Letters to the Editor

Divalproex Versus Olanzapine in Mania

Sir: The article by Zajecka et al.[1] on the efficacy and safety of divalproex sodium versus olanzapine in the treatment of bipolar disorder is interesting, but unfortunately it does not seem to truly support the authors' conclusions.

The first problem is sample size. According to previous experience with divalproex[2] and olanzapine,[3] this study was not clearly powered to show superiority of either drug over the other and it is unclear whether this trial was designed to prove either superiority or noninferiority. The conclusion that both drugs were equally effective goes, then, far beyond the data, as a type II error is very likely. Mean Mania Rating Scale (MRS) score changes from baseline to day 21 were –14.8 for divalproex and –17.2 for olanzapine ($p = .210$), which looks like increasing the sample size might have resulted in significant differences favoring olanzapine. In fact, an Eli Lilly–sponsored trial[4] showed olanzapine to be significantly more efficacious than divalproex ($p < .03$), and the Young Mania Rating Scale (YMRS) total score improvement was –13.4 for olanzapine and –10.4 for divalproex. Although the MRS and the YMRS are different scales, the effect size was strikingly similar in both trials and the main difference in the design was sample size (120[1] versus 251[4]).

More importantly, the absence of a placebo arm in this trial makes it difficult to ascertain whether both drugs were equally effective or rather equally ineffective. The statement that "divalproex and olanzapine demonstrated efficacy for the treatment of acute mania in both trials"[1] goes again beyond the results, as in one trial, divalproex was less efficacious than olanzapine[4] and in the other, neither drug is better but there is no placebo comparator.

There are other concerns that might have biased the results of this trial. The authors argue that they used divalproex and olanzapine doses that approximate clinical practice,[1] but it is unclear whether oral loading of divalproex (20 mg/kg/day as initial medication dosages) and 10 mg/day of olanzapine are truly reflecting clinical practice. Many clinicians would argue that they titrate divalproex dosage and that they would start with 15 to 20 mg/day of olanzapine. Dosage and titration might have influenced the study results.

Other perhaps less important points are the use of lorazepam throughout the study period, which might have reduced putative differences between the tested medications, and the concurrent use of hypnotics, which also may improve the scores in some items such as sleep. It is also unclear how the analysis adjusting for somnolence as an adverse event was performed. Because somnolence was reported in 47% of olanzapine-treated patients and 29% of divalproex-treated patients, there is obviously much less statistical power to find any difference compared with the whole sample.

Finally, it is noteworthy that both in all points in Figure 1[1] and in all psychiatric rating scales olanzapine is consistently numerically better than divalproex. The reason why the authors use analysis of covariance for MRS scores using baseline MRS scores as a covariate is clear for the assessment of MRS ratings differences but less clear for the Brief Psychiatric Rating Scale, Hamilton Rating Scale for Depression, and Clinical Global Impressions-Severity of Illness scale.

In summary, I find this report very informative, but my conclusions are slightly different from the authors'. Experience and evidence from adequately powered trials[4] support that antipsychotics are generally more effective than anticonvulsants in the treatment of acute mania.[5]

Dr. Vieta has served as a consultant to AstraZeneca, Eli Lilly, and Janssen-Cilag; has received grant/research support from AstraZeneca, Bristol-Myers, Eli Lilly, and Janssen-Cilag; and has been on the speakers or advisory boards for AstraZeneca, Bristol-Myers, Eli Lilly, Janssen, Novartis, and UCB Pharma.

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Dr. Zajecka Replies

Sir: Dr. Vieta has raised several concerns regarding our article that reported the results of a recent trial examining the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder.[1] One of Dr. Vieta's concerns relates to the sample size utilized in the trial and the fact that the study was not clearly powered to show superiority of either drug. As the article states quite explicitly, the study was powered to detect differences in weight gain associated with each of the 2 treatments, not differences in efficacy. Both agents have been demonstrated in numerous clinical trials to be effective for the treatment of acute mania associated with bipolar disorder, both agents are approved by the U.S. Food and Drug Administration for this indication, and the a priori assumption was that both agents would have similar efficacy in the current trial.[2–5] As indicated in the article, the sample size

utilized in this trial did provide for an 80% power to detect a 5-point difference in change in Mania Rating Scale (MRS) score between groups, if such a difference in efficacy did exist. The fact that a placebo arm was not included in this study, as Dr. Vieta points out, further emphasizes that this study was not designed to evaluate efficacy differences.

Dr. Vieta's concern that the initial dose of olanzapine (10 mg/day) utilized in this study is lower than what is generally used in clinical practice and may have influenced the study results appears unjustified. Titration of olanzapine in the current study was allowed to a maximum of 20 mg/day, which is consistent with or higher than the olanzapine dosing utilized in previous trials.[4–6] Dose titration in both treatment arms in the current trial was allowed during the first week of the study. Previous trials with divalproex utilizing a conservative initial dose (750 mg/day) have demonstrated significant clinical responses from baseline to final for divalproex-treated subjects compared with placebo-treated subjects, indicating that conservative initial dosing does not impact endpoint analyses.[2,3]

Dr. Vieta's assertion that dosing in clinical practice is typically initiated more conservatively with divalproex and more aggressively with olanzapine (15–20 mg/day) indicates that the statistically significant increase in side effects reported with olanzapine treatment compared with divalproex in the current trial may in fact be an underestimate of what is typically seen in clinical practice. One would expect that by initiating divalproex therapy at 20 mg/kg/day and olanzapine at 10 mg/day, the current study would have minimized side effects associated with olanzapine treatment while potentially maximizing side effects associated with divalproex treatment. The results of the current study indicate that even with a conservative dose titration regimen, olanzapine therapy produces significantly more weight gain and is associated with significantly more side effects than divalproex therapy.

Dr. Vieta raises several additional concerns such as the fact that concomitant use of lorazepam was allowed throughout the duration of the trial. The concomitant use of moderate doses of lorazepam in the current trial is consistent with that seen in other bipolar mania trials.[6] Additionally, Dr. Vieta purports confusion regarding a post hoc analysis that was conducted to examine the role of somnolence on treatment-related antimanic effects. In the current trial, a significantly larger proportion of olanzapine-treated subjects complained of somnolence compared with divalproex-treated subjects (47% vs. 29%, respectively, $p < .05$). As indicated in our article, to evaluate the impact of treatment-related somnolence on antimanic efficacy, a post hoc, 2-way analysis of variance was conducted, with factors for treatment and the presence or absence of somnolence as an adverse event. This was not a subset analysis, but was rather an effort to control for the significant amount of somnolence that occurred in the olanzapine group compared with the divalproex group. The post hoc analysis did in fact demonstrate nearly identical treatment-related improvements in mean MRS scores, as the mean change from baseline to final MRS score was –16.9 for divalproex and –17.6 for olanzapine.

Dr. Vieta's final concern relates to the fact that we reported analysis of covariance results for all secondary efficacy measures. Given the significant differences in the baseline MRS scores, an analysis of covariance was reported for this primary efficacy measure. For the sake of consistency, then, analysis of covariance results were reported for all secondary efficacy measures as well. The analysis of variance results were similar to the analysis of covariance results for all secondary efficacy measures, and had we chosen to report analysis of variance rather than analysis of covariance, the conclusions would be unchanged.

The results of the current study indicate that while divalproex and olanzapine are both effective in treating acute mania associated with bipolar disorder, treatment with olanzapine is associated with significantly more side effects, more weight gain, and a less favorable lipid profile than is divalproex. Clinicians need to carefully consider safety and tolerability, in addition to efficacy, when selecting an antimanic agent for their patients. The long-term risk/benefit ratio of each agent must be considered for each patient, as an unfavorable safety and tolerability profile may jeopardize long-term patient compliance and health.

Dr. Zajecka has received grant/research support from and has served as a consultant to and on the speakers bureau and advisory boards for Bristol-Myers and Wyeth; has served as a consultant to and on the speakers bureau and advisory boards for Abbott and Eli Lilly; has received grant/research support from Alza, AstraZeneca, Cyberonics, Merck, MIICRO, and Pfizer; and has served on the speakers bureau for Pfizer/Roerig, GlaxoSmithKline, and Pharmacia & Upjohn.

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Worsening of Psychosis After Replacement of Adjunctive Valproate With Topiramate in a Schizophrenia Patient

Sir: Topiramate has been suggested as adjunctive therapy to reduce clozapine-induced weight gain and seizures.[1,2] We report here on a schizophrenia patient originally treated with clozapine and valproate who experienced a worsening of psychosis in the context of replacing valproate with topiramate, which remitted when valproate was resumed.

Case report. Mr. A, a 35-year-old man with paranoid schizophrenia (ICD-10), was first admitted to our hospital in 1997 experiencing delusions, disorganized thought, and affective instability, as well as ritualistic behavior that included complex rituals when entering a room or using the bathroom. His family history was free of mental illness, and he had no personal history of seizures or head trauma. He previously participated in a clinical trial of haloperidol versus risperidone, after which he was switched to olanzapine. After 8 weeks of olanzapine treatment, Mr. A had achieved only partial symptom remission.

Introduction of clozapine with titration to 400 mg/day markedly diminished positive symptoms, but residual symptoms (poor concentration, anhedonia, mood swings) and ritualistic behaviors persisted. Sertraline, 100 mg/day, was initiated in 1998 and led to marked improvement of ritualistic behavior and minimal improvement of residual symptoms. During treatment with clozapine and sertraline, the patient gained 25 kg (56 lb) of body weight within 3 years. In 2000, an electroencephalogram (EEG) showed a slowing of background activity as well as frontal delta-theta activity with interposed spikes, requiring anticonvulsant treatment. Valproate was initiated and titrated to 1000 mg/day (serum level > 60 mg/mL), while the clozapine dose was reduced to 300 mg/day. Thereafter, Mr. A showed no evidence of seizures, neither clinically nor in EEGs.

Interestingly, the addition of valproate also led to a significant amelioration of residual symptoms. Over the next 2 months, Mr. A's concentration difficulties and mood clearly improved. In 2001, sertraline was discontinued on the patient's request and his psychopathologic condition remained stable with clozapine and valproate treatment.

Because of hyperlipidemia (cholesterol, 255 mg/dL; triglycerides, 430 mg/dL), gemfibrozil, 450 mg/day, was prescribed in 2002. Through simultaneous dietary advice, Mr. A lost 5 kg (11 lb) within 5 months. To support further weight loss, it was decided to gradually taper and discontinue valproate, and after 3 days valproate was replaced by topiramate, 25 mg/day. At this point, Mr. A's total Positive and Negative Syndrome Scale (PANSS)[3] score was 38 (positive score = 7, negative score = 12, general score = 19). After 4 days of treatment with clozapine, 300 mg/day, plus topiramate, 25 mg/day, the patient showed a worsening of psychosis (ritualistic behavior, thought disorder, agitation, anxiety, social withdrawal, and depressed mood leading to suicidal ideas; PANSS total score = 72, positive score = 12, negative score = 19, general score = 41), which did not improve despite an increase in topiramate dose to a maximum dose of 100 mg/day within 2 weeks and adjunctive treatment with lorazepam. During this time, serum levels of clozapine remained stable (mean ± SD = 165 ± 26 ng/mL). Topiramate was discontinued, and valproate treatment was resumed. Within 1 week, psychotic symptoms decreased significantly and remitted completely after 2 weeks.

Topiramate has been reported to worsen psychosis when added to clozapine in 3 schizophrenia patients who had an unsatisfactory clinical response to clozapine monotherapy.[4] Furthermore, topiramate has been linked to psychosis in patients with epilepsy with and without a prior history of psychiatric illness.[5]

Topiramate antagonizes α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA)/kainate receptors, thus decreasing glutamate-mediated excitation.[6] According to the glutamate model of schizophrenia, inhibition of glutamate receptors in the nucleus accumbens and prefrontal cortex should increase positive and negative symptoms, respectively.[7,8] This mechanism of action could have worsened psychosis in our patient. However, discontinuation of valproate could also have been one reason for worsening of psychosis. It cannot be ruled out that valproate discontinuation may have been the only reason for the worsening of the patient's condition and that the relationship to topiramate was only coincidental.

Although it makes much clinical sense to switch from valproate to topiramate in patients who are gaining weight, as valproate has been shown to induce weight gain and topiramate has been shown to lead to weight loss, our observation suggests the use of caution when considering switching patients from valproate to topiramate.

Dr. Fleischhacker has been a consultant for Janssen and Eli Lilly and has been a speakers/advisory board member for Janssen, Eli Lilly, Pfizer, Sanofi, and Bristol-Myers Squibb. Dr. Hummer has received grant/research support from Eli Lilly and has been a speakers/advisory board member for Janssen, Eli Lilly, Pfizer, and Bristol-Myers Squibb. Dr. Hofer reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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Effect of Bupropion on Sexual Dysfunction Induced by Fluoxetine: A Case Report of Hypersexuality

Sir: Sexual dysfunction (impairment in desire, excitement/erection, or orgasm) is a frequent and important side effect of antidepressant drug treatment[1–3] that has been related to the serotonergic or anticholinergic effect of antidepressant drugs.[4–6] There is a marked difference among antidepressant drugs in the reported rates of sexual dysfunction: bupropion and nefazodone are associated with a lower risk, whereas drugs that inhibit serotonin reuptake (e.g., fluoxetine or venlafaxine) or have an anticholinergic action (e.g., tricyclics) are associated with a higher risk.[2,3]

The adequate management of antidepressant drug–induced sexual dysfunction can be crucial to patient compliance with treatment. Thus, several strategies have been proposed to treat this side effect: waiting for spontaneous remission, changing to another antidepressant with a low incidence of this effect (e.g., bupropion, nefazodone), reducing the dose, instituting drug holidays for short half-life drugs (e.g., sertraline), and using adjunctive drug treatments ("antidotes").[6] Among the "antidotes," bupropion, an antidepressant drug with a dopaminergic and noradrenergic action,[7] has been found to be effective in some case reports and open studies, although contradictory results have been obtained in controlled trials.[1,8–10]

In the present report, we describe a case in which a low dose of bupropion was added to current antidepressant treatment (fluoxetine) and, despite a good initial response (reversal of sexual dysfunction), led to hypersexuality and discontinuation of bupropion.

Case report. Ms. A, a 35-year-old married woman, had a major depressive episode (DSM-IV[11]) without other psychiatric or medical problems. She came to the clinic in October 2001 taking 150 mg/day of clomipramine but still showing residual depressive symptoms (low-to-moderate depressive mood, reduced energy, low self-esteem, anhedonia). Moreover, she complained of reduction of libido that "practically reached zero" since starting clomipramine (she reported normal libido before the introduction of clomipramine, with normal excitement and orgasm when stimulated). Clomipramine was replaced with fluoxetine, 40 mg/day, with total remission of all symptoms except the decreased libido. Thus, the decrease of libido was interpreted as a side effect of the medication and not as a residual depressive symptom since Ms. A reported its onset after she started clomipramine and the symptom did not disappear after the change to fluoxetine, with which all other depressive symptoms remitted.

Bupropion, 100 mg/day, was added to the treatment regimen 3 months after the start of fluoxetine as an antidote for her sexual dysfunction, and 1 month later there was a reversal of the libido reduction. Five months after the beginning of bupropion treatment, Ms. A returned complaining of an exaggerated increase in libido directed both at her husband and at her coworkers, which caused marked distress to her (and thus was ego dystonic), leading her to discontinue all medications of her own initiative. Two months later, her libido returned to normal, although the depressive symptoms also came back. During bupropion treatment, she noted clitoral engorgement only after she had sexual thoughts and she did not report spontaneous orgasms or clitoral priapism. There were no other symptoms according to DSM-IV criteria that could suggest a switch to a manic/hypomanic episode. She was taking no other medication (she refused even over-the-counter medicines). There was no past personal or family history of similar symptoms. After the reintroduction of fluoxetine 2 months after she had discontinued all medications, the patient experienced full remission of depressive symptoms, but her libido fell again.

Among antidepressant drugs, the selective serotonin reuptake inhibitors (SSRIs) are associated with a higher incidence of sexual dysfunction (35%–57%) than other classes.[2,3] There is some clinical evidence suggesting a favorable effect of bupropion on sexual dysfunction induced by SSRIs (although negative results have also been reported), and the rationale for its use in this situation is based on its dopaminergic/noradrenergic–enhancing action, since the increased actions of these neurotransmitters have a positive effect on libido, arousal, and/or orgasm.[4–6] In the case reported here, we cannot attribute the increase in libido solely to bupropion, but to the bupropion-fluoxetine combination. In this line, there is another case report that describes spontaneous orgasm with the introduction of bupropion to treat sertraline-induced sexual dysfunction.[12] Interestingly, it was shown that fluoxetine enhances bupropion-induced dopamine and norepinephrine release in mesocorticolimbic areas.[13] On the other hand, the in vitro biotransformation of bupropion to hydroxybupropion, its major metabolite, was not inhibited by fluoxetine or norfluoxetine.[14] Moreover, bupropion did not alter plasma fluoxetine or norfluoxetine levels.[9] Thus, although we did not determine plasma bupropion or fluoxetine levels, we think that the increased libido was due to a pharmacodynamic rather than a pharmacokinetic interaction between bupropion and fluoxetine. However, there is a case report of spontaneous orgasm and increased libido in a patient with attention deficit disorder treated with bupropion monotherapy,[15] which raises the possibility that the increased libido could be due to the action of bupropion alone.

In conclusion, despite its favorable side effect profile, bupropion can cause increased libido and other sexual side effects that could be distressing to the patient. The small number of case reports in the literature indicates that this side effect may be uncommon or underevaluated. It should be emphasized, however, that prospective controlled studies are required to confirm these case reports of bupropion-induced sexual side effects. Nonetheless, until these data become available, when prescribing bupropion the clinician should be alert to the development of an inappropriate increase in sexual desire that may be associated with a higher potential for painful consequences to the patient.

Dr. Andreatini has been a speakers/advisory board member for GlaxoSmithKline. Dr. Chollet reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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A Word of Caution About the Implied Role for Duloxetine in Pain Management

Sir: A new antidepressant, duloxetine hydrochloride, is soon expected to receive U.S. Food and Drug Administration approval for treatment of major depressive disorder. In premarketing trials, its utility for patients with major depressive disorder accompanied by chronic pain has been a particular focus. Initial conclusions that "duloxetine may be a first-line treatment for patients with major depressive disorder and associated painful physical symptoms"[1(p308)] may be premature. The theoretical rationale for linking its antidepressant efficacy with demonstrations of reducing pain complaints is tenuous. Yet, implying a link between the utility of duloxetine and reduction of pain, a pervasive medical problem, has tremendous commercial implications.

A substantial proportion of depressed patients present with somatic complaints, e.g., 69% of depressed patients reported only physical symptoms as the reason for seeking medical care.[2] Frequently, these are nonspecific pain complaints.[3]

Preliminary evidence suggested that duloxetine mitigates painful somatic complaints, as assessed by using a standard pain assessment instrument, e.g., the visual analog scale (VAS).[1] The VAS, a single-dimension pain-rating measure, is influenced by the vicissitudes of the rater's affect, prevailing mood, cognitions, expectations, and perceptions. Each of these variables can be altered by the presence of major depressive disorder, thereby leading to a magnification of pain severity ratings. The use of the VAS is potentially misleading, as reductions in pain severity ratings can merely be an artifact of the improvements in mood observed when depressed patients are given duloxetine. Thus, as depression is alleviated, so too is the amplification of somatic symptoms reduced. Other studies have corroborated that the degree of physical symptom improvement among depressed patients is correlated with overall reduction of depression severity.[4,5]

Given the experimental paradigms employed to date, it would be erroneous to assume that duloxetine has a direct pain-relieving effect. There is a vast difference between studying analgesic efficacy of duloxetine in patients with chronic pain, who might be clinically depressed, and the effect of reducing "pain" complaints in depressed patients who, by virtue of depression, somatize.

Antidepressants have often been employed as adjunctive agents for the treatment of pain. The mechanism of pain relief is thought to involve the influences on noradrenergic and serotonergic (5-HT) analgesia mediated by descending pain pathways emanating from the brain that modulate incoming pain afferents in the spinal cord. Compelling data for the utility of antidepressants in pain come from studies demonstrating efficacy in pain patients with clear, identifiable disorders who are not depressed[6] and/or demonstrating analgesia at sub-antidepressant doses.[7] Antidepressants with simultaneous noradrenergic and 5-HT influences, e.g., tricyclics, fare better with demonstrating analgesic efficacy than those with more selective neurotransmitter influences, e.g., selective serotonin reuptake inhibitors.[8]

Preliminary animal experimentation does, in fact, suggest that duloxetine may reduce pain-related behaviors.[9] Duloxetine may have a role to play in the management of chronic pain patients, given its simultaneous and direct influence on norepinephrine and 5-HT. What is needed, however, is careful examination of its utility among patients with established chronic pain disorders.

Conversely, depression often complicates the course of illness for patients with chronic pain. The presence of comorbid depression can exacerbate the perceived level of pain and the impact of the pain on patients' level of adaptive functioning.

Duloxetine may be a reasonable consideration for use among chronic pain patients with comorbid depression. It has a desirable safety and tolerability profile, bypassing those side effects limiting the usefulness of other antidepressants, e.g., tricyclics. Adverse effects most commonly associated with the use of duloxetine include nausea, dry mouth, and somnolence.[1]

More convincing evidence of duloxetine's role in pain relief would be established if future empirical investigations included subjects with clinically defined pain disorders. Ideally, demonstration of reductions in pain severity ratings among nondepressed pain patients may be particularly useful. Among pain patients with comorbid depression, duloxetine's efficacy in pain relief may be harder to elucidate, but this is nonetheless possible, particularly if an analgesic effect can be demonstrated before improvement of depression severity or occurs at doses lower than those required to produce mood improvements.

Dr. Leo reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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