

Schizophrenia Symptoms Remain Stable During Decreases From 2 Antipsychotics to Aripiprazole

Sir: Like many others, we have become concerned about the increasing use of more than 1 antipsychotic medication for the maintenance treatment of schizophrenic illness. In an effort to determine whether more than 1 medication was superior to 1 alone, we performed the following small pilot study.

Method. The study was approved by the Massachusetts Mental Health Center Institutional Review Board and was conducted from August 2003 to June 2005. Ten patients with persistent serious but stable DSM-IV–defined schizophrenic illness who agreed to participate and gave written informed consent were enrolled; 3 patients served as controls and 7 as experimental subjects. No subject was in crisis or relapse. All were taking at least 2 antipsychotic medications. Two patients were taking 3 antipsychotics: 1 was taking olanzapine with quetiapine and perphenazine, and 1 was taking olanzapine with risperidone and fluphenazine. Four more patients were taking olanzapine (1 each with ziprasidone, risperidone, fluphenazine, and haloperidol decanoate). Two were taking quetiapine with risperidone, and 1 was taking ziprasidone with fluphenazine. One subject was taking clozapine and risperidone.

After a baseline psychiatric interview to exclude those with concurrent substance abuse, unstable medical illness, or suicidal preoccupation, the subjects had 1 of their antipsychotic medications discontinued. An initial dose-finding phase substituted 15 mg/day of aripiprazole after a first antipsychotic was discontinued. Three of 4 subjects who withdrew from the study did so because of severe agitation. The study was then restarted using a lower starting dose of aripiprazole. As the first antipsychotic drug was tapered and discontinued, either 2.5 or 5 mg/day of aripiprazole was begun. The dose of aripiprazole was increased according to clinician decision as the second antipsychotic medication was tapered and discontinued. Control subjects continued to take their multiple antipsychotic medications as originally prescribed. All subjects were followed over the remaining period until the total study duration of 12 weeks was reached. Subjects were rated pretreatment and posttreatment with the Clinical Global Impressions scale,¹ Brief Psychiatric Rating Scale (BPRS),² and Positive and Negative Syndrome Scale (PANSS).³

Results. All subjects showed a modest decrease in total BPRS scores with no meaningful difference between those who were maintained on treatment with multiple antipsychotics and those who had aripiprazole substituted for both antipsychotics. The 3 control subjects showed a reduction in total scores (mean change = -3.7), and 6 of 7 of the switched patients showed a reduction (mean change = -2.8); the seventh subject did not have baseline ratings performed.

On the PANSS total score, all 3 control subjects showed a reduction in symptoms (mean change = -7.4); 6 of the 7 switched patients showed a reduction (mean change = -9.4). Global scores of psychopathology did not change in either group, although 2 switched patients were rated as improved.

No subjects experienced new side effects or withdrew from the second phase of the study. Abnormal Involuntary Movement Scale⁴ ratings did not change, and there was no evidence of emergent dyskinesia or akathisia. Weight change data were available for the 3 control subjects and 5 of the switch subjects. The control subjects' weight did not change over the 12-week period (-0.3 lb). Five switch subjects lost a mean of 12 lb over

the 12 weeks; 1 subject lost 41 lb during the study period. No measures of cholesterol, triglycerides, weight, or waist size were taken.

On average, therefore, this small number of chronically ill patients did not relapse or demonstrate an increase of symptoms when switched from 2 antipsychotic medications to a single drug over a 12-week period. There were no new side effects, and there were no withdrawal symptoms; weight reduction was associated with the switch to aripiprazole.

On the basis of these few subjects, the usefulness of multiple antipsychotic drugs for the treatment of persistent schizophrenic illness should be further questioned and tested with a rigorous large-scale double-blind controlled study. It should be noted that in this small sample of subjects taking multiple medications, a starting dose of 15 mg of aripiprazole was poorly tolerated by 3 subjects who became severely agitated; all subjects responded well to lower starting doses.

This study was conducted at the Lemuel Shattuck Hospital, Massachusetts Mental Health Center, and was supported by Otsuka/Bristol-Myers Squibb.

The authors report no additional financial or other relationship relevant to the subject of this letter.

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Modafinil: Mischaracterization

Sir: The August 2006 supplement to the *Journal*, titled "New Developments in the Treatment of Attention-Deficit/Hyperactivity Disorder" (ADHD), included an article of the same title by Joseph Biederman, M.D.¹ The supplement, underwritten by "an educational grant" from Cephalon, Inc., was intended to showcase current clinical and basic scientific thoughts about ADHD, including the pharmaceutical alternatives available to treat this condition.²

The individual reports in the supplement were derived from the planning teleconference of the same title as noted above. Dr. Biederman's article provided an introduction and overview to other articles that followed his. Dr. Biederman fully disclosed that he has received research support from Cephalon and that he also serves on the company's speaker's bureau and advisory board.³

In his article, Dr. Biederman stated:

The pharmacologic profile and structure of modafinil are notably different from those of stimulants and other agents used to treat ADHD, and modafinil may reduce the core symptoms of ADHD via the same mechanism by which it improves wakefulness—selective activation of the cortex without generalized effects on the central nervous system. This mechanism results in reduced abuse potential and less likelihood of jitteriness, anxiety, or excess locomotor activity than traditional stimulants.^{1(p4)}

That statement, however, is contradicted by 2 federal drug enforcement agencies. The U.S. Food and Drug Administration (FDA)—approved product label for modafinil (Provigil), in the section “Abuse Potential and Dependence,” states:

In addition to its wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS [central nervous system] stimulants.^{4(p1005)}

Furthermore, the product label continues:

The abuse potential of modafinil (200, 400, and 800 mg) was assessed relative to methylphenidate (45 and 90 mg) in an inpatient study in individuals experienced with drugs of abuse. Results from this clinical study demonstrated that modafinil produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate).^{4(pp1005–1006)}

Additionally, the Drug and Chemical Evaluation Section of the Drug Enforcement Administration (DEA), Office of Diversion Control, evaluation previously stated:

Modafinil is a central nervous system stimulant that is being considered for approval by the FDA, under the trade name Provigil®. Modafinil is being considered for marketing as a prescription drug product for the treatment of excessive daytime sleepiness associated with narcolepsy. Modafinil produces many of the same pharmacological effects and adverse reactions as classic psychomotor stimulants. . . .⁵

Our concern with Dr. Biederman's commentary is that it appears to seriously misrepresent modafinil's neuropharmacologic characteristics, contradicting the science-based evaluation of the data by the U.S. FDA and DEA. Dr. Biederman may have misrepresented modafinil's pharmacologic (stimulant) properties and minimized modafinil's abuse potential—as described in the authoritative FDA-approved product label. Dr. Biederman's misrepresentation of the serious risks posed by this drug, whose target population is children with ADHD, requires reexamination and correction.

Of note, if Cephalon, Inc., were to directly mischaracterize modafinil's pharmacocharacteristics—as Dr. Biederman has—they could be prosecuted under federal law.

Dr. Klotz is on the speaker's bureau of Pfizer Inc and has been a speaker for and consultant to Bristol-Myers Squibb/Otsuka. As of 2007, Dr. Kruszewski does not have any current business or financial arrangements with any pharmaceutical company. Dr. Kruszewski previously participated on the speakers bureaus of the following companies: Pfizer Inc, GlaxoSmithKline, Janssen (Johnson & Johnson),

AstraZeneca, Wallace Labs, Eli Lilly, and GE-Amersham Biosciences; and he previously served on an Eli Lilly Northeast Advisory Panel (1998). Dr. Kruszewski served as general and case-specific expert for national OxyContin MP litigation. Dr. Kruszewski owns less than a \$25,000 holding of Millennium pharmaceuticals.

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Dr. Biederman Replies

Sir: The background research to support the claims of Drs. Kruszewski and Klotz begins and ends with the manufacturer's package insert. However, the manufacturer's package insert is neither a standard of care nor the most comprehensive and up-to-date review of the preclinical or clinical science about a molecule. Were that so, new knowledge or findings would never be able to be conveyed to the field until the company or the U.S. Food and Drug Administration (FDA) determined to alter the manufacturer's package insert. Further, the labeling reflects information provided to the FDA at the time of submission of the compound and not necessarily the universe of scientific information available.

A search of the scientific literature indicates that there have been numerous studies conducted with modafinil which report that modafinil blunts cocaine-induced euphoria,^{1–4} does not produce amphetamine-like effects,^{5,6} and is indistinguishable from the subjective stimulant effects of caffeine.⁷ Additionally, all of the evidence from the literature on the abuse liability of modafinil suggests a much lower potential for abuse and dependency than for amphetamine-like stimulants.⁸ As an independent clinician-researcher and not the agent of the manufacturer, I am compelled to base my teaching on all the information and knowledge available to me.

The authors' primary concern appears to be what they believe are the “serious” consequences of abuse and addiction associated with modafinil (hence, “mischaracterization”). However, both the FDA and the Drug Enforcement Administration (DEA) documents are in complete agreement with my very clear position that modafinil has reduced abuse potential and less likelihood for jitteriness, anxiety, and locomotor activity than traditional stimulants. In fact, the key supporting evidence could be taken directly from those documents:

- First and perhaps most importantly, the definitions of Schedule II and Schedule IV clearly make my statements consistent with DEA documentation and their own determination about the relative potential abuse liability for modafinil compared to traditional stimulants. Traditional stimulants are classified in Schedule II (“the drug or other substance has a high potential for abuse”), while modafinil is in the less-restricted Schedule IV (“the drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule [I, II, and] III”).⁹
- The authors mischaracterize the evaluation of the Drug and Chemical Evaluation Section of the DEA, Office of Diversion Control,¹⁰ by including a partial quotation in their letter. The full quotation reads as follows:

Modafinil is a central nervous system stimulant that is being considered for approval by the FDA, under the trade name Provigil®. Modafinil is being considered for marketing as a prescription drug product for the treatment of excessive daytime sleepiness associated with narcolepsy. Modafinil produces many of the same pharmacological effects and adverse reactions as classic psychomotor stimulants, *but appears to have chemical properties that may limit its abuse (i.e., not water soluble, decomposes in heat). DEA is unaware of any reports of modafinil abuse.*¹⁰ [Italics added to highlight omitted text.]

- The FDA labels for methylphenidate and amphetamines include a black box warning for a high potential for abuse and dependence, and modafinil’s label does not.
- Methylphenidate and amphetamines have contraindications for agitated states and patients with a history of drug abuse in their product information^{11–14}; modafinil has no such contraindication.
- Methylphenidate is contraindicated in patients with marked anxiety, tension, and agitation^{12–14}; modafinil has no such contraindications.
- Finally, as stated in my remarks, the pharmacologic profile and structure of modafinil are notably different from those of stimulants and other agents used to treat attention-deficit/hyperactivity disorder (ADHD). As stated, modafinil is a chemically unique molecule unrelated to stimulants or other treatments for ADHD.

The letter by Drs. Kruszewski and Klotz seriously misrepresents the facts, shows ignorance about the neuropharmacologic characteristics of modafinil, and demonstrates a failure to understand the clinical significance of alternative treatments for ADHD. The accusation that my statement may have misrepresented modafinil’s pharmacologic (stimulant) properties and minimized modafinil’s abuse potential is baseless.

Dr. Biederman receives or has received research support from, is or has been a speaker for, or is or has been on the advisory board for Shire, Eli Lilly, Pfizer, McNeil, Abbott, Bristol-Myers Squibb, New River, Cephalon, Janssen, Novartis, UCB Pharma, AstraZeneca, Forest, GlaxoSmithKline, and Neurosearch and has received research support from Stanley Medical Institute, Lilly Foundation, Prechter Foundation, the National Institute of Mental Health, the National Institute of Child Health and Human Development, and the National Institute on Drug Abuse.

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Aripiprazole Augmentation of Clomipramine-Refractory Obsessive-Compulsive Disorder

Sir: Antipsychotic augmentation strategy is relevant in obsessive-compulsive disorder (OCD), as half of patients fail to respond to an initial adequate trial of serotonin reuptake inhibitors.¹ Aripiprazole is an antipsychotic drug that acts as a partial agonist at dopamine D₂ and serotonin 5-HT_{1A} receptors. The drug is also a serotonin 5-HT_{2A} receptor antagonist that might be of therapeutic value in OCD, as suggested by an open-label aripiprazole monotherapy study.²

Unlike for other atypical antipsychotics, no aripiprazole augmentation study or case series in refractory OCD has yet been reported. We report the first case of clomipramine-refractory OCD that responded to the addition of aripiprazole.

Case report. Mr. A, a 37-year-old white man, was referred to our clinic in January 2006 for worsening of OCD, which was diagnosed 16 years previously. Mr. A was never in a psychotic state and always had good insight into his mental problem. He received behavior therapy and several selective serotonin reuptake inhibitors (SSRIs), with modest results due to a lack of good compliance. He fulfilled DSM-IV-TR criteria for OCD

and major depressive disorder, recurrent, severe episode, with partial remission between episodes. He scored 32 on the Yale-Brown Obsessive Compulsive scale (YBOCS)³ and 26 on the Hamilton Rating Scale for Depression 17-item (HAM-D 17-item).⁴

Clomipramine was progressively initiated over the course of 2 weeks with clonazepam (1–3 mg/day at the patient's discretion) and maintained at a fixed dose of 225 mg/day during 8 weeks with adequate plasmatic dosage. Despite a meaningful clinical response of the patient's depression (HAM-D 17-item score = 12), Mr. A's YBOCS score was stable at 30 to 32. Aripiprazole (fixed dose of 15 mg/day) was then added to clomipramine (225 mg/day) for 16 weeks. Mean YBOCS scores and percentage reductions in score from baseline with the aripiprazole augmentation strategy were as follows: week 1, 27 (10.0%); week 2, 21 (30.0%); week 4, 16 (46.7%); week 6, 16 (46.7%).

Because of this meaningful clinical response ($\geq 35\%$ improvement in baseline YBOCS total score), Mr. A was able to leave our clinic. No change in plasmatic clomipramine dosage was observed. This response was maintained at week 10 (YBOCS score = 16), and Mr. A was in remission (YBOCS score = 15) at week 16. The 16-week augmentation treatment was well tolerated, and optional clonazepam treatment was stopped after 3 weeks. During the aripiprazole treatment, no change in the severity of depression (stability of HAM-D 17-item scores) was reported. At week 16, Mr. A fulfilled the DSM-IV-TR criteria for partial remission of major depressive disorder with a HAM-D 17-item score of 11.

Although we cannot rule out a delayed effect of clomipramine after 8 weeks, the addition of aripiprazole to ongoing clomipramine appears to be a promising strategy for clomipramine-refractory OCD patients. The beneficial effect of aripiprazole augmentation, irrespective of the course of depression, may be attributable to a direct pharmacodynamic action. Nevertheless, further larger controlled studies are required to evaluate the therapeutic potential of aripiprazole augmentation in patients suffering from SSRI-refractory OCD with or without comorbid major depressive disorder.

The authors report no financial or other affiliation relevant to the subject of this letter.

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Lack of Mania Prophylaxis Associated With Lamotrigine Monotherapy in Manic-Predominant Bipolar I Disorder

Sir: Unlike all other mood-stabilizing drugs, lamotrigine does not have an indication for acute mania. The maintenance indication for lamotrigine is based on two 18-month studies evaluating time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in bipolar I patients treated for acute mood episodes with standard therapy. Only when these 2 studies were analyzed together (a priori determined to increase statistical power) was the superiority of lamotrigine over placebo in delaying the time to intervention for a manic episode evident.¹

As the following case reports highlight, lamotrigine may have limitations as monotherapy for mania prophylaxis in DSM-IV manic-predominant bipolar I disorder.

Case 1. Ms. A, a 23-year-old student, was treated with olanzapine 10 mg and lamotrigine 250 mg daily for her first manic episode in April 2005. On this regimen, she became euthymic, with no evidence of postmanic depressive symptoms. Due to weight gain and sedation, olanzapine treatment was discontinued in January 2006. On lamotrigine monotherapy, Ms. A showed no evidence of depressive relapse or recurrence.

One week after the 2006 spring equinox, her parents noted a return of decreased sleep, racing thoughts, pressured speech, emotional lability, and increased goal-directed activities. This episode confirmed a spring equinox vulnerability and manic-predominant bipolar I disorder. Lamotrigine was augmented with olanzapine 7.5 mg daily, with symptom resolution.

Case 2. Mr. B, a 22-year-old student, was hospitalized and treated with divalproex 2000 mg daily for his first manic episode in August 2005. One month after discharge, he discontinued divalproex treatment, believing his persistent depressive symptoms were drug related. Observing no improvement, his psychiatrist started lamotrigine treatment. At a dose of 200 mg daily, he was euthymic, with no evidence of depressive relapse or recurrence.

Mr. B was brought to the emergency room in April 2006 for grandiosity, pressured speech, racing thoughts, insomnia, and impulsive high-risk behaviors. Although not as clearly demarcated as Ms. A's, Mr. B's second episode led to a high suspicion that his manic-predominant bipolar I disorder had a spring/summer seasonal pattern. He was restabilized on treatment with divalproex 2000 mg and lamotrigine 100 mg daily.

Despite pooled data supporting mania prophylaxis, these cases suggest that lamotrigine monotherapy was inadequate for mania prophylaxis in manic-predominant bipolar I disorder. Conversely, the data for lamotrigine, as monotherapy^{2,3} and adjunctive to lithium maintenance therapy,⁴ suggest acute antidepressant effect; the data are much more solid evidence for its efficacy as a maintenance treatment in preventing depression.⁵ Furthermore, the reasons for choosing lamotrigine for these patients were common ones (i.e., weight gain associated with olanzapine and postmanic depressive symptoms ineffectively treated with divalproex).

Clinical practice has evolved into identifying "above baseline" (mania, mixed states, hypomania) and "below baseline" (depression) treatments.⁶ In addition, assessing prior episode burden or pole-predominance may help clarify when, for example, lamotrigine could be utilized as a primary mood stabilizer.

These cases also highlight several areas of further research. First, the merits of long-term combination treatment (i.e., lamo-

trigine with an atypical antipsychotic or divalproex) versus single-agent therapy should be evaluated for ongoing mood stability and tolerability; this is a common community practice with little controlled literature to guide clinicians. Second, when seasonal vulnerability for mania can be established and if lamotrigine is the treatment of choice in a bipolar patient, adjunctive short-term augmentation with an "above baseline" treatment should be evaluated for mania prophylaxis.

Dr. Gitlin is a member of the speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, and Pfizer. Dr. Frye is a consultant for Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon (unpaid consultancy), Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Novartis, Ortho-McNeil, Otsuka, Pfizer, Shire, Solvay, and Wyeth; has received grant/research support from Abbott, American Foundation for Suicide Prevention, Cephalon, GlaxoSmithKline, National Institute of Mental Health, Pfizer, Solvay, and Stanley Medical Research Institute; and is a member of the speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Otsuka, and Pfizer. Drs. Dossett and Land report no financial or other affiliations relevant to the subject of this letter.

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A Different Mechanism to Understand Activation/Sedation Side Effects of Ziprasidone

Sir: The supplement article by Stahl and Shayegan¹ on the psychopharmacology of ziprasidone was a nice review and is still the standard, but I would like to make exception to one well-accepted mechanism. As I review my clinical experience, I see that patients who were started on 40 mg b.i.d. of ziprasidone and then went on to receive 60 mg b.i.d., as suggested by Pfizer on the basis of the article by Stahl and Shayegan, often complained of restlessness and stopped the drug. This is contrary to the explanation of the article indicating that getting to

D₂ blockade balances out the putative serotonin-2C (5-HT_{2C}) effect, which is the basis of the side effect.

Ziprasidone is an antagonist at the 5-HT_{2C} receptor² or, more precisely, an inverse agonist lowering the nonstimulated activity of the receptor.³ The clinical correlation mentioned in the article by Stahl and Shayegan was, however, to fluoxetine, which can have "activating actions in some patients that range from desirable relief of fatigue to undesirable dysphoria, hypomania, and panic. Low doses of ziprasidone could potentially have such activating behavioral effects . . ." (p⁸) However, fluoxetine's behavioral effects seem to express 5-HT_{2C} receptor agonism.⁴ Taking the hypothesis as serotonin activation, Corne et al.⁵ first reported that a head twitch behavior in mice followed the injection of high doses of serotonin. This was opposed by neuroleptic drugs. Jacobs and Klemfuss⁶ found that twitch behaviors occurred in animals sectioned at the level of the pons-medulla, casting doubt on this as an appropriate comparison with human restlessness. Green⁷ noted that the head weaving and allied behaviors "are probably 5-HT₂-receptor-mediated whilst the hyperactivity and hyper-reactivity are not."^(p336) Thus, even if ziprasidone were an agonist at the 5-HT_{2C} receptor, which it is not, this mechanism would not seem to explain restlessness.

In "dissecting out" the complex behavioral syndrome that occurs with serotonergic stimulation, Green⁷ found it is agonism at the 5-HT_{1B} receptor that was responsible for hyperlocomotor behavior. And what is the activity of ziprasidone at the 5-HT_{1B} receptor? It is a partial agonist.⁸ In contrast, a variety of other antipsychotics tested lower activity at this receptor. Thus it may not be surprising that clinical experience with regard to restlessness and sedation with ziprasidone does not conform well with the "classical model" described by Stahl and Shayegan.

Dr. Brophy serves as a local speaker for Pfizer and is a stock shareholder in Johnson & Johnson.

Dr. Brophy is also currently employed at Baylor Medical Center at Irving in Texas. This letter grew out of reading done by Dr. Brophy while he served as a volunteer in Psychiatry Research at the Dallas VA Medical Center, Dallas, Tex.

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Dr. Stahl Replies

Sir: When the mechanism of action of psychotropic drugs can successfully explain their clinical actions, this generally means that the best of the science of receptor pharmacology has been thoughtfully combined with the best of the art of clinical observation. Mr. Shayegan and I reviewed the receptor binding properties of ziprasidone¹ and all atypical antipsychotics² and provided hypotheses about which receptor binding actions were common to all atypical antipsychotics, which were unique for some agents and not others, and, finally, which receptor binding properties could feasibly be related to efficacy versus side effects of the various drugs in this class. Brophy has used this approach in an attempt to explain his clinical observations of motor restlessness with ziprasidone and hypothesizes that the serotonin-1B (5-HT_{1B}) actions of ziprasidone, but not the 5-HT_{2C} actions that we propose to account for behavioral activation of ziprasidone, may account for these observations.

Our hypothesis is that 5-HT_{2C} antagonist properties of ziprasidone may account for its activating behavioral side effects (such as agitation, anxiety, hypomania, and panic) at low doses.^{1,2} These adverse experiences generally occur without concomitant antipsychotic therapeutic effects at low doses, and we explain this as due to the more potent actions of ziprasidone at 5-HT_{2C} receptors than at dopamine D₂ receptors.^{1,2} We point out that such actions would be expected to disinhibit dopamine and norepinephrine release in the cortex without adequate simultaneous blockade of D₂ receptors^{1,2} and that the same pharmacologic profile has been described for fluoxetine, an agent that can also cause similar activating behavioral side effects.³⁻⁷

We further propose that raising the dose of ziprasidone recruits additional D₂ receptor blockade in the presence of already saturated 5-HT_{2C} receptors, resulting in loss of behavioral activation and production of antipsychotic effects, and therefore, to avoid behavioral activation and in order to get robust antipsychotic effects, we advise against utilizing low doses of ziprasidone.^{1,2}

We believe that this pharmacologic explanation for the induction of activating behavioral side effects of low-dose ziprasidone remains valid and that it may also explain the motor restlessness observed with ziprasidone and why increasing the dose of ziprasidone (perhaps with short-term use of benzodiazepines) may be the appropriate clinical response when motor restlessness is observed with ziprasidone. However, Brophy makes several points to argue that this hypothesis does not adequately explain restlessness associated with ziprasidone: fluoxetine is an agonist and not an antagonist at 5-HT_{2C} receptors; ziprasidone is an inverse agonist rather than an antagonist at 5-HT_{2C} receptors; ziprasidone's actions as a partial agonist at 5-HT_{1B} receptors explain its motor activation since this fits with animal data on hyperlocomotor behavior; and, finally, and most importantly, raising the dose of ziprasidone from 40 mg b.i.d. to 60 mg b.i.d. does not improve motor activation.

We respond here to each of these in turn. Although there is some evidence that fluoxetine may be an agonist at 5-HT_{2C} receptors, this is countered by others that suggest it may be an antagonist.³⁻⁶ It may matter little clinically which is true, since both agonists and antagonists of 5-HT_{2C} receptors rapidly down-regulate these receptors,³⁻⁶ and thus multiple dose effects of both may be similar. We agree that ziprasidone may be an inverse agonist rather than an antagonist at 5-HT_{2C} receptors in some assay systems, but this is perhaps a distinction without a clinical difference, since both silent antagonists and inverse agonists antagonize 5-HT actions at 5-HT_{2C} receptors and inverse agonism is defined for receptor systems with high den-

sities of receptors that have detectable constitutive activity, which may not apply in the cerebral cortex, where 5-HT_{2C} receptor density is low. Although some evidence is consistent with partial agonist actions of ziprasidone at 5-HT_{1B} receptors (previously called 5-HT_{1D} receptors in humans and so labeled in references 1 and 2), other data suggest that it may be an antagonist, which would not be consistent with the idea that ziprasidone causes restlessness by stimulating 5-HT_{1B} receptors.⁷ To the extent that ziprasidone does stimulate 5-HT_{1B} receptors, as these receptors are located on serotonergic axon terminals, this would prevent the release of serotonin onto 5-HT_{2C} receptors (and others), creating a net but indirect 5-HT_{2C} antagonist action, consistent with our original hypothesis. Finally, clinical observations of what happens with dosage increase with ziprasidone in patients with motor restlessness are variable, with some patients failing to improve, especially after small dosage increases as observed by Brophy, but with a growing consensus also suggesting that there is not only greater efficacy but overall paradoxically lower motor side effects of ziprasidone at higher doses than lower doses (reference 8 and Anthony Loebel, M.D., data on file, Pfizer Inc, 2002–2005), particularly when comparing 160 mg daily with lower doses.

The bottom line here is, What does a clinician do with this receptor binding information to become informed about what starting dose to use for ziprasidone and what dosing adjustments to make if behavioral or motor restlessness emerges, especially at low doses? One never says "always" in clinical psychopharmacology, since some patients do indeed seem to have more rather than less tolerability to higher doses of ziprasidone, including motor restlessness. Thus, we agree with Brophy that activating motor symptoms may not always improve with a dose increase, perhaps because in some patients the 5-HT_{2C} receptor mechanism does not explain their side effects. However, we stand by our original recommendation on the basis of both receptor profile^{1,2} and emerging clinical experience (reference 8 and Anthony Loebel, M.D., data on file, Pfizer Inc, 2002–2005) that ziprasidone's tolerability and efficacy may be enhanced by not starting the dose too low and, when there are activating side effects, raising the dose. When this intervention reduces side effects as suggested by recent data analyses and clinical experience (reference 8 and Anthony Loebel, M.D., data on file, Pfizer Inc, 2002–2005), this otherwise counterintuitive result is nevertheless consistent with the hypothesis that increased doses recruit D₂ antagonism to counter the activation caused by 5-HT_{2C} antagonism.

The best merger of art and science may be to start ziprasidone at mid-dose range, 80 mg a day, either as 40 mg b.i.d. or 80 mg once at night, increasing the next day to 160 mg a day, either as 80 mg b.i.d. or 160 mg at night, always with food, and even in the face of behavioral or motor activating side effects. One can always use more time at a given dose or the addition of a benzodiazepine when experiencing side effects during initiation or dosing adjustment of ziprasidone as well. The idea is to use receptor pharmacology to guide clinical dosing of various agents and then to tailor specific dosing for individual patients on the basis of good clinical observation.

The supplement in which the article described above appeared was sponsored by Pfizer Inc.

Dr. Stahl has received grant/research support from AstraZeneca, Biovail, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Neurocrine, Organon, Pfizer, Sepracor, Shire, Somaxon, and Wyeth and has been a consultant for or received honoraria from Acadia, Asahi, AstraZeneca, Avera, Biovail, Boehringer Ingelheim, Bristol-Myers Squibb, Cephalon, CSC Pharma, Cyberonics, Cypress Bioscience, Eli Lilly, Fabre Kramer, Forest, GlaxoSmithKline, Neurocrine Bioscience, Neuromolecular, Neuronetics, Nova Del Pharma, Novartis,

Organon, Otsuka, Pfizer, Pierre Fabre, Sanofi Synthelabo, Sepracor, Shire, Solvay, Somaxon, Tetraxen, and Wyeth.

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Attention-Deficit/Hyperactivity Disorder, Binge Eating, and Obesity

Sir: We read with special interest the article by Surman et al.¹ In their analysis of 4 previous case-control studies, the authors found significantly higher rates of bulimia nervosa in women with attention-deficit/hyperactivity disorder (ADHD) versus women without. As stated by the authors, this finding may have important implications for the clinical management of patients with ADHD and bulimia nervosa. We would like to discuss another potentially interesting finding that might come from the data collected in the reviewed studies.¹

Preliminary evidence from empirically based studies suggests a possible comorbidity between ADHD and obesity, at least in clinical settings.^{2–6} The potential mechanisms underlying this putative association are still unclear and unexplored. A possibility is that ADHD leads to or contributes to obesity via impulsive abnormal eating behaviors such as binge eating. Both impulsivity and inattention (2 cardinal symptoms of ADHD) might cause difficulties in adhering to a regular eating pattern, favoring abnormal eating behaviors, including binge eating, which is often found in obese populations, especially in severely obese individuals.⁷

Since eating disorders were specifically evaluated in the 4 studies analyzed by Surman et al.,¹ we suggest that the authors may want to compare the mean body mass index in patients with and without ADHD and look for a potential association between binge-eating behaviors and ADHD symptoms. The finding of an association between symptoms of binge eating and

ADHD would not prove that ADHD actually contributes to obesity via binge eating, since association cannot establish causality. However, such a result from these large studies would allow us to advance our understanding of the putative comorbidity between ADHD and obesity, providing the basis for further investigations exploring the possible causal mechanisms. This might have relevant implications for the treatment of patients who present with both of these conditions. In fact, if the hypothesis that ADHD contributes to obesity is true, the treatment of ADHD may also reduce obesity.

Given the enormous personal, familial, and social burden associated with both obesity and ADHD, we think that research in this field is noteworthy and should be encouraged.

The authors report no financial or other relationship relevant to the subject of this letter.

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Dr. Surman and Colleagues Reply

Sir: We appreciate the questions raised by Cortese et al. with regard to our article identifying higher rates of bulimia in a clinical sample of women with ADHD relative to control subjects. They suggest we might investigate rates of obesity and binge eating in the same large samples of adults and children in which we assessed rates of bulimia nervosa. Unfortunately, data

on obesity and binge-eating behavior are limited from these clinical populations. Our research group previously reported data on weight in large samples of boys and girls ascertained from psychiatric and pediatric settings, as part of an analysis of their growth characteristics.^{1,2} These studies failed to identify meaningful differences in body mass index between youth with and without ADHD. More work will be needed to further examine these issues in adult samples.

We appreciate Cortese and colleagues' suggestion that ADHD might contribute to dysregulation of eating behavior or correlate in some way with obesity, and we welcome further investigation into the relationship between ADHD and these as well as other health risk factors.

The authors' financial disclosure is listed in the original article [2006;67:351].

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