Letters to the Editor

Olanzapine/Risperidone and Diabetes Risk

Sir: The article by Gianfrancesco et al. from the October 2002 issue of *The Journal of Clinical Psychiatry* concluded that olanzapine was associated with an increased risk of type 2 diabetes, but risperidone was not.[1] As researchers who are also studying the relationship between atypical antipsychotics and diabetes, we felt it was important to caution readers against using these results to draw conclusions about the relative safety of olanzapine and risperidone.[2]

If Gianfrancesco and colleagues' results are to be believed, then one must also believe that patients in the olanzapine and risperidone groups were at equal risk for diabetes at the time they initiated therapy. Unfortunately, patients' risk is unknown because patients were not randomly assigned to the olanzapine and risperidone groups. The study used logistic regression to control for some between-group differences (i.e., age, gender, type of insurance, use of other psychotropic drugs, and type of psychosis), but could or did not control for others. To their credit, the study's authors acknowledged that their study was limited because it could not control for race or weight gain, which are known diabetes risk factors. However, additional diabetes risk factors that were not controlled for include a family history of diabetes, use of certain drugs that are associated with diabetes risk (e.g., α- and β-blockers), heart disease, and hypertension. It is very possible that controlling for these factors would have resulted in a different conclusion about the association between olanzapine/risperidone and diabetes risk.

Another reason to question whether olanzapine and risperidone patients were comparable has to do with the time period over which patients were studied. The date that olanzapine was approved for use in the United States (October 1996) occurred in the middle of the study's observation period (April 1996 through December 1997). Consequently, patients did not have equal opportunity to be placed on olanzapine or risperidone treatment over the time period studied. It is also likely that many patients who started taking olanzapine had already failed risperidone treatment. These olanzapine patients were, by definition, different from risperidone patients.

Other aspects of the analysis also lead us to question the strength of their results. First, the study emphasized results based on 12 months of exposure to olanzapine or risperidone. The 12-month results, however, were not based on data from patients who actually had 12 months of exposure; rather, they were extrapolated from the logistic regression model. The model includes many patients with fewer than 12 months of exposure, including the vast majority (93%) of treated patients. One wonders if the study's conclusions would hold if the analysis were performed only on patients who had at least 12 months of exposure.

Second, logistic regression was used to estimate odds ratios for diabetes onset among risperidone patients compared with untreated patients and among olanzapine patients compared with untreated patients. A different statistical technique (Woolf's method) was then used to demonstrate that the odds of diabetes onset differed significantly between olanzapine and risperidone patients. This technique does not take into account how the 2 estimated odds ratios are dependent on each other. Would the odds ratio of diabetes onset for olanzapine patients relative to risperidone patients have been statistically significant if the significance test was based on the same logistic model that generated the odds ratios?

Third, the results are based on the assumption that the odds of diabetes onset increases exponentially (not linearly) with atypical antipsychotic exposure. The model assumes that the odds of contracting diabetes increase a certain estimated percentage each and every month. This compound effect may not be realistic, especially when extrapolating beyond the observation period of most of the treated patients in the analysis. A linear or other nonincreasing form for this effect may lead to a very different estimated relationship between risperidone/olanzapine and the risk of diabetes.

Fourth, the study measured atypical exposure as months of therapy and controlled for the total number of months a patient was observed. Because these 2 variables are very likely highly correlated for treated patients (exposure and observation time were identical for compliant treated patients), it is also likely that the estimated coefficients on the olanzapine or risperidone exposure variables are reflecting some of the differences in observation time between patients in the 2 groups, or vice versa. The study's finding that diabetes risk roughly doubles for every 6 months of observation among psychosis patients (holding all else constant) is unexpectedly large, which lends support to the possibility that the exposure and observation time variables may not be accurately measuring the effect of either variable on diabetes risk.*

In sum, we believe that substantially more research on the relationship between the use of atypical antipsychotics and diabetes needs to be done before any conclusion regarding a causal relationship can be inferred. Data from existing clinical trials have not shown a causal relationship between atypical antipsychotics and diabetes, although they were probably underpowered to do so. Ideally, new clinical trials that specifically include diabetes onset as an endpoint should be conducted. Barring that, many more retrospective studies that use data from different sources and address some of the methodological concerns we have raised here would be necessary before one could conclude with any confidence that atypical antipsychotics increase patients' risk of contracting type 2 diabetes.

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*The odds ratio on observation time (months) was 1.125. Therefore, the odds ratio after 6 months of observation would be $(1.125)^6 = 2.03$.

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Dr. Gianfrancesco Replies

Sir: I wish to respond to comments by Dr. Lee and Mr. Fowler pertaining to our article.[1] While selection bias associated with diabetes risk factors is a possibility, it is doubtful that it favored risperidone. The higher prevalence of excessive weight gain among olanzapine- versus risperidone-treated patients, as reflected in 2 studies synthesizing data from several clinical trials,[2,3] suggests that physicians may have been more cautious in prescribing olanzapine to patients at higher risk for diabetes. The point about the timing of the data seems irrelevant: (1) among patients treated with risperidone or olanzapine, less than 10% were treated with both of these antipsychotics; (2) patients were screened and eliminated if they showed evidence of diabetes in the 8 months prior to treatment with risperidone or olanzapine; and (3) observation periods were lagged 30 days to avoid assignment to the new antipsychotic of diabetes cases due to the prior therapy.

Lee and Fowler also question the reliability of the logistic estimates:

Method for determining odds ratios: the method (exponential) that was used to determine odds ratios for 12 months of exposure is not an assumption, but standard procedure for all continuous variables in logistic regression.[4] Because antipsychotic treatment durations varied, antipsychotic exposure was appropriately expressed as a continuous rather than a categorical variable. The estimated odds ratios for olanzapine and the other antipsychotics reflect 1 month of exposure. The suggestion that the 12-month odds ratios may be unrealistic because we extrapolated beyond the data is not supported. With 13% (not 7%) of treated patients having durations ≥ 12 months and another 16% having durations of 8 to 11 months, the data are sufficient for the model to give reasonable 12-month estimates. The 3.1 odds ratio indicates that patients treated for 12 months with olanzapine have 3 times the likelihood of acquiring type 2 diabetes than psychosis patients not treated with antipsychotics. This estimate is supported by the raw data in Table 1 of the article.[1] The ≥ 12-month relative frequency of diabetes for olanzapine is 7.1 versus 2.6 for untreated patients. The ratio of these relative frequencies is 2.73. Similarly, the 8- to 11-month relative frequency of diabetes for olanzapine is 4.2 versus 1.3 for untreated patients, with a ratio of 3.2.

Reliability of odds ratio estimates: while for treated patients antipsychotic exposure and length of observations were highly (though not perfectly) correlated, it does not follow that this affected the reliability of the odds ratio estimates for these variables. The estimates depend on the entire sample, which included untreated patients for whom this correlation was 0. Also, the meaning of the odds ratio for length of observation is misinterpreted. Being based on claims data, it does not strictly measure diabetes risk. The estimated odds ratio of 1.125 means that, in a population screened for preexisting diabetes, the odds of finding an individual with a claim for diabetes increased by 12.5% for each additional month of observation. In 6 months, the odds double: $(1.125)^6 = 2.03$. From the raw data in Table 1,[1] this rate of increase is not unrealistic. For untreated patients, who more purely reflect the effect of length of observation, the relative frequency of individuals with diabetes claims among those observed for < 4 months was 0, while it was 2.6 for those observed for ≥ 12 months.

Comparing odds ratios: because a direct test could not be performed with the same logistic model, the Woolf method was used to test whether the odds ratios for risperidone and olanzapine were statistically different from each other. Regardless of the commenters' discomfort with this method, logic should suffice to convince the reader that olanzapine has significantly higher odds of causing diabetes than risperidone. Olanzapine had estimated odds that were greater than untreated (significant at $p < .01$), while risperidone had estimated odds that were less than untreated (not significant). Therefore, it follows that the odds of developing diabetes during risperidone treatment are significantly less than those associated with olanzapine treatment.

I agree with Lee and Fowler that clinical trials are better suited for establishing causal relationships between antipsychotics and diabetes. I also agree that more retrospective studies using different data and different techniques would be helpful in establishing associations. Other retrospective studies have found olanzapine but not risperidone to be associated with higher risks of diabetes.[5,6]

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Evidence That Eicosapentaenoic Acid Is Effective in Treating Autism

Sir: There is evidence that eicosapentaenoic acid (EPA), an omega-3 fatty acid found in some dietary fish oil supplements, may be effective in the treatment of depression[1] and bipolar disorder.[2] There is also some evidence that omega-3 fatty acids may be effective as an adjunct therapy in the treatment of schizo-

phrenia,[3,4] although this evidence appears to be conflicting.[5] Since the symptoms of autism often include depression, affective instability with rapidly fluctuating mood states, and psychotic symptoms, and since pharmacologic treatments specifically target these symptoms, the efficacy of EPA supplementation as an adjunct therapy for autism is worthy of examination. We report a case in which addition of omega-3 fatty acid supplements to an existing pharmacologic regimen dramatically alleviated agitation and anxiety in an autistic child.

Case report. An 11-year-old white boy was diagnosed with autism at age 2.5 years and had had intensive therapy since that time, including applied behavior analysis and pharmacologic interventions. For the past several years, the most serious symptoms involved explosive outbursts and aggression, symptoms of mania and depression, anxiety, and obsessive thoughts. The patient was recently hospitalized in an inpatient psychiatric facility due to the severity of his symptoms. Prior to psychiatric hospitalization, he received paroxetine, 10 mg/day, for 1 year, and addition of lithium carbonate, 450 mg/day, for 9 months ameliorated the alternating manic and depressive symptoms. The explosive outbursts and aggression were partially alleviated with risperidone, 1.25 mg/day, for 3 months' duration, and topiramate, 50 mg/day, was added to help alleviate weight gain; these 2 medications were started 8 months after discharge.

After the patient's condition was stabilized on this regimen, the most significant remaining behavioral symptoms were extremely high levels of anxiety and agitation over insignificant events. This symptom was not extrapyramidal in nature and did not increase after escalation of the risperidone dose. Although risperidone prevented these symptoms from blossoming into violent outbursts, they still interfered significantly with the patient's daily life. He frequently became extremely anxious relating to his compulsive rituals and routines of autism regarding the time of day, repeating over and over, "It's one o'clock." A walk around the neighborhood would result in overwhelming anxiety over the fact that a particular store might be open or closed or a particular streetlight was on or off. He was often unable to complete lessons and other therapies due to his level of anxiety. The patient was also unable to undertake any activity that involved waiting, such as waiting in line in a store or for a movie, without becoming extremely anxious and agitated.

Fish oil supplements with omega-3 fatty acids were added, starting at 1 g/day and building to 3 g/day (540 mg of EPA/day) over a 4-week period. Complete elimination of the anxiety and agitation was reported by parents and clinician observation after 1 week at this level. His fixation and agitation about the time of day disappeared, along with his anxiety over routine, inconsequential events, and observations. Activities involving waiting were no longer a problem, with even extended waiting in line resulting in no increased anxiety. The alleviation of these symptoms led to a significant improvement in the overall quality of life for the patient, who now is able to attend to his lessons and participate in more normal daily life activities. These symptomatic improvements have continued undiminished for 8 months of follow-up.

On the basis of these intriguing clinical observations and other observations in the literature,[6] further controlled study of the efficacy of omega-3 fatty acids in the treatment of agitation, anxiety, and affective instability in autism seems warranted.

Dr. Hollander has been a consultant for, received grant/research support from, and been on the speakers or advisory boards for Solvay, Abbott, Wyeth, Pfizer, UCB Pharma, and Lilly. Mr. Johnson reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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They Could Have Named It "Bupopion"

Sir: Wake up all of you out there who write and pronounce it "buproprion"! If psychiatry is to be accepted fully as a branch of medicine, we should spell drug names correctly (bupropion). Here are a few examples of how off base we can get: a letter in the *American Journal of Psychiatry*, "Buproprion and Sexual Dysfunction"[1]; in a table in the *Lancet*, "Zyban (Buproprion)"[2]; in a letter from the Center for Population, Health, and Nutrition, Agency for International Development, "The buproprion study seems…"[3]; an abstract from the American Psychiatric Association Annual Meeting, "Male Sexual Dysfunction Induced by Buproprion Sustained Release"[4]; and a Web site, Virtual Hospital, Iowa Health Book, "Buproprion/Wellbutrin/Zyban."[5]

Some journals show cross-article consistency, perhaps imposed by copy editors: 3 articles in *Clinical Geriatrics* call it buproprion.[6–8] Some authors equivocate, as if spelling it both ways (buproprion and bupropion) will allow them to be correct half the time.[9(pp44,45)] Other authors appear to strive for fair balance by misspelling many drug names (e.g., citalpram, Ascendin, nefazadone, meclobamide, Tobamax, ozcarbazepine, Stalazine, and flurazaepam, as well as buproprion).[10]

Buproprion has an Internet following (2780 hits on Google) that fortunately is dwarfed by the real McCoy, bupropion (43,400 hits). Unfortunately, another variant, bupoprion turned up 48 times. The National Library of Medicine Internet Database (PubMed) had only 26 buproprions, versus 1013 bupropions, so it appears that formal journal articles usually get it right.

Elsewhere, the preferred generic name for the drug is amfebutamone, not bupropion; perhaps because the word contains no *r*'s so as not to confuse our European colleagues. All in all, I suppose it was probably worse back in the old days where few, if any, knew exactly where to place the *i*'s and *y*'s in amitriptyline (or is it amitryptiline?).

Dr. Jefferson is a consultant for, has received honoraria from, serves on the speakers or advisory boards for, and is a major share stockholder in GlaxoSmithKline.

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Clozapine and Pregnancy

Sir: This report is of a patient with chronic schizophrenia who was stabilized on clozapine and continued clozapine as a monotherapy throughout her pregnancy. The possible side effects of clozapine during pregnancy are highlighted.

Case report. Ms. A, a 22-year-old married woman from a low socioeconomic status and a rural background, presented with a history suggestive of schizophrenia onset 3 years previously, according to ICD-10 guidelines. She had been married for $2^1/_2$ years and had relapsed within 3 months of marriage. Following a lack of positive response to various typical antipsychotic drugs and electroconvulsive therapy, she was switched to clozapine, initially 12.5 mg/day, which was later increased to 75 mg/day with proper monitoring of leukocyte counts. Her negative symptoms subsided with treatment, and she was less withdrawn at follow-up.

One year ago, after remaining well stabilized on clozapine treatment for 3 months, Ms. A conceived for the first time, but her pregnancy was not detected until the end of the first trimester. The patient and her husband were counseled on the possible risk to the fetus; however, they decided to continue the pregnancy along with clozapine therapy. On 2 occasions the patient's dose was reduced—once from 75 mg to 50 mg and once from 75 mg to 62.5 mg—during the first and second trimesters, respectively, but both times she relapsed within 72 hours of dose reduction. Her relapses were characterized by withdrawn behavior, refusal to eat, insomnia, lying in a prone position, and sitting in one place continuously for 3 to 4 hours. These exacerbations continued for 4 days; therefore, the patient's dose was increased, and she was maintained at 75 mg/day. Even during the recovery phases she was indifferent toward her pregnancy, particularly in eating. She was registered in an antenatal clinic in the 13th week of pregnancy but stopped attending after the 5th month of pregnancy.

Routine laboratory investigations, including blood sugar, were performed and all the findings were within the normal range. The relatives of the patient reported that her weight gain was appropriate to the gestational age of her fetus; however, she never reported fetal movements. She attended a psychiatry clinic once every 4 to 6 weeks until the eighth month of gestation, and hematologic monitoring was performed every 6 to 8 weeks.

She was brought to the hospital in labor with leaking per vagina at 9 months and 9 days of gestation. Ultrasound examination confirmed a fetus of 32 weeks' gestation with intrauterine growth retardation, oligohydramnios, and absence of fetal heart sound. She delivered a macerated stillborn male baby weighing 2.2 kg (4.9 lb) with no gross congenital anomalies.

The introduction of atypical antipsychotic drugs such as clozapine and the increasing pregnancy rate among women with psychotic disorders have led to greater attention being paid to the treatment of such cases and the effects of such treatment on the fetus. A review of clozapine exposure during pregnancy revealed 10 cases of congenital malformations or perinatal syndromes in 61 children.[1] This review is not conclusive, however, as some of the mothers had also taken other medications during pregnancy. Further, it was suggested that the accumulation of clozapine in fetal serum might be a risk factor for floppy infant syndrome[2] and neonatal seizure.[3] New onset or worsening of gestational diabetes with shoulder dystocia has also been reported in patients taking clozapine.[4,5] In contrast, some case reports have shown no congenital anomalies with clozapine therapy in animals and humans.[6] We suggest that the approach to clozapine use during pregnancy should be cautious.

In conclusion, in our case it is not clear whether clozapine, the disease process, poor nutrition, or lack of antenatal care or a combination of all these factors contributed to the outcome of this pregnancy.

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

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Nonalcoholic Steatohepatitis: A Possible Side Effect of Atypical Antipsychotics

Sir: Some studies and case reports suggest that patients treated with atypical antipsychotics (especially clozapine and olanzapine) are at increased risk not only for weight gain but also for developing diabetes and serum triglyceride elevations.[1,2] The concurrence of obesity, diabetes, hyperlipidemia, and hypertension in the same individual is known as "metabolic syndrome." Another condition with areas overlapping with the metabolic syndrome is nonalcoholic steatohepatitis (NASH), which is defined as fatty liver with histologic features of inflammation and necrosis in individuals who do not drink significant amounts of alcohol.[3] Clinical features of NASH are hepatomegaly and mild-to-moderate elevations of serum glutamate pyruvate transaminase (SGPT) and/or serum glutamic-oxaloacetic transaminase (SGOT). Obesity, diabetes mellitus type 2, hyperlipidemia, and treatment with several drugs are the main risk factors for the development of NASH. Until now, amineptine and sodium valproate have been the only psychotropic drugs known to be possible causes of NASH.[4] The following case report describes 3 patients who developed NASH during treatment with atypical antipsychotics.

Case report. Patients were selected from a sample of 51 outpatients with ICD-10 schizophrenic disorder who had normal liver function before treatment with atypical antipsychotics was started. Data were gathered from 1997 to 2001. Demographic, clinical, and laboratory data are summarized in Table 1. Increase of liver enzymes was detected by routine laboratory testing in months 5, 9, and 15 of treatment. Weight gain and hyperlipidemia were clinically significant in all 3 patients. Ultrasound showed hepatomegaly and "bright liver."* Alcoholic, viral, and immunologic reasons for steatohepatitis were excluded. In patients 1 and 2, liver enzyme elevation was slowly progressive. Patient 3 succeeded in reducing his weight. Both NASH and hyperlipidemia improved within 4 months in patient 3.

Transient liver enzyme increase during the first weeks of treatment with atypical antipsychotics is a well-known side effect of olanzapine and risperidone. To our knowledge, increase of liver enzymes after months of treatment with new atypical antipsychotics has not been reported until now. The main argument strongly suggesting that NASH was induced by antipsychotic treatment is the association with weight gain and hyperlipidemia. NASH is probably mediated by metabolic changes as a result of antipsychotic treatment.

In many cases, NASH is a benign condition. However, progression from steatohepatitis to cirrhosis is possible. Clinicians should be aware that patients who need long-term treatment with atypical antipsychotics might be at increased risk for NASH.

Dr. Haberfellner has been an advisory board member for Eli Lilly, Pfizer, and AstraZeneca. Dr. Honsig reports no financial affiliation or other relationship relevant to the subject matter of this letter.

*The term *bright liver* is used in 2 ways: (1) an ultrasonographic pattern with evident contrast between hepatic and renal parenchyma and (2) the so-called bright echotexture where the liver is more echogenic than the kidneys, produced by fatty droplets within the hepatocytes.

Table 1. Demographic, Clinical, and Laboratory Data for 3 Patients With Nonalcoholic Steatohepatitis

Variable	Patient 1	Patient 2	Patient 3
Sex	Male	Male	Male
Age at study entry, y	24	30	31
Pretreatment drug	Flupenthixol	Flupenthixol	None
Antipsychotic drug	Olanzapine, 10 mg	Risperidone, 8 mg	Olanzapine, 10 mg
Observation period	48 mo	45 mo	46 mo
Liver test results, maximum values, U/L			
SGOT	48	22	21
SGPT	91	72	47
GGT	52	26	40
Cholesterol, mg/dL	256	360	351
Triglycerides, mg/dL	477	403	339
Weight gain (%), kg	31 (26.7)	21 (24.7)	20 (26.7)

Abbreviations: GGT = γ-glutamyltransferase, SGOT = serum glutamic-oxaloacetic transaminase, SGPT = serum glutamate pyruvate transaminase.

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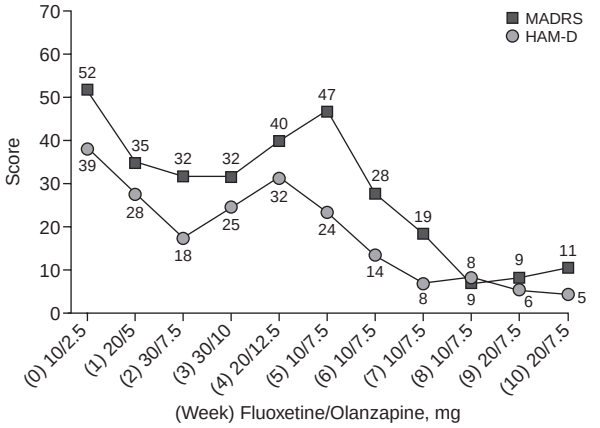
Fluoxetine Augmentation With Olanzapine for Treatment of Chronic Resistant Depression in an Elderly Patient: A Case Report

Sir: Recent consensus treatment guidelines for resistant geriatric depression suggest various multiple antidepressant combination strategies after failed trials with single agents.[1] Thus, we read with interest the article by Shelton et al.[2] about the augmentation of fluoxetine with olanzapine for resistant major depression. We describe the case of a geriatric patient with depression who had been poorly responsive to all treatments over the past 18 years.

Case report. Mr. A, a 76-year-old man, was forced into premature retirement in 1984 due to DSM-IV major depressive disorder, recurrent. He experienced recurrent acute psychiatric hospital admissions with multiple medication trials (e.g., most recently mirtazapine, 45 mg once daily, augmented with quetiapine, 100 mg once daily, and modafinil, 150 mg once daily; citalopram, 40 mg once daily, augmented with quetiapine, 100 mg once daily, and dextroamphetamine, 10 mg b.i.d.) and electroconvulsive therapy (ECT) without ever achieving full remission. Although inpatient and maintenance ECT provided the best results, the patient became ECT refractory. His medical history included a past 46-pack/year cigarette history, hyper-

Figure 1. Ten-Week HAM-D and MADRS Scores With Corresponding Medication Dosages for a 76-Year-Old Patient With Chronic Resistant Depression Treated With Fluoxetine Augmented With Olanzapine



Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

lipidemia, chronic lower extremity venous insufficiency, 1 to 2 daily cocktails, and chronic oral-buccal tardive dyskinesia. Reports from his reliable spouse, liver function tests, and mean corpuscular volume results did not suggest alcohol abuse.

Prior to his most recent psychiatric admission for depression with suicidal ideations, he had stopped his hobbies of painting and playing bridge. He also exhibited insomnia, poor appetite, extreme lethargy, anhedonia, seclusion, hopelessness, and helplessness. On admission, he received inpatient ECT and was started on treatment with venlafaxine extended release (XR). Because he did not have an optimal response on discharge, we switched him to fluoxetine augmented with olanzapine.[2]

Following his last acute psychiatry admission with a poor response to ECT and venlafaxine, his baseline 21-item Hamilton Rating Scale for Depression (HAM-D) score was 39 and his Montgomery-Asberg Depression Rating Scale (MADRS) score was 52. Dosing was started at 10 mg once daily of fluoxetine and 2.5 mg q.h.s. of olanzapine (Figure 1). Extensive clinical and laboratory examinations revealed no cognitive impairment and normal glucose and lipid levels aside from a minimally elevated low-density lipoprotein level (102 mg/dL). The patient was seen weekly for 10 weeks to assess response to the medications based on clinical observation and HAM-D and MADRS results.

At the 2-week follow-up, the patient denied suicidal ideations, exhibited a dry sense of humor, and had markedly improved sleep and reduced somatic complaints. He stood erect, made better eye contact, smiled, and walked with more vigor.

Fluoxetine and olanzapine doses were increased with the goal of continuing the improved mood and affect. However, at weeks 3 and 4 the patient demonstrated a continual increase in agitation and worsening of mood and affect. Therefore, fluoxetine and olanzapine dosages were tapered to 10 mg once daily and 7.5 mg q.h.s., respectively (Figure 1). At week 5, lorazepam, 0.25 to 0.5 mg t.i.d. p.r.n., was added to help modulate the agitation. The patient's wife called the day following the start of the lorazepam to say that the patient had demonstrated a dramatic response. He had resumed driving, spontaneously invited acquaintances in to see his paintings (first time in many years), and demonstrated a marked improvement in mood and affect. While the addition of lorazepam could explain the effect, it was probably incidental. The patient continued to be more spontaneous, without complaints of inner tension, with improved appetite, resolution of insomnia, and cessation of suicidal ideations. At week 10, fluoxetine was increased to 20 mg once daily to improve his energy. Cognitive and laboratory measures were essentially unchanged from baseline levels.

This case demonstrates that the combination of fluoxetine and olanzapine may have potential for geriatric patients with chronic, severe, resistant nonpsychotic depression. As Shelton et al.[2] reported in a younger population, there was a rapid onset of action as evidenced by first and second week HAM-D and MADRS scores (Figure 1). It is hypothesized that the medications have a synergistic effect on increasing central nervous system levels of norepinephrine and dopamine.[2,3]

Olanzapine augmentation of fluoxetine may offer a better tolerated treatment protocol for resistant depression than lithium augmentation of selective serotonin reuptake inhibitors in the geriatric population, given the common finding of comorbid illnesses and polypharmacy problems. The effectiveness of augmenting fluoxetine with olanzapine for resistant depression in geriatric patients merits additional investigation.

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

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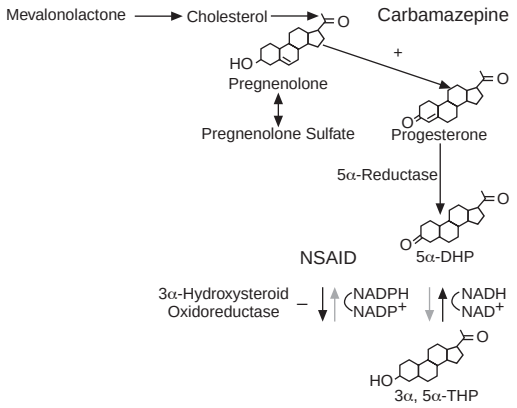
Carbamazepine Treatment of Adverse Psychiatric Effects After Treatment With the Nonsteroidal Anti-Inflammatory Drug Piroxicam

Sir: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of pain. Besides the common gastrointestinal and renal adverse effects of these drugs, there are also reports of psychiatric side effects such as affective disorders, psychotic symptoms, and sleep disturbances.[1] These central nervous side effects of NSAIDs most frequently occur during indomethacin treatment.[2] Nevertheless, there are also some case reports of psychiatric side effects after treatment with other NSAIDs.[3]

The NSAID piroxicam has anti-inflammatory, analgesic, and antipyretic properties. Its mode of action is not fully understood, but like indomethacin it inhibits the biosynthesis of pros-

Figure 1. Biosynthesis of Neuroactive Steroids and Site of Action of NSAIDs and Carbamazepine



Abbreviations: DHP = dihydroprogesterone, NAD^+ = oxidized form of nicotinamide-adenine dinucleotide, NADH = reduced form of nicotinamide-adenine dinucleotide, NADP = nicotinamide-adenine dinucleotide phosphate, $NADP^+$ = oxidized form of NADP, NADPH = reduced form of NADP, NSAID = nonsteroidal anti-inflammatory drug, THP = tetrahydroprogesterone.

taglandins. Possible central nervous side effects are depression, insomnia, agitation, akathisia, hallucinations, and mental confusion. The pathophysiologic mechanisms underlying the psychiatric side effects of NSAIDs remain unclear so far. Thus, only symptomatic treatment has been available.

Certain metabolites of progesterone such as 3α,5α-tetrahydroprogesterone and 3α,5β-tetrahydroprogesterone are potent allosteric modulators of γ-aminobutyric acid A ($GABA_A$) receptors.[4] These 3α-reduced neuroactive steroids have been shown to exert sleep modulatory, anxiolytic, anticonvulsant, and antidepressant properties in animals and humans.[4] A sudden drop in these neuroactive steroids, e.g., during the postpartum period, has been suggested to contribute to the pathophysiology of psychiatric symptoms.[4] 3α-Reduced neuroactive steroids are derived from progesterone by 5α-reduction into 5α-dihydroprogesterone and 5β-dihydroprogesterone.[4] These 5α-pregnane steroids may be further reduced into the GABA-modulating steroids 3α,5α-tetrahydroprogesterone and 3α,5β-tetrahydroprogesterone by 3α-hydroxysteroid-oxidoreductase[4] (Figure 1). NSAIDs such as indomethacin are inhibitors of 3α-hydroxysteroidoxidoreductase. Carbamazepine has been shown to increase the concentrations of progesterone and subsequently of 3α-reduced neuroactive steroids in experimental animals in a dose- and time-dependent fashion[5] (Figure 1). Therefore, we investigated whether treatment with carbamazepine might be an effective way to counteract NSAID-induced disturbances of neurosteroidogenesis and therefore be suitable for the treatment of NSAID-induced psychiatric symptoms.

Case report. Mr. A, a 72-year-old male patient, was hospitalized in 2001 after a 14-day history of acute onset of akathisia, hallucinations, insomnia, agitation, and anxiety. The patient reported free-floating anxiety, feelings of tension, and sleeping difficulties. He did not sleep during the last nights prior to hospital admission, because when he was falling asleep he always experienced fearful visual hypnagogic hallucinations. Due to coxarthrosis, Mr. A was treated with intramuscular injections of piroxicam 3 weeks prior to hospital admission. The patient's symptoms were the second onset of psychiatric symptoms in his life history.

Fifteen years ago, the patient developed a depressive episode with psychotic symptoms during treatment with corticosteroids. At that time, the patient was depressed, agitated, and anxious and suffered from hypochondriacal delusions. None of those symptoms had occurred before. That depressive episode was symptomatically treated with doxepin and benzodiazepines and remitted after 4 weeks, but the patient showed severe withdrawal symptoms after discontinuation of benzodiazepines at that time.

Besides the arthrosis, Mr. A suffered from no other illness, nor did he take any other drugs. All laboratory test results were within normal limits, as were electrocardiogram, electroencephalogram, and magnetic resonance imaging results. In view of the acute onset of psychiatric symptoms together with NSAID treatment and given the fact that the patient experienced only 1 depressive episode in relation to corticosteroid treatment in his lifetime history, we assumed a relationship between psychiatric symptoms and NSAID treatment.

Full remission of symptoms occurred after 7 days of treatment with carbamazepine at a daily dose of 400 mg. The patient's serum carbamazepine level was 5.9 μg/mL after 1 week of treatment. Continuation of carbamazepine treatment was recommended for 6 months.

Our patient responded to treatment with carbamazepine and experienced a complete remission of symptoms within 1 week. It is likely that the reported psychiatric symptoms were a consequence of treatment with NSAIDs, since there were no psychiatric symptoms in the patient's life history without relation to drug treatment. Additionally, the depressive episode reported 15 years ago was a consequence of treatment with corticosteroids.

Although neuroactive steroids were not quantified before and after treatment in our patient, it may be hypothesized that the interference of NSAIDs with the generation of endogenous neuroactive steroids is one of the mechanisms underlying NSAID-induced psychiatric symptomatology. Drugs enhancing the concentration of endogenous neuroactive steroids such as carbamazepine[5] or selective serotonin reuptake inhibitors[6,7] may therefore be suitable for the treatment of NSAID-induced psychiatric symptoms such as anxiety, agitation, depression, or sleep disturbances. Even if NSAID-induced psychiatric side effects are frequently transient and disappear after NSAID withdrawal, an effective treatment is lacking so far for patients with prolonged symptomatology such as our patient, in whom symptoms persisted despite the fact that the last injection of NSAIDs was 3 weeks prior. Moreover, there are a few case reports describing an exacerbation of preexisting psychiatric disorders during NSAID treatment.[3,8] Especially in those vulnerable psychiatric patients, an effective treatment strategy would be essential if NSAID treatment must be continued for clinical reasons.

Although the present case report does not prove that the beneficial effects of carbamazepine in this individual patient are related to the elevation of GABAergic neuroactive steroids, the neurosteroidogenic potential of carbamazepine should be considered a novel therapeutic strategy for the treatment of NSAID-induced psychiatric symptoms that warrants systematic research in clinical trials, including measurements of neuroactive steroids before and after treatment.

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