

Varenicline Treatment for Smokers With Schizophrenia: A Case Series

Sir: Schizophrenia is associated with increased prevalence of smoking, heavy smoking, and smoking-related morbidity and mortality. Standard nicotine dependence treatments have been associated with modest efficacy in patients with schizophrenia and high rates of relapse to smoking upon their discontinuation.¹⁻³ Varenicline was approved for nicotine dependence treatment in 2006. In 2007, 2 case reports were published in which varenicline treatment was temporally associated with exacerbation of psychiatric symptoms in 1 person with schizophrenia and 1 person with bipolar disorder.^{4,5}

These reports prompted the authors to review clinical nicotine dependence treatment with varenicline in smokers with schizophrenia at an urban community mental health clinic with attention to clinical efficacy for nicotine dependence and to signs of clinical worsening that may have occurred secondary to varenicline treatment.

Method. From October 2006 to October 2007, 19 patients with schizophrenia, most of whom had quit smoking in the past but had relapsed to smoking after discontinuation of nicotine dependence treatment with bupropion or nicotine replacement therapy, requested nicotine dependence treatment with the newly available medication, varenicline. These 19 outpatients with schizophrenia were on stable antipsychotic medication regimens and received a standard titration of varenicline as follows: 0.5 mg/day for 3 days, 0.5 mg b.i.d. for 4 days, then 1 mg b.i.d. Each received brief individual counseling at medication visits. Visits were weekly for 2 weeks, then approximately monthly.

Results. All 19 patients reported reduced craving to smoke after initiating varenicline treatment. Four patients discontinued varenicline treatment due to nausea and vomiting. One patient subsequently restarted varenicline and was able to tolerate treatment without vomiting on the second exposure. Thirteen patients tolerated the medication, quit smoking within 10 to 21 days of starting varenicline, and maintained self-reported abstinence for ≥ 12 weeks, verified with periodic expired air carbon monoxide measurements of < 9 ppm at clinical visits. In the period between 12 and 24 weeks, 4 patients had occasional "slips" in which they smoked < 5 cigarettes per day for a period of < 7 days and then regained abstinence.

All 13 patients in this series who quit smoking elected to continue to take varenicline beyond the standard 24-week regimen to prevent relapse to smoking. Patients in this series have remained clinically stable with no clinical evidence of psychotic relapse or significant worsening of psychiatric symptoms or side effects of antipsychotic medications. None of the 19 patients had a psychiatric hospitalization within 24 weeks of starting varenicline. No clinical rating scales were performed as part of this treatment. Likewise, no cognitive tests were performed to assess the effect of varenicline on cognitive performance in these patients.

Varenicline is a partial $\alpha 4\beta 2$ and full $\alpha 7$ nicotinic acetylcholine receptor (nAChR) agonist.⁶ Decreased activity at $\alpha 4\beta 2$ and $\alpha 7$ nAChRs in schizophrenia may underlie the high rates of both nicotine dependence⁷ and relapse to smoking after discontinuation of nicotine dependence treatment observed in this population.³ Because nAChR activity is reduced at baseline, is increased by smoking, and is not expected to return to a normal

baseline after smoking cessation in schizophrenia, as in the general population, it may be reasonable to propose that longer duration, perhaps chronic, agonist or partial agonist therapy may reduce relapse to smoking in schizophrenia. Studies are needed to test this hypothesis.

While we did not observe worsening in psychotic symptoms in 19 stable, medicated outpatients, because activated psychosis in 1 stable patient with schizophrenia⁴ and mania in 1 euthymic patient with bipolar disorder have been reported shortly after initiation of varenicline,⁵ clinicians should proceed with care until further clinical study is completed.

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REFERENCES

1. George TP, Vessicchio JC, Termine A, et al. A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biol Psychiatry* 2002 Jul;52(1):53-61
2. Evins AE, Cather C, Deckersbach T, et al. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *J Clin Psychopharmacol* 2005 Jun;25(3):218-225
3. Evins AE, Cather C, Culhane MA, et al. A 12-week double-blind, placebo-controlled study of bupropion SR added to high-dose dual nicotine replacement therapy for smoking cessation or reduction in schizophrenia. *J Clin Psychopharmacol* 2007 Aug;27(4):380-386
4. Freedman R. Exacerbation of schizophrenia by varenicline [letter]. *Am J Psychiatry* 2007 Aug;164(8):1269
5. Kohen I, Kremen N. Varenicline-induced manic episode in a patient with bipolar disorder [letter]. *Am J Psychiatry* 2007 Aug;164(8):1269-1270
6. Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at $\alpha 4\beta 2$ and a full agonist at $\alpha 7$ neuronal nicotinic receptors. *Mol Pharmacol* 2006 Sep;70(3):801-805
7. Freedman R, Hall M, Adler LE, et al. Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. *Biol Psychiatry* 1995 Jul;38(1):22-33

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Oral Divalproex Sodium Loading for Adolescent Outpatients With Acute Mania/Hypomania: A Report of 2 Cases

Sir: Treatment with divalproex sodium delayed release (DR) of the manic phase of bipolar disorder in adults results in rapid clinical response after a therapeutic serum concentration of 50 $\mu\text{g/mL}$ is achieved.¹ When divalproex treatment was initiated at 750 mg/day and daily dosage was subsequently titrated on the basis of serial serum divalproex sodium concentration determinations (i.e., a standard titration approach), therapeutic levels and corresponding antimanic response were observed in most patients after 5 to 10 days.^{1,2} In contrast, an oral loading strategy of divalproex sodium 20 mg/kg/day produces serum valproic acid concentrations of approximately 80 $\mu\text{g/mL}$ after 1 to 2 days of treatment.^{3,4} In a pooled analysis of 3 double-blind, randomized studies of adults with acute mania associated with bipolar disorder, the onset of antimanic effect with divalproex was

accelerated by oral loading, which was as well tolerated as or better tolerated than other active treatments administered according to a standard titration approach.⁵

Expecting that the same benefits of oral divalproex loading could be realized in younger patients, West et al.⁶ initiated divalproex at 20 mg/kg in 5 adolescent patients with bipolar disorder mixed type who were hospitalized for acute mania. The investigators documented substantial improvement in 3 patients and some improvement in 1 patient as measured by the Young Mania Rating Scale (YMRS) and the Hamilton Rating Scale for Depression. In a study of 15 adolescent patients with mania associated with bipolar disorder, DeBello et al.⁷ also documented benefits with oral divalproex loading, including statistically significant mean changes from baseline in YMRS aggression and irritability items.

We have treated 2 adolescents meeting DSM-IV criteria for bipolar disorder, manic phase, and describe our observations below.

Case 1. Mr. A, a 15-year-old adolescent boy weighing 64.5 kg, had a history of attention-deficit/hyperactivity disorder (ADHD) and depression (both consistent with DSM-IV criteria) but no other medical or substance abuse problems. The patient first presented in 1998 after he was being successfully treated with methylphenidate 20 mg/day and venlafaxine extended-release 75 mg/day for 6 months. He acutely developed manic symptoms characterized by 10 days of decreased need for sleep (1–2 hours of sleep/night), increased irritability, racing thoughts, pressured speech, impulsivity (e.g., he bought 3 guitars and other musical instruments), and delusions of grandiosity (e.g., he planned to quit school, believing that he was meant to be a rock star) after approximately 6 months of euthymia.

The patient was evaluated as an outpatient due to his family's refusal of hospitalization. Five days prior to this evaluation, the parents discontinued administration of methylphenidate. The adolescent was started on divalproex DR 750 mg p.o. twice daily (23.3 mg/kg/day) with no change in the venlafaxine dosage (75 mg/day). His manic symptoms, including acute delusions, decreased significantly by the third day of divalproex therapy. The serum valproic acid level measured on day 5 was 112 µg/mL; other laboratory indices (i.e., liver function tests, complete blood count, thyroid-stimulating hormone) were all within the reference ranges. The symptoms of acute mania had completely remitted by treatment day 10, and the patient was euthymic.

Subsequently, the patient was maintained on divalproex DR 1500 mg/day and venlafaxine 75 mg/day; methylphenidate was reintroduced at 20 mg/day 3 months after the manic episode for persistent symptoms of ADHD (without hyperactivity). At the 6-month follow-up visit, the patient demonstrated a euthymic mood, had returned to his premorbid level of functioning, and reported no side effects of treatment. The patient's weight at 6-month follow-up was 65.0 kg. At 42 months, the patient's treatment was converted from divalproex DR to 2000 mg/day of extended-release (ER) divalproex. Two weeks after switching to divalproex ER at 2000 mg/day, his serum valproic acid level was 104 µg/mL. Neuropsychological testing, requested by his school for academic placement, revealed euthymia and minimal attention difficulties that did not compromise age-appropriate academic and social skills. Follow-up at 46 months demonstrated ongoing euthymia and safety based upon chemistry and hematologic profiles.

Case 2. Ms. B, a 16-year-old adolescent girl weighing 73.6 kg, had a history of intermittent alcohol use over the past 6 months but no other medical or substance abuse problems. The patient had a significant family history of bipolar disorder,

which affected both of her parents as well as her maternal and paternal grandmothers. Ms. B presented in 2000 for outpatient evaluation of hypomania of 3 to 4 weeks' duration characterized by irritability, decreased need for sleep (3–4 hours of sleep/night), impulsivity (e.g., shoplifting), pressured speech, and flight of ideas. No evidence of psychotic symptoms was noted. At the outpatient visit, her urine drug screen was negative and there were no clinically significant results from other laboratory evaluations (i.e., clinical chemistry indices, complete blood count, thyroid-stimulating hormone, urine human chorionic gonadotropin). The patient and family denied alcohol use for the 12 weeks before presentation for her evaluation. The patient was started on divalproex DR 1750 mg daily, given as 250 mg in the morning, 500 mg at noon, and 1000 mg at bedtime (23.8 mg/kg/day). After the first dose, the patient reported mild nausea, which ceased with the addition of famotidine 20 mg for the first 5 days (famotidine was discontinued thereafter).

At a follow-up visit on day 7 of treatment, nearly complete remission of the patient's hypomanic symptoms was noted and a serum valproic acid level of 98 µg/mL was measured. The hypomanic symptoms had completely abated by day 14 after initiating divalproex. The patient had sustained euthymia and no evidence of substance abuse disorder 24 months after the initiation of treatment, at which time chemistry and hematology profiles showed no significant abnormalities.

In summary, divalproex proved to be a safe and effective treatment for acute manic and hypomanic symptoms in 2 adolescents with bipolar disorder in an outpatient setting. Both cases used loading doses of divalproex DR similar to that described in adults with acute mania (20 mg/kg) at the initiation of treatment. Both cases showed good acute tolerability (the second patient reported mild nausea that was transient and responded to a short course of famotidine 20 mg/day). The first patient had his divalproex DR converted to the ER formulation. The conversion was done without titration of either formulation. The dose of the ER formulation was based on the loading dose strategies used in the pivotal acute mania trials in adults with the ER formulation, which was 25 mg/kg on day 1 and an additional 500 mg at day 3.⁸ His weight was 65 kg at the time of conversion to the ER formulation, and he was placed on 2000 mg (30 mg/kg). Our recommendation for initial dosing or conversion to divalproex (ER) is similar to that for adults, initiating at 25 mg/kg, with and subsequent titration as needed to optimize efficacy and minimize side effects.

The evaluation of oral divalproex loading in a controlled study of children/adolescents with manic/hypomanic symptoms is warranted based on the rapid onset of efficacy and good tolerability observed in our 2 adolescent patients.

The case reports described in this letter were presented during a poster session at the 17th annual meeting of the U.S. Psychiatric and Mental Health Congress; November 18–21, 2004; San Diego, Calif.

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REFERENCES

1. Pope HG Jr, McElroy SL, Keck PE Jr, et al. Valproate in the treatment of acute mania: a placebo-controlled study. *Arch Gen Psychiatry* 1991 Jan;48(1):62–68
2. Bowden CL, Brugger AM, Swann AC, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. *JAMA* 1994 Mar;271:918–924
3. Keck PE Jr, McElroy SL, Tugrul KC, et al. Valproate oral loading in the treatment of acute mania. *J Clin Psychiatry* 1993 Aug;54(8):305–308
4. McElroy SL, Keck PE Jr, Tugrul KC, et al. Valproate as a loading treatment in acute mania. *Neuropsychobiology* 1993;27:146–149
5. Hirschfeld RM, Baker JD, Wozniak P, et al. The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine, and placebo in the treatment of acute mania associated with bipolar disorder. *J Clin Psychiatry* 2003 Jul;64(7):841–846
6. West SA, Keck PE, McElroy SL. Oral loading doses in the valproate treatment of adolescents with mixed bipolar disorder. *J Child Adolesc Psychopharmacol* 1995;5:225–231
7. Del Bello MP, Adler C, Strakowski SM. Divalproex for treatment of aggression associated with adolescent mania. *J Child Adolesc Psychopharmacol* 2004;14(2):325–328
8. Bowden CL, Swann AC, Calabrese JR, et al. A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. *J Clin Psychiatry* 2006 Oct;67(10):1501–1510

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Efficacy of Molindone in Treatment-Refractory Agitated Schizophrenia: Three Case Reports

Sir: Agitated behavior of schizophrenic patients refractory to antipsychotic treatment frequently leads to prolonged psychiatric inpatient stays. Difficulty in controlling such behaviors can impede discharge planning more than any other aspect of schizophrenia (e.g., negative symptoms). Treatments that can reduce persistent agitation are thus a key component of helping patients leave the hospital and function in the community.

Following the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and Cost Utility of the Latest Antipsychotics in Severe Schizophrenia (CUtLASS) studies demonstrating comparable efficacy between first- and second-generation antipsychotics,^{1,2} we have been interested in the use of molindone hydrochloride, a dihydroindolone classified as a mid-potency first-generation antipsychotic. We present 3 cases of patients with schizophrenia who had a marked reduction in agitation and violent behavior following treatment with molindone. All cases were considered treatment-refractory to multiple and extensive antipsychotic trials with second-generation antipsychotics and unsuitable for treatment with clozapine.

Case 1. Mr. A is a 39-year-old African American man with a history of DSM-IV schizoaffective disorder, bipolar type; polysubstance abuse; multiple hospitalizations for auditory hallucinations, paranoid ideation, and agitation over the past 12 years; and a history of violent behavior including multiple charges of attempted murder. Despite several consecutive courses of treatment with risperidone, quetiapine, and olanzapine at adequate dosages and at adequate length during his most recent admis-

sion, he remained symptomatic and was transferred to the local state psychiatric center. He continued to be agitated and assaultive and was transferred to our hospital in October 2006.

His initial regimen on arrival was quetiapine 200 mg in the morning and 400 mg at bedtime and divalproex sodium 1250 mg daily. During his first 2 months of hospitalization, Mr. A continued to have episodes of agitation and paranoia requiring intramuscular (IM) medication for behavioral control. His divalproex sodium dose was increased to 1500 mg daily, with serum valproate levels ranging from 75 to 95 mg/mL. Nonetheless, he continued to have both physical and verbal altercations requiring IM medication for behavioral control.

Clozapine treatment was started; however, Mr. A was unable to tolerate the sialorrhea, somnolence, and tachycardia it produced and refused to take it. Instead, quetiapine was tapered off during his third month and replaced with molindone, titrated to a target dose of 100 mg twice daily. Over the next 5 months following cross-taper from quetiapine to molindone, he has had no further episodes of agitation or other behavioral problems and has been able to participate in all rehabilitative activities.

Case 2. Mr. B is a 49-year-old African American man with a history of DSM-IV schizoaffective disorder, depressed type; polysubstance abuse; and multiple hospitalizations including state psychiatric admissions for inappropriate behavior and violence in response to command auditory hallucinations, including a history of criminal charges for menacing, assault, robbery, and rape. The patient also had a history of temporal lobe epilepsy following a motor vehicle accident, which was controlled with phenytoin and lamotrigine. He had a history of poor response to trials of haloperidol, quetiapine, and olanzapine at appropriate dosages and of sufficient duration. He was admitted to another hospital for agitation, sexually inappropriate behavior, and command auditory hallucinations to kill himself and was transferred to a local state psychiatric facility 7 months later for continued treatment and psychiatric stabilization. Mr. B was started on molindone 125 mg at bedtime for treatment of his agitation and psychosis. His seizure prophylaxis of levetiracetam 1500 mg twice daily, lamotrigine 150 mg twice daily, and phenytoin 100 mg 3 times daily was maintained. With this regimen, his agitation and psychosis were reduced substantially, and he was able to participate in ward activities.

He was referred to our hospital 2 months later for a special long-term cognitive rehabilitative treatment program. Unfortunately, after a year and a half in this program, he was hospitalized for an acute coronary syndrome, during which time he was taken off all psychotropic medications. When he returned to the psychiatric ward in April 2004, he was markedly more agitated and psychotic. These symptoms were initially treated with olanzapine 15 mg daily (orally disintegrating tablets) and molindone 75 mg twice daily, but treatment was frequently interrupted by Mr. B's refusal of all medications and complicated further by frequent seizures resulting from his noncompliance with antiepileptic medication.

Clozapine treatment was ruled out due to the patient's frequent seizures and medication refusals. Instead, olanzapine and molindone were replaced with quetiapine, titrated up to a dose of 500 mg twice daily. However, even at this dose, Mr. B continued to be agitated, disorganized, and assaultive. Molindone was again added to his existing quetiapine regimen and titrated up to a target dose of 100 mg twice daily. Since the patient resumed molindone treatment 5 months ago in November 2006, his behavior has improved substantially, with just 1 episode of assaultive behavior occurring in the first month of its reintroduction. Of note, he continued to have seizures every 3 to 4

weeks after resuming molindone treatment despite multiple changes to his antiepileptic drugs, finally settling on a twice-daily dosing regimen of divalproex sodium 1250 mg, lamotrigine 75 mg, phenytoin 160 mg, and clonazepam 1 mg. Nonetheless, he has shown very good behavioral control.

Case 3. Ms. C is a 43-year-old African American, human immunodeficiency virus (HIV)–seropositive woman on highly active antiretroviral therapy with a history of DSM-IV schizoaffective disorder, depressed type; cognitive impairment (mental retardation vs. HIV-related dementia); multiple hospitalizations for disorganized behavior and inappropriate sexual behavior; and a history of suicidal behavior, as well as polysubstance abuse. She was admitted to another hospital after presenting to her mother's home disheveled and with urine and feces on her clothing, responding to internal stimuli. Ms. C was initially treated with ziprasidone, titrated up to 200 mg daily, and clonazepam 2 mg twice daily, with little effect. Ziprasidone was then switched to clozapine, titrated up to 350 mg daily; however, she developed significantly more disorganized speech and behavior. Clozapine was discontinued, and her agitation increased. She was then placed on treatment with molindone 150 mg/day, with marked reduction in violent behavior but still paranoid and delusional.

She was transferred to our hospital 4 months later, in September 2006, for continued treatment. She was tapered off molindone treatment and started on quetiapine treatment, ultimately titrated up to 500 mg twice daily. During this cross-taper, she became substantially more agitated, requiring IM medication to achieve behavioral control. Molindone was restarted and titrated up to 100 mg twice daily. She had a few more episodes over the first 2 weeks during this change, but was able to remain in behavioral control over the next 2 months.

To reduce polypharmacy, molindone was again tapered off, leaving quetiapine 500 mg twice daily as the only antipsychotic. Ms. C again started having more episodes of agitation and paranoia, requiring IM medication for behavioral control every 2 to 3 days. In response, molindone was added back to her regimen and titrated up to 100 mg twice daily. Over the next month during the reintroduction of molindone, Ms. C had 2 more episodes of agitated behavior, but had no further episodes in the following 8 weeks at her current dose.

The 3 cases demonstrate a substantial reduction in symptoms of agitation and assaultiveness following treatment with molindone in patients who had been resistant to previous treatment with multiple antipsychotic medications at appropriate dosages and duration. In the first case, agitation was not controlled until treatment was changed over from quetiapine to molindone, despite concomitant use of divalproex sodium. In the last 2 cases, the agitation episodes were reduced by the use of molindone, recurred when molindone was discontinued, and subsided again after molindone was reinstated. This on-and-off correlation of agitation with molindone use suggests that the changes cannot be adequately explained by use of concomitant medications or other nonspecific effects of treatment. No increased sedation was observed after molindone treatment was started, consistent with molindone's low histamine receptor affinity³ and other clinical data finding less sedation with molindone than with other antipsychotics.⁴ The patients described in the second and third case reports were stabilized ultimately on an antipsychotic combination of molindone and quetiapine. However, in all cases, quetiapine alone had failed to reduce agitation, and in the first case described, quetiapine was not part of the final medication regimen, suggesting that quetiapine is not a required adjunct to molindone to achieve behavioral control. Since in all cases behavioral control was not achieved until mo-

lindone dosage reached 200 mg daily, the inadequate responses to molindone monotherapy observed earlier in the hospital courses of cases 2 and 3 may have been due to subtherapeutic dosing with daily doses of 125 to 150 mg of molindone.

While other typical antipsychotics inactivate neurons in both the substantia nigra zona compacta (A9) and ventral tegmental area (A10) regions, molindone is a potent and selective deactivator of A10 neurons in the ventral tegmental area, a property it shares with clozapine.³ Animal studies have shown that antipsychotic blockade of A9 neurons can facilitate aggressive behaviors,⁵ whereas antipsychotic blockade of A10 neurons can inhibit them.⁶ This selective inactivation of A10 neurons may account for the antiaggressive properties of molindone and clozapine.

The antiagitation and antiaggression effect of molindone has also been shown in children in a randomized, placebo-controlled trial.⁷ It has been effective and well tolerated in treating agitation in HIV-seropositive patients⁸ and elderly patients.⁹ Our case series and the positive reports in patients with other diagnoses suggest that molindone could be effective against aggression. We suggest that molindone warrants further controlled, prospective studies for the treatment of agitation and aggression in treatment-refractory schizophrenia.

Dr. Lindenmayer is a consultant for Eli Lilly and Janssen and has received grant/research support from Eli Lilly, Janssen, AstraZeneca, Pfizer, and Bristol-Myers Squibb. Drs. Ciranni and Gold report no financial or other relationship relevant to the subject of this letter.

REFERENCES

- Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005 Sept;353(12):1209–1223
- Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry* 2006 Oct;63(10):1079–1087
- Owen RR Jr, Cole JO. Molindone hydrochloride: a review of laboratory and clinical findings. *J Clin Psychopharmacol* 1989 Aug;9(4):268–276
- Bagnall A, Fenton M, Kleijnen J, et al. Molindone for schizophrenia and severe mental illness. *Cochrane Database Syst Rev* 2007 Jan 24;(1):CD002083
- Schmidt WJ. Effects of d-amphetamine, maprotiline, L-dopa, and haloperidol on components of the predatory behavior of the ferret, *Putorius furo* L. *Psychopharmacology (Berl)* 1979 Sep;64(3):355–359
- Piazza PV, Ferdico M, Russo D, et al. Facilitatory effect of ventral tegmental area A10 region on the attack behavior in the cat: possible dopaminergic role in selective attention. *Exp Brain Res* 1988;72(1):109–116
- Greenhill LL, Solomon M, Pleak R, et al. Molindone hydrochloride treatment of hospitalized children with conduct disorder. *J Clin Psychiatry* 1985 Aug;46(8 pt 2):20–25
- Fernandez F, Levy JK. The use of molindone in the treatment of psychotic and delirious patients infected with the human immunodeficiency virus: case reports. *Gen Hosp Psychiatry* 1993 Jan;15(1):31–35
- Peper M. Clinical experience with molindone hydrochloride in geriatric patients. *J Clin Psychiatry* 1985 Aug;46(8, part 2):26–29

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Apparent Commercial Bias in Supplement

Sir: I read your recent supplement “Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap”¹ with interest.

As a practicing psychiatrist with experience prescribing the full range of antipsychotics, I recognize the need for detailed information to help clinicians decide among the many choices in our armamentarium. While the supplement was published to address this need, I have serious questions regarding its scientific integrity.

The material in the supplement is based on an “Expert Consensus Survey.” According to the introduction, the survey was constructed to reflect “psychopharmacologic topics not adequately addressed by the evidence-based literature, but which clinicians who use antipsychotic medications need to understand.”^(p6)

I note that the results of 17 specific questions were highlighted in charts throughout the supplement. Of these questions, 8 asked panelists about general treatment strategies, without asking for an endorsement of any specific medication. Nine of the highlighted questions were more specific, asking which of a list of antipsychotics the experts would favor in given clinical situations. It appears that the choice of clinical situations to highlight in the supplement was influenced by the fact that Bristol-Myers Squibb sponsored the production of the article.

This conclusion is based on the following:

- In 7 of 9 (77%) medication comparisons, aripiprazole (Abilify, manufactured by Bristol-Myers Squibb) is ranked number 1 (see page 30 of the supplement).
- In 1 of 9 comparisons, aripiprazole is ranked number 2 (page 21).
- In 1 of 9 comparisons, aripiprazole is ranked number 3 (page 26).

The apparent reason that aripiprazole was so strongly endorsed by the experts was that the questions submitted covered clinical issues in which aripiprazole poses acknowledged advantages over its competitors. Seven of the questions asked specifically which antipsychotic the experts would choose in patients with various medical conditions, including being overweight, having cardiac disease, or having diabetes. Aripiprazole, indeed, has side effect advantages over the majority of competing atypicals regarding all 3 of these issues.

If topics submitted to experts had truly been chosen in the fashion claimed (that is, based on issues not adequately assessed in the literature), I would have expected to see questions addressing the following topics as well:

- Relative efficacy of different atypical antipsychotics
- Relative efficacy of atypical versus conventional antipsychotics
- Choice of antipsychotics in patients with a variety of clinical characteristics, including insomnia, agitation, anxiety, depression, prominent positive symptoms, and prominent negative symptoms

If these questions had been submitted, I believe that many of aripiprazole’s competitors would have been ranked in the first or second spot.

In summary, rather than being an unbiased review of the antipsychotic literature, this supplement appears to be a promotional article commissioned by Bristol-Myers Squibb in order to encourage readers to prescribe more aripiprazole.

Dr. Carlat receives income from the sale of a CME-accredited newsletter and from the sale of several books for psychiatric practitioners.

REFERENCE

1. Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap. *J Clin Psychiatry* 2007;68(suppl 7):1–48

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Dr. Weiden Replies

Sir: As chair of the supplement “Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap,” I would like to personally respond to the concerns put forth in Dr. Carlat’s letter regarding the scientific integrity of this publication.

His letter contends that the selection of items in the survey was “influenced by the fact that Bristol-Myers Squibb sponsored the production of the article.” He disputes our statement of our criteria for item selection. Dr. Carlat’s contention is that we chose specific questions that were likely to show the relative advantages of aripiprazole compared with other medication options. He also states that we avoided focusing on topics that would perhaps show that other antipsychotics might be recommended over and above aripiprazole.

I do not think that there is any way to reply to the content of this letter without first commenting on its tone. I was involved in every step of the Roadmap, from formulation of questions to writing of the supplement, and it seems to me that Dr. Carlat had already prejudged the work, decided his own verdict, and then scrutinized the document to find anything that might support his conclusions.

Let’s examine some of the specific criticisms raised in Dr. Carlat’s letter. It contains some biases and errors, which are addressed below:

- Dr. Carlat implies that we asked only 17 questions of the panel, 9 of which addressed specific medication choices. In fact, we asked a total of 31 detailed, multitiered questions that included use of antipsychotics in a broad range of clinical situations, including those mentioned in his letter. We did not have the space to publish all of these responses; in fact, it was my job as the chair of the project to try to figure out how to convey the results in a way that would be clinically helpful for physicians trying to select medications for their individual patients.
- As Dr. Carlat mentions, the relative weight profiles of the specific agents were indeed well known. But it was not our goal to restate what is already known. The goal of the item selection for this section was to gauge the relative preferences across antipsychotics given varying levels of medical comorbidities. In particular, we wanted to know how various levels of (escalating) baseline metabolic comorbidities would affect antipsychotic selection under a variety of common clinical situations. That item set is *not* the same as asking which antipsychotic has the most favorable weight or metabolic profile. The questions we posed involved balancing multiple and often competing treatment goals, including asking the respondents to the survey to take into consid-

eration their opinion of possible efficacy differences between the medications.

- Dr. Carlat is correct that we decided to highlight 9 questions about specific medication choices, many of which covered weight and metabolic situations, many of which had responses that favored aripiprazole and ziprasidone over the other antipsychotic options. Dr. Carlat is incorrect that the results exclusively “ranked” aripiprazole as “number 1,” since ziprasidone shared the same ranking. The methodology of the Roadmap states that these were not meant as direct head-to-head comparisons. The pattern is that aripiprazole and ziprasidone “move together” and seem to differentiate from the other antipsychotics as a function of a number of metabolic risk factors.
- Dr. Carlat’s letter implies that the graphs were selected because of the sponsor. He was not there when we drafted the supplement. What happened was that we were excited about the pattern of responses that visually showed the degree to which baseline obesity or increased metabolic risk factors affected medication choices. If Dr. Carlat has prejudged our motivation for showing these results, nothing will convince him otherwise. To other readers: please ask yourself which side effects *you* think should be emphasized in a supplement about individualizing antipsychotic medications for persons with serious mental illness. Do you think it was reasonable for us to have emphasized weight and metabolic problems over other comorbidities induced by side effects?

Our goal was to develop a supplement that might help clinicians help their patients achieve better outcomes. What saddens me is that nowhere in Dr. Carlat’s letter is his opinion about whether this Roadmap is a helpful and effective guide for clinicians caring for those suffering from serious mental illness. Our group worked hard to integrate current evidence-based knowledge with expert opinions. We hoped to create a document that would be useful in complex clinical situations. We struggled with how to develop something that would be a real contribution beyond that already available for clinicians. This was our motive, and the Roadmap project should be judged on whether or not we achieved those objectives.

Within the last 3 years, Dr. Weiden has been a consultant for AstraZeneca, Bristol-Myers Squibb/Otsuka America, Janssen, Organon, Pfizer, Shire, Vanda, and Wyeth; has received research support from AstraZeneca, Bristol-Myers Squibb/Otsuka America, Janssen, and Pfizer; and has been a speaker or consultant for AstraZeneca, Bristol-Myers Squibb/Otsuka America, Janssen, and Pfizer. A family member has consulted for Pfizer.

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Is Aripiprazole an Efficacious Adjunct for Unipolar Depression?

Sir: As part of a psychiatry residents’ journal club, we reviewed the recently published study by Berman et al.¹ on the efficacy of adjunctive aripiprazole versus adjunctive placebo in patients with unipolar, nonpsychotic major depression. We identified one potential confounding factor, for which we thought further data might provide some clarification.

Throughout the study, all patients were receiving antidepressants selected by the investigators (escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine). Although the protocol encouraged even distribution of the different antidepressants prior to randomization, the article provides no data showing that there were no differences between the treatment groups after randomization with regard to the number of patients receiving the various antidepressants. This lack of evidence could be relevant given pooled analyses^{2,3} that demonstrate statistically and clinically significant improved remission rates for patients taking venlafaxine as compared to those taking selective serotonin reuptake inhibitors. If, for example, there were more patients in the adjunctive aripiprazole group receiving venlafaxine as compared to patients in the adjunctive placebo group, then this finding would confound the results and may partly explain the difference in efficacy in this study.

Dr. Ghaemi currently received research grants from GlaxoSmithKline and Pfizer. He currently serves on the speakers bureaus of GlaxoSmithKline, AstraZeneca, Pfizer, Janssen, and Abbott and has served on the advisory boards of GlaxoSmithKline, Janssen, Pfizer, Shire, and Abbott. Neither he nor any of his family members hold equity positions in pharmaceutical corporations. Dr. Rakofsky reports no financial affiliation or other relationship relevant to the subject of this letter.

REFERENCES

1. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2007;68:843–853
2. Stahl SM, Entsuah R, Rudolph RL. Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression. *Biol Psychiatry* 2002;52:1166–1174
3. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* 2001;178:234–241

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Dr. Berman Replies

Sir: We thank Drs. Rakofsky and Ghaemi for their inquiry on the recent study published by my colleagues and me.¹ This article reports the first of 2 studies (see also Marcus et al.²) in which we present the efficacy and safety of aripiprazole as adjunctive treatment to standard antidepressant therapy (ADT) in patients with major depressive disorder who have had an inadequate response to ADTs. This study showed that adjunctive aripiprazole, compared with adjunctive placebo, significantly improved depressive symptoms as measured by the change in the Montgomery-Asberg Depression Rating Scale total score from baseline, the primary outcome measure.

Drs. Rakofsky and Ghaemi raise the question as to whether unequal antidepressant distribution between treatment groups could explain the observed efficacy. I provide Table 1 (showing data from the efficacy sample), which describes the distribution of antidepressants between treatment groups.

From Table 1, it is clear that equal distribution between placebo and aripiprazole treatment arms occurred for each ADT in the double-blind phase, and the efficacy data are not confounded by unequal randomization. Of note, no antidepressant-by-treat-

Table 1. Distribution of Antidepressants Received by Patients Taking Either Placebo or Aripiprazole as Adjunctive Treatment for Major Depressive Disorder^a

Adjunctive Treatment	Escitalopram	Fluoxetine	Paroxetine	Sertraline	Venlafaxine
Placebo	50 (29.1)	23 (13.4)	13 (7.6)	35 (20.3)	51 (29.7)
Aripiprazole	54 (29.8)	26 (14.4)	18 (9.9)	36 (19.9)	47 (26.0)

^aValues shown as N (%).

ment interaction effect was apparent in this study ($p = .914$, analysis of covariance).

These data, in addition to those presented in the article,¹ confirm that adjunctive aripiprazole is an efficacious augmentation medication for patients with major depressive disorder who have had an inadequate response to standard ADTs.

The study discussed in this letter was supported by Bristol-Myers Squibb Co. (Princeton, N.J.) and Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan).

Dr. Berman is an employee of Bristol-Myers Squibb.

REFERENCES

1. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2007;68:843–853
2. Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind placebo-controlled study. *J Clin Psychopharmacol* 2008;28:156–165

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Measurement of Pain and Medication Effect in a Study of Duloxetine

Sir: We would like to comment on the November 2007 article by Brecht et al.¹ that addressed the efficacy and safety of duloxetine in treating pain in patients experiencing major depressive disorder. We concur with the authors that co-occurring pain and depression is a clinical issue of utmost importance, one that has only recently begun to gain a level of attention commensurate with its clinical impact. However, we believe that a number of issues potentially limit this investigation's applicability to the clinical setting. The chief concerns involve the unclear description of the clinical problem investigated and the limited impact of duloxetine on pain.

Regarding the unclear description of the problem studied, the methods section indicates that only patients who had a

moderate or greater pain intensity rating on the Brief Pain Inventory-Short Form (BPI-SF) could enter the study. However, the nature of the pain was not described. Thus, we do not know if the majority of the patients who responded experienced neuropathic or musculoskeletal or some other form of pain. In addition, it is noted that these patients must not have been taking analgesics on a "regular basis" in the preceding 6 months. The term "regular basis" is not clearly defined, but, generally speaking, chronic pain patients with a moderate or great level of persistent pain receive some form of regular oral analgesia. Is it possible that the form of pain treated in this study is actually what is termed "somatic equivalents" for depression, whereby pain complaints are serving as a proxy for depression and there is no primary physical pain problem?² Without more information, we cannot know the answer to this question.

Regarding the robustness of the effect of duloxetine on pain, the primary pain measure employed in this study was the BPI-SF measure of pain intensity in the preceding 24 hours. The authors report that there was an almost 50% reduction of pain on this measure. However, the absolute reduction of pain for duloxetine was 2.57 (45%), versus a reduction of 1.64 (29%) for placebo, on an 11-point Likert scale, with 0 being no pain and 10 being the most severe pain. Although there was a statistically significant difference between the drug and control interventions, the rating scale difference between drug and placebo conditions found in this study is not robust from the standpoint of clinical practice.³

In conclusion, we believe that the vagueness of the clinical group studied and the limited separation from placebo hinder a clinician's ability to apply the findings of this study to the clinical setting.

Dr. Brecht was shown this letter and declined to comment.

Drs. Griffith and Severn and Mr. Hasley report no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Brecht S, Courtecuisse C, Debievre C, et al. Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. *J Clin Psychiatry* 2007;68:1707–1716
2. Ohayon MM. Specific characteristics of the pain/depression association in the general population. *J Clin Psychiatry* 2004;65(suppl 12):5–9
3. Forouzanfar T, Weber WE, Kemler M, et al. What is a meaningful pain reduction in patients with complex regional pain syndrome type 1? *Clin J Pain* 2003 Sep–Oct;19(5):281–285

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