Letters to the Editor

Gender Difference in Severity of Schizophrenia

Sir: The summary by Lindamer et al.[1] (January 1999 issue) regarding gender differences and age states that "women overall may develop more severe positive symptoms [of schizophrenia] than men" and ends with a conclusion: "These differences may reflect the influence of sex hormones and menopause . . . or the possible existence of an 'estrogen-related' form of schizophrenia. . . ."[1(p61)]

Neither the summary nor the text itself gives any mention of the fact that a mother-girl experience in infancy may be sufficiently different from a mother-boy experience to influence symptom outcome. Not to also offer this possibility is shoddy science.

References

1. Lindamer LA, Lohr JB, Harris J, et al. Gender-related clinical differences in older patients with schizophrenia. J Clin Psychiatry 1999;60:61–67

Peter D. King, M.D., Ph.D.
Sherman Oaks, California

Bupropion-Amantadine–Associated Neurotoxicity

Sir: The antidepressant drug bupropion is a substituted chloropropiophenone with a structure reminiscent of stimulant and anorectic drugs such as diethylpropion.[1] It exerts both a stimulant profile, as shown by increases in motor activity, and an antidepressant profile.[2] Some data show that bupropion increases dopamine concentration in the mesolimbic system involved in the neural circuitry of reward.[3]

There is noticeable absence of sedation with bupropion treatment, but stimulant effects occur, including excitement, palpitations, tremors, agitation, increased motor activity, occasional toxic confusional state, and, in some patients, seizures when bupropion is given in high doses.[4–7] Because of its dopamine stimulating effect,[8,9] bupropion offers potential unique advantage in elderly patients with depression and dementia, many of whom suffer apathy and motor retardation.

We reviewed the records of 8 nursing home residents treated for major depression with bupropion during 1998. All residents had been diagnosed as having major depressive disorder by their primary care physician and psychiatrist, using DSM-IV criteria[10] and semistructured interviews and verified by the 17-item Hamilton Rating Scale for Depression (HAM-D-17).[11] All patients had been selected for bupropion monotherapy because of symptoms of avolition, apathy, and motor retardation. The mean age of the 8 subjects was 87.4 years (range, 77–96 years) when drug therapy began. Five were men, and 3 were women. Cognitive impairment ranged from mild to moderate, with a mean Folstein Mini-Mental State score of 16.[12] All patients were medically stable at the onset of treatment. The mean dosage of bupropion was 156 mg/day (range, 75–200 mg/day). The mean pretreatment HAM-D-17 score was 18.8.

Of the 8 patients receiving bupropion therapy, 6 were coadministered amantadine for influenza prophylaxis as a result of an influenza outbreak in the facility. The mean duration of bupropion therapy before amantadine was commenced was 2.7 months. Three of the 6 patients developed confusion and neurologic signs within a week of drug coadministration. Symptoms consisted of restlessness, agitation, gross motor tremors, ataxia, gait disturbance, dizziness, and vertigo. Two of the 3 patients had symptoms so severe that hospitalization was required. All 3 patients had a negative medical work-up, including normal CT brain scan results (all had mild preexisting cerebral atrophy). In all cases, symptoms resolved within 72 hours of discontinuation of bupropion and amantadine. One patient was rechallenged with bupropion at the same previous dosage with no recurrence of side effects.

Amantadine is often included in the regimen of antiparkinsonian drugs because of its incidental release of dopamine from intraneural storage sites.[13,14] Its adverse effects include irritability, tremor, dysarthria, ataxia, vertigo, agitation, and delirium.[15]

We propose that the above-noted adverse drug reaction (neurotoxicity) resulted from a synergistic central dopamine effect caused by the coadministration of bupropion and amantadine.

References

1. Ferris RM, Cooper BR. Mechanism of antidepressant activity of bupropion. J Clin Psychiatry Monograph 1993;11(1):2–14
2. Martin P, Massol J, Colin JN. Antidepressant profile of bupropion and three metabolites in mice. Pharmacopsychiatry 1990;23:187–194
3. Nomikos CG, Damsma G, Wenkstern D, et al. Effects of chronic bupropion on interstitial concentration of dopamine in rat nucleus accumbens and striatum. Neuropsychopharmacology 1992;7:7–14
4. Mendels J, Amin MM, Chouinard G, et al. A comparative study of bupropion and amitriptyline in depressed outpatients. J Clin Psychiatry 1983;44(5, sec 2):118–120
5. Chouinard G. Bupropion and amitriptyline in the treatment of depressed patients. J Clin Psychiatry 1983;44(5, sec 2):121–129
6. Settle EC Jr. Bupropion: general side effects. J Clin Psychiatry Monograph 1993;11(1):33–39
7. Davidson J. Seizures and bupropion: a review. J Clin Psychiatry 1989;50:256–261
8. Kane JM, Cole K, Sarantakos S, et al. Safety and efficacy of bupropion in elderly patients: preliminary observations. J Clin Psychiatry 1983;44(5, sec 2):134–136
9. Bodkin JA, Lasser RA, Wines JD, et al. Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. J Clin Psychiatry 1997;58:137–145
10. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
11. Hamilton M. Development of a rating scale for primary depression illness. Br J Soc Psychol 1967;6:278–296
12. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198
13. Parkes JD, Zilkha KJ, Calver DM, et al. Controlled trial of amanta-

dine hydrochloride in Parkinson's disease. Lancet 1970;1:259–262
14. Grelak RP, Clark R, Stump JM, et al. Amantadine-dopamine interaction: possible mode of action in Parkinsonism. Science 1970; 169:203–204
15. Postma JV, Tilburg JW. Visual hallucinations and delirium during treatment with amantadine. J Am Geriatr Soc 1975;23:212–215

Brian Trappler, M.D.
Augusto M. Miyashiro, M.D., C.M.D.
Brooklyn, New York

Sexual Dysfunction on Fluvoxamine Therapy

Sir: I noted with great interest the study by Nafziger et al.[1] (March 1999 issue) entitled "Incidence of Sexual Dysfunction in Healthy Volunteers on Fluvoxamine Therapy." This study's premise is timely and its results could potentially be of significant clinical impact given the sheer number of newer anxiolytics and antidepressants currently being used in practice. It was an interesting article, but I identified a few problems I had with this study.

First, this study was an open-label study. There is a great deal of room for inherent bias that goes along with the use of such a design, which typically can lead to faulty conclusions. I am not implying that open-label studies do not provide important information, because many times they do, but conclusions from such a study should be highlighted and underscored by the limitations of this particular design.

Second, the study was conducted in a "healthy" population, both medically and psychiatrically. Thus, it is not scientifically reasonable to apply the results to the target population that actually takes selective serotonin reuptake inhibitors (SSRIs). It would have been more appropriate to study the effects of fluvoxamine on sexual dysfunction in individuals with anxiety disorders or depression.

Third, the study's design as described would lead to an increased probability of finding a significant result by chance alone because the chi-square tests for adverse effects were not independent. I would suggest using a correction test such as the Bonferroni adjustment or the Duncan multiple range test.

Fourth, there could be a significant "testing effect"[2] being observed in this study. That is, if one administers a test or, in this case, a questionnaire enough times, the test subject will, over time, render an answer that is significant. In this study, the patients completed the questionnaire at least 8 times. With such frequency, it is expected that there would be recall bias and sensitization.

Fifth, the questionnaire used in the study employed a yes-no format. This method of testing is not sensitive enough for the desired purpose of identifying the sexual dysfunction; that is, it is too "all or none" and does not allow for any answer between those extremes for describing the adverse effect. It also would have been a stronger study had it employed more standard assessments for measuring sexual dysfunction such as the Rush Sexual Inventory, the Arizona Sexual Experience Scale, the Changes in Sexual Functioning Questionnaire, or the Derogatis Sexual Function Inventory.

Sixth, and related to the last limitation, is the lack of comparator drugs. How disabling is fluvoxamine compared with fluoxetine or sertraline in terms of sexual dysfunction?

Seventh, the sample size of 20 individuals was exceedingly small. Power was probably not achieved in the study. The authors briefly allude to this, but the study also appears to be an afterthought from another study exploring phenotyping and drug-drug interactions.

Eighth, the steep dosage titration of the fluvoxamine (e.g., tripling the dose in a 7-day period) could easily result in overendorsement of adverse effects, including sexual dysfunction. Again, it would be important to see how patients taking other SSRIs would respond to similar dosage titrations. This also calls to mind the issue of not having comparator arms using other SSRIs.

Finally, it is also probably not totally correct to assume that, although the SSRIs are structurally dissimilar, they have similar mechanisms of action. It is clear they do not look alike in terms of chemical structure. Likewise, we are now beginning to appreciate that they do have subtly different effects at the receptor level (e.g., in affinities and receptor binding),[3] with implications for purported mechanism of action.

The question of how much sexual dysfunction results from using fluvoxamine or any other SSRI is of great importance. The present study prompts us to remember to seek out this information; however, I would recommend that this particular study not be quoted without also citing its significant limitations. I look forward to hearing about future follow-up studies from the authors on this topic.

References

1. Nafziger AN, Bertino JS Jr, Goss-Bley AI, et al. Incidence of sexual dysfunction in healthy volunteers on fluvoxamine therapy. J Clin Psychiatry 1999;60:187–190
2. Campbell DT, Stanley JC. Experimental and Quasi-Experimental Designs for Research. Boston, Mass: Houghton Mifflin Company; 1963
3. Kilts CD. Recent pharmacologic advances in antidepressant therapy. Am J Med 1994;97(suppl 6A):3S–12S

Lyle K. Laird, Pharm.D., B.C.P.P.
Denver, Colorado

Dr. Nafziger and Colleagues Reply

Sir: We thank Dr. Laird for his thoughtful comments about our article.[1] This study was an open-label clinical trial with fluvoxamine used as a hepatic enzyme inhibitor, as clearly stated in our Method section. The problems associated with open-label studies are well known,[2] as are the benefits and problems associated with double- and triple-blind studies. While open-label studies have limitations, we do not believe that this study design led to "faulty conclusions" as Dr. Laird suggests.

We consider the use of healthy volunteers to be a strength rather than a study flaw because it allows assessment of drug side effects as separate from the well-recognized frequent coexistence of depression and sexual dysfunction. In fact, as noted and referenced in our article,[3,4] previous studies of sexual dysfunction as an adverse effect of selective serotonin reuptake inhibitors (SSRIs) have been confounded by study of these medications in patients with coexisting psychiatric disorders.

Generally, use of Bonferroni adjustment (based on Bonferroni's inequality) is a statistical technique done to avoid inflation of the experimental alpha values that occurs with multiple comparisons. These techniques are most typically applied when investigators are evaluating multiple subgroups or several different test treatments. We do not believe that this test should be applied to the data from this study. For this study, the outcome of interest was sexual dysfunction in one group of patients. Data on other adverse events were reported (with statistical testing) for the reader's information. On the basis of a priori knowledge of common SSRI side effects, we could have chosen to evaluate

and present adverse effects only on the neurologic, psychiatric, sexual function, and gastrointestinal systems. If we apply Bonferroni adjustment only to the organ systems of interest, the significance level would be assigned at ≤ .0125, and statistical significance for incidence of sexual dysfunction would still have been met. As discussed in our article, the finding of a high incidence of sexual dysfunction with fluvoxamine use is consistent with other published data. The null hypothesis for our study was rejected, proving that the study had adequate power.

We do not think that a "testing effect" occurred with our data collection. There is no reason to assume that subjects would report sexual dysfunction but not other adverse effects with repeated, self-administered adverse effect questionnaires. One could speculate that healthy volunteers are less likely to self-report sexual dysfunction since it is socially embarrassing.

Our intent was not to identify or describe "extremes of sexual dysfunction." The yes-no questionnaire format is a commonly used and validated method of obtaining self-reported incidence data.[5] In addition, we employed a questionnaire that was referenced and previously validated. The questionnaires suggested by Dr. Laird were not available at the time of study design and conduct. Certainly, they would be useful for future studies, particularly those intended to delineate the range of sexual dysfunction manifestations.

While use of comparator drugs for comparison of type and frequency of sexual dysfunction would be of interest, it was not an aim of this study. It is unlikely that healthy volunteers would agree to undergo repeated courses of medications known to cause such a high incidence of sexual dysfunction since they would not be receiving the drug for treatment of a psychological disorder. We are unaware of data that show that rapid SSRI titration leads to more sexual dysfunction than slower dosage titration. The half-life of fluvoxamine is 15 hours. Therefore, subjects should have reached steady-state concentrations within the first week. The persistence and continued emergence of sexual dysfunction at 4 weeks does not support rapid titration as a reasonable criticism.

As Dr. Laird points out, there are in vitro data showing that the SSRIs have subtly different effects at the receptor level. While we realize that psychiatric caregivers often try numerous antidepressants (even those in the same class) and believe that one may work when others fail, to the best of our knowledge, there are no randomized, crossover trials with SSRIs that provide evidence of clinically different effects on either psychiatric disorders or types of sexual dysfunction.

References

1. Nafziger AN, Bertino JS Jr, Goss-Bley AI, et al. Incidence of sexual dysfunction in healthy volunteers on fluvoxamine therapy. J Clin Psychiatry 1999;60:187–190
2. Meinert CL. Clinical Trials: Design, Conduct and Analysis. New York, NY: Oxford University Press; 1986
3. Simon GE, VonKorff M, Heiligenstein JH, et al. Initial antidepressant choice in primary care: effectiveness and cost of fluoxetine vs tricyclic antidepressants. JAMA 1996;275:1897–1902
4. Mathew RJ, Weinman M, Claghorn JL. Tricyclic side effects without tricyclics in depression. Psychopharmacol Bull 1980;16:58–60
5. Converse JM, Presser S. Survey Questions: Handcrafting the Standardized Questionnaire. Beverly Hills, Calif: Sage Publications; 1986

Anne N. Nafziger, M.D., M.H.S.
Joseph S. Bertino, Jr., Pharm.D.
Angelica I. Goss-Bley
Cooperstown, New York
Angela D. M. Kashuba, Pharm.D.
Chapel Hill, North Carolina

Clozapine Versus Chlorpromazine in Geriatric Patients

Sir: I began my career in clinical research conducting multicenter comparative drug studies of antipsychotic agents in geriatric Veterans Affairs hospital patients. Thus, it was with high expectations that I read the article by Howanitz et al.[1] comparing the old gold standard, chlorpromazine, with the new gold standard, clozapine, in a geriatric Veterans Affairs hospital patient population.

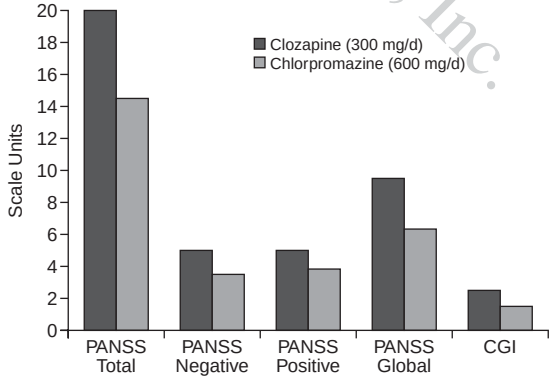
I was disappointed to find, however, certain problems with the authors' interpretations of their study results. Specifically, they stated that "an important finding in our study was the equality of efficaciousness of the 2 medications."[1(p43)] The logic of statistical inference in this context does not allow them to conclude that they proved the 2 medications equal. In fact, they failed to prove that one was superior to the other.

This is more than semantic hairsplitting, since every analysis they performed favored clozapine over chlorpromazine. The presumed "proof of equality" simply reflected sample sizes so small that the true differences between these agents could not possibly be proven. By their methodology, no therapeutically superior agent would ever be discovered, if only the studies could be kept small enough!

Furthermore, the authors point out that of the 43 initial subjects, only 34 met their completion criteria and were part of their comparative efficacy analyses. The rate of completion was twice as high for clozapine patients (21 clozapine completers versus 11 taking chlorpromazine), an immediate clue that perhaps superior efficacy might be accounting for the higher rates of treatment retention with clozapine. Such tiny sample sizes would demand huge differences in measured improvement to meet statistical significance, and the authors correctly point out this deficiency in the "power" of their small study.

A small study of this type should be regarded as preliminary at best, the reasons for differential dropout rates examined qualitatively, and the pattern of actual efficacy outcome differences examined for internal consistency as well as consistency with other published findings. Consider Figure 1, derived from the authors' Table 1, providing a graphic reconsideration of the study results.

Figure 1. Mean Improvement From Baseline on All Efficacy Variables[a]



[a]Data from Howanitz et al.[1] Abbreviations: CGI = Clincal Global Impressions Scale, PANSS = Positive and Negative Syndrome Scale.

Figure 1 makes clear that despite the tiny sample sizes and corresponding lack of statistical significance, in every instance clozapine was found to produce more improvement than chlorpromazine. Improvement rates were 25% to 50% greater with clozapine than with chlorpromazine despite an initial assignment bias against clozapine (these patients started the study with higher levels of pathology in every efficacy variable).

Finally, there is the matter of dosage. Most clinical studies have determined that 300 mg/day of clozapine is the floor of the therapeutic range. The rationale for the 300-mg dose in this study was the older patient group (minimum age = 55 years) and "previous experience" at Pilgrim State Psychiatric Center "that these maximum doses are sufficient to obtain significant therapeutic responses in elderly patients."[1(p42)] While I respect greatly the experience of skilled clinicians, the purpose of clinical research is to test scientifically the validity of such observations. A far better study design would have stratified patients randomly into low- (300 mg/day) and medium-dose (600 mg/day) groups to test prospectively whether the Pilgrim State clinical observations were borne out in this population.

How then to reinterpret these findings? I would characterize this as a useful pilot study at one Veterans Affairs hospital site comparing low-dose clozapine with chlorpromazine in a small number of older patients. In every instance, clozapine patients exhibited markedly higher rates of improvement, despite low daily doses and their having started the study at higher levels of overall psychopathology than the reference patients taking chlorpromazine. Retention rates in the 12-week study were twice as high for clozapine-treated Veterans Affairs hospital patients.

Reference

1. Howanitz E, Pardo M, Smelson DA, et al. The efficacy and safety of clozapine versus chlorpromazine in geriatric schizophrenia. J Clin Psychiatry 1999;60:41–44

Gilbert Honigfeld, Ph.D.
Princeton, New Jersey

Combination of Donepezil and Gabapentin for Behavioral Disorders in Alzheimer's Disease

Sir: Behavioral symptoms are very frequent in patients with Alzheimer's disease, and management of these symptoms is a primary goal of therapy.[1] Several drugs may be used with benefit, including atypical neuroleptics, selective serotonin reuptake inhibitors, anticonvulsants, tacrine, and the newer acetylcholinesterase inhibitors such as donepezil, recently indicated for the symptomatic treatment of Alzheimer's disease. Indeed, there are conflicting reports in the literature about the action of donepezil in behavioral disorders associated with Alzheimer's disease, with some authors reporting a benefit[2] and others reporting a worsening of the symptoms.[3]

Gabapentin, an anticonvulsant reported to be effective in treating behavioral agitation in Alzheimer's disease,[4] is characterized by a good safety profile and a clear pharmacokinetic profile, making it a good therapeutic option for elderly people on polytherapy. We report 2 cases of Alzheimer's disease in which donepezil provided some benefit for cognitive symptoms, but increased behavioral problems, which were then successfully controlled by adding gabapentin.

Case 1. Mr. A, a 75-year-old man, had been diagnosed with Alzheimer's disease for 1 year when he came to our treatment center. At that time, he had a Mini-Mental State Examination (MMSE) score of 21/30 and a Neuropsychiatric Inventory (NPI) score of 96/120. He began treatment with donepezil, 5 mg/day. After 2 months, Mr. A's MMSE score was 23/30, and his NPI score was 94/120; he complained of anxiety, agitation, irritability, and motor restlessness. Attempted treatment with a benzodiazepine failed because of excessive sedation, and risperidone could not be used because of extrapyramidal side effects. Gabapentin, 300 mg at bedtime, provided benefit; after 1 week, Mr. A's MMSE score was 25/30, and his NPI score decreased to 66/120. At 2-month follow-up, the benefit was maintained and caregivers reported a substantial reduction of stress.

Case 2. Mr. B, an 85-year-old man, had been diagnosed with Alzheimer's disease for 10 months when he came to our treatment center. At that time, he had an MMSE score of 19/30. He began treatment with donepezil, 10 mg/day. After 4 months, Mr. B's MMSE score was 22/30, but severe mood swings, anxiety, agitation, lack of impulse control, and sleep-wake cycle alteration had appeared; his NPI score was 86/120. An attempt with a benzodiazepine was ineffective, and fluoxetine was not tolerated. Gabapentin, 300 mg at bedtime, was started and provided a substantial reduction of the symptomatology in 48 hours. His NPI score decreased to 52/120. Mild drowsiness was reported.

The use of acetylcholinesterase inhibitors in mild-to-moderate Alzheimer's disease is steadily increasing. Even with improvement in cognitive symptoms, behavioral problems remain a major concern, particularly for caregivers. Gabapentin is a drug well known for its safety profile; it is not metabolized and does not interact with liver enzymes. If the effect of gabapentin in controlling the behavioral symptoms in Alzheimer's disease is confirmed by well-designed controlled studies, the use of gabapentin with donepezil in mild-to-moderate Alzheimer's disease might be considered in those patients in whom behavioral symptoms worsen with a cholinesterase inhibitor.

References

1. Mega MS, Cumming JL, Fiorello T, et al. The spectrum of behavioral changes in Alzheimer's disease. Neurology 1996;46:130–135
2. Levy ML, Cummings JL, Kahn-Rose R. Neuropsychiatric symptoms and cholinergic therapy for Alzheimer's disease. Gerontology 1999; 45(suppl 1):15–22
3. Wengel SP, Roccaforte WH, Burke WJ, et al. Behavioral complications associated with donepezil. Am J Psychiatry 1998;155: 1632–1633
4. Regan WM, Gordon SM. Gabapentin for behavioral agitation in Alzheimer disease [letter]. J Clin Psychopharmacol 1997;17:59–60

Carlo Dallocchio, M.D.
Carlo Buffa, M.D.
Novi Ligure, Italy
Paolo Mazzarello, M.D., Ph.D.
Pavia, Italy