

Letters to the Editor

Respiratory Infections Rather Than Antibiotics May Increase Clozapine Levels: A Critical Review of the Literature

Sir: Approximately 70% of clozapine metabolism is explained by the cytochrome P450 1A2 (CYP1A2).¹ The CYP1A2 can be inhibited by respiratory infections. Decreased theophylline (a CYP1A2 substrate) clearance during upper respiratory infections has been described in asthmatic children^{2,3} and in adults with chronic bronchitis.⁴ Cytokines released during infection decrease CYP1A2 activity and synthesis.⁵ Expert pediatricians recommend decreasing theophylline doses by half during severe respiratory infections.³

Two cases of increased plasma clozapine concentrations during respiratory infection were recently published.^{6,7} The English-language literature was reviewed in October 2003 with a PubMed search using all searchable years and several term combinations including *clozapine and CYP3A*, *clozapine and macrolide*, and *clozapine and fluoroquinolone*. All the references listed in the newly found articles and in those gathered over the course of my more than 7 years of interest in the subject were also reviewed to obtain all relevant articles. This critical review of the literature suggests that 3 prior clozapine toxicity cases attributed to drug interactions with erythromycin^{8,9} or ampicillin¹⁰ are better explained by 1 pharyngitis case⁸ and 2 sinusitis cases.^{9,10} Ampicillin does not inhibit the CYPs.¹¹ Erythromycin inhibits CYP3A, but a study of a single clozapine dose in 12 healthy males failed to show any effects of erythromycin.¹² Similarly, itraconazole, another potent CYP3A inhibitor, did not influence clozapine metabolism.¹³ Therefore, in 2 patients taking erythromycin,^{8,9} CYP1A2 inhibition associated with a respiratory infection was probably the major factor contributing to clozapine toxicity, although some small effects of erythromycin cannot be ruled out. Assuming that clozapine follows linear pharmacokinetics,¹⁴ clozapine concentration-to-dose ratio associated with the respiratory infection decreased by a factor of 2 to 3 times (3.3,⁶ 2.0,⁷ 1.9,⁸ and 3.0⁹).

Clinicians caring for adult patients taking clozapine must therefore be careful should a patient develop serious respiratory infection with fever; they must pay particular attention to any signs suggesting clozapine toxicity (severe sedation, myoclonus, or even seizures). If any of these signs appear, the physician may need to decrease the clozapine dose, at least by half, until the patient has recovered from the infection. Obviously, this recommendation is limited by the small amount of published information supporting it (4 case reports); however, prospective studies in patients who are taking clozapine and having serious respiratory infections are unlikely to happen due to ethical and practical issues. The aim of this letter is to raise clinician awareness and stimulate the publication of new case report data that may or may not support the recommendation of decreasing the dose by half in clozapine-treated patients suffering a serious respiratory infection and showing signs of clozapine toxicity.

CYP1A2 also metabolizes olanzapine, an antipsychotic agent used more frequently than clozapine. The limited experience my colleague and I⁷ reported in 1 patient taking both clozapine and olanzapine suggests that olanzapine levels increased by a factor of 1.7 during severe respiratory infection. An increase by a factor of 2 (or 1.7) in olanzapine level may not have the same clinical implications as in clozapine levels; olanzapine has a much wider therapeutic window.

Finally, 3 clarifications are needed. (1) Not all antibiotics are free of drug interactions with clozapine; ciprofloxacin, a CYP1A2 inhibitor, can increase clozapine levels.¹⁵ (2) Smoking withdrawal for a few days during a respiratory infection may not have major effects on clozapine levels; the published case reports of clozapine toxicity after smoking cessation suggest that the increase of clozapine levels after smoking cessation usually takes at least 2 to 4 weeks to manifest.¹⁶ (3) Severe respiratory infections in patients taking clozapine can be associated with clozapine-induced agranulocytosis. According to data from the Clozaril National Registry, recent U.S. estimates suggest that agranulocytosis is less frequent (0.6%)¹⁷ than previously thought. Moreover, clozapine-induced agranulocytosis is very rare after 18 months of treatment¹⁷ and can be easily ruled out by drawing a white blood cell count.

The author received no financial support for writing this letter. In the past 2 years, he has been on the advisory board of Bristol-Myers Squibb and AstraZeneca, received researcher-initiated grants from Eli Lilly and Roche Molecular Systems, Inc, and gave a lecture supported by Eli Lilly.

REFERENCES

1. Bertilsson L, Carrillo JA, Dahl M, et al. Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. *Br J Clin Pharmacol* 1994;38:471-473
2. Chang KC, Bell TD, Lauer BA, et al. Altered theophylline pharmacokinetics during acute respiratory viral illness [letter]. *Lancet* 1978;1:1132-1133
3. Shilalukay K, Robieux I, Spino M, et al. Are current pediatric dose recommendations for intravenous theophylline appropriate? *J Asthma* 1993;30:109-121
4. Clark CJ, Boyd G. Theophylline pharmacokinetics during respiratory viral infections [letter]. *Lancet* 1979;1:492
5. Abdel-Razzak Z, Loyer P, Fautrel A, et al. Cytokines down-regulate expression of major cytochrome P-450 enzymes in adult human hepatocytes in primary culture. *Mol Pharmacol* 1993;44:707-715
6. Raaska K, Raitasuo V, Arstila M, et al. Bacterial pneumonia can increase serum concentration of clozapine. *Eur J Clin Pharmacol* 2002;58:321-322
7. de Leon J, Diaz FJ. Serious respiratory infections can increase clozapine levels and contribute to side effects: a case report. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;27:1059-1063
8. Funderburg LG, Vertrees JE, True JE, et al. Seizure following addition of erythromycin to clozapine treatment [letter]. *Am J Psychiatry* 1994;151:1840-1841
9. Cohen LG, Chesley S, Eugenio L, et al. Erythromycin-induced clozapine toxic reaction. *Arch Intern Med* 1996;156:675-677
10. Csik V, Molnar J. Possible adverse interaction between clozapine

- and ampicillin in an adolescent with schizophrenia. *J Child Adolesc Psychopharmacol* 1994;4:123-128
11. Gillum JG, Israel DS, Polk RE. Pharmacokinetic drug interactions with antimicrobial agents. *Clin Pharmacokinetics* 1993;25:450-482
 12. Hagg S, Spigset O, Mjorndal T, et al. Absence of interaction between erythromycin and a single dose of clozapine. *Eur J Clin Pharmacol* 1999;55:221-226
 13. Raaska K, Neuvonen PJ. Serum concentration of clozapine and *N*-desmethylclozapine are unaffected by the potent CYP3A4 inhibitor itraconazole. *Eur J Clin Pharmacol* 1998;54:167-170
 14. Choc MG, Lehr RG, Hsuan F, et al. Multiple-dose pharmacokinetics of clozapine in patients. *Pharm Res* 1987;4:402-405
 15. Raaska K, Neuvonen PJ. Ciprofloxacin increases serum clozapine and *N*-desmethylclozapine: a study in patients with schizophrenia. *Eur J Clin Pharmacol* 2000;56:585-589
 16. Zullino DF, Delessert D, Eap CB, et al. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. *Int Clin Psychopharmacol* 2002;17:141-143
 17. Alvir JMJ, Lieberman JA, Safferman AZ, et al. Clozapine-induced agranulocytosis: incidence and risk factors in the United States. *N Engl J Med* 1993;329:162-167

Jose de Leon, M.D.

University of Kentucky Mental Health Research Center at Eastern State Hospital
Lexington, Kentucky

Psychotic Symptoms Associated With Topiramate: Cognitive Side Effects or Worsening of Psychosis?

Sir: Hofer et al.¹ report worsening of psychosis in a patient treated with topiramate. There are anecdotal reports in the literature suggesting this adverse effect of topiramate. However, the pathophysiologic mechanism cited by the authors to explain this worsening of psychosis is contrary to what the literature suggests. Inhibition of glutamate receptors is a hypothesized cause of schizophrenia, but it is the hypofunction of the *N*-methyl-D-aspartate (NMDA) receptor that has been implicated in schizophrenia.² Topiramate, on the other hand, is an antagonist at the α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate receptor. The latter action has been hypothesized to reduce neuronal excitability and is used in the treatment of seizure disorders.

One of the consequences of NMDA receptor hypofunction in schizophrenia is the excessive and unregulated stimulation of AMPA/kainate receptors, which in turn results in excitotoxic damage; Deutsch and colleagues² have explained this mechanism in detail. On the basis of this hypothesis, topiramate has been used to treat negative symptoms of schizophrenia.³ This use is further supported by a study⁴ which showed that topiramate attenuates a well-characterized behavior elicited by MK-801, a phencyclidine analogue and an antagonist at the NMDA receptor. Moreover, AMPA antagonists have been suggested to possess an atypical antipsychotic profile.⁵ Therefore, the mechanism of action of topiramate suggests that, rather than causing worsening of psychosis, it has potential use in treating at least some patients with schizophrenia.

Then how does one explain the presentation described by Hofer and colleagues? Topiramate does cause cognitive side effects including word-finding difficulty, psychomotor slowing, difficulty with concentration, somnolence, and fatigue. It has also been shown to cause memory problems and exacerbation of mood disturbance (e.g., irritability and depression).⁶ Some of the symptoms cited as worsening of psychosis in the report may be due to these cognitive side effects of topiramate. One patient of ours (with a history of psychotic disorder) developed such

severe word-finding difficulty due to topiramate that she was misdiagnosed as having a thought disorder. This symptom resolved completely when topiramate treatment was discontinued. Cognitive side effects of topiramate can thus falsely elevate both negative and positive scores on the Positive and Negative Syndrome Scale in patients with schizophrenia. Negative scores may theoretically be more elevated, as most of the cognitive side effects of topiramate fall under this domain; not surprisingly, elevation of negative scores was observed in the reported case.¹ Therefore, caution should be exercised when a patient with psychosis worsens on treatment with topiramate, as this might be misconstrued as worsening of the underlying disorder, leading to unnecessary increase in the dose of topiramate, as happened with Hofer and colleagues' patient. Tapering or slower titration of this drug should be tried before adding other medications to counter psychotic symptoms.

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

REFERENCES

1. Hofer A, Fleischhacker WW, Hummer M. Worsening of psychosis after replacement of adjunctive valproate with topiramate in a schizophrenia patient [letter]. *J Clin Psychiatry* 2003;64:1267-1268
2. Deutsch SI, Rosse RB, Schwarz BL, et al. A revised excitotoxic hypothesis of schizophrenia: therapeutic implications. *Clin Neuropharmacol* 2001;24:43-49
3. Drapalski AL, Rosse RB, Peebles RR, et al. Topiramate improves deficit symptoms in a patient with schizophrenia when added to a stable regimen of antipsychotic medication. *Clin Neuropharmacol* 2001;24:290-294
4. Deutsch SI, Rosse RB, Billingslea EN, et al. Topiramate antagonizes MK-801 in an animal model of schizophrenia. *Eur J Pharmacol* 2002;449:121-125
5. Svensson TH. Dysfunctional brain dopamine systems induced by psychotomimetic NMDA-receptor antagonists and the effects of antipsychotic drugs. *Brain Res Rev* 2000;31:320-329
6. Topamax (topiramate). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 2003:2503

Harpreet S. Duggal, M.D., D.P.M.
Western Psychiatric Institute and Clinic
Pittsburgh, Pennsylvania

Dr. Hofer and Colleagues Reply

Sir: We appreciate the comments of Dr. Duggal regarding our data concerning worsening of psychosis after replacement of adjunctive valproate with topiramate in a patient with schizophrenia. We agree completely with Dr. Duggal concerning hypotheses suggesting that *N*-methyl-D-aspartate (NMDA) receptor hypofunction, dampened γ -aminobutyric acid (GABA)ergic inhibition, and excessive stimulation of the kainic acid/ α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) class of glutamate receptors occur in at least some patients with schizophrenia. Such a condition of "hypoglutamatergia" has been hypothesized to result in "paradoxical" excessive stimulation of the kainic acid/AMPA receptors and excitotoxicity, which in turn might explain the progressive psychosocial and cognitive deterioration seen in a subgroup of schizophrenia patients.¹ Topiramate, a kainic acid/AMPA receptor antagonist and GABA potentiator, has been suggested to be an effective means of treating olanzapine-refractory schizophrenia by decreasing negative symptoms. Positive symptoms showed no changes in one patient² and worsened in another.³ On the other hand, piracetam, which acts an AMPA agonist, has

also been suggested to be of therapeutic benefit in treating schizophrenia patients in combination with conventional antipsychotics.⁴ Therefore, it remains uncertain at present whether AMPA agonists, antagonists, or partial agonists/modulators should be pursued further in this indication.⁵

Similar to our findings, Millson et al.⁶ have reported worsening of psychosis when topiramate was added to clozapine treatment in 3 schizophrenia patients. In addition, a psychiatric history has been described to be a potential risk factor for topiramate-related psychiatric adverse events in patients with epilepsy.⁷ The most common neuropsychiatric symptoms associated with topiramate include somnolence, dizziness, tiredness, ataxia, headache, depression, and cognitive impairment such as mental confusion, slow reasoning, speech difficulty, and disturbance of memory.^{8,9}

We agree with Duggal's point that some of the symptoms cited as psychosis in our report might be confused with these cognitive side effects of topiramate. However, the patient in the reported case was diagnosed with acute psychotic disorder according to ICD-10 criteria, and his clinical features were similar to those he had shown when he experienced the first episode of the illness. The Positive and Negative Syndrome Scale was administered to quantify the degree of worsening of psychosis. There is no doubt that the patient developed a psychotic episode, which quickly remitted after topiramate treatment was discontinued and valproate treatment was resumed.

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.

REFERENCES

1. Deutsch SI, Rosse RB, Schwartz BL, et al. A revised excitotoxic hypothesis of schizophrenia: therapeutic implications. *Clin Neuropharmacol* 2001;24:43-49
2. Drapalski AL, Rosse RB, Peebles RR, et al. Topiramate improves deficit symptoms in a patient with schizophrenia when added to a stable regimen of antipsychotic medication. *Clin Neuropharmacol* 2001;24:290-294
3. Levy E, Margolese HC, Chouinard G. Topiramate produced weight loss following olanzapine-induced weight gain in schizophrenia [letter]. *J Clin Psychiatry* 2002;63:1045
4. Noorbala AA, Akhondzadeh S, Davari-Ashtiani R, et al. Piracetam in the treatment of schizophrenia: implications for the glutamate hypothesis of schizophrenia. *J Clin Pharm Ther* 1999;24:369-374
5. Carlsson A, Waters N, Holm-Waters S, et al. Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annu Rev Pharmacol Toxicol* 2001;41:237-260
6. Millson RC, Owen JA, Lorberg GW, et al. Topiramate for refractory schizophrenia [letter]. *Am J Psychiatry* 2002;159:675
7. Kanner AM, Wu J, Faught E, et al. A past psychiatric history may be a risk factor for topiramate-related psychiatric and cognitive adverse events. *Epilepsy Behav* 2003;4:548-552
8. Stella F, Caetano D, Cendes F, et al. Acute psychotic disorders induced by topiramate. *Arq Neuropsiquiatr* 2002;60:285-287
9. Lee S, Sziklas V, Andermann F, et al. The effects of adjunctive topiramate on cognitive function in patients with epilepsy. *Epilepsia* 2003;44:339-347

Alex Hofer, M.D.
W. Wolfgang Fleischhacker, M.D.
Martina Hummer, M.D.
 Department of Biological Psychiatry
 Innsbruck University Clinics
 Innsbruck, Austria

Successful Treatment of Sexual Dysfunction With Dronabinol: A Case Report

Sir: There have been numerous reports of the sexually enhancing effects of tetrahydrocannabinol (THC),¹ and this letter reports positive outcome in a female bipolar patient after dronabinol use. Dronabinol, a medication currently labeled as Schedule III, is approved by the U.S. Food and Drug Administration (FDA) for treating nausea and increasing appetite. Δ^9 -tetrahydrocannabinol is the sole synthetic psychoactive ingredient of dronabinol. While dronabinol may still require the additional supervision needed for a controlled substance, because of its Schedule III classification in the controlled substances list of the Controlled Substances Act, the medication is not as restricted as a medication from the Schedule II list. In practical terms, dronabinol may be prescribed by telephone with up to 6 refills in a 6-month time period.

Case report. Ms. A, a 43-year-old married African American woman employed as a midlevel manager for a federally funded organization, had a history of bipolar disorder, mixed type (DSM-IV criteria), with numerous hospitalizations in the past 5 years for manic or depressive episodes that were always triggered by noncompliance with her medications. After her last relapse, she had readily admitted that the single most important factor in her noncompliance was sexual dysfunction secondary to her psychotropic medications (olanzapine, valproic acid, and paroxetine). In the past, bupropion, methylphenidate, and yohimbine had been tried, but the patient had experienced no relief from her major complaint of anorgasmia. She had no history of substance abuse.

In November 2001, Ms. A was instructed to use dronabinol 10 mg p.r.n. 1 hour before sex. She was advised that she should not drive a vehicle for 24 hours after using dronabinol and that treatment of sexual dysfunction was a non-FDA-approved use of dronabinol.

Ms. A completed self-rating of her sexual function on a scale from 0 to 10, with 0 representing the worst and 10 representing the best, and her ratings after 2½ weeks showed remarkable overall improvement. Dronabinol improved the patient's sexual function on all of the domains assessed, including libido, arousal, lubrication, orgasm, and overall quality of her sex life.

Two years after her last hospitalization, Ms. A remains functional, employed, fully compliant with her medication, symptom-free, and sexually satisfied. There is no evidence that she has abused dronabinol. She has been using dronabinol an average of 2 times weekly.

An interesting and potentially serious complication occurred during the course of treatment. In routinely administered testing at her workplace, Ms. A tested positive for THC and was immediately suspended from work, but, fortunately, after a second opinion from a university-based colleague and a medical report from me addressing the rationale for her pharmacotherapy, the medical director of her company ruled in her favor, and she resumed her job.

Dronabinol's potential for producing sexually enhancing effects that reverse psychotropic-induced sexual dysfunction is probably multifactorial. Dronabinol causes euphoria and relaxation, and because these emotional states may promote sexual pleasure, it is likely that the positive sexual response is due in part to this very avenue. Most likely, there are other unknown mechanisms involved in dronabinol's sexually enhancing effects. Particular attention must be paid to patients with bipolar disorder due to the greater risk of substance abuse among bi-

polar patients. Further double-blind, placebo-controlled studies are needed to establish the efficacy of dronabinol as an enhancer of sexual function. The potential for abuse is a risk and must be considered. Further, because Δ^9 -THC is the sole psychoactive ingredient of dronabinol and cannabis, clinicians must remain aware of the adverse physiologic consequences of cannabis use,²⁻⁵ and the clinical decision to prescribe dronabinol should rest on the overall risks and benefits of side effect management of bipolar patients.

Dr. Salerian has served as a consultant for and received honoraria from Eli Lilly, Pfizer, Janssen, Wyeth-Ayerst, SmithKline Beecham, and Shire.

REFERENCES

1. Powell J, Fuller WR. Marijuana and sex: strange bed partners. *J Psychoactive Drugs* 1983;15:269-280
2. Kolodny RC, Masters WH, Kolodner RM, et al. Depression of plasma testosterone levels after chronic intensive marijuana use. *N Engl J Med* 1974;290:872-874
3. Besch NF, Smith CG, Besch PK, et al. The effect of marijuana (delta-9-tetrahydrocannabinol) on the secretion of luteinizing hormone in the ovariectomized rhesus monkey. *Am J Obstet Gynecol* 1977;128:635-642
4. Smith CG, Moore CE, Besch NF, et al. The effect of marijuana on the secretion of sex hormones in the mature male rhesus monkey. *Clin Chem* 1976;22:1120
5. List A, Nazar B, Nyquist S, et al. The effects of Δ^9 -tetrahydrocannabinol and cannabidiol on the metabolism of gonadal steroids in the rat. *Drug Metab Dispos* 1977;5:266-272

Alen J. Salerian, M.D.
Washington Center for Psychiatry
Washington, D.C.

Withdrawal Reactions Associated With Low-Dose Venlafaxine Treatment in a Patient With Premenstrual Dysphoric Disorder

Sir: It has recently been demonstrated that venlafaxine, a serotonin-norepinephrine reuptake inhibitor, is effective for the treatment of premenstrual dysphoric disorder (PMDD).^{1,2} However, withdrawal reactions with venlafaxine have been reported.³⁻⁷ Most of these withdrawal reactions were noted in patients with depressive disorder and associated with daily venlafaxine doses of 150 mg or more. We describe the development of withdrawal symptoms after discontinuation of low-dose venlafaxine treatment in a patient with PMDD.

Case report. Ms. A, a 25-year-old single woman, visited our premenstrual syndrome (PMS) clinic in February 2003 due to premenstrual mood problems that had persisted for 2 years. She met the DSM-IV research criteria for a diagnosis of PMDD. After a series of laboratory tests and prospective daily recording of symptoms with the 35-item Prospective Record of the Impact and Severity of Menstrual Symptomatology (PRISM) calendar⁸ for 2 menstrual cycles, the diagnosis of PMDD was confirmed. No other psychiatric diagnosis was noted, and the patient denied any family history of mental illness.

Ms. A was treated with venlafaxine 18.75 mg/day for the first 5 days, then the dosage was titrated to 37.5 mg/day for the rest of the treatment course. The patient's PMDD symptoms were much improved during the first cycle. The PRISM calendar revealed more than 70% improvement in late-luteal-phase

dysphoria. Comparison of the patient's pretreatment and post-treatment premenstrual condition revealed that her Hamilton Rating Scale for Anxiety⁹ score dropped from 16 to 4, while her Hamilton Rating Scale for Depression¹⁰ score dropped from 13 to 3. Ms. A's Clinical Global Impressions-Severity of Illness scale¹¹ score decreased from 5 (markedly ill) to 1 (not at all ill), and her Clinical Global Impressions-Improvement scale¹¹ score was 1 (very much improved) in the second cycle after beginning treatment.

Unfortunately, after 2 months of effective treatment with low-dose venlafaxine, Ms. A missed taking a single 37.5-mg venlafaxine tablet one night. The apparent withdrawal reactions developed 14 hours after the missed dose. Clinical manifestations included disequilibrium features (dizziness, vertigo, ataxia), gastrointestinal symptoms (nausea, irritation), sensory disturbances (paresthesia, shocklike sensations), and sleep and psychological symptoms (anxiety, jitteriness, insomnia). The patient could not work and had to rest in bed for the next 2 days. She refused to take the agent again and did not seek any medical help. The withdrawal reactions progressively disappeared over the next 4 days.

Although the possibility of a withdrawal reaction is mentioned in the manufacturer's data sheet,¹² the implication is that such reactions are observed with daily doses of 150 mg or more. An important issue that should be addressed is the occurrence of withdrawal reactions with even such low doses of venlafaxine as the one in the present case.

Newer antidepressants for PMDD have acute-phase efficacy,¹³ and recent preliminary studies have also revealed similar efficacy with intermittent doses of selective serotonin reuptake inhibitors in the symptomatic premenstrual phase in comparison to full-cycle treatment.¹³⁻¹⁶ Given this fluctuating, phase-dependent sensitivity to antidepressants, antidepressant withdrawal reactions become an important consideration in the treatment of PMDD.

It seems reasonable to suggest that clinicians should be aware of the risk of withdrawal reactions for novel antidepressants, especially venlafaxine, during both intermittent and long-term treatment of PMS/PMDD patients.

Supported by grant NSC-90-2314-B-182-054 from the National Science Council, Taipei, Taiwan, and grant CMRP-1267 from Chang Gung Memorial Hospital, Taoyuan, Taiwan.

Dr. Liu has received grant/research support from Eli Lilly, Wyeth, and GlaxoSmithKline and has participated in speakers/advisory boards for GlaxoSmithKline, Wyeth, and Pfizer.

REFERENCES

1. Freeman EW, Rickels K, Yonkers KA, et al. Venlafaxine in the treatment of premenstrual dysphoric disorder. *Obstet Gynecol* 2001;98:737-744
2. Hsiao MC, Liu CY. Effective open-label treatment of premenstrual dysphoric disorder with venlafaxine. *Psychiatry Clin Neurosci* 2003;57:317-321
3. Farah A, Lauer T. Possible venlafaxine withdrawal syndrome [letter]. *Am J Psychiatry* 1996;153:576
4. Louie AK, Lannon RA, Kirsch MA, et al. Venlafaxine withdrawal reactions [letter]. *Am J Psychiatry* 1996;163:1652
5. Benazzi F. Venlafaxine withdrawal symptoms [letter]. *Can J Psychiatry* 1996;41:487
6. Dallal A, Chouinard G. Withdrawal and rebound symptoms associated with abrupt discontinuation of venlafaxine [letter]. *J Clin Psychopharmacol* 1998;18:343-344
7. Parker G, Blennerhassett J. Withdrawal reactions associated with venlafaxine. *Aust N Z J Psychiatry* 1998;32:291-294
8. Reid RL. Premenstrual syndrome. *Curr Probl Obstet Gynecol Fertil*

- 1985;8:43–67
9. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50–55
 10. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62
 11. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
 12. Effexor [package insert]. Philadelphia, Pa: Wyeth; 2004
 13. Yonkers KA. Antidepressants in the treatment of premenstrual dysphoric disorder. *J Clin Psychiatry* 1997;58(suppl 14):4–10
 14. Wikander I, Sundblad C, Andersch B, et al. Citalopram in premenstrual dysphoria: is intermittent treatment during luteal phases more effective than continuous medication throughout the menstrual cycle? *J Clin Psychopharmacol* 1998;18:390–398
 15. Freeman EW, Rickels K, Arredondo F, et al. Full- or half-cycle treatment of severe premenstrual syndrome with a serotonergic antidepressant. *J Clin Psychopharmacol* 1999;19:3–8
 16. Jermain DM, Preece CK, Sykes RL, et al. Luteal phase sertraline treatment for premenstrual dysphoric disorder: results of a double-blind, placebo-controlled, crossover study. *Arch Fam Med* 1999;8:328–332

Mei-Chun Hsiao, M.D.
Chia-Yih Liu, M.D.

Department of Psychiatry
Chang Gung Memorial Hospital and
Chang Gung University School of Medicine
Taoyuan, Taiwan

Measuring Efficacy of Polypharmacy in Schizophrenic Inpatients

Sir: McCue et al.¹ compare a number of indirect parameters assessing the effectiveness of polypharmacy in the treatment of acutely ill inpatients with schizophrenia. While we all welcome data that would support the safety and rationality of polypharmacy in schizophrenia treatment, the data the authors present are difficult to interpret. Their study carries some methodological flaws and uses a number of indirect parameters that most likely have alternative explanations.

The authors compared 459 and 584 inpatients discharged in 2 different years. They indicate that in each group some patients had several discharges in the same year; presumably, they chose only 1 discharge for such patients, as their final number of subjects is smaller than the number of discharged patients for the particular year. By what criteria did they choose the particular discharge data of a multiply discharged patient, and were the criteria applied in the same manner in the 2 time periods under investigation?

Two parameters were chosen as proxy measures of the effectiveness of polypharmacy: the length of stay and the discharge rates to state facilities. Both of these parameters are more likely to reflect outside, nonpharmacologic factors, such as administrative hospital pressures on length of stay. In fact, the Office of Mental Health, which regulates the rates of transfers to long-term state facilities in the state of New York, significantly decreased the flow of transfers to its facilities between the 2 timepoints under investigation, making this particular measure clinically useless.² Furthermore, comparing the number of adverse events between the 2 time periods is not very meaningful, as the reported rates in the 2 cohorts are unusually low (18 vs. 6).

The heuristically safe and limited conclusion of the authors' data is to state that polypharmacy in acute inpatients with schizophrenia was increased in 2000 as compared with 1995.

Dr. Lindenmayer has been a consultant for Janssen; has received grant/research support from Novartis, AstraZeneca, and Eli Lilly; has received honoraria from Janssen and Abbott; and has participated in speakers/advisory boards for Bristol-Myers Squibb and Janssen.

REFERENCES

1. McCue RE, Waheed R, Urcuyo L. Polypharmacy in patients with schizophrenia. *J Clin Psychiatry* 2003;64:984–989
2. Office of Mental Health. OMH Admission Data for Brooklyn, 1995 vs 2000. Available at: <http://www.omh.state.ny.us/omhweb/chartbook>. Accessed July 27, 2004

Jean-Pierre Lindenmayer, M.D.
Manhattan Psychiatric Center
Psychopharmacology Research Unit
New York University
New York, New York

Dr. McCue and Colleagues Reply

Sir: We welcome all comments on our report, the methodological limitations and tentative conclusions of which are outlined in the Discussion section of the article. A more careful reading of the Method section by Dr. Lindenmayer would have addressed his concern about our using only 1 admission of patients with multiple admissions. In fact, we used all discharges with the diagnosis of schizophrenia in 1995 and 2000. The number of unique patients in these samples was noted in the article.

It is true that the number of admissions to state facilities decreased between 1995 and 2000 because of a concerted effort by the state of New York to reduce the number of beds. However, this decrease did not affect the number of patients in need of intermediate- or long-term care, but only the availability of beds in state facilities for these patients. As a result, if fewer patients in need of intermediate- or long-term care were transferred to state facilities in 2000, then they would have remained hospitalized at our acute service until ready for discharge. Length of stay at our facility would have increased if all else remained the same. In fact, our patients with schizophrenia had a reduced length of stay in 2000, even with the reduced availability of state hospital beds. Other factors affected our patients' readiness for discharge; the change we found in prescription practices may be one of them.

In addition, there was a significant reduction in adverse drug reactions between 1995 and 2000 that was very likely attributable to fewer extrapyramidal effects because of the increased use of atypical antipsychotics. We leave it to the reader, including Dr. Lindenmayer, to decide whether this reduction is meaningful. We thought it was.

We appreciate Dr. Lindenmayer's restatement of our primary conclusion that polypharmacy increased in acute patients with schizophrenia between 1995 and 2000. We believe that our other observations about fewer adverse drug reactions and improved patient outcome require stronger counter-arguments before being dismissed.

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

Robert E. McCue, M.D.
Rubina Waheed, M.D.
Leonel Urcuyo, M.D.
Department of Psychiatry
Woodhull Medical and Mental Health Center
Brooklyn, New York

Development of Guidelines for Preventing and Managing Obesity and Diabetes in Mentally Ill Patients

Sir: I would like to thank you for publishing in *The Journal of Clinical Psychiatry* the proceedings from the consensus development conference held in November 2003 between the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity.¹ Though originally published in *Diabetes Care*,² publication in the psychiatric literature ensures that the proceedings are viewed by the majority of psychiatrists and mental health clinicians who are the primary prescribers of antipsychotics, including the second-generation agents.

Obesity is a significant national health concern and cannot be divorced from type 2 diabetes mellitus. The monitoring protocol suggested in the proceedings is impressive and will help detect metabolic syndrome early. Increased waist circumference and elevated diastolic blood pressure are good early clinical indicators of metabolic syndrome. In our outpatient practice, we have been monitoring fasting glucose and lipid profiles in the chronically mentally ill for over 2 years (including those not treated with second-generation agents) and have found that we are detecting younger individuals with diabetes and dyslipidemia. In light of this discovery, we have instituted establishment of a fasting lipid profile for inpatients, including those admitted to our child and adolescent unit.

We have been measuring patients' abdominal girth (at the level of the umbilicus) in addition to weight, pulse, and blood pressure in one of the day treatment programs for approximately 1 year. Abdominal girth measurement has turned out to be an intervention, as patients begin to inquire about the reason for measurement and subsequently want to know what they could do to reduce their waist size. We have specifically suggested replacing soft drinks with water (some patients drink up to 4 L/day; liquid carbohydrate content can approach close to 600 g) and walking 30 minutes per day.

Finally, we are instituting these guidelines so that more patients will be screened and diabetes and lipid disorders (whether due to second-generation agents or to other factors) will be detected earlier, to hopefully prevent patients from developing ketoacidosis. We also suggest that patients presenting with vague complaints, especially visual ones, should have a random blood glucose test (high levels of unstable sugars cause visual changes). It appears that the evidence is mounting that chronic psychiatric illnesses (e.g., schizophrenia and bipolar disorder) should be considered as independent risk factors for type 2 diabetes mellitus, and the consensus conference should also have made a statement on this issue.

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

REFERENCES

1. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *J Clin Psychiatry* 2004;65:2:267-272
2. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care* 2004;27:596-601

Sanjay Gupta, M.D.
Bradford L. Frank, M.D., M.P.H., M.B.A.
 Department of Psychiatry
 University of Buffalo School of
 Medicine and Biomedical Sciences
 Buffalo, New York

Effect of Mirtazapine Versus Fluoxetine on "Sleep Quality"

Sir: As a psychiatrist in clinical practice, I appreciate the importance of restoring sleep quality in my depressed patients. I therefore read with interest the recent article by Winokur et al.¹ comparing the sleep physiology effects of mirtazapine versus fluoxetine. Unfortunately, the authors seemed to demonstrate only that a drug with a sedative side effect causes more drowsiness than a drug without it.

In the study, mirtazapine not surprisingly helped depressed patients fall asleep more quickly and stay asleep longer. In other words, the patients showed a decrease in sleep latency, increased total sleep time, and thus improved sleep efficiency throughout the 8 weeks. The fact that most of these changes were statistically significant as early as week 1 seems merely to reflect mirtazapine's well-known sedative side effect; there was no basis for linking this effect to the more slowly developing improvement in sleep quality associated with antidepressant benefit. Indeed, the authors liken sleep alterations with mirtazapine to those produced by the hypnotic compounds zolpidem and zaleplon, two drugs with no claim to antidepressant efficacy.

Moreover, the study seems to draw an unfair comparison, since the doses of the two drugs were not comparable. While 45 mg of mirtazapine at bedtime is appropriate, the fluoxetine subjects were moved up to 40 mg daily—twice what the package insert² states is sufficient for most patients and, in my opinion, actually 4 times what is usually necessary. With this excessive dose comes increased risk for at least 2 adverse effects that can unfavorably impact the parameters of this study. Subjects who experience activation with fluoxetine will, of course, have greater trouble falling asleep at bedtime. On the other hand, there are some individuals who feel somnolence with a fluoxetine dose this high; presumably, they will be more inclined to take daytime naps (apparently not prohibited in the study), and this, in turn, could prolong sleep latency at bedtime. The incidence of these two side effects, excessive activation and daytime somnolence, was not noted.

Bearing out these concerns, the authors' data indicate that sleep latency in the fluoxetine group was actually slightly improved at week 1, when the dose was 20 mg and there had not yet been much accumulation of this slowly metabolized drug. It is only after week 8 that we see worsening in sleep latency, reflecting the high drug levels accumulated during 4 weeks of taking a daily dose of 40 mg.

The authors make several references to the fluoxetine-associated increases in stage 1 sleep, "generally interpreted as a disruption of sleep continuity."^{1(p1227)} However, there is no explanation for, or even mention of, the considerable disparity between the baseline amounts of stage 1 sleep: 38.7 minutes for the fluoxetine group and 66.2 minutes for mirtazapine subjects. Further, while stage 1 sleep climbed to a mean of 67.9 minutes by week 8 on fluoxetine treatment, the amount of stage 1 sleep eventually achieved by the mirtazapine subjects was a remarkable 111.2 minutes. In other words, stage 1 sleep increased by 75.4% with fluoxetine and 68.0% with mirtazapine. I will take the authors' word that the former increase was statistically significant while the latter was not, but spending almost 2 hours per night in stage 1 does not speak to a great sleep benefit from mirtazapine.

The authors conclude, "These alterations in sleep physiology [with mirtazapine] are indicative of improvement in sleep quality."^{1(p1228)} However, this statement begs the question of what is truly meant by the concept of "sleep quality" when we

consider the enhancement of energy, motivation, concentration, and mood associated with antidepressant-restored sleep. The authors correctly point out that "both the mirtazapine- and the fluoxetine-treated patients demonstrated robust antidepressant responses . . . [and] both groups had substantial reductions in the total scores for the 3 HAM-D sleep items."¹(p1228) In other words, there was no difference between groups with respect to subjective self-assessment of improved sleep quality. As has been found previously,³ there is a significant disconnect between what researchers might wish to call "sleep quality," based on the parameters we have thus far discovered (i.e., electro-somnography), and the restored sleep enjoyed by patients as they recover from depression.

Dr. Winokur was shown this letter and declined to comment. Dr. Lawrence has been a consultant and speaker for Eli Lilly, GlaxoSmithKline, and Forest; has been a speaker for Wyeth-Ayerst; and has received grant/research support from Pfizer.

REFERENCES

1. Winokur A, DeMartinis NA III, McNally DP, et al. Comparative effects of mirtazapine and fluoxetine on sleep physiology measures in patients with major depression and insomnia. *J Clin Psychiatry* 2003;64:1224-1229
2. Prozac [package insert]. Indianapolis, Ind: Eli Lilly and Company; 2004
3. Rush AJ, Armitage R, Gillin JC, et al. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. *Biol Psychiatry* 1998;44:3-14

Robert Wm. Lawrence, M.D.
Private Practice
Fort Collins, Colorado

Possible Impact of Dropout in a Study of High-Dose Olanzapine and Prolactin Levels

Sir: Prolactin elevation as a consequence of antipsychotic drug therapy may result in decreased sexual desire, difficulties in sexual performance, and gynecomastia in men and in amenorrhea, infertility, breast engorgement, and lactation in women.¹ Karagianis and Baksh² studied 24 patients to determine whether high-dose (20–40 mg/day) olanzapine was associated with prolactin elevation. They found that there was no correlation between dose of olanzapine and prolactin level, that the highest elevation of prolactin was 20 ng/mL, and that only 21% of patients had (mildly) elevated prolactin levels. They concluded that prolactin elevation may not be a significant problem with olanzapine at the doses studied.

Karagianis and Baksh² admitted several limitations to their study. However, they did not note that the most serious limitation was that the mean duration of olanzapine therapy was 15.3 months, which raises the possibility that patients who experienced prolactin-related problems may have dropped out of

treatment and may thereby have been preselected out of the sample. Therefore, conclusions about the effect of high-dose olanzapine on prolactin levels must remain guarded.

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

REFERENCES

1. Andrade C. Psychopharmacology. In: Bhugra D, Ranjith G, Patel V, eds. *Handbook of Psychiatry*. New Delhi, India: Foundation Books; 2004. In press
2. Karagianis JL, Baksh A. High-dose olanzapine and prolactin levels. *J Clin Psychiatry* 2003;64:1192-1194

Chittaranjan Andrade, M.D.
Department of Psychopharmacology
National Institute of Mental Health and Neurosciences
Bangalore, India

Drs. Karagianis and Baksh Reply

Sir: While we agree that dropouts could potentially influence this type of study, in this particular study they did not. All patients were from the senior author's (J.L.K.'s) clinical practice, and no patient meeting the inclusion criteria dropped out. All patients had to be taking at least 20 mg/day of olanzapine for at least 4 months. Furthermore, any patient who would have dropped out prior to meeting inclusion criteria could not have been considered to be on high-dose, long-term treatment. This study was not intended to address the issue of prolactin elevation after low-dose or short-term treatment with olanzapine. Among all of the senior author's olanzapine patients (hundreds), only 2 have ever stopped olanzapine treatment due to side effects related to prolactin elevation, and these patients were receiving low-dose, short-term therapy.

Dr. Karagianis is now an employee of Eli Lilly Canada; however, neither the original article nor this letter was supported by Eli Lilly. Dr. Baksh reports no financial affiliation or other relationship relevant to the subject matter of this letter.

James L. Karagianis, M.D., F.R.C.P.C.
Anton Baksh, M.D., F.R.C.P.C.
Faculty of Medicine
Memorial University of Newfoundland
St. John's, Newfoundland, Canada

Correction

In the article "Health-Related Quality of Life in Patients With Schizophrenia During Treatment With Long-Acting, Injectable Risperidone" by Henry A. Nasrallah, M.D., et al. (April 2004 issue, pp. 531-536), the population of the placebo group in Figure 3B on page 534 should be 28.