

QT Interval Prolongation in Patients on Methadone With Concomitant Drugs

To the Editors:

A variety of well-known cardiac and noncardiac medications like psychotropic drugs prolong the QT interval and can trigger episodes of ventricular arrhythmia such as torsade de pointes (TdP). Blockade of a human cardiac K^+ channel is a frequent underlying mechanism through which many drugs produce QT interval prolongation and associated ventricular arrhythmia.

As the occurrence of TdP could be enhanced by increased drug concentration, any pharmacokinetic drug interaction leading to a reduction of the clearance of the responsible drug may increase the risk of TdP.¹ Predisposing factors such as long QT syndromes may result from mutations of genes encoding ion channels or proteins modulating channel function. These mutations can lead to phenotypic polymorphism, and a normal QT interval could become prolonged in presence of additional factors disturbing cardiac repolarization like electrolytes abnormalities or drugs modifying the QT interval.¹

We report a QT interval prolongation in 10 patients (8 males and 2 females) on oral methadone maintenance treatment with daily doses ranging from 14 to 360 mg/d (Table 1). These cases were collected over a period of 3 years (2000 to 2002) in the Geneva University Hospital. Three patients presented a TdP, 2 presented a ventricular tachycardia, and 1 presented a bigeminy. In the 4 asymptomatic patients, an electrocardiogram was done as a routine investigation because of an infection in

3 of them and dizziness in 1. Pharmacokinetic or pharmacodynamic drug interactions likely to enhance methadone cardiac adverse effect were present in 9 patients.

As the hepatic metabolism of methadone is mainly mediated by CYP3A4, a pharmacokinetic interaction was assumed with the use of inhibitors such as clarithromycin, fluconazole, indinavir, nifedipine, ritonavir, and valproate. Pharmacodynamic cardiac interaction was suspected with concomitant medications described as prolonging the QT interval: chlorprothixen, citalopram, clarithromycin, cocaine, cotrimoxazole, efavirenz, fluconazole, mianserine, olanzapine, and sertraline.²⁻⁵ In some patients, the QT interval prolongation decreased either when the methadone dosage was reduced or when the suspected concomitant drug was stopped as clarithromycin in 1 case. A switch from methadone to morphine was decided in 6 patients on a persistent QT interval prolongation. An important observation was that QT interval returned to normal values in all patients in whom a switch from methadone to morphine was done. Thus, QT prolongation is an adverse effect that occurs with methadone and its structurally related congeners, acetylmethadol and propoxyphen,^{6,7} but this phenomenon is not a feature seen with "natural" opioid.

The impact of some opioids on cardiovascular arrhythmic events has been suspected for years. Based on published reports on fatalities related to methadone maintenance treatments, a review pointed out that about half of the deaths occurred during the dose-finding period,⁸ and a report mentioned 10 heroin addicts' deaths at the start of a methadone maintenance program.⁹ A retrospective review of electrocardiogram recordings of patients treated with intravenous methadone reported a QT prolongation in 17% of them, and a sudden death was observed in 2 patients.

The authors showed that methadone and the chlorbutanol used as a preservative agent caused dose-dependant blockage of HERG current.¹⁰ A recent retrospective case series documented 17 TdP in patients from a methadone maintenance program or from a chronic pain clinic receiving high doses of methadone.¹¹ As patients on maintenance treatment may still use illicit drugs, it is important to note that cocaine and cocaethylene, a potent metabolite of cocaine and alcohol, both inhibit HERG channels at concentration similar to what might be observed in plasma of humans who simultaneously ingest these drugs.^{4,12,13} Thus, cocaine as well as cocaethylene inhibition of HERG channels may prolong the long QT interval and contribute to potentially lethal cardiac arrhythmia. An online search of the World Health Organization database showed that among 2294 spontaneously reported adverse effects with the use of methadone, 66 (2.8 %) reactions were classified as heart rate and rhythm disorders [among these were TdP (n = 8), ventricular tachycardias (n = 3), QT prolongations (n = 5), ventricular fibrillations (n = 2), and cardiac arrests (n = 20)], but the scarcity of data prevented the interpretation of the causal relationship.

In conclusion, these clinical observations supply further evidence that methadone prolongs the QT interval in some patients and can lead to arrhythmias such as torsade de pointes particularly when using high doses, after direct intravenous administration, or when associated with concomitant medication inhibiting methadone hepatic clearance. Pharmacodynamic interactions may also increase the risk of arrhythmia when concomitant medications modifying cardiac repolarization are used as well as in the presence of other risk factors for QT prolongation. Despite the lack of a control group, the reversible QT prolongation seen in our patients is highly suggestive of a clinically important and

TABLE 1. Patients' Characteristics and Medication

Gender/Age	Drugs	ECG Modifications and Symptoms	Comorbidities	Evolution
M/36	M (360) Bromazepam (50) Cocaine*	QTc: 0.66; bigeminitis after cocaine injection	Hepatitis C	↓M (200), QTc: 0.54 Stop M switch to Mo (300), QTc: 0.40
F/31	M (230) Atenolol (25) Clorazepate (40) Magnesium (15) Sertraline* (50)	QTc: 0.62 (after sertraline) asymptomatic	Hepatitis C, HIV+	Stop M and sertraline; switch to Mo (900), QTc: 0.39
F/36	M (180) Chlorprothixene* (15) Efavirenz* (600) Fluconazole* [†] (week) Flunitrazepam (1 g) Lopinavir (1064) Lormetazepam (2 g) Mianserine* (30) Oxazepam (15) Ritonavir [†] (264) Zidovudine (600)	QTc: 0.64; VT, TdP	Hepatitis C, AIDS grade C2	↓M (160) Stop tritherapy and fluconazole and mianserine, QTc: 0.55; stop M, switch to Mo (660), QTc: N; at 1 year Mo (660), QTc, 0.45
M/40	M (140) Abacavir (600) Ceftriaxone (2 g) Clarithromycin* [†] (1 g) Flurazepam (30) Lamivudine (300) Lopinavir (800) Lorazepam (2.5) Olanzapine* (10) Ritonavir [†] (200)	QTc: 0.48; asymptomatic	Hepatitis C, AIDS grade A2, hypokalemia	Stop clarithromycin; QTc: N
M/38	M (130) Furosemide (40) Omeprazole (20) Vitamin K (10)	QTc: 0.5; VT	Hepatitis C, cirrhosis, AIDS grade B2, hypokalemia, and magnesiumemia	No change after correction of electrolytes; stop M, switch to Mo (160), QTc: 0.42
M/39	M (115) Oxazepam (200) Valproate [†] (1 g)	QTc: 0.48; VT, TdP	Hepatitis C, AIDS grade A2, chronic alcoholism	Stop M, QTc: 0.41, rechallenge with M (40), QTc: 0.49; stop M switch to Mo (400), QTc: 0.44
M/42	M (90) Cotrimoxazole* (3/w) Indinavir [†] (600) Lamivudine (300) Zidovudine (500)	QT prolongation; VT, TdP	AIDS (grade unknown)	Stop M & tritherapy, correction hypomagnesemia no change ad pacemaker
M/33	M (80) Butamirate (45) Citalopram* (20) Midazolam (15) Nifedipine [†] (60) Omeprazole (20) Oxazepam (60) Rofecoxib (50)	QTc: 0.59; VT	Hepatitis B and C, “long time nonprogression” HIV, hemophilia, minor thalassemia, chronic alcoholism	↓M (50 mg/d) associated to Mo (200), QTc: 0.44

(continued)

TABLE 1. (Continued)

Gender/Age	Drugs	ECG Modifications and Symptoms	Comorbidities	Evolution
M/40	M (45) Atovaquone (7.5) Azithromycine (1250/w) Fluconazole*† (200)	QTc: 0.51; asymptomatic	Hepatitis C, AIDS grade C3	No change after correction of electrolytes; stop fluconazole, maintenance of M (45), QTc: 0.51
M/41	M (14) Amoxicilline-clavulanate (1.8 g) Cotrimoxazole* (3/w) Hydroxyzine (25) Imipenem (2 g) Midazolam (15) Omeprazole (40)	QTc: 0.54; asymptomatic	Hepatitis C, AIDS grade A3, chronic alcoholism	Stop M, switch to Mo (40), QTc: 0.41

QT interval corrected by heart rate (QTc) according to Bazett formula expressed in seconds.¹⁴

Abbreviations: ECG indicates electrocardiogram; N, normal; M, methadone; Mo, morphine, (dose mg/d); TdP, torsade de pointe; VT, ventricular tachycardia; hepatitis were all chronic active.

*Pharmacodynamic interaction.

†Pharmacokinetic interaction.

independent effect of methadone on cardiac repolarization. Therefore, further studies should determine whether electrocardiogram monitoring would be mandatory when introducing or increasing methadone doses as well as when suspecting any pharmacokinetic or pharmacodynamic interactions.

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Amoxapine in Schizophrenia

A Negative Double-Blind Controlled Trial

To the Editors:

Several lines of evidence suggest that the antidepressant medication amoxapine may have therapeutic potential as an atypical antipsychotic including receptor occupancy studies showing that it blocks serotonin 5HT₂ receptors as well as dopamine D₂ and D₄ receptors.^{1,2} In an open-label study of amoxapine in patients with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* schizophrenia, amoxapine had a beneficial effect on positive and negative symptoms with minimal side effects.³ The aim of this study was to assess the therapeutic efficacy of amoxapine in patients with schizophrenia using double-blind trial methods.

Ten patients with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of schizophrenia were recruited from 2 general catchment area-based psychiatric services who had moderately severe psychotic symptoms and who did not have significant depression or other comorbid conditions. The study was approved by the Human Research and Ethics Committees of Southern Health and The Alfred Hospital. Patients were randomized to identical capsules containing either 75 mg of amoxapine or 5 mg of olanzapine. All subjects received 1 capsule for 5 days followed by 2 capsules for 9 days. From day 14 until the end of the trial (8 weeks), the dose could be adjusted based on clinical need between 2 and 4 capsules per day (150 to 300 mg/d of amoxapine or 10 to 20 mg/d of olanzapine). Other antipsychotic medications as well as antidepressants and mood stabilizers were not allowed during the trial after the first week allowing preexisting medications to be ceased. Concomitant treatment with benzodiazepines was allowed. Assessments made by blind raters included the Positive and Negative Syndrome scale,⁴ Montgomery-Åsberg depression rating scale,⁵ Simpson Angus scale for extrapyramidal symptoms,⁶ and the Barnes Akathisia scale.⁷ Recordings were also made of weight, plasma prolactin, triglycerides, and cholesterol.

Five patients were randomized to each group. There were no differences between the 2 groups in age or sex. There were no differences between the groups in baseline Positive and Negative Syndrome scale total scores, positive, or general symptom scores, but the olanzapine group had a greater degree of negative symptoms (24.8 ± 5.5 vs. 17.2 ± 4.3 , $t(8) = 2.4$, $P < 0.05$). All 5 of the patients in the olanzapine group completed the 8 weeks of the trial. Across the 8 weeks, there was a significant improvement in positive symptoms [baseline 20 ± 4.5 vs. 8 weeks 13.8 ± 4.5 , $t(4) = 6.1$, $P < 0.005$], negative symptoms [24.8 ± 5.5 vs. 19.4 ± 4.9 , $t(4) = 5.8$, $P < 0.005$], and general symptoms [40.4 ± 3.5 vs.

34.4 ± 2.5 , $t(4) = 6.3$, $P < 0.005$]. Of the 5 patients receiving amoxapine, none completed the 8 weeks of the trial. Four of the subjects were withdrawn between weeks 4 and 7 due to lack of efficacy. A fifth subject was withdrawn due to pending imprisonment due to an offence unrelated to the trial or his illness. At the time of his withdrawal (after 6 weeks of treatment), there had been a worsening of his overall condition (11-point increase in total Positive and Negative Syndrome scale score from baseline). Analysis of change in psychopathology scores for this group (last completed visit vs. baseline) showed no change in positive, negative, or general symptoms or total Positive and Negative Syndrome scale scores. Comparing clinical response between the 2 groups (change from baseline to study end, last observation carried forward), the olanzapine group achieved a significantly greater improvement in positive ($P < 0.005$) and negative symptoms ($P < 0.05$). There was no significant difference between the groups in any side effect measure.

The major limitation of the study is the sample size and the high withdrawal rate in the amoxapine group. The planned sample size was 30 patients (15 in each group); however, due to the high discontinuation rate in the first 10 patients recruited, an interim analysis was performed. Once it became apparent that all of the discontinuations had occurred in 1 group and the differences between the groups were statistically reliable, the blind was broken and the study ceased. While the small sample size urges caution regarding a firm conclusion, lack of sufficient power is unlikely to be a major confound as no subject receiving amoxapine made any significant degree of response and all received at least 4 weeks of treatment. It is also possible that despite these negative results, amoxapine would show therapeutic potential in other circumstances. For example, the patients in this study had a considerably longer duration of illness (approximately 9 years) than those in the study of Apicquian et al³

(approximately 2 years), and the escalation of the dose was also slower. While the dose range for amoxapine used in this study was lower than that in which it was commonly prescribed as an antidepressant (225 to 450 mg/d), it was similar to the dose shown to produce atypical antipsychotic equivalent levels of dopamine D₂ and 5HT₂ receptor occupancy in normal controls. It is possible that higher doses may be required in patients with longer histories of antipsychotic exposure due to receptor up-regulation secondary to previous treatment.

The results of this pilot study do not support the antipsychotic effectiveness of amoxapine in schizophrenia. It is unclear why its "antipsychotic" pattern of receptor occupancy has not resulted in more substantial clinical effects.

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Brain Activation During Affective Visual Cues in Schizophrenia A Pilot Study Using fMRI

To the Editors:

Affective symptoms such as anhedonia and affective blunting are core features of schizophrenia. The neural basis of these symptoms has been studied¹ but remains incompletely characterized. The current generation “atypical” antipsychotic medications are more effective in this symptom domain than were first generation antipsychotics, although treatment effect size remains modest.² While much is known about the neurochemistry of these medications at the receptor level,³ the effects of antipsychotic treatment on brain function are less clear. Advances in the treatment of these symptoms would be welcome, as reduction of affective symptoms results in improved social function and enhanced quality of life for individuals with schizophrenia.⁴

Functional magnetic resonance imaging (fMRI) has emerged as a useful tool for exploring the neural basis of affective processing in normal individuals and in individuals with psychiatric illnesses, including schizophrenia.^{5–9} While many fMRI studies of schizophrenia have tested subjects who were receiving antipsychotic medication, only a few have directly addressed the effects of pharmacotherapy.^{10–12} Pharmacologic

fMRI studies of disorders other than schizophrenia demonstrate the utility of the methodology and suggest approaches that could be adapted to the study of antipsychotics. For example, Davidson et al¹³ studied the brain activation induced by negative affective stimuli in depressed patients and noted components of the response that change within 2 weeks of treatment with antidepressants. The degree of anterior cingulate activation in response to negative stimuli before treatment predicted subsequent response to antidepressant treatment.

Our group is developing fMRI studies regarding the treatment of affective symptoms in schizophrenia. We are reporting a pilot study designed to assess the feasibility of using moderately pleasant or unpleasant pictures to differentiate brain processing of hedonic responses in subjects with schizophrenia and normal controls by use of fMRI. Our hypothesis for this study has been that differential processing of pleasant and unpleasant pictures in subjects with schizophrenia and controls would be demonstrable by fMRI. The literature suggested limbic structures (particularly the amygdala and cingulate cortex) and frontal cortex as areas of particular interest.

This study was approved by the Oregon Health & Science University institutional review board. All subjects gave written informed consent. Images were selected from the International Affective Picture System¹⁴ in 3 categories based on population norms of the affective valence of each picture: pleasant, neutral, and unpleasant. The pictures resembled those found in general interest magazines.

Subjects were scanned at 1.5 T with a GE scanner. Two moderate-resolution anatomic scans were followed by 6 runs of functional scanning using a block design (TR = 2000 milliseconds, 8 slices, axial orientation, slice width 10 mm, matrix 64 × 64, FOV 24, most superior slice coverage beginning just cephalad of the cingulate gyrus). During functional runs, images were presented

on video goggles. Each run consisted of 6 groups of 5 sequential pictures of similar affective valence (pleasant, neutral, or unpleasant). Within each sequence, each picture appeared for 2 seconds. A 10-second fixation screen (blank field with a centered fixation cross) preceded the first sequence of pictures. Following each block of pictures, a 6-second text screen prompted subjects to rate the preceding pictures as very pleasant, somewhat pleasant, somewhat unpleasant, or very unpleasant, by pressing corresponding buttons on a box which rested under the subject’s right fingers. Each scanning run presented 2 sequences of pictures from each of the 3 affective valence categories. The order of the affective category sequences was counterbalanced between the runs.

Data were analyzed with Brain-Voyager 4 software (Brain Innovation BV, Maastricht, The Netherlands). Following visual inspection for integrity of data and gross head motion, minor head motion was corrected using a 3-dimensional preprocessing algorithm. Statistical 2-dimensional maps were prepared for each slice from each subject showing linear correlation analysis of sequences of unpleasant versus pleasant pictures. Two-dimensional data were combined to form a 3-dimensional data set, spatially transformed into Talairach space, and the statistical analysis was repeated.

(See Table 1). Five subjects who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for chronic schizophrenia (1 female, 4 male; age = 25.2 ± 8.1 [mean ± SD] years, range 19 to 35 years) completed the scanning protocol. Positive and Negative Syndrome Scale scores indicated moderate psychotic symptoms: total Positive and Negative Syndrome Scale score = 62.2 ± 18.7 (mean ± SD, range 48 to 88). All of these subjects were living in the community and were receiving pharmacologic treatment. Five control subjects with no history of psychiatric disorder also completed the scanning protocol

TABLE 1. Areas of Differential Brain Activation While Viewing Pleasant or Unpleasant Pictures

Subjects No.	Group	Age (Year)	Sex	Total PANSS Score	Medication*	Location and Direction of Activation [†]	<i>P</i> [‡]
1	Control	26	M	—	—	R frontal	P>U 0.006
						Post cingulate	P>U 0.004
						R basal ganglia	P>U 0.006
2	Control	29	M	—	—	L temporal	P>U 0.007
						L occipital	U>P 0.004
						R occipital	U>P 0.005
3	Control	33	M	—	—	R frontal	U>P 0.02
						R post cingulate	P>U 0.01
						R occipital	P>U 0.001
4	Control	32	F	—	—	L caudate	U>P 0.01
						R occipital	U>P 0.024
5	Control	26	M	—	—	R parietal	P>U 0.002
						R occipital	U>P 0.009
						L occipital	U>P 0.004
6	Schiz	19	M	52	Quetiapine, 150 mg every other day	R basal ganglia	P>U 0.0001
						L basal ganglia	P>U 0.0002
						R occipital	U>P 0.0002
						L occipital	U>P 0.0002
7	Schiz	19	M	48	Ziprasidone, 40 mg daily	R parietal	U>P 0.0001
						R occipital	U>P 0.0001
8	Schiz	33	M	47	Ziprasidone, 20 mg daily	L frontal	P>U 0.005
						R temporal	P>U 0.01
						R Post cingulate	U>P 0.009
						L parietal	U>P 0.01
9	Schiz	20	F	76	Ziprasidone, 160 mg/d	L frontal	U>P 0.001
						L/R midcingulate	P>U 0.0003
						Cerebellum	U>P 0.0005
10	Schiz	10	M	88	Ziprasidone, 160 mg/d	L/R midcingulate	P>U 0.02
						R temporal	U>P 0.008
						L temporal	U>P 0.02
						R occipital	U>P 0.006

PANNS, positive and Negative Syndrome Scale.

*Self report of actual use, doses below the usual therapeutic range (subjects 6 to 8) reflect partial compliance with prescribed treatment.

[†]With 1-cm slice width, locations are approximate. L indicates left; R, right, Post, posterior; P>U, increased activation during pleasant picture sequences compared to unpleasant sequences; U>P, decreased activation during pleasant picture sequences compared to unpleasant sequences.

[‡]Linear correlation analysis.

(1 female, 4 male, age = 29.2 ± 3.3 [mean ± SD] years, range 26 to 33 years).

Subjects and controls rated affective valence of the picture sequences in accordance with expectations (Pearson correlation 0.835; *P* = 0.0000). That is, sequences selected as pleasant from International Affective Picture System were rated by the subjects as somewhat

or very pleasant, and sequences selected as unpleasant were rated by the subjects as somewhat or very unpleasant. In each subject, at least one brain area showed significantly different activity during blocks of unpleasant and pleasant pictures.

Differential brain activity occurred in response to moderately pleas-

ant and unpleasant pictures in each control subject and each subject with schizophrenia. Differential activation was noted in frontal, occipital, or medial cortical areas, and in subcortical structures. However, each subject appeared to have his own pattern. Inspection of the activation revealed no group patterns of activation that might separate the

subjects with schizophrenia from controls. Nor was there a pattern of activation that would distinguish pleasant from unpleasant stimuli for either group. Sample size was insufficient to test for subtler group differences by more sophisticated statistical methods.

The precision and accuracy of this study were limited by the relatively small data storage capacity of the particular fMRI system, limiting brain coverage, and requiring the use of thick (1 cm) slices for coverage of the areas of interest. The use of a system with sufficient data storage for full brain coverage at high resolution will be necessary to truly localize activation patterns. Higher magnetic field strength may also be advantageous in reducing the signal-to-noise ratio and time in the scanner.

During data collection, we became aware of another group using similar methods with a more advanced fMRI machine. Takahashi et al¹⁵ found that, in comparison with neutral pictures, unpleasant pictures caused activation in the amygdala, thalamus, anterior cingulate, and caudate nucleus in controls, but activated only the anterior cingulate and left amygdala in patients. Their findings are consistent with our hypotheses.

This pilot project's finding of demonstrable differences in brain processing of moderately pleasant and unpleasant pictures in all of the subjects and controls suggests that fMRI studies of affective response in schizophrenia are feasible using similar methods. Issues to be addressed in future studies include plasticity, the relationship of brain activation to the severity of affective symptoms in schizophrenia, patterns of brain activation associated with therapeutic response, and activation patterns at baseline that may be predictors of treatment response.

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The Effect of Hypertension and Obesity on the Development of Diabetes Mellitus in Patients Treated With Atypical Antipsychotic Drugs

To the Editors:

Clozapine, olanzapine, quetiapine, risperidone, and ziprasidone are designated as atypical antipsychotic drugs because they produce fewer extrapyramidal symptoms at clinically effective doses than do typical agents, for example, haloperidol. These drugs, however, produce metabolic side effects, such as weight gain and emergence of diabetes mellitus (DM).¹ It is still controversial whether obesity or weight gain during treatment with an atypical antipsychotic drug is associated with increased risk of the development of DM.

Individuals with DM have increased risk of cardiovascular diseases, such as hypertension. On the other hand, it has been suggested that cardiovascular risks are correlated with blood glucose levels in nondiabetic subjects as well.² Nondiabetic range of hyperglycemia has been regarded as a risk factor for atherosclerosis. These observations indicate the presence of common predisposing factors for DM and cardiovascular diseases, such as hypertension. Therefore, we hypothesized that hypertension, a common disease in the general population, would be a risk factor for developing DM during treatment with atypical antipsychotic drugs.

The goals of the present study were to determine if subjects with pre-existing hypertension have a higher incidence of new-onset DM during treatment with atypical antipsychotic drugs, and if baseline weight or BMI, or change in these measures during

treatment, was predictive of the development of DM.

Patients who visited an outpatient community mental health center (Mental Health Cooperative at Nashville, TN) during February 2001 to May 2002 were randomly assessed. A patient was included in this study if s/he was receiving clozapine, olanzapine, quetiapine, or risperidone. For these subjects, retrospective chart review was conducted to obtain clinical and demographic information.³ For each patient, an "index date" was designated as the date for initiation of treatment with the atypical antipsychotic drug that the patient was receiving at the time assessment was initiated. A date of diagnosis of DM was defined as when s/he had either a medical or facility claim with DM (corresponding to ICD codes 250.00 to 250.99) for the first time. Subjects who had already the DM diagnosis before the index date (N = 19) were excluded from the study. This study was approved by the Institutional Review Board of Vanderbilt University, and written informed consent was obtained from the subjects.

Presence of hypertension and/or heart disease at the time of index date was also identified through examination of the diagnoses on medical or facility claims. The effect of comorbidity of

these circulatory diseases, as well as weight and BMI, on the development of atypical antipsychotic drug-induced DM was evaluated.

Clinical data were obtained from 116 subjects meeting the study criteria (Table 1). Fourteen subjects were found to have developed DM following treatment with one of the atypical antipsychotic drugs. Age, gender, race, and the ratio of patients diagnosed with schizophrenia, did not differ between subjects who developed DM and those who did not (N = 102). There was no overall difference in the frequency of DM among these atypical antipsychotic drugs.

Seven subjects had a diagnosis of hypertension⁴ at the time of index date. The subjects comorbid for hypertension showed a significantly greater incidence of DM during treatment with an atypical antipsychotic compared to those who were not hypertensive (Table 1). Age, sex, race, weight, or BMI (baseline, current, change) was not different between the 7 subjects with hypertension and those without (data not presented).

Baseline BMI, but not weight of patients who developed DM, was significantly greater than that in the subjects who did not develop DM (Table 1). A logistic regression model was used to

predict the risk of DM using age, gender, race, and one of the following variables: baseline or current weight (or BMI), or change in weight (or BMI). Table 2 shows the effect of the weight and BMI variables in these models. The results indicated significant effects of baseline and current BMI, as well as marginal influence of baseline and current weight, on the development of DM. On the other hand, change in weight or BMI was not found to be associated with the development of DM. Gender, age, or race was not a significant covariate in the models with baseline or current BMI to predict the development of DM, as revealed by logistic regression estimates (data not shown).

The results of this study provide the first suggestion that individuals with hypertension are at an increased risk for the development of new-onset DM during treatment with atypical antipsychotics compared to those without hypertension.

Coutinho et al² argued that the cutoff point for DM would be lower if increased risk of cardiovascular events was used to define the condition. Therefore, it is possible that the subjects with hypertension reported here may have had increased vulnerability to develop DM, which was rendered clinically overt

TABLE 1. Demographic Data

	Subjects Who Developed Diabetes	Subjects Who Did Not Develop Diabetes	<i>t</i>	χ^2	<i>P</i>
Sample size	14	102	—	—	—
Age, year	46.1 (11.5)	42.4 (10.5)	-1.20	—	0.23
Male/female	8/6	58/44	—	0.00	1.00
Race (White/non-White)	9/5	61/41	—	0.10	0.75
Schizophrenia/nonschizophrenia	9/5	45/57	—	2.01	0.16
Clozapine/risperidone/ olanzapine/quetiapine	5/4/5/0	18/19/50/15	—	5.16	0.16
Baseline weight (lb)	206.2 (49.5)	182.5 (47.9)	-1.27	—	0.13
Baseline BMI (kg/m ²)	28.0 (8.8)	25.5 (8.1)	-2.25	—	0.03
Comorbidity of hypertension or cardiovascular disease	7/14 (50%)	0/102 (0%)	—	—	<0.0001

Values represent mean (SD) for continuous variables.

*Fisher's exact test.

TABLE 2. Odds Ratio for the Risk of Diabetes

Parameters	Odds Ratio	95% Confidence Interval	P
Baseline weight	1.015	1.000 to 1.031	0.06
Current weight	1.011	0.998 to 1.024	0.09
Change in weight	0.997	0.973 to 1.021	0.78
Baseline BMI	1.106	1.011 to 1.210	0.03
Current BMI	1.085	1.009 to 1.166	0.03
Change in BMI	0.993	0.851 to 1.159	0.93

by subsequent treatment with atypical antipsychotics. Alternatively, as preexisting hypertension has been reported to play an important role in the progression of DM-related renal diseases, possibly via altered activity in glomerular intrinsic antioxidant enzymes,⁵ subjects with hypertension may be more likely to develop DM-associated complications, such as renal dysfunction, which, in turn, may increase the likelihood of diagnosis of DM.

Obesity has been associated with insensitivity to the action of endogenous leptin,⁶ which may provide a mechanism underlying association between obesity and increased incidence of new-onset DM in patients taking atypical antipsychotic drugs. The results of the present study point to the need for more frequent blood monitoring in obese patients, irrespective of change in weight, during treatment with atypical antipsychotic drugs.

This study might not necessarily support a role for atypical antipsychotic drugs in the induction of DM. To address this issue, a comparable group of patients treated with conventional antipsychotics would have been required, which is beyond the scope of this study.

The limitations of the present study include a relatively small sample number and the lack of clinical information related to the risk of DM, such as family history of DM. Further investigations controlling for these variables are warranted. Also, analyses of quantitative data to predict the development of DM in a larger number of subjects deserve further study.

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Comparative Evaluation of Olanzapine Efficacy in the Maintenance Treatment of Bipolar Disorder

To the Editors:

Lithium and valproate are currently used in the maintenance treatment of bipolar disorder (BD). Although these drugs are effective to reduce the incidence of recurrences, they can have important adverse effects and need repeated determinations of plasma levels because of their low therapeutic index. Another important problem is the lack of response to these treatments or the possibility of developing of resistance in the long-term treatment.¹

In the last few years, clinical researchers have been looking for new safer molecules effective in the maintenance treatment of BD.

As alternative to lithium or valproate, atypical antipsychotics are a new class of compounds, whose pharmacodynamic profile is wider than that of some typical antipsychotics.²

These compounds showed efficacy both in acute mania³ and, from preliminary data, in the maintenance treatment of BD as adjunctive therapy⁴ or monotherapy.⁵

Olanzapine is an atypical antipsychotic with a good tolerability profile; it blocks 5HT_{1A}, 5HT_{1C}, D₁, and D₄ receptors.

To date, studies on olanzapine efficacy in the maintenance treatment of

BD have all considered this drug as an adjunctive therapy.⁶ Our study is the first to evaluate olanzapine efficacy as monotherapy in the maintenance treatment of bipolar patients, euthymic at the moment of recruitment. Tohen et al⁷ recently reported a double-blind study comparing olanzapine versus valproate in the treatment of acute mania, with a continuation phase of 44 weeks: during the 3-week acute phase olanzapine treatment group showed significantly greater mean improvement of mania ratings and significantly greater proportion of patients achieving protocol-defined remission, compared with the divalproex treatment group, although results from the extension phase have not been yet reported.

An additional study on olanzapine efficacy in relapse prevention of bipolar disorder has been recently presented.⁸ In this trial, following 6 weeks of acute therapy, patients remitting on olanzapine combined with lithium or valproate were randomized to olanzapine or placebo concomitant with ongoing valproate or lithium. Time to relapse was evaluated in these groups for a 18-month period. During the follow-up period, 55.3% of placebo-treated patients and 36.7% of olanzapine-treated patients relapsed into either mania or depression.

The aim of our study was to compare the efficacy of olanzapine and valproate monotherapy in the maintenance treatment of BD, observing the clinical course, in an open-label fashion, for 6 months. The study included patients with a diagnosis of BD type I or II or schizoaffective disorder bipolar type, euthymic at the moment of recruitment. Diagnoses were obtained with the administration of Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, Axis I. The study had institutional review board approval, and all patients gave their written informed consent to participate into the study. Patients taking concomitant psychotropic compounds except for benzodiaze-

lines or with medical or physiologic conditions (pregnant women, fertile women not on adequate contraceptive methods, and breast-feeding women) contraindicating the administration of olanzapine or valproate were excluded.

Twenty-three outpatients were randomly assigned to olanzapine (OLZ group) or valproate (VPA group) treatment, both at flexible doses. Twenty outpatients (9 males and 11 females) completed the study. Three patients assigned to OLZ group prematurely discontinued the study because of the occurrence of side effects (weight gain, sedation). At baseline, mean age of patients was 40.2 (± 13.5) for OLZ group and 51.0 (± 13.9) for VPA group. Mean age at onset was 22.5 (± 8.5) for OLZ group and 34.6 (± 13.5) for VPA group; 6 patients had a diagnosis of BD I (5 in OLZ group and 1 in VPA group), 11 of BD II (2 in OLZ group and 9 in VPA group), and 3 of schizoaffective disorder bipolar type (OLZ group).

Olanzapine and valproate doses were adjusted according to the clinical needs. The final mean dosage was 9 mg (± 3.2) for olanzapine and 415 mg (± 16.39) for valproate. At the end of the study, the mean valproate plasma level was 62.7 (± 19.5) $\mu\text{g/mL}$; therapeutic level required was 50 $\mu\text{g/mL}$. Clinical course of BD was evaluated at the beginning of the study (T0) and every month by using the Brief Psychiatric Rating Scale (final version by Overall and Hollister, 1986) and the Clinical Global Impression (CGI), administered by blind raters with respect to the treatment group patients had been assigned. Data were analyzed using analysis of variance with repeated measures on the rating scales in the 2 treatment groups. Baseline mean scores of Brief Psychiatric Rating Scale were 9.2 (± 2.1) for OLZ group and 7.3 (± 2.5) for VPA group. Brief Psychiatric Rating Scale scores showed a significant decrease over time ($F = 6.055$; $P = 0.007$) without significant differences between the 2 groups ($F = 3.917$; $P = \text{ns}$). Clinical Global Impression mean scores at

baseline was 2.9 (± 0.7 SD) for OLZ and 3.1 (± 0.5 SD) for VPA group. The same analysis done on CGI scores (severity of illness item) showed no score changes ($F = 0.820$; $P = \text{ns}$) and no significant differences between the 2 groups ($F = 0.312$; $P = \text{ns}$).

We compared the percentage of patients who relapsed during the follow-up with that of the 6-month period before the beginning of the study, during which patients did not take any mood stabilizer. During the follow-up, we observed a reduction of the percentage of patients with depressive relapse (from 70% to 50% in OLZ group and from 50% to 20% in VPA group). The percentage of patients with manic relapse changed from 20% to 10% in OLZ group and from 10% to 20% in VPA group. Relapse was defined as a patient fulfilling *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for a major mood episode (depressive, manic, or mixed).

Results from this preliminary study suggest a comparable efficacy of olanzapine and valproate in the first 6 months of maintenance treatment of BD. In addition, our observation allowed to confirm the overall good tolerability profile of olanzapine. The adverse effects occurring during olanzapine treatment were dry mouth and weight gain (3.8 ± 7.2 kg). We are aware that our study is a preliminary one and that larger samples with a longer follow-up are needed before drawing any definitive conclusion. However, these findings appear promising.

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Comments on Article by Harrigan et al: “A Randomized Evaluation of the Effects of Six Antipsychotic Agents on QTc, in the Absence and Presence of Metabolic Inhibition.”

To the Editors:

I read with interest the report in the February 2004 issue of the *Journal* by Harrigan et al¹ on the effects of 6 antipsychotic drugs on the QTc interval. The authors point out that because CYP3A4 is responsible for only one third of ziprasidone's clearance, inhibition of this enzyme by ketoconazole caused no clinically meaningful change in the QTc interval. They further state that two thirds of ziprasidone clearance “is mediated by aldehyde oxidase, a pathway

with no known clinically relevant inhibitors or inducers.” In support of this statement, they cite a report by Beedham et al.²

Recently, however, an in vitro study of human liver aldehyde oxidase of which Beedham was one of the authors found substantial aldehyde oxidase inhibition (greater than 80%) by 36 of 239 drugs that were tested.³ These included phenothiazines, clozapine, olanzapine, amlodipine, erythromycin, ethinyl estradiol, raloxifene (most potent), and metoclopramide. The authors suggest that zaleplon which is metabolized by aldehyde oxidase might produce excessive sedation in the presence of one of the more potent inhibitors. While they do not mention ziprasidone, one must wonder whether some of the more potential aldehyde oxidase inhibitors could cause problematic QTc interval prolongation in combination with this drug, especially if CYP3A4 was also inhibited.

Clearly, in vitro data may not accurately predict what occurs in vivo. In fact, while ketoconazole was found to be one of the more potent aldehyde oxidase inhibitors and while it is also a potent CYP3A4 inhibitor, it only increased the C_{max} of ziprasidone by a bit over 31% and did not significantly alter the QTc interval. Also, it should be noted that the study of inhibitors dealt only with aldehyde oxidase-catalyzed oxidation, whereas ziprasidone is metabolized by reduction. Whether these inhibitors also affect aldehyde oxidase-catalyzed reduction is not known, but should be subjected to future study.

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Melatonin Treatment of Day-Night Rhythm Disturbances and Sundowning in Alzheimer Disease An Open-Label Pilot Study Using Actigraphy

To the Editors:

Half of patients with severe Alzheimer disease (AD) develop day-night rhythm disturbances or agitated behavior during the evening hours (so-called sundowning).¹ When these symptoms occur in the context of home care, they can become a great burden to professional caregivers and family members. In fact, day-night rhythm disturbances and sundowning are the number one cause of long-term hospitalization in patients who suffer from AD.² Current treatment options involve the use of benzodiazepines or neuroleptics.³ However, in addition to low response rates, these drugs have serious side effects and are therefore only of limited use.

It has been suggested that day-night rhythm disturbances and sundowning are both a result of perturbations in the circadian timing system. A number of preliminary studies suggest that chronobiologic treatment methods involving light therapy or the administration of exogenous melatonin may be effective in the management of day-night rhythm disturbances and sundowning.^{4,5} Indeed, there have been reports that exogenous melatonin improves clinical symptoms such as disturbed nighttime sleep and agitation in patients suffering from AD or other cognitive disorders.^{6–8} However, these improvements have yet to be

measured in an objective manner (eg, using polysomnography or actigraphy). The aim of this pilot study was to obtain, for the first time, actigraphic data on the effects of melatonin in the treatment of day-night rhythm disturbances and sundowning in patients with AD.

A total of seven consecutive patients (3 females, 4 males, mean age 75.6 years, SD 10.6) who met the NINCDS-ADRDA criteria for probable AD and were suffering from day-night rhythm disturbances or sundowning were included in our open-label, uncontrolled pilot study. All patients were living at

home. The mean score of the Mini-Mental State Examination was 4.3 (SD 6.2). On the Global Deterioration Scale, all patients were at level 6 (severe cognitive decline). Additional patient characteristics are given in Table 1. None of the patients suffered from sleep apnea syndrome, restless legs syndrome, or other illnesses that can be accompanied by evening or nighttime agitation.

After a 7-day baseline period, patients received 3 mg melatonin every evening over a period of 3 weeks. The supraphysiologic dose of 3 mg melatonin was used because the hypothesized

mode of action in these patients was a supposed increase of output amplitude of the 24-hour variation in motor activity levels. Family members were instructed to administer melatonin to the patients between 8:45 PM and 9:15 PM. Melatonin was not to be administered at all on evenings when it could not be taken within this time frame. Using actigraphy, motor activity levels were assessed both during the 1-week baseline period and the 3-week treatment period. Primary outcome parameters were evening, nocturnal, and diurnal motor activity. For each parameter, measurements were made both

TABLE 1. Anamnestic Data, Clinical Changes, and Actometer Activity

No.	Gender/ Age	Diagnosis* (Years)	Medication (Daily Dose)	CBS [†] (Months)	Result	Activity Counts [‡]					
						Diurnal (6 PM to 9 PM)		Evening (3 PM to 9 PM)		Nocturnal (9 PM to 6 PM)	
						b	m	b	m	b	m
1	M/62	PSDAT (7)	Donepezil 5 mg; risperdal 3 mg	SD; D/N (2)	Remitted	109472	127234	22980	28180	26176	16762
2	M/66	PSDAT (7)	Donepezil 5 mg; valproic acid 150 mg	D/N (6)	Unchanged	52404	63783	28070	29862	39160	22604
3	F/87	SDAT (5)	Isosorbide dinitrate 40 mg; piracetam 800 mg	D/N (6)	Remitted	96243	74298	51480	30046	42648	27554
4	M/67	PSDAT (7)	Donepezil 10 mg; valproic acid 600 mg	SD D/N (2)	Improved Unchanged, but wife's (!) sleep improved	46629	49533	20941	21735	35162	32532
5	F/81	SDAT (8)	Digitoxin 0.07 mg; acetylsalicylic acid 100 mg; amitriptyline 25 mg; haloperidol 1 mg; clomethiazole 250 mg	D/N (2)	Remitted	91605	66591	47082	27636	33812	13911
6	F/87	SDAT (5)	Verapamil 120 mg; digitoxin 0.07 mg; thyroxin 25 µg; furosemide 40 mg; captopril 37.5 mg	D/N (2)	Remitted	375562	301123	141822	143473	42012	37960
7	M/81	SDAT (2)	Risperidone 1mg; galantamine 16 mg	SD (1) D/N (4)	Remitted Little improved	196616	198412	93609	90644	21132	18024
						<i>P</i> > 0.05		<i>P</i> > 0.05		<i>P</i> = 0.018	

*PSDAT indicates presenile dementia of the Alzheimer type; SDAT, senile dementia of the Alzheimer type.

[†]CBD indicates circadian behavioral disturbance; SD, sundowning; D/N, day-night rhythm disturbance.

[‡]Counts per day in baseline week (b) and last treatment week (m), *P* value: Wilcoxon rank sum test.

during the baseline week and the 3-week melatonin treatment period. Time periods were defined as diurnal (6 AM to 9 PM), nocturnal (9 PM to 6 AM), and evening activity (3 PM to 9 PM).⁴ Family members provided their own assessments of patients' well-being using the Nurses' Observation Scale for Inpatient Evaluation.

Patients wore an actometer during all study procedures and tolerated melatonin well, without any complaints. Table 1 shows the clinical changes of target symptoms during melatonin treatment. Four patients (nos. 1, 3, 5, and 6) experienced complete remission of day-night rhythm disturbances or sundowning. Clinical improvements were uncertain in patient no. 4; nevertheless, his wife reported that she experienced improved sleep. After melatonin, patient no. 7 showed no further symptoms of sundowning but continued to suffer from day-night rhythm disturbances. Caregivers did not report any change in behavior in patient no. 2. Nurses' Observation Scale for Inpatient Evaluation-30 positive factors improved in 5 patients (not in nos. 2 and 7), and Nurses' Observation Scale for Inpatient Evaluation-30 negative factors did not change significantly in any of the patients. Before the study, full hospitalization was planned for 5 of the patients but was no longer necessary in 3 patients after melatonin treatment.

As noted above, clinical observations were substantiated by measuring objective motor activity levels using actimetry. Five patients showed a marked reduction in nocturnal activity, whereas evening and diurnal activity changed differentially (Table 1). The reduction in nocturnal activity was significant despite the small number of patients ($P = 0.018$).

The effects of exogenous melatonin in our patients corroborate evidence that day-night rhythm disturbance and sundowning in AD patients may be linked to perturbances in the circadian timing system.⁹ However, which part of the circadian axis¹⁰ is disrupted has yet to be determined. It is still unclear

whether we are dealing with (1) an impairment in the transmission of the daily light-dark signal from the retina to the suprachiasmatic nucleus, known as the site of the central biological clock, 2) a dysfunction of the biological clock itself, 3) an impairment of the transmission of signals from the biological clock to the pineal gland, or 4) a disruption of melatonin production and secretion in the pineal. AD patients have been shown to have pronounced degenerative changes in the suprachiasmatic nucleus.¹¹ This may explain AD-related disturbances of the circadian secretory profiles. Changes in the pineal gland point to a reduced capacity for melatonin production in AD patients.¹² Exogenous melatonin bypasses the retina-suprachiasmatic nucleus-pineal axis and has proven to be effective in various disturbances of the circadian timing system.¹³ On the other hand, bright light requires a fully intact circadian axis to be effective. This may explain the low response rates obtained with light therapy in the treatment of day-night rhythm disturbance and sundowning in AD patients.⁴

Exogenous melatonin has been shown to be useful in the treatment of a variety of disorders that involve increased nighttime motor activity levels.^{14–16} Locomotor activity in animals clearly exhibits a circadian pattern and can be strongly influenced by exogenous melatonin. In studies of nonhuman primates, similar findings have been seen with regard to the influence of melatonin on locomotor activity during sleep.¹⁷

The results of our pilot study clearly support the idea that exogenous melatonin, as an easily administered, inexpensive drug with few side effects, may be an attractive treatment option for patients with these difficult-to-treat complications of AD. Important, too, is the prospect that exogenous melatonin may help alleviate the burden borne by professional caregivers and family members and thus lower long-term hospitalization and improve patients' quality of life.

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Gabapentin and Behavioral Disorders in Severe Alzheimer Disease

To the Editors:

Behavioral symptoms are common in Alzheimer disease and are often difficult to manage because of poor response to therapies or unacceptable side effects. Gabapentin is a new, antiepileptic drug with some interesting properties: improvement of behavioral disorders was described in single case reports or in small series of patients with dementia. We treated 5 men and 4 women with gabapentin, mean age 81.5 years, range 77 to 93 years, all but one were residents in the special care unit (Nucleo Alzheimer) of the nursing home. The diagnosis of probable Alzheimer disease was made according to NINCDS-ADRDA criteria; the severity of dementia was evaluated by the extended Clinical Dementia Rating Scale and the Bedford Alzheimer Nursing Severity Scale, and the psychiatric symptoms by the Neuropsychiatric Inventory (UCLA).¹ In

all patients, the behavioral symptoms were the major problem; environmental modifications or use of psychotropic drugs was ineffective or had unacceptable side effects. Gabapentin was started at a dosage of 300 mg at bedtime, increasing the dosages gradually every 2 to 3 days to avoid side effects. Routine hematologic tests and urinalyses were performed at baseline and after 1 and 4 months.

At baseline, 1 patient scored 2, and 8 patients scored 3 on the Clinical Dementia Rating Scale; the mean score of Bedford Alzheimer Nursing Severity Scale was 13.6, range 10 to 19, and the mean score of UCLA was 7.7, range 0 to 20. One patient scored 0 at UCLA: gabapentin was administered for manipulation of stool. After 1 month, the mean scores of the Clinical Dementia Rating Scale and Bedford Alzheimer Nursing Severity Scale were unchanged (3 and 14, respectively), whereas the mean score of UCLA was 3.6, range 0 to 20. Namely, the UCLA score was 0 in 4 patients and was about half than at baseline in 3 patients; 2 patients were unchanged, and therefore the drug was discontinued. Improvement was maintained for 4 or 5 months, but behavioral symptoms reappeared in several patients; so after 6 months, improvement was maintained in only 2 patients. An attempt to increase the dosages was ineffective or failed because of excessive sedation. In one patient, a second

attempt with gabapentin 600 mg/d was made some months apart but failed because of the appearance of hallucinations that subsided after the drug was discontinued. In patients with good response to gabapentin, small doses of other drugs (benzodiazepines, thioridazine, or trazodone) were occasionally required. No modifications in hematologic tests or urinalysis were observed. The results are summarized in Table 1.

In 1997, Regan and Gordon² referred to a dramatic improvement of behavioral symptoms in a patient with Alzheimer disease with gabapentin 600 mg/d. Since then, several case reports and small series have been published on the utility of gabapentin in the treatment of behavioral symptoms in dementias.^{3–10} On the whole, 60 demented patients have been treated: 37 with Alzheimer disease, 2 with mixed dementia (degenerative and vascular), 7 with vascular dementia, and 14 with other dementias (alcoholic, anoxic, in Parkinson disease, posttraumatic, or not specified). In all case reports,^{2–4,6,10} in the case report of Roane et al,⁷ and in the Moretti et al⁹ series, gabapentin was very effective at dosages between 300 mg/d and 2400 mg/d at the follow-up between 8 and 32 weeks. In the 2 largest series, the response is more variable. Thirty-six patients were treated with gabapentin at dosages between 100 mg/d and 3600 mg/d with follow-up between 4 weeks and 2 years (1 patient). Of

TABLE 1. Study Results

Patient	Sex	Age	UCLA, Baseline	UCLA, 1 Month	Gabapentin, mg/d	Follow-up
1	M	83	9	0	900	Good after 6 months
2	F	77	6	0	900	Worse after 5 months
3	M	81	6	0	600	Worse after 5 months
4	M	80	4	0	600	Good after 6 months
5	F	77	8	4	900	Worse after 5 months
6	F	93	8	2	600	Worse after 6 months
7	F	85	16	8	600	Worse after 5 months
8	M	77	20	20	1,200	Drug discontinued
9	M	81	0	0	600	Drug discontinued

(manipulation of stool)

twenty-four patients in Hawkins et al⁵ series, 17 were much or greatly improved, 4 were minimally improved, 1 unchanged, and 2 dropped out because of excessive sedation. Of twelve patients in the Herrmann et al⁸ series, 2 were much improved, 3 somewhat improved, 6 unchanged, and 1 minimally worse. Of 9 patients in this series at follow-up at 1 month, 4 were much improved (0 at UCLA), 3 greatly improved (the score at UCLA was about half than at baseline), and 2 unchanged. Improvement was maintained for about 5 months, and then worsening of behavioral symptoms was observed in several patients and the increase of dosages was ineffective or caused excessive sedation. Therefore, at follow-up at 6 months, improvement was maintained in only 2 patients. According to the literature in our series, the drug was well tolerated at dosages lower than 900 mg/d. Early in the study, mild sedation was observed, and 1 patient became a little disinhibited, but withdrawal of the drug was not required. In 1 patient, a second attempt with gabapentin induced the appearance of hallucinations.

Another unusual side effect was observed in a patient not included in this series: a nondemented female aged 88 years taking gabapentin as an antiepileptic developed compulsive masturbation at a dosage of 300 mg/d; the symptom disappeared after the drug was withdrawn.

Our patients and those described in the literature were poorly responsive to other drugs, and so any little or temporary improvement may be important. Presently, there are only case reports or small open studies, but results are encouraging, and more controlled studies are warranted to define indications, effectiveness, dosages, and side effects.

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Anorgasmia in a Patient Treated With Bupropion SR for Smoking Cessation

To the Editors:

Bupropion SR is the first non-nicotine product licensed for the treatment of nicotine dependence and considered a first-line therapy for smoking cessation in the United States and Europe.¹ It appears to be a safe, well-tolerated, and effective medication when combined with smoking cessation counseling for a wide range of smokers as shown in several multicenter double-blind, placebo-controlled clinical trials.^{2,3} In addition, it is widely used as an

antidepressant in the United States for over 12 years. Bupropion is generally well tolerated both when used as an antidepressant and as a smoking cessation aid.

The 2 adverse events that have been reported to be significantly more frequent with bupropion SR (300-mg dose) than with placebo were insomnia and dry mouth.¹ Previous reports have described the occurrence of increased libido and spontaneous orgasm associated with bupropion SR treatment.^{4,5} Moreover, adjunctive bupropion has been suggested as a treatment for all the major categories selective serotonin reuptake inhibitors-induced sexual side effects.⁶ Although there are some rare case reports of sexual side effects in patients taking bupropion SR with other medications for depression,⁷ to our knowledge, this is the first report of sexual dysfunction associated with bupropion SR when used for smoking cessation.

CASE REPORT

The patient is a 36-year-old married man who self-referred to our smoking cessation clinic. On arrival to the unit, patients are thoroughly assessed before deciding the treatment option considered more appropriate for each patient.

He had been smoking since he was 16 years old and was smoking 20 cigarettes per day. He had 3 prior quit attempts, twice on his own without any help and once using nicotine replacement products and the help of his local community pharmacist. The longest he had ever been abstinent from cigarettes in his 20-year smoking career was for 3 weeks, with the nicotine replacement products, 4 years before coming to our clinic. He had no relevant past medical history and neither had he any past psychiatric history. He drank less than 5 standard units of alcohol per week and was not taking any medication at present. Physical and mental state examinations were normal.

Following the initial assessment and considering there were no contraindications, he was prescribed bupropion SR in conjunction to a series of planned visits for individual relapse prevention counseling.

Bupropion SR was commenced at the recommended initial dose of 150 mg to be taken daily for 6 days, with a view to increase it to 150 mg twice daily on day 7. The second visit was planned 10 days later, on the third day after the "target quit date." However, the patient returned to the clinic 6 days after initiating the medication, while still on a 150-mg/d dose. He complained that since he started on bupropion SR, he had been completely unable to have an orgasm during each of the 3 times he had attempted to have sexual intercourse, which had upset both the patient and his wife. While the anorgasmia experienced by the patient was associated with ejaculatory failure, desire and arousal were preserved. He denied any prior sexual problems in his 5 years of marriage and reported to have sex an average of 3 times per week. There were no further adverse events. It was subsequently decided to stop the medication to reassess the situation 10 week later. At the following clinic visit, he reported that the sexual dysfunction had resolved 3 days after stopping bupropion. He continues to be followed up at our clinic and at present remains 12 weeks smoke-free using relapse prevention counseling and without pharmacologic aids.

Bupropion is a pharmacologic agent with a low propensity for inducing sexual dysfunction. This has partly explained through its alleged mode of action. Bupropion has been reported to be a relatively weak inhibitor of the neuronal reuptake of noradrenaline and dopamine with minimal effect on the reuptake of 5-HT and decreased prolactin concentration,⁸ although it has also been suggested to exert an excitatory action on 5-HT neuron firing.⁹ While the mechanisms underlying sexual dysfunction in general and anorgasmia in particular are complex and multifactorial, it appears that central serotonergic hyperactivity as caused by selective serotonin reuptake inhibitors may exert a crucial role. It is possible that the reported anorgasmia could be mediated through bupropion's serotonergic effects.

Interestingly, the patient experienced the anorgasmia, while still on a small dose of 150 mg/d and before steady-state plasma concentrations were

achieved, which may also suggest a particular susceptibility of the patient to the reported adverse event. It is possible, as well, that the patient may have been anxious and worried, and this could simply be an adverse placebo effect. However, not only did he express interest in medication and specifically bupropion SR during the initial assessment, but this was also considered and ruled out during subsequent visits to the clinic by a psychiatrist (J.M.-R.).

Anorgasmia may be a rare side effect in some individuals being treated with bupropion for smoking cessation, although it remains unclear if this side effect was due to the medication itself. Clinicians ought to be aware of this potential side effect of bupropion, which may cause additional stress to patients attempting to quit smoking and may contribute to an early relapse.

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A Follow-up Study of Male Sexual Disorders The Neurophysiological Assessments, Anxiety-Depression Levels, and Response to Fluoxetine Treatment

To the Editors:

Erectile dysfunction and premature ejaculation are the most common reasons for seeking help for male sexual disorders.^{1,2} It has been well documented that these are related to depression and anxiety.^{3,4} Treatment has mainly focused on pharmacotherapy and cognitive-behavioral therapy.^{5,6} The serotonergic system is thought to be a primary means through which ejaculation is controlled and modified. Selective serotonin reuptake inhibitors especially are found to be useful as a treatment for premature ejaculation.^{5–8}

It is generally considered that erectile dysfunction is related to organic factors, while premature ejaculation is related to psychological factors.^{1,2} A detailed history, physical examination, and laboratory tests are insufficient for differential diagnosis in 15% to 20% of cases. Therefore, the role of neurophysiologic assessment is important.^{9–12} As indicated in our previous study, neurophysiologic methods might be useful for differential diagnosis in revealing suspicious organicity, generally believed to be due to psychologic factors in male sexual disorders.¹²

In the present study, we investigated the relationship between neurophysiologic measures and anxiety-depression levels in patients with sexual dysfunction who were treated with fluoxetine, a selective serotonin reuptake inhibitor, and treatment outcome during a 6-month follow-up period.

Samples were selected consecutively from patients with premature ejaculation and erectile dysfunction who presented to the urology and psychiatry outpatient clinics between January and December 2002. Patients were interviewed individually and screened by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (American Psychiatric Association: Washington, DC, American Psychiatric Press; 1994) diagnostic criteria for premature ejaculation and erectile dysfunction. Twelve male patients who met fulfilling criteria were included in this study (mean age: 46.83 ± 14.48 years; min: 27, max: 69).

All patients were informed and gave consent and completed the State-Trait Anxiety Inventory (STAI) and Beck Depression Inventory (BDI) at the onset of the study.^{13,14} Neurophysiologic examinations were performed by a team of a neurologist, a psychiatrist, and an EMG technician. Recordings were done with a Premiere Plus Model EMG device developed by Medelec Limited (TECA Corporation, UK). Neurophysiologic examinations were performed with three different tests: a hand and genital sympathetic skin responses (SSR), pudendal somatosensory evoked potentials, and bulbocavernosus reflex latency, in a semidarkened room with the temperature of 23°C to 25°C (for details, see references¹⁰⁻¹²).

All patients then received a fixed dose of fluoxetine (20 mg/d) during the study period. No patients dropped out. At the end of the sixth month, STAI, BDI, and neurophysiologic examinations were performed again, treatment responses were evaluated based on the patients' self-reports, and fluoxetine was stopped.

The data analyses were performed using the Wilcoxon test and paired-samples *t* test on a Pentium PC with SPSS statistical package.

Seven patients had premature ejaculation (58.3%), 3 patients had erectile dysfunction (25%), and 2 patients had both (16.7%), according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnostic criteria.

The fluoxetine treatment was not useful for the 5 patients who had a physical illness before the study (3 with diabetes mellitus, 1 with colon cancer, and 1 with an inguinal hernia).

The BDI and STAI-state scores of the patients who were responsive to fluoxetine treatment significantly decreased at endpoint compared to baseline (Table 1).

The difference between baseline and endpoint BDI scores (16.71 ± 8.44 and 10.29 ± 5.74 , respectively) was significant in the 7 patients without physical illnesses ($P < 0.05$, $z = 2.120$). Also, STAI-trait scores of those patients significantly decreased at endpoint compared to baseline (68.29 ± 10.59 and 61.43 ± 6.60 , respectively; $P < 0.05$, $z = -2.207$).

The STAI-state and STAI-trait scores of the 7 patients with premature ejaculation significantly decreased at endpoint compared to baseline. No statistically significant differences were found in the other sexual dysfunction groups.

Genital SSR of 7 patients were positive. In 5 patients, no genital SSR could be obtained; moreover, these patients were not responsive to fluoxe-

tine treatment and all of the patients had a physical illness associated with their sexual dysfunction. The STAI-trait scores of the patients with positive genital SSR latencies significantly decreased at endpoint compared to baseline (69.86 ± 10.14 and 61.14 ± 6.91 , respectively; $P = 0.027$, $z = -2.207$, Wilcoxon test). BDI and STAI-state scores did not show differences over time in those patients.

When considering psychologic factors, it has been reported that male sexual dysfunctions are influenced by generalized anxiety, castration anxiety, passive aggressive personality disorder, narcissism, and unconscious fears about women.⁹ In this context, it was emphasized that neuroticism plays a basic role especially in premature ejaculation.² Also, anxiety increases sympathetic response and leads to shortening duration of the ejaculation time.⁹ Review of current literature implies that anxiety and depression are often associated with premature ejaculation and erectile dysfunction.^{1,2,4,9}

It has been well known that selective serotonin reuptake inhibitors which are used for the treatment of sexual dysfunctions are also effective for anxiety and depression.⁵⁻⁷ The results of the present study showed significantly lower BDI and STAI-state scores at endpoint especially in the patients who were responsive to the fluoxetine treatment. According to our study, it supports a close relationship between sexual dysfunction and anxiety-depression. However, state anxiety scores were not significantly different at endpoint from

TABLE 1. BDI and STAI Scores of Treatment Responsive Patients at Baseline and End Point (n = 7)

Variables	Baseline	Endpoint (Sixth Month)	P (Wilcoxon Test)
	Mean \pm SD	Mean \pm SD	
BDI	19.43 \pm 6.48	10.86 \pm 6.09	$P = 0.034$; $z = -2.123$
STAI-state	69.57 \pm 7.25	61.8 \pm 7.58	$P > 0.05$
STAI-trait	71.57 \pm 6.08	62.0 \pm 6.00	$P = 0.028$; $z = -2.196$

Abbreviations: BDI indicates Beck Depression Inventory; SD, Standard deviation; STAI, State-Trait Anxiety Inventory.

the onset. This may be explained by testing anxiety. In the sexual dysfunction groups, the premature ejaculation group's significantly decreasing anxiety scores support the relationship between anxiety and premature ejaculation.⁹

The depression and anxiety scores of the patients who did not have physical illness decreased at the end of the sixth month. However, the depression and anxiety levels of the patients with physical illness did not change at end point and those patients did not respond to pharmacotherapy.

When the relationship between the presence of genital SSR with anxiety levels and treatment response was examined, the anxiety levels of the patients with no genital SSR did not change at the end of the follow-up period and those patients did not respond to the fluoxetine therapy. We observed that the patients who did not have genital SSR had suffered from primary or secondary erectile dysfunction. In our previous study, we found that an organic factor such as polyneuropathy and diabetes mellitus can explain their erectile dysfunction.¹² Taken as a whole, these findings may be considered as evidence that supports the relationship between physical illnesses and erectile disorders. Also, genital SSR seems to be helpful in revealing underlying suspicious organicity. The majority of patients with positive genital SSR suffered from premature ejaculation. At the end of the follow-up period, these patients responded to fluoxetine therapy and their anxiety levels decreased significantly. In conclusion, it is suggested that pharmacotherapy may be effective in treating sexual dysfunctions presenting predominantly with anxiety.

Finally, our results suggest that neurophysiologic examinations, especially genital SSR, can be useful for differentiation of the underlying organicity and prediction of the treatment response in male sexual dysfunction disorders.¹² The results of the present study support that fluoxetine has therapeutic effect in premature ejaculation

which is associated with anxiety and psychogenic factors.^{7,8}

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Panic Attacks With Spontaneous Ejaculation Successfully Treated With Citalopram and Clonazepam

To the Editors:

Panic attacks are associated with increased plasma levels of norepinephrine and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG).^{1,2} Therefore, during a panic attack, there is an overactivation of the sympathetic nervous system. It has also been shown that premature ejaculation is associated with high levels of anxiety and that there is a high prevalence of premature ejaculation in patients with panic disorder and social phobia.^{3,4} I report here a case of spontaneous ejaculation frequently manifesting during panic attacks.

CASE REPORT

Mr A is a 42-year-old single male who presented for treatment of spontaneous panic attacks and generalized social phobia. He reported frequent panic attacks occurring in and out of social contexts 5 to 6 times per day. In addition, 2 to 3 times per day, he would experience an ejaculation during a panic attack. He denied having an erection or feeling sexually aroused before or during the ejaculations and experienced them as highly embarrassing as well as socially and occupationally limiting. He would frequently need to change clothes and avoid social situations due to the fear that he would ejaculate.

Mr A had no prior psychiatric treatment and had been suffering with these symptoms for approximately 5 years. He had no panic attacks or spontaneous ejaculations

before this time. A routine laboratory work-up, including a complete blood count, electrolytes, liver function tests, and thyroid stimulating hormone, was performed, and all were within normal limits. Mr A reported no other symptoms and had a normal physical examination.

One week after starting treatment with citalopram (Celexa; Forest Laboratories; St. Louis, MO) 10 mg/d and clonazepam 0.5 mg twice daily, Mr A reported a significant reduction in panic attacks and spontaneous ejaculations. He reported that the frequency of both had gone down to one to two times per week. The dose of citalopram was increased at that time to 20 mg per day and the dose of clonazepam was increased to 1.0 mg twice daily. At these dosages, Mr A reported a complete remission of panic attacks and no further spontaneous ejaculations. He also experienced much less social anxiety and was able to engage in social activities that he formerly avoided. He tolerated both medications well and denied any side effects, including a decrease in libido or delayed ejaculation during sexual activity. This improvement was still present 6 months later.

Based on studies in humans and primates, the male ejaculatory response is dependent upon peripheral norepinephrine release and can be blocked by a high dose of guanethidine, a peripheral adrenergic blocking agent.⁵ Also, premature ejaculation can be treated by the administration of alpha 1-adrenergic blockers.⁶ Therefore, the sympathetic nervous system, through its effect on alpha 1-adrenergic receptors, mediates a substantial part of the ejaculatory response. In addition, central nervous system control of the ejaculatory response involves the anterior hypothalamus. More specifically, the magnocellular neurons of the hypothalamic paraventricular nucleus mediate ejaculation. It has been demonstrated that an increase in extracellular serotonin in the anterior hypothalamus following ejaculation inhibits subsequent ejaculation and is responsible for the ejaculatory refractory period. In contrast, increased dopamine in the anterior hypothalamus facilitates the male sexual response, including ejaculation.⁷ Thus, it suggests that sympathetic nervous system over-

activity, including increased dopamine and norepinephrine activity, in addition to reduced serotonergic activity, as is present in panic disorder, can lead to spontaneous ejaculation.^{8,9}

Alpha 1-adrenergic blockers such as prazosin have been shown to inhibit the pressure response in the seminal vesicles from electrical nerve stimulation. This has resulted in delayed and, at times, inhibited ejaculation. Similarly, fluoxetine, clomipramine, and serotonin itself have been shown to reduce the pressure response in the seminal vesicles to electrical nerve stimulation.¹⁰ It is unknown whether the successful treatment of spontaneous ejaculation in this patient was secondary to the successful treatment of panic attacks or an increase in serotonin neurotransmission or both. It will require further study and specific sampling of plasma or CSF levels of norepinephrine, MHPG, serotonin, and the serotonin metabolite 5-hydroxyindoleacetic acid to elucidate the mechanism by which the successful treatment of panic attacks leads to a resolution of spontaneous ejaculation.

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Changes in Energy After Switching From Daily Citalopram, Paroxetine, or Sertraline to Once-Weekly Fluoxetine

To the Editors:

Depression is often accompanied by low energy, listlessness, and fatigue. In fact, these symptoms afflict more depressed patients than do anxiety and nervousness.¹ However, although treatment of comorbid anxiety-related symptoms has received significant attention recently as an important consideration in the selection of an antidepressant, the value of energy restoration in listless depressed patients has been relatively neglected.² Moreover, baseline fatigue is a risk factor predictive of a chronic course for depressive illness,³ and residual symptoms of fatigue often remain after an acute antidepressant response has been achieved.⁴ Failure to treat the symptoms of low

energy that accompany depression may impede the path to full recovery and remission.

Daily treatment with fluoxetine has been shown to be effective in restoring energy in depressed patients suffering from concomitant listlessness and fatigue.⁵ Once-weekly fluoxetine is an effective alternative to daily dosing for the continuation/maintenance treatment of depression.⁶ To assess whether this weekly regimen also provides benefit for the target symptoms of fatigue and low energy, we have analyzed measures of energy in an open-label study in which patients were switched from a daily selective serotonin reuptake inhibitor (SSRI) antidepressant other than fluoxetine to enteric-coated fluoxetine 90 mg once weekly. Although patients had already achieved an antidepressant response to a daily SSRI other than fluoxetine when switched to fluoxetine once weekly, patients experienced an improvement in energy according to the MOS 36-Item Short-Form Health Survey (SF-36) Vitality scale.

A full report, including methods of this study, has been published previously.⁷ The study was a multicenter, open-label trial of patients currently undergoing treatment for major depressive disorder with an SSRI other than fluoxetine. Patients had received at least 6 weeks, but no more than 52 weeks, of treatment with citalopram (20 to 40 mg/d), paroxetine (20 mg/d), or sertraline (50 to 100 mg/d) for a current episode of depression and had demonstrated a response to treatment (Clinical Global Impression-Severity scores of ≤ 2 and modified HAMD₁₇ scores ≤ 10). The study consisted of two periods. The first was a one-week assessment phase (Study Period 1) during which all patients continued taking their prescribed medication (citalopram, paroxetine or sertraline). This was followed by a twelve-week, open-label treatment phase (Study Period 2) during which all patients received enteric-coated fluoxetine 90 mg once weekly. Written informed consent was obtained from all

the patients in accordance with the Helsinki conventions.

The primary measure of energy improvement for this analysis was the Vitality subscale of the MOS 36-Item Short-Form Health Survey (SF-36).^{8,9} The Vitality subscale reflects daily energy levels; individual items are described in Table 1. Higher scores on this scale represent better health status and functioning. Energy improvement was also assessed with the Hamilton Depression Rating Scale (HAMD) Retardation factor score, which consists items 1 (depressed mood), 7 (work and activities), 8 (retardation), and 14 (genital symptoms) of the HAMD₂₈ scale. Overall depression was assessed using the modified HAMD₁₇ total score.

Baseline measurements were collected before patients received treatment with enteric-coated fluoxetine (visit 1 or 2). A patient's endpoint measure is defined as their last measure available in study period 2. The change from baseline to endpoint (intent-to-treat, last observation carried forward) within each previous therapy was assessed with a Wilcoxon signed rank procedure for all parameters measured. The change from baseline to endpoint was compared among the previous therapy groups with analysis of variance with prior SSRI therapy and investigator as effects in the model for the same parameters.

Full efficacy and safety results for this study are presented by Miner et al⁷; this current analysis focuses on measures of energy. Baseline SF-36 Vitality subscale scores (\pm SD) were 45.9 ± 21.3 for citalopram, 48.9 ± 23.8 for paroxetine, and 44.1 ± 20.49 for the sertraline treatment group; there were no significant differences between prior treatment groups in baseline scores. From baseline to endpoint, a significant improvement (increase in scores) was seen in the Vitality subscale of the SF-36 for all previous treatment groups (Table 1). No statistically significant difference in change was seen between the 3 prior SSRI treatment groups.

When all 3 prior therapy groups were pooled, a statistically significant improvement was seen in each of the individual items of the Vitality subscale (Table 1). Significant improvement was seen in all 3 prior treatment groups for each of the individual items except for item 9a, for which an increase in score was seen in the paroxetine and sertraline groups that did not reach statistical significance.

Baseline HAMD retardation scores (\pm SD) were 1.2 ± 1.3 for citalopram, 0.7 ± 1.1 for paroxetine, and 0.9 ± 1.07 for sertraline. No significant change was seen in the HAMD Retardation subscale for any prior treatment group. Mean change \pm SD for the HAMD Retardation subscale was 0.3 ± 1.8 for citalopram, 0.1 ± 1.6 for paroxetine, and 0.4 ± 2.1 for sertraline ($P = 0.355, 0.592, \text{ and } 0.252$, respectively). Of the individual items of the Retardation subscale, item 1 (mood) increased significantly for patients previously treated with sertraline (mean change 0.23, $P = 0.029$). No other significant change was seen in any individual item for any prior treatment group.

Symptoms of low energy, listlessness, and fatigue frequently accompany depression and can be troubling residual symptoms after an acute antidepressant response is achieved. Identification of these symptoms and selection of an appropriate antidepressant for acute treatment can enhance patient perception of antidepressant efficacy and may increase compliance.² In addition, resolution of residual symptoms may reduce the risk of relapse in patients being treated for depression.¹⁰

In this study, patients who exhibited an antidepressant response to treatment with a daily SSRI other than fluoxetine according to the HAMD₁₇ rating system experienced a significant improvement in energy levels, as measured by the SF-36 Vitality scale, when switched from their daily SSRI to fluoxetine once weekly. The mean SF-36 Vitality score for the general US population is 50, according to the

1998 National Survey of Functional Health Status.¹¹ Baseline SF-36 Vitality scores were slightly below average, suggesting residual presence of impairment in energy despite demonstrated response to the subjects original SSRI, while endpoint scores were slightly above average for all prior treatment groups. The difference between baseline and endpoint scores may represent resolved residual symptoms of the primary depressive disorder or may be related to adverse events associated with the baseline medication.

Of the other health concepts measured in the SF-36, statistically significant improvements were seen in “general mental health” and “role limitations due to emotional problems” for all prior treatment groups after switching to fluoxetine once-weekly.⁷ These improved health perceptions may have been due, in part, to the decreased burden of fatigue on these patients once they were switched to fluoxetine once weekly from their daily SSRI.

The HAMD Retardation subscale has been used previously as a measure of energy levels in depressed patients.⁵ In the current analysis, no significant change was seen in HAMD Retardation scores after the switch to once-weekly fluoxetine. Several possibilities for this discrepancy exist. First, patients were required to have a HAMD₁₇ total score of ≤ 10 to enter this study. The low HAMD₁₇ criterion for study entry may have introduced an unintentional bias towards those patients who had low HAMD Retardation subscale scores at study entry, leaving little possibility for improvement in these scores to evaluate changes in energy. This finding on the HAMD Retardation subscale is inconsistent with the increase in patient energy levels that was detected after the switch to once-weekly fluoxetine using the SF-36 Vitality scale as a measure of energy.

An additional explanation for why an increase in energy levels was not detected with the HAMD Retardation

subscale, while a significant improvement was observed using the SF-36, may be in the design of the measurement tools. The HAMD₁₇ is a physician-rated scale that is primarily used in a clinical setting to rate depressive symptoms. The SF-36 scale is patient-rated and is predominantly focused on assessment of general quality of life. Patients responding to self-rated questions on the SF-36 scale may be more attentive to the effects of low energy and fatigue on their daily quality of life than those same patients responding to questions by a physician in the course of a clinical assessment of depression.

In conclusion, patients in this study experienced an increase in energy levels after switching from daily citalopram, paroxetine, or sertraline to enteric-coated 90 mg fluoxetine once weekly, according to the SF-36 Vitality subscale. This quality of life improvement is especially notable because patients had already achieved an antidepressant response to their daily SSRI before

TABLE 1. Mean Change the SF-36 Vitality Scale and Individual Items*

Measure	Prior Treatment [†] (n)	Mean Change	P
SF-36 Vitality scale total score	Citalopram (81)	7.4 ± 21.8	0.012
	Paroxetine (72)	9.3 ± 26.0	<0.001
	Sertraline (82)	8.5 ± 23.4	0.002
Item 9a: did you feel full of pep?	Citalopram (80)	0.13 ± 1.26	0.379
	Paroxetine (72)	0.22 ± 1.51	0.238
	Sertraline (81)	0.35 ± 1.32	0.022
	Overall [‡] (233)	0.23 ± 1.36	0.012
Item 9e: did you have a lot of energy?	Citalopram (81)	0.33 ± 1.29	0.017
	Paroxetine (72)	0.40 ± 1.58	0.024
	Sertraline (82)	0.48 ± 1.34	0.003
	Overall [‡] (235)	0.40 ± 1.40	<0.001
Item 9g: do you feel worn out?	Citalopram (81)	0.43 ± 1.45	0.005
	Paroxetine (72)	0.64 ± 1.55	<0.001
	Sertraline (82)	0.33 ± 1.40	0.031
	Overall [‡] (235)	0.46 ± 1.46	<0.001
Item 9i: do you feel tired?	Citalopram (81)	0.58 ± 1.51	<0.001
	Paroxetine (72)	0.60 ± 1.49	<0.001
	Sertraline (82)	0.52 ± 1.60	0.004
	Overall [‡] (235)	0.57 ± 1.53	<0.001

*Higher scores represent better functioning.

[†]No statistically significant difference was seen among the 3 prior SSRI groups for the Vitality subscale or any item.

[‡]Pool of all 3 prior therapies.

switching to fluoxetine once weekly. Improvement in energy levels may increase compliance; it may also represent resolution of residual symptoms of depression in these patients, which may reduce the risk of depression relapse.

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Serum Cholesterol in the Continuation Phase of Pharmacotherapy With Fluoxetine in Remitted Major Depressive Disorder

To the Editors:

A growing number of studies report that patients with depression may differ in terms of their cholesterol levels from nondepressed psychiatric patients or normal controls.¹ In a previous study conducted by our group, we found that major depressive disorder (MDD) patients with random pretreatment serum cholesterol levels greater than or equal to 200 mg/dL were less likely to respond to an 8-week, fixed-dose, open-trial of 20 mg of the selective serotonin reuptake inhibitor (SSRI) fluoxetine¹ or a 6-week open trial of nortriptyline.² To offer an explanation for this finding, we speculated that excess cholesterol may have an adverse impact on the function of the serotonergic system, in general, or, more specifically, the serotonin transporter (5HTT).³ In support of this hypothesis, we reported that MDD patients with elevated cholesterol levels had evidence of 5HTT dysfunction by way of a blunted cortisol response to fenfluramine.⁴ To lend further support to the argument that hypercholesterolemia may have an adverse impact on the treatment of MDD with SSRIs, we chose to extend our clinical findings by investigating the impact of serum cholesterol on the outcome of continued treatment with fluoxetine among outpatients with MDD in remission following an acute trial with fluoxetine treatment. Patients who achieved remission at the end of the 8-week trial

had their fluoxetine dose increased to 40 mg/d and were enrolled in a 28-week continuation phase of treatment. In the present study, we tested whether greater cholesterol levels or hypercholesterolemia predicted relapse in these patients during the continuation phase of treatment.

Three hundred eighty-six outpatients, ages 18 to 65 years, who met the criteria for a current major depressive episode according to the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*,⁵ who were medication-free for at least 2 weeks, with a baseline 17-item Hamilton Depression Rating Scale⁶ score of ≥ 16 , were eligible to enroll into an 8-week, fixed-dose, open-label trial of 20 mg fluoxetine conducted at the Massachusetts General Hospital Depression Clinical and Research Program. Further details on the inclusion/exclusion criteria and methods for this open trial are reported elsewhere.⁷ After signing an institutional review board-approved written informed consent form and immediately before patients were started on medications, patients had random (non-fasting) serum cholesterol measurements performed. Patients were then started on 20 mg of fluoxetine daily. At the completion of the acute phase, remission was defined as a 17-item Hamilton Depression Rating Scale score of ≤ 7 for at least 3 weeks. A total of 134 patients at the end of the open phase met criteria for remission and were entered into the 28-week continuation phase. For the continuation phase, all patients had their fluoxetine dose of 20 mg increased to 40 mg/d, were randomized to cognitive-behavior therapy or medication management, and followed monthly. Further details of the continuation-phase protocol have been described elsewhere.⁸ Depressive relapse was defined as meeting criteria for a new episode of major depression at any continuation visit or a 17-item Hamilton Depression Rating Scale score of ≥ 15 at 2 consecutive visits. Relapse was confirmed by a

follow-up visit 1 week later with another clinician, blind to treatment status. All subjects who took at least a week of study medication and had at least one postbaseline efficacy assessment in the continuation phase were included in the intent-to-treat analysis. In line with our previous studies, cholesterol levels were classified as elevated if greater than or equal to 200 mg/dL and normal if less than 200 mg/dL.^{1,2,4} Separate logistic regressions we used to assess the relationship between (1) elevated versus normal cholesterol levels and (2) cholesterol levels entered as a continuous measure and relapse, controlling for age, gender, and body mass index at baseline.

Of the 134 patients enrolled in the continuation phase, 111 (82.8%) had random serum cholesterol levels at baseline; 56 of 111 of the present sample were female. The mean age of our sample was 40.4 ± 10.2 years, the mean body mass index in kg/m^2 was 26.2 ± 5.0 , the mean duration of the current major depressive episode in years was 3.2 ± 5.5 , the mean number of lifetime major depressive episodes was 5.1 ± 8.0 , the mean age of onset of the first major depressive episode in years was 23.4 ± 12.0 , and the mean severity of depression during the baseline visit of the open trial as reflected by the 17-item Hamilton Depression Rating Scale total score was 18.9 ± 2.9 . Of the 111 patients enrolled in the continuation phase with cholesterol levels measured at baseline, 52 (46.8%) had elevated cholesterol levels, while 59 (53.2%) had normal levels. Seven (6.3%) of the 111 patients relapsed, while 104 (93.7%) did not. The mean cholesterol level for the entire sample was 201.1 ± 42.6 mg/dL. The mean cholesterol level for patients that relapsed was 233.4 ± 55.2 mg/dL, while the mean level for patients who did not relapse was 198.9 ± 41.0 mg/dL ($P = 0.0377$). When cholesterol was used as a continuous variable, greater serum cholesterol level at baseline was found to predict relapse, controlling for

age, gender, and body mass index ($P = 0.0409$, $\chi^2 = 4.180$, Coef/SE = 2.044, 95% CI = 1.001 to 1.043). There was a nonsignificant trend for patients with elevated cholesterol levels at baseline had higher rates of relapse during the continuation phase ($P = 0.2$). Of the 52 patients with elevated cholesterol levels, 5 (9.1%) relapsed, while of 64 patients with normal cholesterol levels, 2 (3.4%) relapsed.

The results of the present study reveal a significant relationship between serum cholesterol levels at baseline and the risk of subsequent relapse in patients with remitted MDD during the continuation phase of treatment with fluoxetine. Specifically, the presence of higher cholesterol levels at baseline was found to confer an increased risk of depressive relapse in these patients. The present results are important in that they extend previous findings of our group, namely, that elevated cholesterol levels have an adverse impact on outcome to continued treatment with the SSRI fluoxetine, in fluoxetine-remitted MDD patients, and lend indirect support to the hypothesis that elevated cholesterol levels may have a direct adverse impact on 5HTT or 5HT-receptor functioning.⁴ How would hypercholesterolemia adversely impact 5HTT function? Incorporating cholesterol into the neuronal phospholipid bilayer leads to a reduction in membrane fluidity.⁹ Neurotransmitter receptors are concentrated and precisely localized in specific areas of the neuronal membrane, referred to as lipid rafts, and this precise localization is critical for neurotransmission. Excessive cholesterol may indirectly manipulate the conformation and function of membrane-bound proteins and receptors such as the 5HTT by reducing neuronal membrane fluidity and thereby altering or disrupting the function of lipid rafts. Altering the membrane cholesterol content of cells containing the 5HTT, for instance, has been shown to lead to concomitant changes in the affinity for serotonin and function of the transporter.¹⁰ In parallel, several clinical trials reveal a relationship between

5HTT affinity before treatment and clinical response to SSRIs.^{11,12}

The following reasons may account for why the relationship between elevated cholesterol levels (assessed dichotomously) did not reach statistical significance as in the previous study. First, increasing the dose of fluoxetine to 40 mg/d in patients who responded to 20 mg/d may have obscured this relationship by decreasing the rate of relapse during the continuation phase, as the overall rate of relapse during that phase was less than 10%.⁸ There was a selection bias, since patients with elevated cholesterol levels were less likely to achieve remission, therefore less likely to be enrolled in the continuation phase, further reducing the power of the present study to detect a difference in relapse rates between the 2 groups. Compared to 44.2% of patients in the continuation phase, 51.6% of patients in the acute study had elevated cholesterol levels. Alternatively, that continuous rather than dichotomous levels-predicted relapse may represent a chance finding. Further studies are necessary to study the relationship between cholesterol and antidepressant response.

A limitation of this study is its very low relapse rate. This is likely to have been related to the study design, which included an increase in the dose of fluoxetine from 20 to 40 mg/d following acute treatment and also the exposure to cognitive-behavior therapy for half of the subjects enrolled in the continuation phase. It is interesting that, despite the relatively small number of relapsers, the impact of cholesterol was still statistically significant. Hypothetically, in a less vigorously treated sample, other factors would have obscured the effect of greater cholesterol levels on relapse rates. In addition, our sample reflects a clinical trial population. The degree to which these findings generalize to a more heterogeneous population of depressed patients, including those with severe suicidality, psychosis, bipolar disorder, or substance abuse, remains to be determined. Further

studies are needed to study the relationship between cholesterol and treatment with SSRIs in MDD.

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Differential Time Course Efficacy on Dysphoric and Physical Symptoms of the Intermittent Dosing of Fluoxetine in the Premenstrual Dysphoric Disorder

To the Editors:

Premenstrual dysphoric disorder (PMDD) is a well-defined and clinically different clinical entity from other widely diagnosed disorders, such as major depression, panic disorder, etc.¹ Diagnosis of PMDD requires the presence of at least 5 of the 11 listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* symptoms like depressive mood, irritability, and physical symptoms, among others. The symptoms should be severe on a daily basis before menstruation and mild or absent after it, with a significant failure in functioning during the symptomatic premenstrual cycle for 2 or more menstrual cycles.

The primary objective of this study was to evaluate the efficacy and safety of intermittent treatment with 20 mg daily

of fluoxetine administered during 3 consecutive menstrual cycles in the luteal phase in patients diagnosed with PMDD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnostic criteria. Forty-one patients [mean age = 33 (SD ± 8.9)] with the diagnosis of PMDD and without a previous major depressive episode at entry into the study volunteered for the study after providing written informed consent. They were at least 18 years old, had regular menstrual cycles of about 25 to 31 days, and used a medically approved contraceptive method different from hormonal contraceptives. Thirty patients concluded the study and provided the information used in the statistical analysis.

This was a prospective, open, not controlled study with a follow-up period of 4–menstrual cycle duration (3 under medication) and 10 visits. Visit 1 was made at any time of the menstrual cycle. However, only those that obtained a total score of visual analogue scales of >50 (for mood and physical symptoms, scored from 0 to 100)² during the luteal phase (visit 3) with minimal or no symptoms during the follicular phase (visit 2) went on to visit 4. The treatment period included 3 menstrual cycles with 2 visits for each one [follicular phase (between days 5 and 11) and luteal phase (within 6 days before the beginning of menstruation and the first day of the next menstruation)]. In visit 4, patients were instructed to take 20 mg of fluoxetine per day during the luteal phase, from 14 days before (12 to 16 days before) the expected beginning of the menstruation until the first complete day of menstrual bleeding. Visit 10 (last visit) was in the follicular phase after menstrual cycle 4.

The Calendar of Premenstrual Experiences (COPE)³ was designated a priori as the primary efficacy instrument. The COPE's values obtained by the patients during the first luteal period (visit 3) were used as a baseline score for the data analysis. Those values were compared with those obtained during the treatment luteal periods to visit 9. All

data were evaluated using intent-to-treat analysis; data from all patients were included in the analysis. For the efficacy analysis, a reduction in the COPE score of $\geq 50\%$ from baseline (visit 3) to endpoint and a score of <40 at endpoint were considered a positive response criteria. To simplify the interpretation of the results and to expand the efficacy analysis, we determined the mean change per visit of COPE subscores based on groups of symptoms: (1) block 1—dysphoric symptoms: depression, irritability, easy crying, grief attacks, anxiety, tension, and feeling nervous; (2) block 2—other affective symptoms: fatigue, confusion, difficulty concentrating, motor disability, craving for some kind of food, forgetfulness, increased appetite, and mood swings; (3) block 3—physical symptoms: heavy feeling, breast pain, abdominal pain, headache, numbness (hands, ankles, and breast); and (4) block 4—relational symptoms: changes in sexual life and feeling lonely. Changes in those specific symptoms and the COPE's total score were analyzed in comparison with the basal visit (V3) using an analysis of variance.

Table 1 shows the results of the analysis of the COPE scores. According to response parameters established beforehand in the protocol, 95% of the patients had a reduction higher than 50% at V9 in comparison with the initial COPE score in the luteal phase and a final score

of <40 in the same scale. During the 10 visits of the study, no significant changes in the vital signs (blood pressure, pulse, and weight) were reported in any of the patients. No alterations in the electrocardiogram taken in visits 3 and 9 were observed. The analysis of laboratory tests results (hematology, blood biochemistry, and urinalysis) did not show significant statistical changes in any of the patients. The most common spontaneous adverse events reported by patients were headache (10%) and dizziness (6.6%).

Very little is known about the etiology of premenstrual syndrome. One of them is that hypersensitive steroid receptors in the central nervous system may exist as consequence of disturbances in neurotransmitters outputs, such as serotonin and the mediator mechanisms of the gamma-aminobutyric acid (GABA).⁴ In rats, the consecutive injection of progesterone (P4) results in an increase in serotonin reuptake (5-HT) in several brain areas.⁵ That progesterone effect could explain a diminution in the synaptic levels of serotonin and its metabolite 5-HIAA in urine during the late luteal phase.⁶ As consequence, it is postulated that 5-HT receptors in hypothalamus and other brain areas must experience cyclic fluctuations, undergoing desensitization after ovulation. A recent article investigated that the long-term treatment of cycling female rats with fluoxetine showed a hypothalamic

desensitization of postsynaptic 5-HT_{1A} receptor signaling.⁷ Evidence that antidepressant serotonergic agents are effective treatment for women with severe premenstrual irritability and dysphoria supports this hypothesis.^{1,8-10}

As far as we know, this is the third published study about the intermittent use of 20 mg of fluoxetine daily during 3 consecutive luteal phases. Although this is an open study with a small number of patients with PMDD, it corroborates the efficacy and safety findings reported in the studies of Steiner et al¹¹ and Cohen et al¹² and offers the first data about the efficacy and safety of intermittent therapy with fluoxetine in Latino patients (Colombians). Nevertheless, it is important to point out that the use of the COPE as a primary measure of efficacy reflects a progressive response from the first cycle of treatment that increases more as the cycles of treatment continue. The analysis of the blocks that group the COPE's symptoms lets us conclude that the effect of the intermittent treatment with fluoxetine is faster in the reduction of the dysphoric symptoms, irritability, and tension. However, other affective and physical symptoms show statistically significant changes only from the second cycle of treatment onwards. This progressive response does not correspond to an antidepressant effect because in this study, all the eligible subjects were screened by experienced

TABLE 1. Observed Mean Change and for Each Visit in the Total Score and in the Blocks of Symptoms in the COPE During Luteal Phases

Scale	V3 (n = 21)	V5 (n = 21)	V7 (n = 21)	V9 (n = 21)
Total COPE	164.35	103.21 (37.8)*	74.95 (54.4) [†]	37.81 (77) [†]
Block 1 (%)	65.10	34.14 (47.5) [‡]	21.33 (67.2) [†]	9.19 (85.9) [†]
Block 2 (%)	45.14	33.19 (26.5) (NS)	24.14 (46.5) [†]	12.62 (72) [†]
Block 3 (%)	48.52	34.38 (29.1) (NS)	27.43 (43.5) [†]	14.95 (69.2) [†]
Block 4 (%)	5.59	1.50 (73.2) [§]	2.05 (63.3) [†]	1.05 (81.2) [†]

Block 1, dysphoric symptoms; block 2, other affective nondysphoric symptoms; B3, physical symptoms; B4, relational symptoms.

%, change percentage in comparison with the evaluation in visit 3; P values in comparison to V3.

NS indicates not significant.

*P = 0.06.

[†]P < 0.006.

[‡]P = 0.02.

[§]P = 0.008.

psychiatrists or psychologists to prevent the inclusion of patients with major depressive or dysthymic disorders.

Surprisingly, the fast antidysphoric effect beginning in the first cycle of treatment has not been described in those studies using an intermittent administration of short half-life selective serotonin reuptake inhibitors like citalopram and sertraline. In the study of Alpay and Turhan¹³ with sertraline, 22 of the 23 patients that received intermittent therapy withdrew because of adverse events; in the study of Wikander et al¹⁴ with citalopram, only irritability was evaluated by a visual analogue scale with statistical improvement in the intermittent group respect to placebo since the first cycle of treatment, but other dysphoric symptoms were only present in a subgroup of patients and the changes in this symptoms did not reach statistical significance. Finally, in the Halbreich et al¹⁵ trial with intermittent low doses of sertraline, a progressive improvement in the total score of Daily Record of Severity of Problems is also observed, but in the report, the impact of sertraline over dysphoric symptoms at the first cycle of treatment is not mentioned.

Therefore, we speculate that the increase of serotonin levels in the synaptic gap at the hypothalamus is not enough to explain the improvement of all the PMDD symptoms. The fast antidysphoric effect of fluoxetine could be due to that mechanism and also, perhaps, to the increase in alopregnanolone levels, which is a progesterone metabolite with anxiolytic and antidysphoric effects, probably related to fluoxetine's interaction with GABA_A receptors.¹⁶ It must also be considered that the long half-life of fluoxetine and its active metabolite could offer some level of response over symptoms like fatigue, difficulty concentrating, secondary mood changes, and physical symptoms, which require postsynaptic changes not only in the hypothalamus but also in spinal-thalamic pathways and in different areas of the limbic system. Comparative, randomized studies between different selective

serotonin reuptake inhibitors, with focus on groups of stratified symptoms of PMDD, are needed to confirm the hypothesis stated here.

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Mutation Analysis of the Ryanodine Receptor Gene Isoform 3 (RYR3) in Recurrent Neuroleptic Malignant Syndrome

To the Editors:

Neuroleptic malignant syndrome (NMS) is a rare and life-threatening complication of antipsychotic medication. It is characterized by hyperthermia and muscular rigidity; optional symptoms include CK elevations, lowered

consciousness, and symptoms of autonomic dysregulation.¹ Despite extensive research efforts, the molecular pathways underlying NMS remain elusive. The hypodopaminergic state vulnerability and the Universal Field Hypothesis represent current pathophysiologic concepts.^{2,3} A further hypothesis postulates that a dysregulated hyperactivity of the sympathetic nervous system might constitute a trait vulnerability which, when coupled with state variables, produces that clinical syndrome.⁴ NMS shares several core symptoms with malignant hyperthermia and catatonic schizophrenia (hyperthermia, increased muscle tone, and catatonic symptoms), suggesting similar pathophysiologic mechanisms.^{1,4-7} In particular, the striking symptomatic and pathophysiologic overlap between malignant hyperthermia and NMS supports the hypothesis that NMS might be a neurogenic form of malignant hyperthermia and that vulnerability to both disorders is attributed to mutations in genes involved in the regulation of intracellular calcium homeostasis.^{4,5}

The ryanodine receptors (RYRs) are a family of intracellular Ca^{2+} release channels that play a pivotal role in the regulation of intracellular Ca^{2+} homeostasis in muscle cells and neurons.⁸ The *RYR* genes encode 3 isoforms with different properties and tissue distributions: *RYR1* (skeletal muscle), *RYR2* (cardiac muscle and brain), and *RYR3* (brain and some smooth muscle). So far, 22 different mutations in the *RYR1* gene have been identified to play a causative role in the pathogenesis of malignant hyperthermia, but none of these *RYR1* mutations have been found in NMS.⁹ Taking into account that the sympathetic nervous system might be the pathophysiologic basis of NMS,⁴ the most interesting candidate gene for NMS is the brain-expressed *RYR3* gene. *RYR3* has been localized on the chromosomal segment 15q14-q15,¹⁰ to which periodic catatonia¹¹ as well as a neurophysiologic trait marker for schizophrenia¹² have been mapped. With at least

102 exons coding for a cDNA of approximately 15.5 kb, the genomic organization of *RYR3* is one of the most complex genes in the human genome,¹³ making large-scale screening efforts of *RYR3* a time-consuming and cost-consuming task. We therefore performed a pilot study to screen for mutations in conserved *RYR3* coding sequences in 2 patients with recurrent NMS induced by different antipsychotics.

The diagnosis of NMS was assessed by the diagnostic research criteria for NMS according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (333.92; APA, 1994). Both NMS patients were ascertained through a study on the Genetic Determinants of Neuroleptic Malignant Syndrome, which we have established in collaboration with the Drug Commission of the German Medical Association (Cologne). Blood samples of the patients and clinical details were obtained after written informed consent was obtained. The study was approved by the ethic committee of the Charité, Humboldt University of Berlin. The following casuistic of both patients reports characteristics and clinical features of their first NMS episode and summarizes pharmacologic details on their subsequent NMS episodes.

Patient 1: 44-year-old German female with a 29-year history of schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, 295.3). No family history of psychiatric diseases. Her first psychotic episode (paranoid ideation, massive anxiety, and acoustic hallucinations) occurred at 15 years of age. Four months after initiation of benperidol (10 mg), flurazepam (15 mg), and chlorprothixene (100 mg) treatment, she experienced hyperthermia (38.5°C to 39.5°C), tachycardia (140/min), rigor, and leukocytosis. Rapid discontinuation of all drugs led not only to full remission of clinical NMS features, but also to exacerbation of paranoid delusions after 4 weeks. So far, 6 subsequent NMS episodes according to *Diagnostic and Statistical Manual*

of Mental Disorders, Fourth Edition research criteria occurred at ages 18, 28, 32, 35, 37, and 40 during medication with clozapine, levopromazine, clozapine, haloperidol, haloperidol, and fluphenazine, respectively. Since 2 years, the patient is fully remitted under quetiapine treatment (700 mg) and did not develop any drug-related side effect.

Patient 2: 25-year-old German male diagnosed with paranoid schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, 295.3). Family history with 3 schizophrenic relatives. First prodrome at 16 years, 6 years later, he had his first psychiatric admission to a hospital due to psychotic symptoms (paranoid delusion, acoustic hallucinations, and formal thought disorder), and elevated systolic blood pressure (RR: 205/80 mm Hg), hyperthermia (38.0°C), rigor, and tachycardia were experienced during fluphenazine and lorazepam treatment (dosages unknown) for 50 days. Subsequently, 3 additional NMS episodes occurred during the same year (medications: benperidol, risperidon, thioridazin, respectively) and another 1 year later (medication: haloperidol). Actually, the patient receives risperidon treatment (6 mg) and exhibited no psychotic or NMS features since 2 years.

To search for *RYR3* mutations predisposing to NMS in these 2 patients with recurrent NMS episodes, we sequenced directly the conserved coding sequences and adjacent intron/exon boundaries of the functionally most important *RYR3* domains. The genomic sequence of *RYR3* was derived by in silico-sequence comparison using the BLAT search function of the UCSC Genome Bioinformatics Site (www.genome.ucsc.edu) and the published cDNA sequence (GenBank accession number: NM_001036). Intronic primer pairs were designed and optimized for the amplification of 40 *RYR3* exons (5-6, 8-28, 31-34, 39-43, 51-58), covering a total of 5.56 kb of coding sequences. Primer sequences and assay conditions for the polymerase chain reaction will

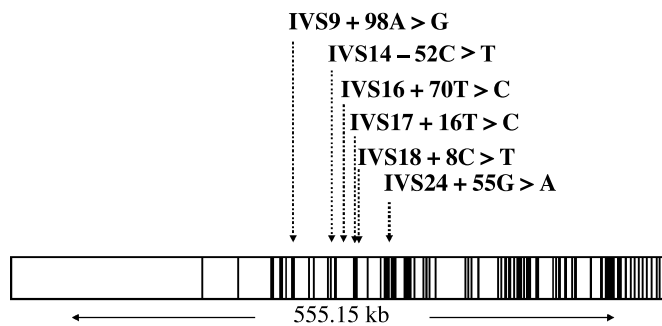


FIGURE 1. Schematic representation of the *RYR3* gene. Vertical bars indicate *RYR3* exons, thick bars represent several exons. Spaces between bars indicate introns larger than 6 kb. Introns and exons are not drawn to scale. The positions of the intronic single nucleotide polymorphisms identified in the present study are given.

be provided on request. Polymerase chain reaction products were directly sequenced on an ABI 377 sequencer (Applied Biosystems, Foster City, CA).

To our knowledge this is the first study searching for *RYR3* mutations in NMS patients. The present mutation analysis of the conserved *RYR3* coding sequences and adjacent intron/exon boundaries did not reveal sequence variants that are likely to confer vulnerability to NMS. No exonic sequence variants were identified, but we detected several intronic single nucleotide polymorphisms (Fig. 1), including IVS9 + 98A → G, IVS14 - 52C → T, IVS16 + 70T → C, IVS17 + 16T → C, IVS18 + 8C → T, and IVS24 + 55G → A, of which none is likely to alter splice mechanisms. Due to the complex genomic organization of the *RYR3* gene, the search for NMS mutations was focused on the conserved *RYR3* sequence motifs, which express the functionally most important *RYR3* domains. Accordingly, it is still possible that we have missed NMS mutations outside the conserved *RYR3* coding sequences in the investigated 2 NMS patients. In particular, target regions for an extended mutation screening should include regulatory elements of the *RYR3* gene, such as the promoter region. In addition, lack of mutations in 2 NMS patients does not exclude the possibility that causative *RYR3* mutations will be identified in other NMS patients, especially those with a familial occurrence of

NMS. Nevertheless, the identified intronic single nucleotide polymorphisms provide valuable tools to search for undetected vulnerability alleles by linkage disequilibrium mapping in larger samples of NMS patients and in other neuropsychiatric disorders, in which the *RYR3* gene is a plausible candidate gene.

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Further Comments on the Effects of Nitrous Oxide Treatment on Alcohol Withdrawal

To the Editors:

Controlled studies show the nitrous oxide technique as an effective alcohol withdrawal treatment but not when used incorrectly and as an isolated pharmacologic agent without the correct therapeutic milieu.

Alho et al have acknowledged that their technique "...may differ from the method of Gillman et al."¹ We wonder why this possibility was not raised in their initial work^{2,3} and had to await a public request for clarification.⁴

Our method titrated to a clinical endpoint⁴ and they titrated to a “thumbsuck” end-tidal volume of nitrous oxide of 30%.¹⁻³ That this is indeed a “thumbsuck” concentration can be readily seen.

First, there is no evidence in the literature that an end-tidal volume of nitrous oxide of 30% results in the amelioration of the alcoholic withdrawal state. We have never alluded to such a concentration and we are not aware of any publications that do so. Indeed, as illustrated by Alho et al,^{2,3} this excessive concentration is no better than placebo.

To justify this “thumbsuck” concentration, they have mistated the literature in 2 instances.^{1,3}

In one of their previous articles, Alho et al³ explained their use of an end-tidal (Et) volume of 30% N₂O by referring to a Cochrane Protocol entitled “Conscious sedation for dental anxiety,”⁵ in which this concentration was said to be recommended for safe conscious sedation.

After perusing the review,⁵ we found no such reference. We contacted Dr Adair (né McGoldrick) who referred us to Dr A. de Jongh, one of her co-authors.⁵ Dr de Jongh agreed with us that Alho et al³ had mistated the Cochrane review (personal communication, Dr A. de Jongh, 2003).

Dr Alho et al also state “Several references on sedative effects in dental surgery and pediatric care of nitrous oxide refer to concentrations between 30% and 50% (inspiratory) in oxygen, as noted in the textbook by Goodman-Gilman et al.”¹ Here, Alho et al quote (as their reference 11) the seventh edition of this standard textbook of pharmacology,⁶ but these concentrations are nowhere mentioned in the pages noted by Alho et al in relation to conscious sedation.¹ Indeed, the textbook states the reverse: “...some patients lose consciousness when breathing 30% nitrous oxide in oxygen.”⁶

The fifth edition of Goodman and Gilman’s textbook states when referring to analgesia (not sedation or relaxation)

that “The optimal concentration of nitrous oxide to produce a maximal degree of analgesia and *yet maintain the co-operation* (our italics) of the subject approximates 35%.”⁷ Furthermore it also states: “As little as 10 volumes % can produce a substantial effect...”⁷

We must emphasize that these are inhaled concentrations of nitrous oxide.^{6,7} And it is well known that the end-tidal volume of the gas both with a nasal mask⁸ or face mask⁹ is much lower.

We are therefore not surprised that the nurse had to make “...sure that the subjects who were receiving N₂O treatment remained fully conscious at all times...”³ This complication is avoided with our technique.¹⁰ We match the concentrations of nitrous oxide to the patients’ clinical state and not the other way round, as done by Alho et al.¹⁻³

In our paradigm, the patient breathes through a nasal mask¹⁰ and through an open system so that concentrations reflected on the flowmeter rotameters are approximately double the values actually reaching the lungs.⁸

Alho et al¹ state and re-state,^{2,3} that “heavily sedating doses”¹ (ie, higher than the 30% end-tidal volume of nitrous oxide) might ameliorate the alcoholic withdrawal state. The continued reference to the possibility that higher doses than the excessive doses they have already used^{2,3} might ameliorate withdrawal is, in our opinion, a “red herring.” This, because we have made it clear to these investigators⁴ that their work^{2,3} has demonstrated that their arbitrarily chosen dose is excessive for almost all patients.^{10,11} They never suggest that lower doses of nitrous oxide than they used could be therapeutic.¹⁻³

We are dealing with an entire technique or paradigm and *not* the isolated use of a pharmacologic agent, in this case nitrous oxide; a technique or paradigm that involves using very low concentrations of nitrous oxide in oxygen. Indeed, rotameter flow rates of as little as 15%,¹⁰ which as mentioned above, results in approximately half this concentration (ie, 7.5%) reaching the lungs⁸

reinforced by a positive milieu¹⁰ and administered by a trained nurse or physician who is aware of the exact, but subtle, clinical endpoint to which they are aiming, is therapeutic.¹⁰

We^{10,11} and other colleagues,¹²⁻¹⁶ do not use the gas merely as a pharmacologic agent, detached from positive clinical support at an excessive concentration, where an arbitrarily chosen end-tidal volume of nitrous oxide is used,^{2,3} a concentration which is clearly much higher than is necessary to get effective relief of the alcoholic withdrawal state.^{4,10,11} The vast majority of patients respond positively at rotameter settings of less than 50% nitrous oxide¹¹ and, in some cases, as low as 15% (ie, approximately 7.5% in the alveoli).¹⁰ This means that only a small minority of patients require nitrous oxide rotameter settings of 60%,^{10,11} which would be approximately equivalents to the 30% end-tidal volume used by Alho et al.^{2,3}

Alho et al have suggested that their inability to reproduce our technique¹⁰ ‘is a basic flaw in the current evidence-based era where all interventions should be described in such a detailed way that independent workers can repeat them.’¹ In theory this may apply, but in practice this is open to question. It is for this reason that scientists and physicians travel to learn hands-on techniques with which they are not familiar, despite detailed descriptions of these techniques in scientific papers. We know personally of 3 colleagues in South Africa and 3 in the United States who have been able to successfully repeat our work in the clinical setting by only reading our papers.

Alho et al¹⁻³ also make the claim that their work is the first “controlled and *detailed* (our italics) reported study with nitrous oxide on alcohol withdrawal signs”¹ and dismiss our work¹⁷ which was published 6 months before their article² “...as not really placebo-controlled, double-blind...”¹

We generally do not believe that it is wise to use a placebo in a trial of the therapeutic efficacy of pharmacologic agents in human subjects, except perhaps

in very special circumstances. Instead, we compared the effects of nitrous oxide against a benzodiazepine, which is regarded as the gold standard^{3,17} for current treatments of the alcoholic withdrawal state, in a randomized double-blind manner.^{17,18} In our work,^{17,18} the trained nurse was unaware of the gas she administered, which is clearly of utmost importance for reasons discussed earlier.⁴ This was not the case in the work of Alho et al.^{2,3}

We believe that the work of Alho et al^{2,3} is, nevertheless, extremely important because they have demonstrated unequivocally that training in our paradigm is almost always essential to repeat our successful use of nitrous oxide for alcohol withdrawal.^{4,10,11,17,18} and that excessive concentrations of nitrous oxide are no better than placebo.^{2,3}

We trust that the debate sparked by the work of Alho et al¹⁻³ will encourage others to test our technique using low doses of nitrous oxide in oxygen on the alcoholic withdrawal state. Our previous offer¹⁶ to arrange training to any interested investigators remains open.

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