TT<sub>4</sub> = total serum thyroxine.

unstable thyroid disease. A total of 382 patients with schizophrenia (DSM-IV criteria) were randomly assigned to treatment with risperidone, quetiapine, or placebo in a 2:2:1 fashion. Thyroid function tests were performed at baseline and week 6 endpoint. During the last 4 weeks of this trial, subjects could receive additional psychotropics to treat persistent symptoms. The thyroid function analysis was performed on subjects who remained on monotherapy throughout the 6-week study period (placebo N = 35; quetiapine N = 79; and risperidone N = 101). The thyroid function results of the entire population have been reported elsewhere<sup>6</sup> and are fully consistent with these findings.

Consistent with the prior reports, the results of the present study showed a statistically significant decrease in TT<sub>4</sub> for patients receiving quetiapine, but not in those receiving risperidone or placebo (Table 1). The change with quetiapine was also significant when compared to those observed with risperidone or placebo. Total serum triiodothyronine (TT<sub>3</sub>) levels were similarly affected. It is important to note that free T<sub>4</sub> and T<sub>3</sub> levels were not collected in this trial, so it is challenging to rule out alterations in protein binding as the cause of the decreases observed. In this case, TSH levels may be elucidating, as effects on protein binding should not influence TSH. After 6 weeks of treatment, TSH levels significantly increased only in quetiapine-treated patients. To our knowledge, these data represent the first report of changes in TSH levels with an atypical antipsychotic. These TSH findings differ from those reported by Kelly and Conley.<sup>1</sup> This may, in part, reflect differences in the patient populations (treatment-resistant in Kelly and Conley) and/or the larger number of patients included in our study.

Although Kelly and Conley<sup>1</sup> acknowledge that the full clinical impact of the effects observed in their study cannot be conclusively determined through a post hoc analysis, their report adds to the growing body of literature that thyroid hormone levels change significantly with quetiapine. With the new evidence that TSH may be affected as well, prospective studies designed

specifically to study the potential consequences of thyroid hormone dysfunction, particularly in patients with severe mental illness, are appropriate. Important research questions that merit investigation are (1) the long-term clinical consequences of drug-induced thyroid dysfunction, (2) the persistence versus reversibility of the abnormalities, and (3) the impact on children who receive these medications.

*Drs. Greenspan and Gharabawi are employees of Janssen Pharmaceutica. Dr. Kwentus reports no financial or other relationship relevant to the subject of this letter.*

## REFERENCES

- Kelly DL, Conley RR. Thyroid function in treatment-resistant schizophrenia patients treated with quetiapine, risperidone, or fluphenazine. *J Clin Psychiatry* 2005;66:80-84
- Roberts CG, Ladenson PW. Hypothyroidism. *Lancet* 2004;363:793-803
- Peuskens J, Link CG. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatr Scand* 1997;96:265-273
- Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. *Biol Psychiatry* 1997;42:233-246
- Small JG, Hirsch SR, Arvanitis LA, et al, and the Seroquel Study Group. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry* 1997;54:549-557
- Greenspan A, Kosik-Gonzales C, Bossie C, et al. Readiness to discharge among inpatients with schizophrenia: effects of risperidone, quetiapine, and placebo [poster]. Presented at the Collegium Internationale Neuro-Psychopharmacologicum; June 20-24, 2004; Paris, France

**Andrew Greenspan, M.D.**  
**Georges Gharabawi, M.D.**

Janssen Pharmaceutica Products, L.P.  
Titusville, New Jersey  
**Joseph Kwentus, M.D.**  
Department of Psychiatry  
University of Mississippi  
Jackson, Mississippi

## Weight Gain, Sexual Dysfunction, and Bupropion

**Sir:** In their recent (May 2005) article, Zimmerman et al.<sup>1</sup> reported that bupropion is not associated with weight gain or sexual dysfunction. I disagree with their assertion for the following reasons.

Concerning weight gain, the package insert for bupropion extended-release (XL)<sup>2</sup> states that 9% of patients treated with the immediate-release (IR) form of bupropion gained weight, a rate higher than that found with placebo. At least 1 case report noted weight gain with bupropion treatment.<sup>3</sup>

The package insert for bupropion XL<sup>2</sup> also disclosed decreased libido, increased libido, impotence, abnormal ejaculation, dyspareunia, and painful erection as infrequent side effects. In addition, the literature contains case reports of bupropion-associated sexual dysfunction.<sup>4-8</sup> Furthermore, a cross-sectional, observational study of 6297 adult outpatients receiving antidepressant monotherapy reported a 22% prevalence of sexual dysfunction with bupropion IR and a 25% prevalence with bupropion sustained-release.<sup>9</sup> A naturalistic study of outpatients with nonpsychotic, unipolar depression treated with



bupropion observed a 6.7% incidence of anorgasmia, a 20% incidence of increased libido, and a 6.7% incidence of decreased libido.<sup>10</sup> Finally, a meta-analysis of randomized, double-blind, controlled clinical trials of bupropion versus selective serotonin reuptake inhibitors (SSRIs) for depression in adults noted that sexual arousal disorder, orgasmic dysfunction, and decreased sexual desire occurred with bupropion, although less frequently when compared with SSRIs.<sup>11</sup>

In conclusion, bupropion treatment is indeed associated with weight gain and sexual dysfunction.

*Dr. Menaster reports no financial or other relationship relevant to the subject of this letter.*

#### REFERENCES

1. Zimmerman M, Posternak MA, Attiullah N, et al. Why isn't bupropion the most frequently prescribed antidepressant? *J Clin Psychiatry* 2005;66:603–610
2. Wellbutrin XL [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2005. Available at: [http://us.gsk.com/products/assets/us\\_wellbutrinXL.pdf](http://us.gsk.com/products/assets/us_wellbutrinXL.pdf). Accessed June 19, 2005
3. Workman EA, Short DD. Bupropion-induced carbohydrate craving and weight gain [letter]. *Am J Psychiatry* 1992;149:1407–1408
4. Martinez-Raga J, Sabater A, Cervera G. Anorgasmia in a patient treated with bupropion SR for smoking cessation [letter]. *J Clin Psychopharmacol* 2004;24:460–461
5. Chollet CA, Andreatini R. Effect of bupropion on sexual dysfunction induced by fluoxetine: a case report of hypersexuality [letter]. *J Clin Psychiatry* 2003;64:1268–1269
6. Ramasubbu R. Bupropion treatment-related sexual side effects: a case report [letter]. *Can J Psychiatry* 2000;45:200
7. Berigan TR. Possible sexual dysfunction associated with bupropion for smoking cessation: a case report [letter]. *Prim Care Companion J Clin Psychiatry* 1999;1:193
8. Labbate LA. Bupropion-SR-induced increased libido and spontaneous orgasm [letter]. *Can J Psychiatry* 1998;43:644–645
9. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* 2002;63:357–366
10. Vanderkooy JD, Kennedy SH, Bagby RM. Antidepressant side effects in depressed patients treated in a naturalistic setting: a study of bupropion, moclobemide, paroxetine, sertraline, and venlafaxine. *Can J Psychiatry* 2002;47:174–180
11. Nieuwstraten CE, Dolovich LR. Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. *Ann Pharmacother* 2001;35:1608–1613

**Michael J. Menaster, M.D.**  
Private Practice  
San Francisco, California

#### Dr. Zimmerman and Colleagues Reply

**Sir:** Our recent article<sup>1</sup> examining the factors influencing psychiatrists' prescription of bupropion was based on 3 propositions: (1) all antidepressant medications are generally equally effective<sup>2</sup>; (2) weight gain and sexual dysfunction are the 2 side effects that are of greatest concern to patients and have the greatest impact on long-term compliance; and (3) bupropion is not associated with either weight gain or sexual dysfunction. Dr. Menaster questioned the accuracy of our third proposition and concluded that bupropion is associated with weight gain and sexual dysfunction. He cited 4 lines of evidence supporting his conclusion: (1) case reports; (2) reports of weight gain in the package insert for bupropion extended-release (XL); (3) reports from naturalistic, observational studies; and (4) the results of a

meta-analysis comparing bupropion and selective serotonin reuptake inhibitors (SSRIs).

In our original article, we reviewed the literature on the efficacy of bupropion, but we did not cite any studies to support our assertion that bupropion is not associated with either weight gain or sexual dysfunction. Herein we review this literature because if Dr. Menaster's conclusion is correct, then one of the central premises upon which our study was based is undermined. We first review the literature on bupropion and weight gain and then review the literature on bupropion and sexual dysfunction.

#### Weight Gain

**Short-term trials.** In our article, we identified 10 published placebo-controlled studies of bupropion, 6 of outpatients<sup>3–8</sup> and 4 of inpatients.<sup>9–12</sup> Five of the 10 studies reported the mean change in weight in the medication and placebo groups. In 4 of these studies, the mean change in weight was lower in the bupropion group than in the placebo group,<sup>6–8,10</sup> and in 1 study, there was no change in weight in either the bupropion or placebo group.<sup>9</sup> In 4 of the 5 studies, the mean change in weight was less than zero in the bupropion group, thereby indicating that the medication tended to cause weight loss rather than weight gain. No study reported the percentage of patients who gained a clinically significant amount of weight.

We also identified 14 published studies comparing bupropion with another medication.<sup>3–6,13–22</sup> Ten of the 14 studies reported the mean change in weight in the bupropion and active comparator groups.<sup>3,6,14–20,22</sup> In each of these studies, the mean change in weight was lower with bupropion than with the active comparator, and in each study, the mean change in weight was less than zero in the bupropion group.

These results are consistent with the findings reported in the 2005 edition of the *Physicians' Desk Reference* (PDR).<sup>23</sup> The package insert for bupropion XL, referenced by Dr. Menaster, is an abbreviated version of the description in the PDR. Dr. Menaster correctly noted that 9% of patients taking bupropion were reported to have experienced weight gain. However, he did not fully describe the information provided in the package insert and the PDR. The PDR discusses weight gain separately for the immediate-release (IR), sustained-release (SR), and XL preparations of bupropion. For bupropion IR, the text notes that 9.4% of patients gained weight, which was lower than the 34.5% rate in patients receiving tricyclic antidepressants (TCAs). Table 1 of the PDR description reports that in placebo-controlled studies, the rate of weight gain was lower in patients treated with bupropion IR compared with the rate in the patients who received placebo (13.6% vs. 22.7%). The definition of *weight gain* was not given. In the section on bupropion SR, the incidence of weight gain, defined as an increase > 5 lb, in placebo-controlled trials was nearly identical in patients treated with 300 mg/day (3%) and 400 mg/day (2%) of bupropion SR and placebo (4%). No data were reported on the frequency of weight gain in patients treated with the XL version.

In summary, the results of the placebo-controlled studies of bupropion IR and bupropion SR clearly indicate that the medication does not cause weight gain, at least in the short run. This does not belie the fact that some patients gain weight while taking the medication, just as some gain weight while taking placebo. Because weight gain is multifactorially determined, it is necessary to conduct placebo-controlled trials to determine whether the incidence is attributable to the medication. Dr. Menaster selectively abstracted the 9% statistic from the package insert without indicating that this was reported in studies comparing bupropion with TCAs, and he omitted the

package insert data that compared rates of weight gain in patients treated with bupropion SR versus placebo.

**Longer-term trials.** The studies summarized above were short-term trials, generally under 2 months of duration. Perhaps bupropion causes weight gain when prescribed over a longer period of time. We identified 3 studies examining weight changes in patients taking bupropion for at least 6 months.<sup>24-26</sup> Harto-Truax and colleagues<sup>25</sup> reported an average weight loss of 7.4 lb after 32 weeks of treatment, although they suggested that much of the weight loss was attributable to the discontinuation of TCAs. Gardner<sup>24</sup> followed 58 depressed outpatients treated with bupropion IR for at least 3 months up to 1 year after initiating treatment. The mean treatment duration was 9 months. The last recorded weight for each patient showed a mean terminal weight change of -6.8 lb. Nearly three quarters of the patients lost weight, and one quarter gained weight. Of the 14 patients who gained weight, half had gained less than 5 lb. Croft et al.<sup>26</sup> conducted the only analysis of weight change in a placebo-controlled, double-blind maintenance study of bupropion. Patients were treated with bupropion SR in an open-label fashion for 8 weeks and lost an average of 3.1 lb. Treatment responders were randomly assigned to receive placebo or bupropion SR (150 mg twice daily) for 44 weeks. The mean changes in body weight from baseline to the end of the maintenance phase in the bupropion SR and placebo groups were -2.5 lb and -0.4 lb, respectively. Thus, the bupropion SR group maintained the modest weight loss that occurred during the initial 8-week open phase, whereas in the placebo group the patients' weight returned to baseline levels. Croft et al. also found that the amount of weight loss was associated with patients' pretreatment body mass index—higher baseline body weight was associated with greater weight loss.

On the basis of this review of acute and maintenance studies, we stand by our initial proposition that bupropion is not associated with weight gain.

### Sexual Dysfunction

The question of whether bupropion causes sexual dysfunction is somewhat more complicated because it is well recognized that the rates reported in the PDR, which are based on global inquiries of side effects attributable to the medication, grossly underestimate the true prevalence of sexual side effects.<sup>27</sup> Accordingly, to evaluate whether bupropion is associated with sexual dysfunction, it is necessary to examine studies that systematically assessed this domain.

Sexual dysfunction, like weight gain, can be the result of many different factors. Loss of libido is frequent in depressed patients, and in earlier diagnostic systems it was considered as part of the diagnostic criteria for depression.<sup>28</sup> In the absence of a placebo control group, it is not possible to determine how much of the reported sexual dysfunction is due to the medication and how much is due to other, nonmedication factors such as the depressive disorder itself, relationship problems, physical illness, or sexual disorders or to other medications.

**Naturalistic studies.** Dr. Menaster cited 2 naturalistic, observational studies that reported that 6.7% to 25% of patients receiving bupropion experienced some form of sexual dysfunction. In one of these studies, Clayton et al.<sup>29</sup> used the Changes in Sexual Functioning Questionnaire<sup>30</sup> to compare the prevalence of sexual dysfunction in 6268 primary care patients taking antidepressant medication. (The sample size of 6297 cited by Dr. Menaster represented the total sample enrolled in the study. Because of missing data, only 6268 patients were included in the sexual functioning analyses.) A subset of 802 patients (798 of whom were included in the analyses) were prospectively identified as being free of other probable causes of sexual dysfunction

such as comorbid medical illnesses or concomitant medications. As noted by Dr. Menaster, in the overall sample the prevalence of sexual dysfunction was 22% in patients taking bupropion IR and 25% in patients taking bupropion SR. However, he did not indicate that these rates were the lowest among the 10 medications examined. He also did not indicate that in the subset of patients without other probable causes of sexual dysfunction, the rate of dysfunction in the bupropion SR group dropped to 7%, which again was lower than rates for all other medications studied. In fact, the rate of sexual dysfunction in this group was less than one third of the 23% prevalence rate in the group with the second lowest rate.

The difference in the rates of sexual dysfunction between the total sample and the subset of patients without other probable causes of sexual dysfunction highlights the reasons for being cautious in interpreting the results from naturalistic, observational studies. Because sexual dysfunction can be due to a variety of factors, it is necessary to have a placebo control group for comparison. Without such a control group, it is not even possible to know whether the 7% rate of dysfunction in the bupropion group is due to the medication. The same limitation applies to the other naturalistic study of antidepressant side effects cited by Dr. Menaster, although it should again be noted that the rates of anorgasmia, decreased libido, delayed ejaculation, and erectile dysfunction were each below 7% and lower than the rates reported for sertraline, paroxetine, and venlafaxine.<sup>31</sup>

Dr. Menaster indicated that the meta-analysis of controlled trials comparing bupropion and SSRIs concluded that sexual dysfunction occurred in patients treated with bupropion, although less often than in patients receiving SSRIs. This is a misrepresentation of the conclusions of the review. Nieuwstraten and Dolovich<sup>32</sup> did not suggest that bupropion was associated with sexual dysfunction, presumably because they did not compare rates in patients treated with bupropion with rates in patients treated with placebo. Rather, they limited their conclusions to a comparison with the SSRIs.

**Placebo-controlled studies.** There are 3 published placebo-controlled studies examining whether sexual dysfunction is associated with bupropion.<sup>4-6</sup> Each of these studies used the same methods. A noteworthy inclusion criterion was the requirement that patients had to be in a stable relationship and participate in sexual activity at least once every 2 weeks. Patients were systematically interviewed about sexual functioning during the course of the trial, and sexual dysfunction was diagnosed according to DSM-IV definitions. In addition, patients made global ratings of their satisfaction with sexual functioning. Five types of sexual dysfunction were examined: sexual desire disorder, sexual arousal disorder, orgasm dysfunction, premature ejaculation (in 2 of the 3 studies), and global satisfaction with sexual functioning.

Each of the 3 studies was 8 weeks in duration; patients were evaluated at weeks 1, 2, 3, 4, 6 and 8; and statistical analyses compared the groups at each timepoint. Thus, there were a total of 84 statistical comparisons between the bupropion and placebo groups. (In fact, there were more than 84 statistical tests because Coleman et al.<sup>5</sup> also conducted a secondary analysis and compared sexual dysfunction rates in patients who responded or whose illness remitted from treatment. They reported a significantly higher rate of orgasm dysfunction at one of the treatment weeks in the patients whose illnesses remitted with placebo than in patients whose illnesses remitted with bupropion.) Five (6.0%) of the 84 comparisons showed a significant difference. On the basis of an alpha level of .05, this number of significant differences would be expected by chance. In the study by Croft et al.,<sup>6</sup> bupropion was associated with a

significantly lower rate of sexual desire disorder at endpoint and week 7, and a significantly higher rate of sexual arousal disorder at endpoint. In the study by Coleman et al.,<sup>5</sup> bupropion was associated with a significantly higher rate of sexual desire disorders at weeks 1 and 2, although this difference was due to the pretreatment differences between groups. Thus, the results of these 3 placebo-controlled studies do not suggest that bupropion is associated with sexual dysfunction. In fact, as we noted in our original article, some studies have found that bupropion may be particularly beneficial to patients who experience sexual dysfunction.<sup>33–39</sup>

### Conclusion

In conclusion, our review of the literature is consistent with the statement made in our article that bupropion is not associated with either weight gain or sexual dysfunction. Some patients might have idiosyncratic reactions, just as they might to other medications; however, on the basis of the available published data, we do not believe that clinicians need to discuss the possibility of weight gain and sexual dysfunction when initiating treatment with bupropion.

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### REFERENCES

- Zimmerman M, Posternak M, Attiullah N, et al. Why isn't bupropion the most frequently prescribed antidepressant? *J Clin Psychiatry* 2005;66:603–610
- American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder [Revision]. *Am J Psychiatry* 2000;157(suppl 4):1–45
- Branconnier RJ, Cole JO, Ghazvinian S, et al. Clinical pharmacology of bupropion and imipramine in elderly depressives. *J Clin Psychiatry* 1983;44(5 pt 2):130–133
- Coleman C, Cunningham L, Foster V, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. *Ann Clin Psychiatry* 1999;11:205–215
- Coleman CC, King BR, Bolden-Watson C, et al. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. *Clin Ther* 2001;23:1040–1058
- Croft H, Settle E, Houser T, et al. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. *Clin Ther* 1999;21:643–658
- Lineberry CG, Johnston JA, Raymond RN, et al. A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients. *J Clin Psychiatry* 1990;51:194–199
- Reimherr F, Cunningham L, Batey S, et al. A multicenter evaluation of the efficacy and safety of 150 and 300 mg/d sustained-release bupropion tablets versus placebo in depressed outpatients. *Clin Ther* 1998;20:505–516
- Fabre L, McLendon D. Double-blind placebo-controlled study of bupropion hydrochloride (Wellbutrin) in the treatment of depressed in-patients. *Curr Ther Res* 1978;23:393–401
- Feighner J, Meredith C, Stern W, et al. A double-blind study of bupropion and placebo in depression. *Am J Psychiatry* 1984;141:525–529
- Pitts WM, Fann WE, Halaris AE, et al. Bupropion in depression: a tri-center placebo-controlled study. *J Clin Psychiatry* 1983;44(5 pt 2):95–100
- Merideth CH, Feighner JP. The use of bupropion in hospitalized depressed patients. *J Clin Psychiatry* 1983;44(5 pt 2):85–87
- Chouinard G. Bupropion and amitriptyline in the treatment of depressed patients. *J Clin Psychiatry* 1983;44(5 pt 2):121–129
- Davidson J, Miller R, Van Wyck Fleet J, et al. A double-blind comparison of bupropion and amitriptyline in depressed inpatients. *J Clin Psychiatry* 1983;44(5 pt 2):115–117
- Masco H, Kiev A, Holloman L, et al. Safety and efficacy of bupropion and nortriptyline in outpatients with depression. *Curr Ther Res* 1994;55:851–863
- Mendels J, Amin MM, Chouinard G, et al. A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry* 1983;44(5 pt 2):118–120
- Shopsin B, Soper R, Tyrer S, et al. Bupropion (Wellbutrin) imipramine study: a single-blind comparison in depressed outpatients. *Curr Ther Res* 1983;33:339–361
- Feighner J, Hendrickson G, Miller L, et al. Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. *J Clin Psychopharmacol* 1986;6:27–32
- Weisler RH, Johnston JA, Lineberry CG, et al. Comparison of bupropion and trazodone for the treatment of major depression. *J Clin Psychopharmacol* 1994;14:170–179
- Feighner JP, Gardner EA, Johnston JA, et al. Double-blind comparison of bupropion and fluoxetine in depressed outpatients. *J Clin Psychiatry* 1991;52:329–335
- Kavoussi RJ, Segraves RT, Hughes AR, et al. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J Clin Psychiatry* 1997;58:532–537
- Weihls KL, Settle EC Jr, Batey SR, et al. Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. *J Clin Psychiatry* 2000;61:196–202
- Physicians' Desk Reference. 59th ed. Montvale, NJ: Thomson PDR; 2005
- Gardner E. Effects of bupropion on weight in patients intolerant to previous antidepressants. *Curr Ther Res* 1984;35:188–199
- Harto-Truax N, Stern WC, Miller LL, et al. Effects of bupropion on body weight. *J Clin Psychiatry* 1983;44(5 pt 2):183–186
- Croft H, Houser T, Jamerson B, et al. Effect on body weight of bupropion sustained-release in patients with major depression treated for 52 weeks. *Clin Ther* 2002;24:662–672
- Montejo-Gonzalez A, Llorca G, Izquierdo J, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther* 1997;23:176–194
- Feighner JP, Robins E, Guze SB, et al. Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry* 1972;26:57–67
- Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* 2002;63:357–366
- Clayton A, McGarvey E, Clavet G. The Changes in Sexual Functioning Questionnaire (CSFQ): development, reliability, and validity. *Psychopharmacol Bull* 1997;33:731–745
- Vanderkooy J, Kennedy S, Bagby R. Antidepressant side effects in depression patients treated in a naturalistic setting: a study of bupropion, moclobemide, paroxetine, sertraline, and venlafaxine. *Can J Psychiatry* 2002;47:174–180
- Nieuwstraten C, Dolovich L. Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. *Ann Pharmacother* 2001;35:1608–1613
- Modell J, May R, Katholi C. Effect of bupropion-SR on orgasmic dysfunction in nondepressed subjects: a pilot study. *J Sex Marital Ther* 2000;26:231–240
- Segraves R, Croft H, Kavoussi R, et al. Bupropion sustained release (SR) for the treatment of hypoactive sexual desire disorder (HSDD) in nondepressed women. *J Sex Marital Ther* 2001;27:303–316
- Rowland D, Myers L, Culver A, et al. Bupropion and sexual function: a placebo-controlled prospective study on diabetic men with erectile dysfunction. *J Clin Psychopharmacol* 1997;17:350–357
- Ashton AK, Rosen RC. Bupropion as an antidote for serotonin reuptake inhibitor-induced sexual dysfunction. *J Clin Psychiatry* 1998;59:112–115
- Gitlin M, Suri R, Altshuler L, et al. Bupropion-sustained release as a treatment for SSRI-induced sexual side effects. *J Sex Marital Ther* 2002;28:131–138
- Kennedy SH, McCann SM, Masellis M, et al. Combining bupropion



SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. *J Clin Psychiatry* 2002;63:181-186

39. Clayton A, Warnock JK, Kornstein SG, et al. A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor-induced sexual dysfunction. *J Clin Psychiatry* 2004;65:62-67

**Mark Zimmerman, M.D.**  
**Michael A. Posternak, M.D.**  
**Naureen Attiullah, M.D.**  
**Michael Friedman, M.D.**  
**Robert J. Boland, M.D.**  
**Scott Baymiller, M.D.**  
**Stacie Lauro Berlowitz, M.D.**  
**Shahzad Rahman, M.D.**  
**Kirsten K. Uy, M.D.**  
**Steve Singer, M.D.**  
**Iwona Chelminski, Ph.D.**  
**Tavi Thongy, M.D.**

Department of Psychiatry and Human Behavior  
 Rhode Island Hospital, Brown Medical School  
 Providence, Rhode Island

### Treatment-Emergent Psychosis With Aripiprazole

**Sir:** Aripiprazole, the latest atypical antipsychotic to receive approval by the U.S. Food and Drug Administration, is unique in its action as a partial agonist at dopamine receptors.<sup>1</sup> Partial agonists can function as net agonists or net antagonists, depending on the amount of naturally occurring full agonist neurotransmitter that is present. Aripiprazole has antagonist activity at dopamine-2 (D<sub>2</sub>) receptors in a hyperdopaminergic environment and agonist activity in a hypodopaminergic environment. There is no complete blockade of dopamine neurons by aripiprazole.<sup>2,3</sup> In different areas of the brain, aripiprazole can simultaneously boost deficient dopamine activity and block excessive dopamine activity.

We report a case in which aripiprazole's unique mechanisms of action may have contributed to recurrence of psychotic and manic symptoms.

**Case report.** Ms. A, a 57-year-old woman, has long suffered from schizoaffective disorder, bipolar type (DSM-IV criteria). For the 2 years prior to the time of this report, she had been treated daily in a partial hospital program by the same geriatric psychiatrist (N.H.). Her condition was stable while she was on 8 mg daily of the liquid form of perphenazine, a high-potency first-generation antipsychotic. When the manufacturer discontinued the liquid form of perphenazine, it was decided to convert this patient's medication to aripiprazole.

In August 2004, Ms. A was started on aripiprazole, 10 mg daily, and the dose was titrated to 20 mg daily after 2 weeks. While on 20 mg daily, Ms. A was noted to engage in increasingly bizarre behaviors. She dug holes in the backyard of her boarding home and ate grass. Her mood was irritable and her affect labile. She became hypersexual and displayed inappropriate sexual behaviors in public. After 3 weeks, Ms. A required an emergency department evaluation. She was given an intramuscular injection of ziprasidone and discharged home.

The next day, in accordance with the strategy described by Casey et al.,<sup>4</sup> aripiprazole was increased to 30 mg daily. Ms. A's symptoms progressed and she became more paranoid, with severely delusional thinking and increased agitation. After 3 days

on 30 mg daily of aripiprazole, Ms. A began to suffer from insomnia, and on the fifth day of treatment at this dosage, she was admitted to the hospital. While Ms. A was at the inpatient unit, aripiprazole was discontinued, and she was started on quetiapine 200 mg/day. Her condition was stabilized, and on her discharge from the inpatient unit, her quetiapine dosage was 350 mg/day.

This patient's acute onset of psychotic and manic symptoms was temporally related to increasing doses of aripiprazole, suggesting the medication may have played a key role. Since Ms. A had previously been on long-term treatment with a high-potency dopamine antagonist (perphenazine), it is conceivable that her relapse was triggered by the discontinuation of perphenazine. However, one would expect the emergence of psychotic symptoms to have happened earlier than 3 weeks into the aripiprazole treatment. One might also argue that insomnia, a common side effect of aripiprazole, might have triggered the emergence of psychosis. However, if the information provided by the patient and the staff of the boarding home is correct, the onset of insomnia began after the emergence of psychotic symptoms.

A possible explanation could be that the chronic administration of the high-potency D<sub>2</sub> receptor antagonist perphenazine created a state of decreased dopamine-mediated neurotransmission in which aripiprazole acted as an agonist, thus causing a worsening of psychotic symptoms. Alternatively, the chronic D<sub>2</sub> blockade may have caused hypersensitivity of the D<sub>2</sub> receptors in the mesolimbic system,<sup>2</sup> creating a situation in which the partial agonist properties of aripiprazole were inadequate to control the emergence of psychotic symptoms. Manic-like symptoms emerging in the context of atypical antipsychotics have previously been reported.<sup>5</sup> Our case adds another to the small number of reports thus far of worsening of psychotic and manic symptoms by aripiprazole.<sup>6-8</sup>

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### REFERENCES

- Abilify [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2004
- DeLeon A, Patel NC, Crismon ML. Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. *Clin Ther* 2004;26:649-666
- Stahl S. *Essential Psychopharmacology*. 2nd ed. New York, NY: Cambridge University Press; 2002
- Casey DE, Carson WH, Saha AR, et al, for the Aripiprazole Study Group. Switching patients to aripiprazole from other antipsychotic agents: a multicenter randomized study. *Psychopharmacology (Berl)* 2003;166:391-399
- Rachid F, Bertschy G, Bondolfi G, et al. Possible induction of mania or hypomania by antipsychotics: an updated review of reported cases. *J Clin Psychiatry* 2004;65:1537-1545
- DeQuardo JR. Worsened agitation with aripiprazole: adverse effect of dopamine partial agonism? [letter] *J Clin Psychiatry* 2004;65:132-133
- Ramaswamy S, Vijay D, William M, et al. Aripiprazole possibly worsens psychosis. *Int Clin Psychopharmacol* 2004;19:45-48
- Reeves RR, Mack JE. Worsening schizoaffective disorder with aripiprazole [letter]. *Am J Psychiatry* 2004;161:1308

**Matthew E. Barnas, M.D.**  
**Najeeb Hussain, M.D.**  
**Georgios Petrides, M.D.**

Department of Psychiatry  
 New Jersey Medical School-U.M.D.N.J.  
 Newark, New Jersey