Respiratory Dyskinesia as Discontinuation Effect of Risperidone

To the Editors:

Atypical antipsychotics, among them risperidone, cause less extrapyramidal side effects, including tardive dyskinesia (TD), than conventional antipsychotics.\(^\text{1}\) One of the many presentations of TD reported is respiratory dyskinesia (RD) which is characterized by involuntary movements of respiratory muscles, irregular respiration, grunting, dyspnea, and reactive hyperventilation.\(^\text{2}\) To the best of our knowledge, there are no reports of risperidone causing RD. We present a case of RD after the discontinuation of risperidone in a demented elderly patient.

CASE REPORT

An 84-year-old woman with dementia was referred to the geriatric psychiatric outpatient clinic. The Mini-Mental State Examination score was 16/30, and the Cambridge Cognitive Examination score was 55/105. She had visual hallucinations, was prone to falls, and presented with fluctuations in cognitive functioning. We diagnosed dementia with Lewy bodies (DLB).\(^\text{3}\) Her current medication was 10 mg donepezil, and 2 mg risperidone in the previous 3 months. During this period, the only nonpsychotropic substance she received was ranitidine 150 mg. There was no record or indication of prior use of psychotropic medication.

During examination, rigidity in the upper limbs with cogwheel phenomenon was noted.

Risperidone was gradually withdrawn over a period of 1 week, and quetiapine was introduced at a dose of 25 and, later, 50 mg/d. Three days after risperidone withdrawal, the caregivers reported that the patient's condition deteriorated. Reported symptoms included anxiety with bouts of hyperventilation. During examination, she displayed involuntary movements of the respiratory musculature. She grunted and displayed signs of distress resulting from irregular respiration. No additional dyskinetic symptoms were noted. We diagnosed RD and restarted 2 mg risperidone. This resulted in immediate symptom alleviation. Risperidone dosage was reduced in 0.5-mg intervals over a period of 3 months, during which respiratory symptoms were subjectively reported as being much less severe with no accompanying discomfort. The treatment with quetiapine remained unchanged. Six months after the initial observation of RD, no symptoms remained.

To our knowledge, this is the first report on RD after risperidone treatment. This condition is most often observed in patients displaying symptoms of TD after treatment with antipsychotics. In our patient with DLB, it occurred as discontinuation effect. The prevalence of RD is 2.3% in chronic inpatients and 7.4% among those with TD.\(^\text{4}\) It is often underrecognized or misdiagnosed as anxiety or restlessness.\(^\text{5}\) Patients with Parkinson disease can also develop spontaneous RD.\(^\text{6}\) This is worth considering because Parkinson disease and DLB seem to share important neuropsychiatric and pathobiologic features, including degeneration of the dopaminergic nigrostriatal system.

Some authors have reported low incidence of TD with the administration of risperidone in dementia,\(^\text{1}\) but our case underlines the high vulnerability for side effects on antipsychotics in patients with DLB.

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REFERENCES


Plasma Risperidone Levels and Clinical Response in Patients With First-episode Psychosis

To the Editors:

Risperidone (RSP) is an atypical antipsychotic with antagonistic properties at serotonin 5-HT\(_2\) and dopamine D\(_2\) receptors. Orally administered RSP is readily absorbed and extensively metabolized to various metabolites including the main metabolite 9-hydroxyrisperidone (9-OH-RSP) by cytochrome P450 enzymes, especially CYP2D6\(^*\) and CYP3A.\(^\text{2}\) 9-OH-RSP may reach the brain at substantial concentrations and contribute importantly to pharmacological actions and subsequent clinical outcomes after RSP doses.\(^\text{3}\) Therefore, previous studies suggest that it is important to measure steady-state plasma levels of total active moiety by analyzing both RSP and 9-OH-RSP for plasma drug monitoring.\(^\text{4}\)

The pharmacokinetics of RSP shows a wide interindividual variability under the influence of various physiological, genetic, and environmental factors such as age, CYP2D6 genotype, and so on.\(^\text{5–7}\) In a recent study, Spina et al.\(^\text{8}\) assessed the relationship between plasma levels of RSP and 9-OH-RSP and clinical response in 42 schizophrenic patients who experienced an acute exacerbation of the disorder. In this open-label study, the authors concluded that the plasma levels correlated with the occurrence of extrapyramidal side effects (EPSs), but not with the degree of clinical improvement.

The aim of this study was to assess the relationship between plasma levels of RSP and its active metabolite, 9-OH-RSP, and the clinical response in drug-naive Asian patients with first-episode psychosis.

The study population comprised 19 consecutive referrals to the inpatient and outpatient services of the Early Psychosis Intervention Programme,
Singapore. Drug-naive patients with first-episode psychosis who were started on RSP monotherapy and who gave a written informed consent were recruited. Patients were excluded if they had received concomitant therapy with other antipsychotic, antidepressant, or mood stabilizer medication, as well as if they had a history of current substance use or serious medical illness. Diagnosis was made using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I disorders.\(^8\)

Patients were assessed at baseline before being started on RSP and then at weeks 2, 6, and 12. Each assessment included the following measures: Positive and Negative Syndrome Scale (PANSS) to assess the psychopathology\(^9\) and Simpson-Angus Scale for Extrapyramidal Side Effects\(^10\) to rate the severity of EPSEs. The assessments were done by experienced psychiatrists who were trained in the use of the rating instruments. Interrater reliability coefficient among the raters was established at 0.80.

RSP was started at a dose of 0.5 to 1 mg/d and increased gradually to a target dose of 1 to 3 mg/d, based on the therapeutic response and development of side effects. The patients were administered the entire dose at night before sleep.

Blood samples for the determination of RSP and 9-OH-RSP levels were obtained at the end of week 12. Blood samples were taken in the morning, 12 hours after the last dose. The determination of the RSP and 9-OH-RSP levels was performed by high-performance liquid chromatography method using ultraviolet detection.\(^11\)

Spearman rank correlation coefficient was used to test the correlations between the dose and plasma drug levels, between the dose and clinical response, and between plasma levels and clinical response. Statistical significance was set at \(P < 0.05\).

Nineteen Chinese patients (10 men and 9 women) with a mean (SD) age of 28.74 (6.7) years and mean (SD) duration of untreated illness of 11.91 (22.04) months completed the study. The mean (SD) daily dose of RSP prescribed was 1.47 (0.56) mg. The mean (SD) reduction in PANSS score was from 64.58 (3.33) at baseline to 41.32 (2.20) at week 12. Only 2 patients developed EPSE as defined by Simpson-Angus Scale for Extrapyramidal Side Effects score of 0.3 or more.\(^12\)

The mean (SD) plasma levels were as follows: RSP, 2.77 (3.66) ng/mL; 9-OH-RSP, 9.62 (6.10) ng/mL; and active moiety (RSP + 9-OH-RSP), 12.39 (8.21) ng/mL. There was a significant correlation between plasma levels of RSP and 9-OH-RSP \((r = 0.66, P = 0.002)\). We also observed a significant correlation between the dose of RSP per kilogram of body weight at week 12 and plasma levels of 9-OH-RSP \((r = 0.46, P = 0.046)\), but not with plasma levels of RSP and active moiety. After adjusting for dose, there were no significant correlations between age or sex and plasma levels of RSP, 9-OH-RSP, and active moiety. After adjusting for dose, there were no significant correlations between age or sex and plasma levels of RSP, 9-OH-RSP, and active moiety.

We did not find a significant correlation between plasma levels of RSP, 9-OH-RSP, and active moiety with improvement in PANSS scores (%) (Fig. 1). Two patients (9.50%) developed EPSE as defined by Simpson-Angus Scale for Extrapyramidal Side Effects score of 0.3 or more.\(^12\) Patients who developed EPSE did not have significantly higher plasma levels of RSP, 9-OH-RSP, and active moiety than patients who did not develop EPSE.

**DISCUSSION**

Atypical antipsychotic drugs are gradually becoming the first-line agents in the treatment of first-episode psychosis. By examining the correlation between the dose, plasma levels, and clinical response, we sought to better understand the role of therapeutic plasma drug monitoring for RSP in patients with first-episode psychosis.

There was a significant correlation between weight-normalized dose of RSP and 9-OH-RSP plasma levels, but not RSP plasma levels. This finding suggests that 9-OH-RSP is an important and clinical active metabolite of RSP and needs to be measured in the therapeutic plasma monitoring.

We did not find a significant correlation between dose of RSP and clinical response. We also did not find a correlation between plasma drug levels and clinical response. However, a closer look at the scatterplot figure indicated that this was because of 2 subjects who were nonresponders, and when they were not included in the correlational analysis, there was indeed a significant correlation between clinical response and plasma levels of RSP, 9-OH-RSP, and active moiety. A closer clinical look at these 2 patients indicated that one of them showed a delayed response (after the end of study period). In the second patient, the psychotic symptoms had resolved; however, there was an emergence of depressive and anxiety symptoms, and this increased the PANSS scores. Hence, there may be a trend toward a correlation between plasma drug levels and clinical response. However,
To the Editors:

In chronic psychotic illnesses such as schizophrenia, oral antipsychotic medications are administered daily during maintenance treatment. Efforts to reduce exposure through prolonged drug holidays (eg, intermittent treatment) or use only when symptoms emerge (eg, targeted therapy) have been associated with increased relapse rates.1–3

Several recent lines of investigation, however, caused us to rethink the issue of daily administration. Dopamine D2 receptor blockade appears to be the sine qua non of antipsychotic activity,4 and more recent work involving positron emission tomography indicates that the optimal chance of clinical response occurs when D2 occupancy exceeds 65%.5 Therapeutic doses of risperidone and olanzapine demonstrate D2 occupancy in the range of 70% even 48 hours after the last administration.6 In addition, drugs such as quetiapine achieve antipsychotic response with only transiently high D2 daily occupancy.7 Along similar lines, haloperidol decanoate maintains response despite D2 occupancy levels dropping to less than 65% by the end of the injection interval.8 It has also been demonstrated that the injection interval for fluphenazine decanoate can be extended from every 2 weeks to every 6 weeks without compromising response.9 Postulating that extended (but regular) dosing may be sufficient to maintain antipsychotic response, we conducted a pilot study as proof of principle.

Subjects were recruited from the Schizophrenia Program at the Centre for Addiction and Mental Health, a tertiary care setting associated with the University of Toronto. The study was approved by the human subjects review committee, and subjects provided written informed consent after receiving detailed information about the protocol.

Inclusion criteria included (i) outpatient status, (ii) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnosis of schizophrenia or schizoaffective disorder, (iii) stabilization on a single oral antipsychotic 3 months or longer with no change on the Clinical Global Impression Scale over 2 weeks before study entry, (iv) no depot antipsychotic use in the last year, (v) no current history of substance-related disorders, and (vi) antipsychotic compliance; that is, both study candidate and treating clinician independently assessed compliance with current antipsychotic treatment to be greater than 90%.

Subjects could be on any oral antipsychotic, typical or atypical, except clozapine and quetiapine, based on current thinking regarding their D2 binding profile, that is, rapid dissociation10,11 and anecdotal evidence linking abrupt discontinuation of such agents with rapid relapse.12

The trial was open, and at baseline, participants were instructed that their antipsychotic would be decreased in 2 phases, each 3 months in duration. The plan was to administer the medication at the current dose every second day for the first 3 months, and should the patients remain stable, the interval was to increase to every third day. A calendar detailing the schedule was provided, and follow-up visits were scheduled every 2 weeks, with the primary outcome measure being change in clinical symptoms using the Brief Psychiatric Rating Scale and Clinical Global Impression Scale.13

Thirteen subjects were recruited, with individual data summarized in Table 1. Six individuals completed the pilot study as proof of principle.

REFERENCES


"Extended" Antipsychotic Dosing Rationale and Pilot Data

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<th>Other Psychotropic Drugs/Daily Dose at Baseline</th>
<th>Trial (wk)</th>
<th>Baseline BPRS</th>
<th>CGI</th>
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*DSM-IV* indicates *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression.

†Benzodiazepine prescribed for insomnia in initial weeks of trial (clonazepam 0.5 mg or lorazepam 1 mg nightly, as needed).

At 3 months, subject was stable but requested to continue alternate day dosing for the second 3 months.
were prescribed benzodiazepine as needed for sleep disturbance on the drug-free nights.

Data analysis included 11 subjects, excluding the individual who relapsed because of noncompliance and a subject who withdrew consent and did not attend beyond the first visit. Paired t tests using baseline versus end point scores for the Brief Psychiatric Rating Scale and Clinical Global Impression Scale failed to show significant differences for each: \( t_{11} = 0.50, P = 0.63; \) and \( t_{11} = 0.00, P = 1.0, \) respectively. Scales to evaluate extrapyramidal symptoms were completed; however, scores at baseline were so low that statistical analyses were not carried out.

Because antipsychotics have also been linked to the induction of depression and secondary negative symptoms, Brief Psychiatric Rating subscales addressing withdrawal/retardation, anxiety/depression, and activation were analyzed, but again, paired t tests failed to show significant differences: \( t_{10} = 1.20, P = 0.26; \) \( t_{10} = 0.11, P = 0.92; \) and \( t_{10} = 1.15, P = 0.28, \) respectively.

Advances in understanding regarding the relationship between \( D_2 \) blockade, clinical response, and side effects\(^{6,6}\) led us to hypothesize that efficacy of antipsychotic drugs might be maintained with intermittent but regular, that is, extended, antipsychotic dosing, and these pilot data suggest that this may be possible. Only 1 of the 13 individuals enrolled in the study, who stopped his antipsychotic completely, relapsed.

Why would we entertain extended dosing that is, in practice, more complex than regular daily medication administration? The goal in antipsychotic treatment is one of minimizing exposure without compromising efficacy. All currently available antipsychotics have dopamine-blocking properties and can adversely influence cognition, affect, and motivation,\(^{14}\) even at relatively low doses. Reducing antipsychotic dose is therefore beneficial in this regard, but the \( D_2 \) occupancy data would suggest that there is a threshold, in the level of 65%, below which response may be compromised.\(^5\) In contrast, it appears that sustained \( D_2 \) occupancy above this threshold is not required, offering another means of decreasing overall antipsychotic exposure.\(^7,8\)

Although we were unable to establish improvement in these other clinical domains with the current measures, various participants did describe subjective improvement and a preference for the extended dosing approach. In addition, issues such as weight gain, metabolic disturbances, and lipid dysregulation have come to the fore with the atypical agents, and while it is not known yet whether decreasing exposure can reduce such effects, it is a reasonable possibility to explore. Finally, studies such as this have important theoretical implications regarding the underlying mechanisms of action necessary to maintain response.

We highlight the preliminary nature of these data and their limitations. This was a small, open, pilot study, and the patient sample represented a select subgroup: stable, has minimal polypharmacy, reasonable to excellent symptom control, compliant, and has no concomitant substance abuse. Whereas only one individual relapsed, that is, the person who stopped his medication completely, 5 others discontinued for other reasons, resulting in 6-month data on only 6 subjects. It can also be argued that a longer follow-up interval is required to fully evaluate the risk of relapse.

We are, however, encouraged by the findings and have now undertaken a larger double-blind trial to better evaluate our hypothesis.

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ACKNOWLEDGMENTS
The authors thank the patients for their participation.

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The Prevalence of Hyperprolactinemia After Long-term Haloperidol Use in Patients With Chronic Schizophrenia

To the Editors:
Chronic prolactin elevations should be a major focus in clinical practice...
because of the potential risk of serious chronic medical problems such as menstral abnormalities, gynaecomastia, galactorrhea, osteoporosis, and cardiovascular disease. However, there have been few studies on the prevalence of chronic hyperprolactinemia in the patients with schizophrenia. To examine the prevalence of hyperprolactinemia in the chronic schizophrenia with long-term haloperidol use, serum prolactin levels were examined. All patients with oral haloperidol monotherapy in 2 large psychiatric facilities in Korea were evaluated. Inclusion criteria included subjects with a Diagnostic and Statistical Manual of Mental Disorders diagnosis of schizophrenia and between the ages of 18 to 45 years. In addition, only those on haloperidol monotherapy (~1 year) and who received the same dosage for at least 3 months (mean dose, 15.7 ± 10.9 mg/d; median dose, 15.0 ± 12.5 mg/d) were included. Benzotropine and benzodiazepine were the only concomitant medications permitted. Sixty subjects (28 women and 32 men) were enrolled in this study. The mean illness duration was 15.5 ± 7.8 years. Hyperprolactinemia was defined as a serum prolactin level of more than 20 ng/mL for men and more than 24 ng/mL for women. Two-tailed Student t tests were used to evaluate the clinical variables. Spearman rank correlation was used to examine the relationship of prolactin level to haloperidol dose and weight. All tests were 2-tailed, and significance was defined as an r less than 0.05. All patients were enrolled into this study after giving written consent. This study was approved by the institutional review board of Busan Paik Hospital, Inje University.

Overall, 66% of the subjects had hyperprolactinemia. Prolactin levels were not significantly related to body mass index. There were no significant differences in age (38.9 ± 5.0 vs. 40.6 ± 4.6 years), duration of haloperidol treatment (86.5 ± 62.2 vs. 95.5 ± 55.5 months), and dose of haloperidol (15.0 ± 12.1 vs. 16.3 ± 10.0 mg/d) between women and men (Table 1). However, the mean prolactin level for women was significantly higher than that for men (73.8 ± 46.2 vs. 24.15 ± 15.56 ng/mL, t58 = −5.52, P < 0.0001). The prevalence of hyperprolactinemia for women (93%) was significantly higher than that for men (47%; χ²1 = 14.59, P < 0.0001; Table 1). A significant correlation was observed between haloperidol dose and serum prolactin level in women (r = 0.4262, P = 0.021), but not in men (r = 0.15, P = 0.414). Among women of reproductive age and men, the percent of hyperprolactinemia was 69.6% and 42.4%, respectively. By drug group, among women, this corresponded to 88% with risperidone treatment and 47.6% with conventional drug. This prevalence is noted to be lower than our results; however, dose in our study is higher than the dose reported by Kinon et al which may explain some of the variance. Mean antipsychotic dosing in our subjects was 14.9 ± 12.1 mg/d of haloperidol versus 401.9 ± 398.6 mg/d chlorpromazine equivalents reported in the other study. Although the dose of both groups was sufficient to block most D2 receptors in the tuberoinfundibular tract, it is difficult to compare their results directly with ours, because they included a host of conventional antipsychotics. Interethnic difference from a pharmacogenetic standpoint should also be considered to explain the higher rate of prolactin elevations found in our study. It is known that the activity of cytochrome P450 enzyme such as CYP2D6 is different between Asians and whites, and this can cause an interethnic difference in therapeutic outcome, adverse effects, and toxicity in subjects of different ethnic origin undergoing antipsychotic drug treatment.

<table>
<thead>
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<th>TABLE 1. A Comparison Between Women and Men</th>
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<td><strong>Women (n = 28)</strong></td>
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<td>% With hyperprolactinemia (n)</td>
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<td>% With menstrual disturbances (n)</td>
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Values given are mean ± SD, median ± interquartile range. NA indicates not assessed.
It is interesting whether Aw et al reported that patients with hyperprolactinemia showed early peaks in prolactin with haloperidol which then decreased, yet still remained above the reference range after completing the early phase. Our findings support that prolactin elevations with haloperidol are at least sustained and can be cumulative; however, this should be confirmed with further prospective studies.

A few limitations should be considered in interpreting the findings of this report. First, it is a cross-sectional study with no comparator. Next, the sample size was small. Lastly, the dose of haloperidol was higher than doses used in other clinical studies, because of chronic nature of patients of sample.

Our study suggests that hyperprolactinemia with long-term haloperidol treatment is more frequent and serious than in short-term treatment. Schizophrenia is a chronic mental disorder, and most patients with schizophrenia need antipsychotic drug throughout their lifetime. While more long-term studies are needed to characterize the risk of hyperprolactinemia with adverse consequences, a few recent studies have demonstrated bone loss and breast cancer. Furthermore, poor subjective well-being regarding hormonal side effects and sexual dysfunction related to hyperprolactinemia can complicate the clinical outcomes of treatment. Our findings also suggest that sex specificity must be considered when one interprets the prolactin response to antipsychotic drug in the clinical practice as well as in the research setting. Because of the importance of long-term health outcomes for patients, more attention should be paid to the minimized impact of this adverse effect in both sexes.

ACKNOWLEDGMENTS
This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (0412-CT02-0704-0006).

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Delusional Disorder With Delusions of Parasitosis and Jealousy After Stroke
Treatment With Quetiapine and Sertraline

To the Editors:
Delusional parasitosis is a rare psychiatric disorder characterized by the false and persistent belief of being infested by parasites. Pimozide usually has been considered the treatment of choice, although the increasing and successful use of atypical antipsychotics with a more favorable side effects profile has raised doubts about this practice. We report the case of a 74-year-old woman with very mild vascular dementia who developed a mixed delusional disorder that included delusions of parasitosis secondary to stroke. Partial clinical remission was achieved with relatively low quetiapine and sertraline, with no significant side effects. Few reports on the use of quetiapine or olanzapine in delusional parasitosis have been published.2,3 Aw et al did not find quetiapine to be useful in 2 cases. However, Kim et al and Wenning et al reported isolated successful cases. Thus, to our knowledge, the present report offers the first evidence of the successful combined use of quetiapine and sertraline in patients with delusional parasitosis.

CASE REPORT
Mrs A., a 74-year-old woman, had right hemispheric stroke at age 71 years (November 2001), resulting in left hemiparesis and confinement to a wheelchair. She was moved to an old people’s home for appropriate medical care. One year later, she referred itching particularly around orifices. She thought that this was due to being infested by minute but macroscopic black insects smaller than lice which she claimed to be able to catch and try to kill off by using ammonia. In July 2003, 2 months after her husband began to live in the same old people’s home, she began to accuse him of cheating on her despite the lack of objective data. Secondly, she
became depressed, with difficulties initiating and maintaining sleep, and had dysphoria, depressed mood most of the day, frequent thoughts of death (although without suicidal ideation), decreased appetite, and markedly diminished pleasure in most of her activities. She firmly stated that all depressive symptoms were due to her husband cheating on her, and she based her accusation on the observation that he spoke with other women in the residence. Previously, no affective symptoms had been reported. Finally, in September 2003, she began to explain that she kept a gold medallion which was very precious to her in one of her shoes, in an attempt to prevent it from being stolen. This was when a first psychiatric assessment was carried out. Her medical history comprised hypertension, type II diabetes mellitus, and 2 previous right hemispheric strokes. No previous psychiatric antecedents were found. Her mental status was consistent with mild dementia, and brain magnetic resonance imaging disclosed diffuse cortical retraction, a hypodense zone in the right lobe, multiple hypodensities suggestive of cerebrovascular disease, and a lesion in the right brainstem and mesencephalic region. Laboratory testing revealed the following: blood glucose, 398 mg/dL; cholesterol, 369 mg/dL; folate, vitamin B₁₂, iron, and thyroid hormones, all within reference range; and negative syphilis testing. Mild vascular dementia and a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision) diagnosis of psychotic disorder secondary to general medical condition were established. She was put on sertraline 100 mg/d, ziprasidone 40 mg/d, and bromazepam 3 mg/d. Two weeks later, both ziprasidone and bromazepam were discontinued due to confusional state and irritability. As she continued showing the preceding psychiatric symptoms, the sertraline dose was increased to 150 mg/d, and quetiapine was introduced at an initial dose of 25 mg. This was progressively increased in 25-mg steps every 3 days to avoid potential hypotension, to a maximum of 300 mg/d. Two months later, no evidence of depressive syndrome was observed. She was also able to fully criticize her jealousy delusion and partially her delusional parasitosis and spent much less time scratching herself (having been convinced that she had eliminated the insects).

**DISCUSSION**

Although few controlled studies have been carried out, pimozide continues to be considered the treatment of choice in delusional parasitosis, based mainly on case-report series. Full recommendation with pimozide is between 28%1,2 and 50%8 to 82%.9 However, treatment with pimozide is limited by its side effects profile, and atypical antipsychotics have also proven effective—especially risperidone.3,10,11 Sertindole has been mentioned as useful only in a single case file12 and has not been proven to be particularly effective. In addition, the drug has been withdrawn from the market.

It has been proposed that atypical antipsychotics may be considered early in the management of patients diagnosed with delusional parasitosis, because these patients are very reluctant to accept psychiatric treatments, and atypical antipsychotics offer a better side effects profile.4,8 However, caution has been advised with the use of risperidone, due to the risk of extrapyramidal reactions.1,3 Moreover, considering that, in the present case report, delusional parasitosis was secondary to vascular dementia and that, recently, the Committee on Safety of Medicines recommended avoiding risperidone and olanzapine in patients with dementia due to concerns over the excess risk of stroke,13 and despite the fact that another recent publication found both drugs to pose no statistically significant increase in the risk of cerebrovascular accidents versus typical antipsychotics,14 it seems mandatory to question whether the rest of atypical antipsychotics could be an alternative in these patients. In a preliminary work, Schneider et al15 reported no evidence of an increased risk of cerebrovascular adverse events associated with the use of quetiapine in elderly patients with dementia.

It should also be taken into account that, in our patient, vascular dementia was probably secondary to previous hypertension, type 2 diabetes, hypercholesterolemia, and 2 previous right hemispheric strokes. It seems that type-2 diabetes is an independent risk factor for cognitive decline and dementia.16 Indeed, in a 6-year follow-up of 274 elderly participants (36 with diabetes and 238 without diabetes), Hassing et al17 found type 2 diabetes to be associated with accelerated cognitive decline in old age that may result in dementia.

Quetiapine is a second-generation antipsychotic of demonstrated efficacy in application to schizophrenia18 and bipolar disorder.19 Although the labeled dose range is 400 to 800 mg/d, higher doses have been used with good clinical outcome and a favorable side effects profile.20 Blockade of the 5-HT receptors—specifically of 5-HT₂ receptors—has been hypothesized to be important in delusional parasitosis.1,3 However, quetiapine is a relatively low—5-HT₂ affinity antipsychotic and was found to be useful in this case report—although the potential role of sertraline should also be taken into account, because the patient was treated with both sertraline and quetiapine at the time of improvement.21 In addition, clomipramine monotherapy has been found to be effective in the treatment of somatic-type delusional disorders, thus suggesting some association between somatic-type delusional disorder and serotoninergic dysfunction.22 Clomipramine may have been a potentially useful treatment in this case report, because the patient also presented secondary depression due to delusions of jealousy. The absence of prior depressive symptoms after stroke and the chronological coincidence of the depressive symptoms with her husband beginning to live with her in the same residence led us to diagnose secondary depression due to delusions of jealousy and not poststroke depression, because the disturbance was better accounted for by the former diagnosis. Furthermore, both the delusions of jealousy and the depressive episode subsided at the same time after the treatment was started. On the other hand, only a weak relationship has been described between poststroke depression and right hemispheric lesions.23

Quetiapine offers several advantages in the treatment of delusional states in the elderly, due to its favorable side effects profile, with a lack of anticholinergic activity,24 extrapyramidal symptoms, or cardiovascular adverse outcomes.25 Moreover, the most common side effects of quetiapine—drowsiness, dizziness, and postural hypotension—rarely result in withdrawal from therapy in elderly patients with psychotic disorders.1,3 However, the potential use of quetiapine in nonschizophrenic psychotic syndromes and nonpsychotic disorders remains unexplored,12,13,26 and further research is needed to consider quetiapine as a first-line treatment option.
for delusional parasitis and other psychotic syndromes in the elderly.

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Periodic Restless Legs Syndrome Associated With Quetiapine Use

A Case Report

To the Editor:

Restless legs syndrome (RLS) is a common disorder with prevalence ranging from 2% to 15% of general adult population but is often undiagnosed or misdiagnosed. Some second-generation antipsychotics such as risperidone and olanzapine have been reported to cause secondary RLS, whereas others have been reported to help it. No cases of RLS attributed to quetiapine were found on MEDLINE and EMBASE searches done on February 28, 2005. We report a case of RLS possibly induced by quetiapine.

A 68-year-old white female with bipolar I disorder, manic with psychotic symptoms, developed parkinsonian symptoms of cogwheel rigidity, bradykinesia, and tremor on a combination of risperidone and lithium (serum level, 1.2 mEq/L). There was no akathisia at that time. The parkinsonian symptoms resolved completely on tapering off the risperidone and reducing the dose of lithium. Two months after discontinuing risperidone, she was started on quetiapine 100 mg/d for insomnia, depressed mood, and mild agitation. The dosage was titrated up by 50 mg/d. Within 24 hours of receiving 200 mg/d, she complained of uncomfortable and annoying sensations in both her legs that were worse at rest and at night and relieved on moving the legs. These sensations worsened the initial and middle insomnia, and the patient would walk about at night to relieve her symptoms. Neurological examination did not show abnormalities. There was no prior history of RLS, and other causes including increased caffeine intake, anemia, renal failure, and other medication use were excluded. Serum ferritin level was within reference range at 50 ng/mL. Polysomnography could not be done because of short duration of symptoms. There was history of idiopathic RLS in a second-degree relative. Quetiapine was reduced to 150 mg/d, and the sensations, restlessness, and sleep disturbance resolved completely within 48 hours.

Six weeks later, an attempt was made again to increase the dose of quetiapine to 200 mg/d to control mild agitation as there was lack of efficacy with 150 mg/d. Within a day, she had recurrence of unpleasant sensations in her legs that were worse in the evening and at night and relieved with movement of legs, and her sleep was disturbed. After 3 days, she reduced the dose to 150 mg/d with complete resolution of the symptoms, and she remains symptom-free at 6 months.

The case described satisfies the RLS diagnostic criteria established by...
International Restless Leg Syndrome Study Group. Restless leg syndrome has to be differentiated from akathisia as the 2 conditions share some clinical features, and quetiapine has been reported to cause akathisia. The symptoms of dysesthesias in the legs, desire to move because of the dysesthesias rather than internal restlessness, increased severity at rest, diurnal variation with worsening at night, significant sleep disturbance from dysesthesias, and a family history of RLS suggest a diagnosis of RLS.

Restless leg syndrome is frequently associated with periodic limb movement disorder that can only be diagnosed with polysomnography. Polysomnography was not done in this instance, and hence, the association with periodic limb movement disorder cannot be ascertained. Close temporal relation between use of quetiapine 200 mg/d, complete resolution with a decrease in dose, and reemergence on rechallenge with higher dose indicate that quetiapine was the likely etiologic agent and that it was a dose-dependent side effect. Dopaminergic dysfunction is considered to be a pathophysiologic mechanism in the development of RLS, and drugs that block dopamine receptors are likely to induce RLS. Of the second-generation antipsychotics, quetiapine has lower and more transient D2 dopamine receptor occupancy of 58% to 64% and may be least likely to induce RLS. It has also been shown to improve RLS induced by other second-generations antipsychotics such as risperidone. However, physicians should be aware that quetiapine could cause RLS when there are associated risk factors such as family history, older age, and female sex, and reduction in dosage or discontinuation of the medication may be adequate to resolve the RLS.

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Lisinopril May Augment Antidepressant Response

To the Editors:
The ability of the central nervous system to maintain euthymic mood requires a number of structural features, including:
- Anatomic integrity of the neural circuitry involved in maintenance of normal mood;
- Intact regulation of neurotransmitter synthesis, storage, and release;
- Biochemical regulation of second and subsequent messenger pathways;
- Functional neuroendocrine regulation; and
- Ability of the blood flow system at the cellular level to provide glucose and oxygen for oxidative phosphorylation and energy to operate.

A number of medications prescribed mainly for the treatment of cardiovascular disorders are known to have effects on mood and cognition. A historically early antihypertensive, reserpine, was soon shown to have a significant effect in causing major depressive disorder (MDD) in some patients. On the other hand, there is no clear relationship between whether compounds raise or lower blood pressure, and the nature of influence mood or cognition. A number of antihypertensives also do not clearly influence mood or cognition, such as diuretics. Two other antihypertensives, clonidine and guanfacine, have been reported to improve performance in many patients diagnosed with mood-lifting properties. In replicated trials, verapamil, a calcium-channel blocker, has been shown to have mood-stabilizing properties.

It is our preliminary observation in 10 patients that the angiotensin-converting enzyme (ACE) inhibitor lisinopril may also demonstrate mood-stabilizing potential. It is our purpose in this brief communication to describe some of the characteristics of these patients and the results of their treatment. Internists or cardiologists were treating all 10 patients for hypertension primarily, without reference to their mood disorders. Nine of these patients had had MDD. At least 1 of these 9 had a strong family history of bipolar disorder. The tenth patient had documented bipolar disorder.

The diagnoses in all but 2 of these patients (both of these patients with MDD) were confirmed by one of us (M.H.), using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. Thus, the diagnoses included the required criteria for MDD or bipolar disorder, as well as excluding patients with alternative, or confounding reasons for mood disorders.

Our original observations in the present series were the following:
A 50-year-old white woman was being treated for refractory MDD with

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bupropion, to a dose of 300 mg every day (qd). During the course of treatment, her blood pressure increased, and bupropion was discontinued. At the same time, lisinopril, 10 mg qd, was prescribed for hypertension by her internist. Contrary to expectation, a month later, her mood had improved significantly and has remained so since.

A 60-year-old white man had MDD and a strong family history of bipolar disorder. Lithium, 1200 mg qd, failed to improve his depression and was discontinued. His mood began to improve upon this regimen and provided some additional improvement of mood. At about this time, her internist added lisinopril 10 mg for the first time to treat her hypertension. She has maintained a reasonably stable mood for 1.5 years on lisinopril alone.

The remaining patients also had improved mood with a combination of antidepressant and lisinopril. None of these patients reported significant side effects from lisinopril treatment, whether alone or in combination with other medications.

**DISCUSSION**

To our knowledge, this is the first report of possible mood-stabilizing effects from the ACE inhibitor, lisinopril. In none of these cases was lisinopril deliberately instituted to achieve this effect. However, it appeared to be tolerated well.

The relationship between depressive illness and hypertension is probably complex. Depressive disorders are over-represented in individuals who have hypertension, although no clear evidence supporting a causal relationship has been established. Coffey et al. had demonstrated microvascular changes (unidentified bright objects on T2-weighted magnetic resonance imaging) in depressed patients before electroconvulsive therapy. Dysregulated cortisol release in depressed patients may contribute to increased blood pressure. Robinson et al. have elucidated poststroke depressions, and hypertension is a clear risk factor for cerebrovascular disease.

There is at least some indirect evidence, which may indicate a role for ACE in the central nervous system as a factor in regulating affective state. The central nervous system is rich in receptors for angiotensin II. Such receptors have been demonstrated in preclinical models to be involved in the regulation of dopamine and in the regulation of the balance between dopamine and serotonin. Other studies have implicated angiotensin II receptors in regulation of substance P, a current target for novel antidepressant development. Central nervous system ACE activity has been reported to be increased in suicidal patients.

The relationship of ACE inhibition to successful antidepressant augmentation remains speculative. Bioamine regulation might account for at least some of this effect. An intriguing alternative is that angiotensin II inhibition may promote increases in microvascular cerebral profusion. Such an increase in perfusion might facilitate neuronal activation in circuits where receptor down-regulation by antidepressants acts synergistically to improve mood. Studies in depressed patients suggest region-specific cortical activation derangements, which can be reversed by appropriate frequency transcranial magnetic stimulation.

At the present time, we believe that it is as yet unjustified to treat patients for mood problems with lisinopril alone. However, this small series suggests that expanding the sample of patients with mood disorders who happen then to be placed upon lisinopril coincidentally may render a firmer statement as to the extent to which lisinopril may have mood-stabilizing properties. We are presently expanding the sample under study by having internists and cardiologists prescribe as they ordinarily would, and then obtaining patient self-completed mood rating scales before and during treatment with lisinopril.

This study also opens the question as to whether other ACE inhibitors or, perhaps, other antihypertensive medications may also have mood-stabilizing properties.

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Extrapontine Myelinolysis Resembling Neuroleptic Malignant Syndrome

To the Editors:

Early recognition of neuroleptic malignant syndrome (NMS) is crucial in preventing morbidity and mortality by allowing for discontinuation of triggering drugs and rapid implementation of treatment.1,2 However, a premature diagnosis of NMS can have significant adverse consequences. Overdiagnosis of NMS could result in delayed recognition and treatment of other serious medical disorders that present with similar symptoms.1–3 Furthermore, an incorrect diagnosis of NMS may inhibit future antipsychotic treatment because of unwarranted concerns about recurrent episodes.

The need to carefully consider alternative diagnostic causes of fever and encephalopathy is heightened in patients receiving second-generation antipsychotics (SGAs) because these agents are less likely to induce NMS.4,5 In addition, SGAs may cause a milder or “atypical” form of NMS, which is less specific and therefore more difficult to distinguish from other disorders.4,5 To illustrate these points, we describe a unique case in which NMS was initially considered in a patient receiving quetiapine, who subsequently proved to have extrapontine myelinolysis (EPM).

To our knowledge, this is the first report of EPM mimicking NMS.

CASE HISTORY

A 14-year-old girl, with pan-hypopituitarism and diabetes insipidus, presented with diarrhea, lethargy, and a serum sodium of 106 mEq/L. She had been receiving nasal desmopressin 10 µg twice a day, hydrocortisone 10 mg daily, and levotyroxine 150 µg daily. Significant psychiatric history included pervasive developmental disorder. Diagnosis of NMS became the working diagnosis because of the change in mental status, extrapyramidal symptoms, and elevations in temperature and creatine kinase. She received dantrolene, carbidopa/levodopa, and lorazepam, but her level of consciousness and neurological status deteriorated. Four days later, her creatine kinase increased to 2800 IU, but she became afebrile. A serum quetiapine level was nontoxic.

One week later, a magnetic resonance imaging of the brain showed bilateral high-signal intensity in the caudate and putamen with restricted diffusion. Combined with the history of hyponatremia, these magnetic resonance imaging findings confirmed the diagnosis of EPM. She eventually regained normal motor and sensory function. However, treatment of reemerging behavioral problems with antipsychotics was complicated by concerns over recurrence of NMS due to the possibility of NMS having occurred with quetiapine in this patient.

DISCUSSION

We describe a case in which NMS associated with quetiapine was initially considered in a patient subsequently shown to have EPM. In retrospect, most of her symptoms could be attributed to EPM.

EPM typically presents with obtundation, quadriplegia, and pseudobulbar palsy after correction of hyponatremia.6 Classic signs of EPM, which reflect demyelination of the base of the pons, can be missed because of the limited extent of the lesions or obscured by associated medical conditions. In addition, variants of the syndrome are increasingly recognized with myelinolysis occurring outside the pons, including the basal ganglia (EPM).6 For example, there are several case reports in which EPM presented with levodopa-responsive parkinsonism or catatonia.7–12 These cases showed a consistent clinical pattern that may be helpful in diagnosing EPM; each patient deteriorated after a variable period of improvement in mental status after recovery from hyponatremia.

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Familiarity with the diagnoses of EPM and CPM is relevant to psychiatric practice because water intoxication leading to hyponatremia is a well-known phenomenon that requires treatment in a subgroup of patients with chronic psychiatric disorders. In retrospect, NMS was an unlikely cause of the features in our patient. She did not exhibit generalized rigidity, extreme hyperthermia, labile autonomic signs, or other secondary symptoms of NMS. The elevation of creatine kinase was non-specific and does not confirm the diagnosis of NMS. Although SGAs may produce a mild form of NMS, we believe that quetiapine was not a factor in this case. She received quetiapine for 2 years without incident and previously received more potent antipsychotics without NMS. In fact, there are still few unequivocal reports implicating quetiapine monotherapy in causing NMS. The low affinity and fast dissociation of quetiapine in relation to dopamine receptors should diminish the risk of NMS with this agent.

We previously proposed that the liability of SGAs in causing extrapyramidal symptoms, including NMS, may be significant only when they are administered in high-risk populations. Risk factors for the development of NMS may include hyponatremia and preexisting basal ganglia dysfunction. It follows that patients who sustain basal ganglia damage associated with EPM after hyponatremia and who are also receiving SGAs could be at increased risk of developing NMS. Hence, it can be difficult to distinguish EPM from NMS in these patients, and we cannot exclude entirely the possibility of a transient NMS-like effect of quetiapine in our case.

In conclusion, we report the first case of EPM mimicking NMS. Although these are rare conditions, EPM and CPM have been associated previously with catatonia and parkinsonism and should also be included in the differential diagnosis of NMS. Furthermore, this case underscores the importance of identifying serious medical disorders as well as NMS in patients presenting with fever and neurological changes during treatment with antipsychotic drugs. Errors in excluding either category of illness prematurely can be fatal.

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Impaired Glucose Homeostasis After Imipramine Intake in a Diabetic Patient

To the Editors:

The tricyclic antidepressant (TCA) imipramine is primarily indicated for the treatment of depression, but in practice, it is also used for other disorders. We describe a patient with type II diabetes mellitus, in whom changes in insulin need were closely associated with the use and dose changes of imipramine, which was prescribed for the treatment of urinary incontinence.

CASE DESCRIPTION

A 62-year-old woman was treated for several years for type II diabetes mellitus with the oral hypoglycemic agent glimepiride (4 mg daily). Since November 27, 1998, she additionally used NPH insulin before the night, but the correction of the blood glucose was only moderately successful because the average HbA1C level was 9.0% (normal value, 4.4%–6.1%). On July 13, 2000, a urologist prescribed imipramine (25 mg at bedtime) because of urinary incontinence. On September 12, 2000, the diabetologist switched the oral hypoglycemic treatment in combination with bedtime NPH insulin to intensive insulin therapy (multiple daily injection regimen) with blood glucose self-monitoring and algorithm-based adjustment of insulin dose. Glucose measurements as well as the amount of injected insulin were monitored and registered by the patient on a daily basis in a “diabetes diary.” From September 12, 2000, to May 29, 2002, the average insulin dose was 81 U/d, and the HbA1C level was 8.4% on August 16, 2001, and 6.8% on March 13, 2002. On May 30, 2002, the dose of imipramine was increased from 25 mg once daily to 25 mg twice daily

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Letters to the Editors

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Tissue sensitivity does decrease in response to imipramine. The measured HbA1C level was 6.5% and 7.4%, respectively. We further analyzed the time relationship between the intervention and the change in insulin requirements. Several mechanisms have been described in literature that may be involved in imipramine-induced glucose deregulation. Like most TCAs, imipramine inhibits the synaptic reuptake of norepinephrine and serotonin (5-hydroxytryptamine [5-HT]) at nerve terminals. Norepinephrine may stimulate glycogenolysis and gluconeogenesis resulting in increased blood glucose levels or reduced insulin release. Because these effects occur in a short time span, these mechanisms could not explain the time gap between the interventions with imipramine and effects on glucose homeostasis. Another mechanism encompasses a blockade of TCAs of M2 receptors in beta cells, resulting in suppression of insulin secretion and increased leptin levels, also inhibiting insulin secretion by the pancreas.

**FIGURE 1.** Time relationship between insulin dose and imipramine dose.
This case report illustrates that imipramine can affect glucose homeostasis in diabetic patients. Although the mechanism is still unclear, physicians have to be conscious that imipramine, and probably other antidepressants, can impair diabetes control in some sensitive patients. Further research is needed to elucidate the mechanism for this effect and to find out which patients are at risk.

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Diplopia With Citalopram
A Case Report

To the Editors:

Citalopram is an antidepressant which effects serotonergic neurotransmission through potent and selective inhibition of serotonin reuptake. Neuroendocrine studies suggest decrease of serotonergic responsivity in patients with major depression. Citalopram is (1) superior to placebo in the treatment of depression; (2) is similar to that of the tricyclic and tetracyclic antidepressants and to other selective serotonin reuptake inhibitors; and (3) is safe and well tolerated in the therapeutic dose range of 20 to 60 mg/d.1 Data from 3107 patients from 24 clinical trials2 showed that nausea, dry mouth, somnolence, increased sweating, tremor, diarrhea, and ejaculation failure, mostly of mild to moderate severity, occurred with a significant frequency with citalopram.

However, bruxism, cutaneous reactions, dorsale de pointes, bradycardia and hypotension, hyponatremia secondary to syndrome of inappropriate secretion of antidiuretic hormone, priapism, panic attacks, palpebral twitching, photopigmentation, galactorrhea, and hypertriglyceridemia have been reported rarely with citalopram.

Diplopia is an unusual phenomenon that may occur after citalopram ingestion.3 Diplopia is defined as double vision. Binocular diplopia is a type of double vision that is eliminated when either eye is occluded.4 Causes of binocular diplopia are isolated third, fourth, and sixth cranial nerve palsies, orbital disease, cavernous sinus/superior orbital fissure syndrome, posttraumatic status, intranuclear opthalmoplegia, verteobasilar artery insufficiency, other central nervous system lesions, and spectacle problem.5

Here, we report a 28-year-old man who developed diplopia after citalopram ingestion. To our knowledge, there is no report on the interval after which this side effect is eliminated after discontinuation of the drug.

CASE REPORT

MZ was a 28-year-old, single, medical student, who lived in a university dormitory, and met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition nonpsychotic major depressive disorder criterion for 6 months before his referral. There was no history of past psychiatric problem in childhood and adolescence. His condition deteriorated day by day that led him to drop several courses. He was urged by the university to visit our clinic.

After his referral, he was examined in our clinic. The patient’s score on 21-Item Hamilton Depression Scale was 34. There was a positive history of major depressive disorder in his father.

Citalopram, 20 mg/d in the morning, was prescribed to him. After 12 days, incapacitating diplopia appeared. This condition was accompanied with diarrhea and memory complaints. He was frightened and described the condition as “It is terrible. I see everything in 2. I don’t know which is real and which is artificial. If I concentrate and close one eye, I will be able to differentiate the real one.”

There was no positive finding in neurological and ophthalmologic consultations. Citalopram, the only medication he was taking, was discontinued. After 60 hours, the diplopia disappeared completely, and he felt relaxed.

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How Safe Is Long-term Benzodiazepine Pharmacotherapy?

To the Editors:

One of the more contentious issues in clinical practice concerns the long-term use of benzodiazepines. Many authorities have cautioned against such use because of concerns about dependence, cognitive impairment, and risk of falls in the elderly and have recommended substituting selective serotonin reuptake inhibitors and related agents as first-line treatment for long-term management of anxiety disorders and non-pharmacological treatment for chronic insomnia. Despite the voluminous literature on benzodiazepines, there have been, to my knowledge, no systematic studies on the frequency and type of adverse events occurring in patients populations receiving long-term (ie, >6 months) benzodiazepine pharmacotherapy. The authors of a major review article have said, “While we have an immense body of knowledge about many of the effects of benzodiazepines, we have very little information about either the benefits or the risks of long-term use.”

I recently reviewed the records of my last 22 years of general psychiatric practice in a multispecialty private clinic affiliated with a university hospital health system and wish to share the highlights of my experience with respect to the safety of this form of treatment.

A total of 836 patients received continuous benzodiazepine pharmacotherapy for 6 months or longer. Duration of use ranged from 6 months to 21 years. Median duration was 3.5 years.

Five hundred sixty-one patients received benzodiazepines for daytime treatment of anxiety symptoms and 80 for nighttime treatment of insomnia, and 195 received treatment for both anxiety and insomnia.

All but 85 patients received concomitant psychiatric medication.

In my opinion, the most important finding was that only 7 patients (0.8%) had to have benzodiazepines discontinued because of adverse events, 6 patients for alcohol abuse–related events, and 1 patient for abusing multiple drugs. None of these resulted in death or serious injury.

One hundred forty-four patients (17%) had adverse events not serious enough to require discontinuation of benzodiazepine treatment. Of these, 116 had a concomitant substance abuse diagnosis, and 28 had a psychiatric diagnosis alone at the time of initial evaluation.

In the dual diagnosis group, the commonest types of adverse events were episodes involving abuse of alcohol and street drugs. Other adverse events included motor vehicle accidents (no serious bodily injuries) and abuse or overdose of benzodiazepines. There was an incident each of the following: prescription forgeries, fall, suicide, sudden death (no autopsy), early refill of benzodiazepine prescription, and falling asleep with lighted cigarette (no injury).

In patients without a substance abuse diagnosis, the commonest adverse events were abuse or overdose of benzodiazepines or other drugs, or seeking early prescription refill (19), motor vehicle accidents (6), falls (4), and arrests for driving under the influence (2). Some of these patients probably were incorrectly diagnosed as not having a substance abuse problem at the time of initial evaluation.

In most cases, it was impossible to determine whether the adverse events were caused by benzodiazepines or were related to the underlying psychopathology (particularly substance abuse disorders) and would have occurred anyway had the patient not been receiving long-term benzodiazepine therapy.

Three percent of patients had been prescribed at some time during their treatment a dose higher than the manufacturer’s recommended upper limit for daytime use. Fifteen percent of patients had been prescribed a dose higher than the manufacturer’s recommended upper limit for hypnotic use. None of these latter were higher than twice the upper limit, for example, 60 mg of flurazepam.

Assuming that the experience in my practice is typical of clinical practices in general (which admittedly may not be the case), I conclude that long-term benzodiazepine therapy is relatively safe. In choosing a long-term treatment for anxiety symptoms, for many patients, the relative safety of benzodiazepines may compare favorably with that of selective serotonin reuptake inhibitors and related drugs, taking into account the benefits and risks of long-term use.

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consideration the well-known side effects of the latter such as weight gain and sexual dysfunction, as well as their lack of effectiveness in many cases. With respect to the treatment of chronic insomnia, the relative safety of benzodiazepines needs to be balanced against the frequent ineffectiveness of nonpharmacological treatment and the relatively high rate of accidents and injuries occurring in patients having untreated chronic insomnia.\(^7\)

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Understanding Toxidromes: Serotonin Toxicity
A Commentary on Montanes-Rada et al

To the Editors:
There have been some interesting new articles from toxicology research group (hunter area toxicity service) of WHYTE\(^1\)\(^2\) of providing data from more than 2200 prospectively documented overdoses of serotonergic drugs. These have been published in a series of articles\(^1\)\(^4\) that add greatly to our understanding of serotonin syndrome (SS) or serotonin toxicity (ST), as some authors now prefer to call it. These may be considered, in addition to the discussion by Montanes-Rada et al.,\(^5\) who have made some statements that can be further clarified in the light of this additional data.

The key concept that Whyte’s data confirm is that SS is better conceptualized as a form of poisoning (ie, ST), because progressively increasing serotonergic effects are an inevitable result of the ingestion of overdoses of selective serotonin reuptake inhibitors and serotonergic drug combinations (see Refs 6 and 7 for a full discussion of the spectrum concept of ST and the animal and human evidence that supports it). Whyte’s data from human overdoses demonstrate that approximately 15% of selective serotonin reuptake inhibitors–alone overdoses (which are only ever mild to moderate in severity), increasing to 50% for combined overdoses of monoamine oxidase inhibitors + selective serotonin reuptake inhibitors (which are also much more severe), exhibit ST (ie, have sufficient serotonergic symptoms to cross the arbitrary “diagnostic” threshold). There is a dose-related increase in severity of serotonergic symptoms. This is why toxicity authors are referring to the condition as ST; that emphasizes its inevitable dose-related relationship to the ingestion drugs (ie, poisoning), whereas the term SS implies that it is idiosyncratic, like neuroleptic malignant syndrome (NMS). It may be noted that this does not exclude the observation that some serotonergic effects that can occur with therapeutic doses may have idiosyncratic characteristics, as clinical experience suggests.

However, the criteria for SS resolve the problem excluding SS if an antidopaminergic drug is administered.

There is a strong argument that a fundamental difference between NMS and ST exists. NMS is a rare idiosyncratic reaction that is quite different to the usual toxic effects of neuroleptic overdose.\(^8\) Conversely, ST, after ingestion of serotonergic drugs, is a common progression of serotonergic effects, merging into toxicity. ST is much more strongly statistically associated with serotonergic drugs than NMS is with neuroleptic drugs. The Bayesian theory of “prior probability” indicates that known ingestion of serotonergic drugs is the more important piece of data that would help predict the correct diagnosis in doubtful cases.\(^9\)

The original article of Sternbach\(^10\) made suggestions about diagnostic criteria, which although helpful for our initial understanding, were nevertheless unvalidated proposals derived from a rather selected sample. He duly noted the likelihood of reporting bias in his series, but that qualification has sometimes received insufficient subsequent attention. In the light of the quality data from Whyte’s hunter area toxicology service series, it is now also appropriate to review his other suggestion—that previous ingestion of a neuroleptic should be an exclusion criteria for a diagnosis of ST. A special argument is necessary to logically justify assigning a hierarchical precedence to one feature over another, such as the previous ingestion of a particular drug: such a case of prior probability is stronger for serotonergic drugs, especially mixtures of monoamine oxidase inhibitors and selective serotonin reuptake inhibitors, which we now know have approximately a 50% prior probability for inducing ST. This is reflected in the diagnostic decision (CART) rules derived from Whyte’s data: rule 1 is if serotonergic drugs have been ingested, and clonus is present, a definite diagnosis of ST is highly probable (sensitivity, 84%; and specificity, 97%).

There is no established criteria for serotonin syndrome...the differential diagnosis between SS and NMS is difficult as there is considerable overlap in the symptoms.

Whyte’s data have now established reliable criteria and diagnostic decision rules for ST,\(^3\) as above. Other evidence indicates that ST and NMS are distinct, not only in their in clinical symptoms, but...
also in etiology, course, and treatment response: these differences have been discussed in detail elsewhere.\(^7,11-13\) In summary, they are as follows:

(a) ST is caused by serotonergic drugs (frequently, predictably, and dose-related). NMS occurs in association with neuroleptics (rarely, idiosyncratically, and not dose-related).

(b) ST, rapid onset, and progression (hours). NMS, slow onset, and progression (days).

(c) ST, hyperkinesia, and hyperreflexia/clonus, pyramidal rigidity. NMS, bradykinesia, and extrapyramidal rigidity.

There will always be situations in clinical medicine where confusion is possible, but that should not obscure the fact that, in a great majority of cases, the distinction can be made clearly and confidently.

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Several pilot studies reported that addition of fluvoxamine to antipsychotic treatment was well tolerated and could improve the psychopathology of schizophrenic patients.\(^5,6\) Recently, we conducted a study regarding the inhibitory effect of fluvoxamine on the clozapinerelated weight gain and metabolic disturbances.\(^7\) Plasma levels of N-desmethylolanzapine, but not clozapine, are associated with the increases in weight and serum glucose and triglyceride level. Olanzapine treatment was also associated with weight gain and elevated levels of insulin, leptin, and blood lipids as well as insulin resistance. Metabolic abnormalities and insulin resistance were associated with both clozapine and olanzapine treatments. Levels of insulin and triglycerides increased by increasing clozapine serum concentration and by increasing ratio of olanzapine to N-desmethylolanzapine were revealed recently.\(^8\) It is suggested that the metabolite N-desmethylolanzapine, but not olanzapine, has a normalizing effect on the metabolic abnormalities.\(^9\) In the study of Albers et al.,\(^1\) the 4'-N-desmethylolanzapine/olanzapine metabolic ratio decreased by 44% at week 6. In spite of no significant change in metabolic indices in this 6-week study, the effects on lipid metabolism may be more apparent in the long run. Therefore, this comedication strategy might carry the risk of aggravating the olanzapine-induced metabolic disturbances.

Although the addition of fluvoxamine to olanzapine medication is well tolerated and critical side effects are absent, this augmentation strategy should be applied only after careful evaluation of risks versus benefits.

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Does N-Desmethylolanzapine Increase, or Reduce, the Risk for Antipsychotic-Induced Metabolic Syndrome?

To the Editors:

We appreciate the thoughtful comments by Drs Chiu and Lu on our study dealing with olanzapine and low-dose fluvoxamine combination treatment to reduce the therapeutic dose requirements for olanzapine. They note that this combination requires further monitoring of its clinical benefits and risks, with a focus on metabolic syndrome. Although this is consistent with our study conclusion that our results form a basis for longer term evaluations of olanzapine and adjunct fluvoxamine therapy, the current treatment consensus statement for atypical antipsychotics already indicates the need for routine clinical monitoring for metabolic side effects before and during maintenance therapy.

Drs Chiu and Lu suggest that coadministration of olanzapine and fluvoxamine may improve negative symptoms of schizophrenia, while potentially raising the risk for antipsychotic-induced metabolic syndrome by increasing the olanzapine/N-desmethylolanzapine concentration ratio. Specifically, they indicate that a reduction in the N-desmethylolanzapine metabolite concentration may increase the risk for metabolic side effects. In support of their hypothesis, they cite 2 cross-sectional studies of patients treated with olanzapine.

We note that the latter work by Melkersson et al represents carefully conducted and detailed characterizations of metabolic endpoints in patients with a psychotic illness. The study samples were, however, relatively small (N = 14–16), and the cross-sectional design does not permit an evaluation of the degree of change in metabolic parameters. In one study, for example, only 3 patients had elevated fasting blood glucose levels, and the other 11 patients were normoglycemic. On the other hand, recent prospective studies with a larger sample size support the alternative hypothesis that an increase, rather than a reduction, in olanzapine or N-desmethylolanzapine plasma concentration may lead to an elevated risk for metabolic side effects. For example, Perry et al reported, in the June 2005 issue of the Journal, a threshold olanzapine plasma concentration of 20.6 ng/mL being associated with an increased likelihood of clinically significant weight gain (≥7% baseline weight). This association remained significant after adjusting for age, sex, baseline symptom severity, body mass index, and symptom improvement (odds ratio, 10.1; 95% confidence interval, 1.3–75.0;  P = 0.024; N = 39). In the latter study, N-desmethylolanzapine plasma concentration was not measured. We emphasize, however, that the plasma olanzapine and N-desmethylolanzapine concentration exhibit a positive correlation (r = 0.75,  P = 0.001).

Hence, it is reasonable to anticipate that, for example, the patients with a low olanzapine plasma concentration (eg, less than the 20.6 ng/mL concentration threshold) in the previous prospective study by Perry et al would also tend to display a low N-desmethylolanzapine concentration. Notably, these patients with a low parent drug and (estimated) metabolite concentration were also found to have a lower likelihood of weight gain. In addition, a prospective study by Lu et al found a significant positive correlation between N-desmethylclozapine plasma concentration and antipsychotic-induced increase in body weight, blood glucose, and triglyceride concentrations. Although it is plausible that there may be differences in the biologic direction in which

![FIGURE 1. Time course of fluvoxamine steady state plasma concentration during co-administration with olanzapine in 10 patients with major psychosis. The data are presented in individual patients (open circles) and as the mean value (bold line) at each time point (solid triangles). In subject 10, fluvoxamine concentration data was not available at week 6. As a reference point, the broken line depicts the in vivo inhibition constant of fluvoxamine for CYP1A2. 1.0 ng/mL fluvoxamine = 3.16 nmol/L.](image)
the structurally related N-desmethylclozapine and N-desmethylolanzapine may influence the risk for metabolic side effects, the study by Lu et al. would support the hypothesis that the risk for metabolic syndrome may increase at higher concentrations of the N-desmethylated metabolites of clozapine or olanzapine.

Dose-dependent inhibition of olanzapine clearance by increasing doses of fluvoxamine (50–100 mg/d) was reported by Chiu et al. On the other hand, fluvoxamine displays nonlinear pharmacokinetics at doses 50 mg/d or higher. Figure 1 shows that a 25-mg daily oral dose of fluvoxamine administered in our study produces adequate and sustained concentrations in the plasma that are at or higher than the in vivo inhibition constant for Kiv for CYP1A2. We note, therefore, that fluvoxamine doses higher than 50 mg/d should be avoided to reduce uncertainty in the time course and extent of CYP1A2 inhibition during adjunctive treatment to reduce olanzapine therapeutic dose requirements.

In summary, we would like to emphasize that the cost factor can limit adequate treatment and access of patients to atypical antipsychotics. We agree that longer term and prospective studies are warranted to evaluate the safety and efficacy of the olanzapine and adjunct fluvoxamine combination therapy. The available prospective data appear to suggest that decreasing N-desmethylolanzapine concentration may be associated with a reduced risk for metabolic side effects. However, it remains to be determined whether and to what extent olanzapine, N-desmethylozanapine, or the N-desmethylolanzapine/olanzapine ratio may serve as a marker of the antipsychotic-induced metabolic syndrome.

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Modafinil-Induced Irritability and Aggression?
A Report of 2 Bipolar Patients

To the Editors:

Modafinil is a novel drug with stimulant like properties but without having the abuse potential of stimulants. The drug has been found to be effective for the treatment of narcolepsy. Research hints at the efficacy of modafinil in counteracting the fatigue and sleepiness associated with depression. A recent study exploring the role of this agent in schizophrenia has found it to be helpful in counteracting the symptoms of fatigue and sleepiness. Improvements in cognitive functions and global functioning were also found. Case reports on the use of modafinil as a therapeutic agent for antidepressant-associated sedation have appeared in the literature. However, there has been concern about the psychosis-inducing property of this drug. We hereby report 2 cases of irritability and aggression related to modafinil use in bipolar disorder.

Case 1

Mr. R.K., a 26-year-old single man diagnosed with bipolar affective disorder, with a family history of suicide in a first-degree relative, presented to our tertiary care psychiatric hospital with complaints of feeling low and decreased interest in work. On mental status examination, the patient revealed ideas of helplessness and occasional worthlessness. At the time of presentation, the patient was taking clozapine 100 mg/d and sertraline 50 mg/d. Given the risk of potential manic switch associated with sertraline, it was stopped, and the patient was started on bupropion 150 mg/d. With bupropion, he reported getting easily angry and aggressive, and hence, he stopped it within 3 days; after which, he felt alright. He reported back after 2 weeks with complaint of excessive sedation during daytime, which had started since the initiation of clozapine and was impairing his work. No depressive symptoms or cognitions were found on examination. To counter the sedative effect of clozapine, he was prescribed modafinil 100 mg/d with his consent. He reported after
another week with complaints of feeling irritable and having difficulty in controlling aggressive outbursts leading to verbal alterations in his office. He had no problems with his sleep, appetite, libido, or personal care. Considering that the patient may be having an impending manic switch, modafinil was stopped, and he was advised to continue clozapine in divided doses. The irritability and aggressive outbursts disappeared within 2 days of discontinuing modafinil. The patient has been doing well for 3 months after stopping modafinil, although the problem of sedation continues.

Case 2

Mr V., diagnosed with bipolar affective disorder, presented to us with complaints of daytime sedation with medications. The patient was on valproate 3500 mg/d with injection zuclopenthixol decanoate 200 mg every 10 days. Further interview revealed that the sedation was worse since the addition of zuclopenthixol to valproate. Physical examination revealed no extrapyramidal or cerebellar sign. There were no symptoms suggestive of depression. The serum valproate level was found to be 124 μg/mL. With his consent, he was started on modafinil 100 mg/d to counter the medication-induced sedation. After 1 week of taking modafinil, the patient started feeling angry with minor events. He felt irritable most of the time. At his workplace, he felt as if he was going to pick up fights with his colleagues every now and then. Seeing his irritable mood, his wife requested him to stop going to work and seek consultation. With his psychiatrist’s advice, he stopped modafinil, and after the next 2 days, he felt normal and remained euthymic after that. He recalled that the irritability after starting modafinil was like his past experience with the beginning of manic episodes. The problem of sedation continued, which subsequently led to his valproate dose being reduced gradually to 2500 mg/d and injection zuclopenthixol decanoate 200 mg being spaced out to be administered every 15 days over the next 2 months. The sedation has come down since then without relapse of manic symptoms.

DISCUSSION

Modafinil has been used successfully as an adjunctive agent in the treatment of residual fatigue and sleepiness in depressed patients. Reports of modafinil use to treat valproate-induced sedation in bipolar disorder have appeared recently. The mechanism of its action is unknown, although it is thought to alter the balance of γ-aminobutyric acid (GABA) and glutamate, resulting in activation of the hypothalamus. It is also claimed to act on excitatory histaminergic neurons and to increase the dopamine level in nucleus accumbens through the inhibition of GABA release. Modafinil has been reported to worsen psychosis in schizophrenia patients maintained on clozapine. This may be a reflection of the indirect dopaminergic action of the drug through inhibition of GABA secretion. Considering the role of dopamine in mood regulation, this indirect dopaminergic action of modafinil is worth considering as a potential mechanism underlying the irritability and aggression induced by this drug in the 2 cases cited here. In addition, because the mood stabilizers act through GABAergic mechanism, the inhibition of GABA secretion by modafinil may well play a role in irritability and aggressive behavior observed here.

To our knowledge, this is the first report to illustrate the mood changes caused by modafinil in bipolar patients. Our observations hint at the need for exercising caution while using modafinil in bipolar patients. Further studies may throw some more light on this issue.

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