# Letters to the Editor

## Possible Effects of Ibuprofen Pretreatment on Seizure Duration During Electroconvulsive Therapy

**Sir:** Leung and colleagues[1] recently reported on the pretreatment of patients undergoing electroconvulsive therapy (ECT) with ibuprofen in an apparently successful attempt at reducing the incidence of post-ECT headache. One of the more interesting findings from their data, however, goes unmentioned in their discussion of the otherwise useful study. Table 1[(p552)] in their article compares the placebo group and the ibuprofen group on a number of factors, one of which is seizure duration. Although the difference between the 2 groups did not meet the authors' a priori significance level of .05, it did produce an interesting p value of .16 with those patients given ibuprofen, 600 mg, 90 minutes prior to the ECT treatment averaging a seizure duration almost 5 seconds longer compared with those given placebo. The current literature reveals that high doses of ibuprofen have been shown to induce seizures.[2,3] It is unknown whether therapeutic doses such as those used by Leung and colleagues[1] also increase the likelihood of a seizure or might prolong the duration of an artificially induced seizure.

One possible mechanism by which ibuprofen might be linked to seizure activity is through alterations in extracellular potassium levels. Poirier[4] describes a case in which, in the presence of even therapeutic doses of ibuprofen, an increase in the dose of ibuprofen apparently caused hyperkalemia. Pan and Stringer[5] have demonstrated that increasing potassium can cause neurons in the dentate gyrus to depolarize.

Whether ibuprofen, 600 mg, administered prior to ECT treatment affects seizure duration is an important question in light of Leung and colleagues'[1] study showing likely benefit for patients with post-ECT headaches. The issue of whether there are other effects of administering ibuprofen prior to ECT is an area worthy of further examination.

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## Higher Levels of Anger and Aggressiveness in Major Depressive Disorder Than in Anxiety and Somatoform Disorders

**Sir:** The recent articles by Koh and colleagues[1] and Posternak and Zimmerman[2] highlighted the frequent presence of anger, aggressiveness, and hostility in unipolar depression. Depressed outpatients scored higher on various measures of anger and hostility than outpatients with anxiety or somatoform disorders,[1] and a strong association was found between a diagnosis of major depressive disorder (MDD) and the presence of anger and aggression.[2]

We, too, have recently drawn attention to anger in unipolar depression. In 2 samples of outpatients with various unipolar depressive conditions, we identified through factor analysis a depressive dimension, an anxious dimension, and an "activation" dimension consisting of anger, irritability, aggressiveness, hostility, and psychomotor activation.[3] The samples had been assessed with, respectively, the revised version of the Minnesota Multiphasic Personality Inventory (MMPI-2) (N = 143) and the Scale for Rapid Dimensional Assessment (SVARAD) (N = 380), a validated observer-rated scale for the rapid assessment of the main psychopathologic dimensions. All patients were free of comorbid Axis I or II disorder and were not receiving treatment with antidepressants. Anger and aggressiveness were found to be clinically relevant in more than 20% of patients.

To test whether Italian patients with depression display higher levels of anger and aggressiveness than patients with anxiety or somatoform disorders, we studied patients consecutively admitted from 2000 to 2002 at the psychiatric outpatient clinic of the La Sapienza University of Rome (Rome, Italy).

*Method.* We included all patients with a DSM-IV diagnosis of MDD (N = 222, mean age = 48.9 years, 64% females), anxiety disorder (N = 258, mean age = 40.2 years, 53% females; panic disorder, N = 112; anxiety disorder not otherwise specified, N = 79; generalized anxiety disorder, N = 19; obsessive-compulsive disorder, N = 17; adjustment disorder with anxiety, N = 12; social phobia, N = 9; simple phobia, N = 8; posttraumatic stress disorder, N = 2), or somatoform disorder (N = 26, mean age = 40.9 years, 50% females; undifferentiated somatoform disorder, N = 21; hypochondriacal disorder, N = 5) who had no Axis I or II comorbidity and had not received antidepressants in the preceding 2 months.

At admission, all patients underwent a careful psychiatric examination lasting about 90 minutes and were rated on the SVARAD[4] by resident physicians. All diagnoses were confirmed by 2 faculty psychiatrists who reviewed clinical records. Each of the SVARAD items is rated on a 5-point scale (0–4), with higher scores indicating greater severity. Ten dimensions are assessed by the SVARAD; our analysis focused on item 3, anger/aggressiveness, which is defined as follows: "anger, resentment; irritability, litigiousness, hostility; and verbal or physical violence."

*Results.* The mean anger/aggressiveness score of patients with MDD was 0.82, significantly higher (p < .01) compared with that of patients with anxiety (0.57) or somatoform disorders (0.58). The difference remained significant (p < .01) when multivariate analysis of variance was used to adjust for age and gender. Also, the proportion of patients with clinically relevant anger/aggressiveness (score ≥ 2) was significantly higher (p < .05) among patients with MDD (N = 48, 21.6%) than among patients with anxiety (N = 29, 12.3%) or somatoform disorders (N = 3, 11.5%). The difference remained significant (p < .01) in a multiple logistic regression model including age and gender.

In MDD patients, we found a modest correlation (rho = 0.20, p < .01) between scores on the anger/aggressiveness and sadness/demoralization items. In anxiety disorder patients, this correlation was low and nonsignificant (rho = 0.11, p = .11), and in somatoform disorder patients, it was also nonsignificant, possibly because of the small sample size (rho = 0.25, p = .22).

*Discussion.* This study has some limitations. We did not include a healthy control group. We also relied on single ratings of anger and aggressiveness and were thus unable to separate anger suppression from anger expression. Further, our results were drawn from a single site and have limited generalizability. Strengths of the study are its exclusion of patients with psychiatric comorbidity and of patients recently treated with antidepressants.

Overall, our findings support a link between anger and depression.[1,2] Regarding possible explanations, attachment theory suggests that in some depressed patients anger and aggressiveness can be part of the protest-despair-detachment reaction to a loss, either actual or symbolic.[5] Personality factors might also play a role. Furthermore, both depressed mood and anger or aggression might be related to serotonergic dysfunction.[6]

In conclusion, evidence is accumulating that anger, irritability, aggressiveness, and hostility are often present in unipolar depression. Their proper recognition by clinicians has important implications for treatment.

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

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**Table 1. Characteristics of 109 Patients Treated With Olanzapine[a]**

| Characteristic | Value |
| --- | --- |
| Age, y | 45.4 ± 14.4 |
| Gender, male/female, N | 76/33 |
| Dose of olanzapine, mg/d | 16.6 ± 7.0 |
| Duration of olanzapine treatment, d[b] | 243.6 ± 96.4 |
| Glucose level, mg/dL | |
| Baseline | 96.9 ± 14.5[c] |
| Endpoint[d] | 99.0 ± 3.6[e] |
| Body mass index (kg/m$^2$) | |
| Baseline[f] | 23.4 ± 3.6 |
| Endpoint[d] | 24.1 ± 3.6 |
| Family history of diabetes, N | 14 |

[a]Values shown as mean ± SD unless otherwise noted.
[b]From start of olanzapine treatment to performance of fasting glucose test.
[c]Also includes random glucose level.
[d]Time when fasting glucose test was performed.
[e]Only fasting glucose level.
[f]Body mass index data at baseline were available for 88 of the 109 cases.

## The Incidence of Hyperglycemia in Patients Treated With Olanzapine

**Sir:** Atypical antipsychotics are extensively used for the treatment of schizophrenia and other psychoses. However, several published reports of glucoregulatory abnormalities related to atypical antipsychotics, particularly clozapine and olanzapine, have appeared.[1]

Olanzapine was launched in June 2001 in Japan. In April 2002, it was reported that 9 cases treated with olanzapine developed severe hyperglycemia and diabetic coma, and 2 of the 9 patients died. Quetiapine was launched in February 2001 in Japan. In November 2002, it was reported that 13 cases of severe hyperglycemia and diabetic coma occurred during quetiapine therapy and 1 of the patients died. In response, the Japanese Ministry of Health, Labor, and Welfare modified the package inserts for olanzapine and quetiapine. These 2 drugs are contraindicated for patients with diabetes or a history of diabetes. It is only in Japan that such stringent measures have been taken in response to reports of abnormality in glucose regulation associated with atypical antipsychotics.

We paid particular attention to olanzapine-associated glucoregulatory abnormality for several reasons. Clozapine is not available in Japan; we treat severely ill patients using olanzapine, and we wanted to accurately assess the risk of hyperglycemia during olanzapine therapy.

It has been reported that the incidence of new-onset diabetes associated with olanzapine treatment ranges from 6% to 35%.[2] These incidence estimates were based on small sample sizes, with limited clinical and laboratory details. Regarding the incidence of hyperglycemia associated with olanzapine, the manufacturer of olanzapine calculated an incidence of 3.1%, but used glucose ≥ 160 mg/dL as a diagnostic threshold, which is not an established cutoff.[3] Wirshing and colleagues[4] reported that when a cutoff of 126 mg/dL for glucose was used, 27.3% of patients receiving olanzapine developed hyperglycemia, and when a cutoff of 200 mg/dL was used, 4.6% developed hyperglycemia. However, due to the retrospective nature of their study, it was unknown whether the glucose levels obtained through medical records were fasting measurements. To date, there have

**Table 2. Characteristics of the 5 Patients Who First Developed Hyperglycemia While Receiving Olanzapine**

| Characteristic | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Age, y | 49 | 45 | 25 | 28 | 55 |
| Gender | M | M | F | M | M |
| Dose of olanzapine, mg/d | 20 | 40 | 15 | 20 | 25 |
| Duration of olanzapine treatment, d[a] | 315 | 333 | 327 | 331 | 348 |
| Glucose level, mg/dL | | | | | |
|   Baseline[b] | 125 | 85 | 92 | 82 | 98 |
|   Endpoint[c] | 169 | 160 | 220[d] | 215[d] | 212[d] |
| BMI (kg/m$^2$) | | | | | |
|   Baseline | 27.6 | 27.2 | …[e] | 22.1 | 23.6 |
|   Endpoint[f] | 26.1 | 22.3 | 30.9 | 23.6 | 26.0 |
| Family history of diabetes | + | − | − | − | − |
| Previous antipsychotics taken | Haloperidol, 6 mg/d Fluphenazine, 12 mg/d Levomepromazine, 100 mg/d Fluphenazine decanoate, 62.5 mg/10 d | Quetiapine, 150 mg/d Sulpiride, 100 mg/d | Fluphenazine, 4 mg/d Fluphenazine decanoate, 50 mg/14 d | Zotepine, 300 mg/d Levomepromazine, 10 mg/d | Fluphenazine, 8 mg/d Chlorpromazine, 200 mg/d Levomepromazine, 50 mg/d |
| Concomitant antipsychotics[g] | Haloperidol, 0.75 mg/d Fluphenazine, 10 mg/d Levomepromazine, 50 mg/d Fluphenazine decanoate, 62.5 mg/10 d | Levomepromazine, 50 mg/d | … | Zotepine, 200 mg/d Fluphenazine decanoate, 12.5 mg/14 d | Levomepromazine, 200 mg/d |

[a]From start of olanzapine treatment to diagnosis of hyperglycemia.
[b]It is unclear whether these results are fasting or random glucose levels.
[c]Time of diagnosis of hyperglycemia.
[d]Random glucose level.
[e]No BMI data available at baseline.
[f]Time when fasting glucose test was performed.
[g]Prescriptions at time of diagnosis of hyperglycemia.
Abbreviations: BMI = body mass index, F = female, M = male. Symbols: + = positive, − = negative.

been no large-scale population studies using adequate indicators of glucose metabolism.

*Method.* The sample for our study investigating the association between olanzapine and hyperglycemia consisted of 109 patients treated with olanzapine in Yamanashi Prefectural Kita Hospital (Nirasaki, Japan) who had not been diagnosed with diabetes mellitus before starting olanzapine therapy (Table 1). To clarify the incidence of hyperglycemia related to olanzapine therapy, we performed a fasting glucose test (after obtaining informed consent). We also retrospectively checked glucose values during olanzapine treatment prior to this fasting glucose test. Hyperglycemia was defined as a fasting glucose level $\geq 126$ mg/dL or a random glucose level $\geq 200$ mg/dL. If hyperglycemia appeared more than 2 times, diabetes mellitus was diagnosed.

*Results.* Five (4.6%) of the patients in our study developed hyperglycemia for the first time while receiving olanzapine (Table 2). In 3 of these cases (cases 3, 4, and 5), hyperglycemia was temporary; olanzapine treatment was continued with close monitoring of glucose levels. The other 2 patients (cases 1 and 2) were diagnosed with diabetes mellitus and olanzapine treatment was discontinued. For case 1, hyperglycemia did not improve after discontinuation of olanzapine, and so initiation of glucose-lowering agents was required.

We need to carry out a prospective study with a larger sample size to ascertain the risk of hyperglycemia when using atypical antipsychotics.

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## Searching the Medical Literature for Case Reports

**Sir:** Relan et al.[1] have drawn our attention to priapism as an important and potentially very serious adverse effect of risperidone. However, they were inaccurate in finding only 3 priapism cases linked to risperidone in the literature.

Any case report of an unusual event associated with a drug must include a detailed description of the literature search per-

formed, including the databases searched, date of the search, and details of the search strategy. The elements of a minimum literature search for the purposes of writing a case report are illustrated below by applying them to Relan and colleagues' case.

First, a MEDLINE search using the search terms as "textwords" should be conducted. When I used PubMed to search MEDLINE on May 1, 2003, the terms *priapism* and *risperidone,* with no qualifiers, resulted in 15 citations. Thirteen of these were unique case reports in which priapism/prolonged erection was attributed wholly or partly to risperidone.[1–13]

Second, one should identify the appropriate Medical Subject Headings (MeSH) and use them to perform the search. In many cases, using the MeSH terminology results in a more powerful search, since any synonyms are subsumed under the MeSH term. However, in this example, the MeSH terms are the same as the original terms, and no new citations were obtained. Using *priapism* and *risperidone* as MeSH terms, I obtained 14 citations, presumably because the Relan et al. letter was not classified in the MeSH database yet.

Third, databases other than MEDLINE should also be searched. A search of EMBASE, the electronic version of Excerpta Medica, is particularly recommended because it covers European literature[14] and medications[14,15] especially well. A search of EMBASE using the textwords shown above resulted in 2 additional references.[16,17]

Fourth, one should examine the references cited in the case reports found, which yields additional references at times, though not in this case.

References for the original reports of the cases identified in the literature should be given. Relan et al. instead refer only to a review article[18] that similarly notes only 3 cases of the association of risperidone with priapism. A MEDLINE search using *risperidone* and *priapism* as textwords and limiting the date of publication to 2001 showed that Compton and Miller[18] were correct that only 3 cases[10,11,13] of priapism had been reported on MEDLINE at the time of their review. (A fourth report[12] referred to prolonged erections rather than true priapism, and 1 report[9] was probably published while Compton and Miller's review was in press.) However, this review also missed 1 case report[17] that was indexed on EMBASE but not on MEDLINE.

Giving a brief outline of the search strategy allows the interested reader to duplicate the search, reveals what literature was not searched, and indicates that the value of the case was carefully weighed[15] and put in context. Additional strategies to identify cases of rare adverse events published as case reports should include contacting the manufacturer of the drug and searching the Web site of the U.S. Food and Drug Administration (http://www.fda.gov). Relan and colleagues would have benefited from looking at all of the previously reported cases and learning more about the issues that should have been highlighted in their case report.

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

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## Drs. Gupta and Mattoo Reply

**Sir:** Mago's brief but comprehensive description of the requirements and logistics of a literature search for a psychiatric publication is commendable. Yet, his call for strict adherence to these in the context of our case report is somewhat misplaced and hence debatable.

On May 1, 2003, using the keywords *priapism* and *risperidone*, Mago found 13 case reports and 2 other citations on MEDLINE, 14 citations that were essentially the same using Medical Subject Heading (MeSH) terms, and 2 more on EMBASE.

We[1] missed the 2 EMBASE citations[2,3] found by Mago for the simple reason that we did not have access to this subscription-based source—a common shortcoming for researchers from the developing countries that is often compensated for during the review process by the journals' reviewers. In our case report (which underwent peer review), neither of the reviewers advised addition of further references, possibly for the simple reason that inclusion of further citations would not have significantly affected the content or objective of our case report.

Our case report, submitted in June 2002, was based on a MEDLINE search conducted in April 2002 that had yielded 3 case reports[4–6] and a review article.[7] Thus, we[1] and the authors of that review article[7] missed only 2 publications[2,3] that antedated April 2002 and were quoted by Mago. Understandably, we could not have cited all other references found by Mago, as they postdated our MEDLINE search.

Mago justifies a comprehensive literature search for case reports to identify "issues that should be highlighted." This approach can be followed only up to a point for a number of reasons. Constraint of print space demands that the case reports

be short—most journals now publish case reports only as letters to the editor, with a usual limit of 500 words. Adverse drug reactions are known to be underreported, and the reporting of adverse drug reactions is sufficient in itself[8] (without describing their etiopathogenesis, which demands more print space). In addition, highlighting too many issues in a case report may defeat the very purpose of that report by confounding issues.

Lastly, while quoting citations, Mago includes 2 case reports that describe prolonged erections with risperidone,[4,5] which are not the same as priapism.[7]

*Drs. Gupta and Mattoo report no financial affiliation or other relationship relevant to the subject matter of this letter.*

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## Visual Hallucinations With Sertraline

**Sir:** Selective serotonin reuptake inhibitors (SSRIs) have been known to cause visual hallucinations (VHs): 1 case each for fluvoxamine[1] and paroxetine,[2] 4 cases with sertraline,[3–6] and 5 cases with fluoxetine[3,7–9] have been reported. On the other hand, a case of VHs following fluoxetine discontinuation has also been described.[10] We report a case of a patient who experienced VHs while on therapy with sertraline.

*Case report.* Ms. A, a 70-year-old woman, was evaluated in July 2001 for memory loss and attention deficits and depressed mood and severe anxiety. Delusional thoughts, visual or auditory hallucinations, and behavioral disorders were absent. Neurologic examination results were normal. The patient's Mini-Mental State Examination (MMSE)[11] score was 22/30, showing mild temporal disorientation, retrieval memory impairment, and sustained attention deficit. No additional psychological testing was performed. Blood tests proved to be within normal limits. A brain magnetic resonance scan showed mild frontal atrophy compatible with age.

Ms. A's medical history was positive for recurrent depressive episodes. In 1967, the patient was admitted to the psychiatric hospital for depressed mood, feelings of guilt, and penance rituals. Moreover, the patient expressed a religious delusion characterized by themes concerning the search for her children's salvation. During her stay in the hospital, she was treated with neuroleptic therapy and electroconvulsive therapy. No hallucinations were ever reported during her stay in the hospital or in the following decades. The patient has been treated for several years with 10 mg of once-daily amitriptyline and 4 mg of once-daily perphenazine.

At the present examination, the patient was not on drug treatment. To exclude a case of depressive pseudodementia, a treatment with sertraline (50 mg q.d.) was started. About 3 weeks later, although her cognitive and psychiatric symptoms had improved (MMSE score = 26/30), the patient started to experience VHs, which were present almost daily, lasting from seconds to minutes. The hallucinations usually concerned unknown people enjoying themselves by hiding the patient's personal objects. On one occasion, the patient saw a tiger seated in her daughter's car. The patient's visions were quite realistic and were accompanied by no auditory hallucinations or delusional thoughts. The VHs would frighten her at first, but she would gain insight into their false nature within a few seconds.

As a consequence of these symptoms, it was decided to discontinue sertraline. The VHs disappeared a few days after, but the depressive symptoms recurred, and therefore citalopram was started.

Currently, after a 1-year follow-up, the patient is still on therapy with citalopram, and her depressed mood and cognitive deficits have improved. Since the sertraline discontinuation, the patient has experienced no further VHs.

Complex VHs occur in several neuropsychiatric conditions. The pathophysiology of VHs is still debated; nevertheless, a release of inhibition phenomena of the association cortex has been suggested.[12] In particular, 3 principal neurotransmitters seem to be involved in VHs: serotonin (5-HT), acetylcholine (ACh), and dopamine.

It has been suggested that in predisposed patients, SSRIs may induce psychotic symptoms by a $5\text{-HT}_2$ and $5\text{-HT}_3$– mediated dopamine release in ventral striate.[4,5,7,8,13] Dementia, Parkinson's disease, head injury, depression with psychotic symptoms, and bipolar disorders have been proposed as risk factors for developing SSRI-related VHs.[4,5,7,8,14] Of note, the symptoms of our patient did not satisfy the diagnostic criteria for any neurodegenerative disease. In most cases, other drugs might have precipitated VHs in patients on therapy with SSRIs through different mechanisms: anticholinergic drugs by worsening the 5-HT/ACh imbalance,[5,7] oxycodone by increasing 5-HT release in the forebrain,[6] dextromethorphan by inhibiting the cortical glutamatergic projections,[9] and zolpidem by a pharmacodynamic potentiation involving 5-HT and omega receptors.[15]

In view of the aforementioned cases and the literature-reported hypotheses concerning the pathophysiology of VHs, we propose that the VHs experienced by our patient may be related to sertraline treatment. Sertraline, as suggested with other SSRIs, may have produced VHs via dopamine release in the mesolimbic pathway by stimulation of $5\text{-HT}_2$ and $5\text{-HT}_3$ receptors. This effect could have been enhanced by a direct action exerted by sertraline on the dopamine receptors, as sertraline has a greater affinity for dopamine receptors than do other SSRIs.

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

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