Safety in Overdose of Mirtazapine: A Case Report

Sir: The new antidepressant mirtazapine (Remeron) has a unique mode of action, combining an increase of noradrenergic and 5-HT_{1A}-mediated serotonergic neurotransmission with a specific blockade of 5-HT_2 and 5-HT_3-receptor subtypes.[1] So far, a single case of overdose with mirtazapine[2] has been reported since its introduction in The Netherlands in September 1994; I now report the second case.

Case report. A 45-year-old female patient with a DSM-III-R diagnosis of recurrent major depressive episode and known compulsive personality traits was admitted to the Intensive Care Unit (ICU) approximately 6 hours after ingestion of 810 mg of mirtazapine and 300 mg of the tricyclic antidepressant dosulepin. [Dosulepin (also known as dothiepin) is not marketed in the United States but is available in other countries, including The Netherlands. It is an established tricyclic that is equipotent with other tricyclics, and it has significant sedative effects and known toxicity in overdose.[3] The defined daily dose of dosulepin is 150 mg/day.]

At admission, the patient's blood level of mirtazapine was 206 µg/L; according to the manufacturer, the recommended therapeutic daily doses usually result in blood levels of 20 to 50 µg/L. The blood level of dosulepin including metabolites was 222 µg/L, which is within the recommended range of 100–200 µg/L. The patient presented with symptoms of anxiety and confusion. No neurological symptoms or other signs/symptoms typical for psychiatric disorder were registered. Her respiratory and cardiac function (as assessed by electrocardiograph recordings) was considered to be normal. A slight increase was registered in systolic blood pressure and heart rate in comparison with preadmission values (130/70 mm Hg vs. 150/70 mm Hg and 76 bpm vs. 85 bpm, respectively). During a 12-hour stay in the ICU, the patient underwent gastric lavage and was treated with laxatives and active charcoal. She was subsequently transferred to the psychiatric ward. After 2 weeks, her psychic and somatic condition was stable, and she was discharged.

The patient had started treatment with mirtazapine 6 weeks prior to overdose and had substantial clinical improvement. The dosage was gradually increased from 15 mg/day to 75 mg/day within 4 weeks, because a dosage of 45 mg/day provided insufficient relief of anxiety symptoms and sleep disturbances. One week prior to overdose and without consulting her physician, the patient added dosulepin 150 mg/day because of continuing panic attacks.

The dose of mirtazapine used in this patient was higher than the maximum of 45 mg/day as stated in the U.S. labeling. The dosing was based on the labeling in The Netherlands, which states that "the starting dose is 15 mg/day, and for optimal therapeutic effect in general higher dosage is needed. Effective dose is usually between 15–45 mg/day." Mirtazapine has been used in trials in doses up to 80 mg/day[1] without any additional tolerability problems compared with those found in studies using lower doses, and its pharmacokinetics are linear in a dose range between 15–75 mg/day.[1]

In contrast to the previously reported overdose case,[2] the patient reported here showed no somnolence despite the large quantity of both drugs taken. The absence of seizures and the fact that no deleterious effects were observed on respiratory and cardiac function or vital signs indices indicate the safety of mirtazapine when taken in overdose. This finding is in agreement with a previously reported case of overdose in The Netherlands[2] and cases occurring during clinical trials.[1,4]

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Lamotrigine Treatment of Refractory Bipolar Disorder

Sir: Lamotrigine represents a new class of anticonvulsant for the treatment of adult patients with refractory partial seizures. Lamotrigine is chemically unrelated to carbamazepine and phenytoin, but is thought to act at voltage-sensitive sodium channels to stabilize neuronal membranes and inhibit transmitter release, principally glutamate and aspartate,[1] similar to the inhibition of neuronal activity produced by phenytoin and carbamazepine.[2] Further, lamotrigine has been shown to possess efficacy similar to that of carbamazepine in control of onset of partial seizures and primary generalized tonic-clonic seizures.[3] The half-life of lamotrigine in adults receiving monotherapy is approximately 24 hours, although its half-life is decreased by approximately 50% when it is used in combination with enzyme-inducing anticonvulsants, such as phenobarbital, carbamazepine, or phenytoin.[4] Valproate, in contrast, extends the half-life of lamotrigine by twofold to threefold,[4] and can lead to toxic levels of lamotrigine and encephalopathy.[5] The usual maintenance dose of lamotrigine is 100 to 500 mg daily given in two divided doses, while the most frequently reported adverse effects are headache, fatigue, nausea, dizziness, drowsiness, and insomnia, with skin rashes occurring in up to 10% of patients and leading to withdrawal of lamotrigine in 2% of patients. In less than 0.1% of patients, severe skin rashes, including angioedema and Stevens-Johnson syndrome, have been reported.[4]

Valproate and carbamazepine are used as alternative agents to lithium in the treatment of bipolar disorders,[6] with case reports suggesting that patients unresponsive to one of these anticonvulsants may respond to the other.[7] Some patients suffer from bipolar disorders refractory to lithium, carbamazepine, valproate, or combination therapies, underscoring the need for new treatments. Just as some patients may respond to valproate and not to carbamazepine, there is preliminary evidence that patients refractory to these agents may respond to lamotrigine.[8–10]

One abstract[8] reported improvement with lamotrigine treatment in two bipolar patients, one with an atypical onset of

Table 1. Seven Cases of Treatment-Refractory Bipolar Disorder Treated With Lamotrigine*

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Diagnosis	Bipolar I, rapid cycler	Bipolar I, rapid cycler	Bipolar I, rapid cycler	Bipolar I rapid cycler	Schizoaffective, bipolar	Bipolar I	Bipolar I
Age at onset (y)	27	24	25	18	17	15	12
Current age (y)	34	52	33	54	28	40	35
Sex	Female	Female	Female	Female	Male	Female	Male
Preceding treatments (mg/d), duration	Lithium 1200, 3 mo; carbamazepine 1200, 1 y; verapamil 240 and haloperidol 1, 1 mo	Carbamazepine 1000 and lithium 900, 19 mo; added valproate 2500, 3 y; added risperidone 3, 3 mo	Lithium 1350, 11 mo; carbamazepine 1600, lithium 750, and T_4 0.1, 3 mo; acetazolamide 750 and carbamazepine 1500, 4.5 mo	Lithium 900, valproate 1500, and carbamazepine 800, 44 wk; clozapine 475, 10 wk	Lithium 1800, 1 y; valproate 1750 and lithium 1800, 2 y; valproate 1750, lithium 1800, thiothixene 10, 1 y	Valproate 750, 5 mo; valproate 750 and bupropion 225, 3 mo; venlafaxine 75, 2 mo	Valproate 1500, lithium 1350, and bupropion 175, 14 wk
Immediate preceding treatment (mg/d), duration	Zolpidem 10 and valproate 2000, 19 mo; and brief trials of bupropion and dexedrine	Carbamazepine 1800, 6 mo	Valproate 750 and acetazolamide 875, 2 mo	Verapamil 180, valproate 500, and lithium 675, 3 y	Valproate 1500, lithium 675, risperidone 1, and levothyroxine 0.15, 3 y	Sertraline 100, fenfluramine 60, and trazodone 50, 7 mo	10 bilateral ECT
Lamotrigine mg/d and other treatments	Lamotrigine 400	Lamotrigine 200 and carbamazepine 1600, 6 wk	Lamotrigine 100 bid and acetazolamide 500	Lamotrigine 50 qid and lithium 675	Lamotrigine 150 bid, risperidone 6, and lithium 900	Lamotrigine 200 bid and lithium 1350	Lamotrigine 150 bid, lithium 1500, dextroamphetamine 10, and trazodone 400
Presenting mood state	Manic, severe, nonpsychotic	Hypomanic	Depression	Mixed mania, severe, nonpsychotic	Depression	Hypomanic and visual illusions	Euthymic
4-Week response[a]	1	0	3	3	0	2	Euthymic
8-Week response[a]	3	0	3	3	0	2	2, moderate depression
Long-term outcome	3 at 65 wk	Discontinued at 8 wk due to nausea	2 at 28 wk	3 at 38 wk	0 at 17 wk, remains psychotic	2 at 22 wk, moderate depression	0 at 14 wk remains depressed

*All doses are mg/day.
[a]Outcome was rated using a modified version of McElroy and associates' scale[14]: 0 = no improvement; 1 = minimal improvement, but not enough to warrant continuation of treatment; 2 = moderate improvement and significant amelioration of symptoms with improved social or vocational functioning; and 3 = marked improvement with complete remission of symptoms.

mania at age 67 and the other with rapid-cycling bipolar II disorder, the former treated for 9 months, the latter for an unspecified duration. Another report[9] noted the beneficial use of lamotrigine in one patient with rapid-cycling bipolar I disorder in the depressed phase, who had been lithium refractory, while another abstract[10] reported on 67 refractory bipolar patients in depressed or manic phases and found that lamotrigine possessed a broad spectrum of efficacy in bipolar disorders. We extend these findings by reporting the use of lamotrigine in six patients with treatment-refractory bipolar I disorder and in one patient with bipolar schizoaffective disorder.

Case reports. Between June 1995 and October 1996, seven adult patients suffering from treatment-refractory mood disorders participated in an open trial of lamotrigine. All had failed "adequate treatment trials" (defined as dosages within the package insert guidelines, usually the maximum tolerated, for at least 6 weeks) of at least six different antidepressants, mood stabilizers, or combinations thereof. An "adequate trial" of a mood stabilizer followed the American Psychiatric Association practice guidelines for bipolar disorders.[11] Actual duration and dosage of the most recent treatment trials are presented in Table 1. DSM-IV diagnoses[12] were made by using a semistructured interview based on the Structured Clinical Interview for DSM-III-R.[13] Outcome was rated by using a scale proposed by McElroy and associates,[14] and slightly modified as follows: 0 = no improvement; 1 = minimal improvement, but not enough to warrant continuation of treatment; 2 = moderate improvement and significant amelioration of symptoms and improved social or vocational functioning; and 3 = marked improvement with complete remission of symptoms. Reports of treatment-emergent side effects were noted. Subjects gave informed consent after the use of lamotrigine as an experimental agent in the treatment of mood disorders was explained, and they were informed of the possible risks associated with this treatment such as headache, tiredness, and rash. The diagnoses, demographics, and results of treatment are presented in Table 1.

These case reports suggest that lamotrigine may be an effective treatment for some treatment-refractory mood disorders. Two rapid-cycling bipolar I patients had marked improvement with this treatment, in spite of failing previous trials of valproate and carbamazepine, suggesting that patients unresponsive to two different anticonvulsants may yet respond to a third anticonvulsant. Of the remaining patients, two had a moderate response, one discontinued the medication due to nausea, and t

wo had no response to lamotrigine. Although the small sample size and open nature of these cases require cautious interpretation of the findings, these cases coupled with three prior reports[8–10] suggest that lamotrigine may be an effective agent in treatment-refractory mood disorders or in patients unable to tolerate lithium, carbamazepine, or valproate alone or in combination. Conceivably, lamotrigine may also be an effective treatment in "nonrefractory patients," suggesting that controlled trials of lamotrigine be conducted.

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Comparison of Valproic Acid and Lithium in Mania

Sir: In their discussion, Frye et al.[1] failed to account for several crucial effects that undermine the results of their study that compared valproic acid and lithium.

First, because every patient taking lithium was also taking a neuroleptic and a benzodiazepine at hospital discharge, the study population was lithium-resistant. Lithium resistance is also suggested by the long duration of illness prior to hospitalization. Simply, lithium does not work in lithium-resistant patients, and subject selection biased the results against lithium.

Second, lithium was not used according to best practices. By Day 5 only two thirds of lithium patients had blood levels drawn, and only 17% showed therapeutic levels. This indicates that early lithium doses were routinely too low. Accordingly, the results reflect prescribing practices rather than efficacy. With loading doses,[2] we have routinely achieved therapeutic serum lithium levels in 3 days and discharge with remission in 5 to 7 days on lithium therapy alone.

Third, variable mixtures of neuroleptic and benzodiazepine tranquilizers were given, and these agents have antimanic actions. Because the actions of tranquilizers were not accounted for, antimanic effects cannot be attributed to only the lithium or valproic acid used with them.

Finally, 52 lithium patients were compared with only 5 valproic acid patients. Five subjects are too few for the results to apply to patients elsewhere, in view of the complexities noted above. Statistical significance can be achieved with results from a group of just two subjects, but clinical significance is another matter.

In sum, it seems that the authors studied their own prescribing practices rather than differences in efficacy between antimanic agents. Improvements in the treatment of mania are important, and impartial methods are needed for useful results.

In July 1996, this manuscript and a commentary reprising it were mass-mailed with funding from the pharmaceutical firm that makes a patented form of valproic acid. The limitations we noted were not mentioned; we saw no balance. It appears that this report was disseminated for commercial purposes; accordingly, its shortcomings need similarly wide appreciation.

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Drs. Altshuler and Frye Reply

Sir: We thank Drs. Townes and Swartz for their letter regarding our paper. We wish to respond to the important issues they raised.

First, Townes and Swartz assert that our patient population on lithium treatment must have been lithium-resistant because they received antipsychotics and benzodiazepines. However, (1) we found that it was standard clinical care at UCLA from 1989 to 1992 to administer one or both of these agents at admission for mania, depending on patient symptoms, and (2) all treatment groups received equivalent doses of these medications. While concern may be raised that an overprescription of adjunctive agents occurred in these bipolar patients, it does not *explain* our findings, since there were no group differences in the prescription of these agents, nor does it implicate the lithium group as being treatment resistant. While all groups were on polydrug treatment with adjunctive benzodiazepines and/or antipsychotics, these additional drugs were taken into account in the statistical model as potential confounders and were not

found to explain the findings. Interestingly, of the 52 patients in the lithium-treatment group, 45 had classic (euphoric) mania, and only 7 had mixed mania. Classic mania has been shown to be predictive of a positive antimanic response to lithium. Further, as presented in the demographic table, the lithium group had the fewest years of previous illness, suggesting greater likelihood of lithium response with fewer preceding episodes. When the hospital length of stay was broken down in lithium-treated patients by manic subtype (assuming the mixed group might be less responsive to or fail lithium over time), the group with classic mania (N = 45) had a mean ± SE length of stay of 17.02 ± 1.08 days when treated with lithium, and the mixed group (N = 7) had a length of stay of 18.37 ± 2.96 days. Thus, the diagnostic subtype per se (mixed vs. manic) was not differentially responsible in the lithium-treated sample for the longer length of stay in the lithium group.

As Townes and Swartz point out, and as we discuss in our paper, by Day 5 only 26% of the lithium-treated patients who had blood levels drawn were at therapeutic lithium levels. This suggests, as they note, that usual care does not accord with textbook "best clinical practice." We were also surprised to find so many patients with low lithium levels at Day 5. Review of the study records suggested a number of reasons for this, including the inability of patients to tolerate a faster titration of lithium. Thus "best clinical practice" (i.e., titration to therapeutic levels) was unable to be rapidly effectuated. We encourage others to look at their hospital's "standard of care" to see if rapid lithium titration is actually able to be instituted in the clinical (as opposed to research study) setting. We agree that our study may tell us less about the efficacy of each drug (all of which we know to be efficacious in mania) than about the ability of patients to differentially tolerate rapid titrations of drugs. This, however, ultimately influences the rate at which patients improve and the resultant hospital length of stay.

We agree that five and six patients are very small numbers in the divalproex sodium and carbamazepine/lithium groups, respectively. As we have indicated in our report, ours was a small, retrospective study, with clinician-chosen assignment to medications and all the methodological limitations inherent in such a study. We chose to put our preliminary observations into writing because the results were striking and highly clinically relevant. It is our hope that further prospective studies will ensue to determine the best approach to rapid treatment and stabilization of our bipolar patients.

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Refractory Depression, Cardiovascular Risk Factors, and Leukoariosis

Sir: Dr. Goodnick and colleagues recently provided a comprehensive and practical review of the fascinating interface between depression and diabetes.[1] Patients with diabetes are more prone to suffer from depression than people in the general population. Depressed diabetics are eight times more likely to suffer depressive relapses. The level of hyperglycemia has a direct bearing on the severity of depression.[1] This is not surprising, considering that diabetes has recognized vascular complications,[2] and cerebrovascular disease is often associated with depression.[3] Magnetic resonance imaging (MRI) studies reveal that a subgroup of depressed patients has subcortical white matter hyperintensity lesions, otherwise known as leukoariosis.[4] These lesions are considered to be ischemic in origin. They tend to correlate with cardiovascular risk factors, new onset of depression in the elderly, and poor treatment response.[5,6] The purpose of the present study was to examine the magnitude of the contribution of various cardiovascular risk factors, such as diabetes, in the development of cerebral leukoariosis in patients with depressive illness.

The authors completed a retrospective naturalistic review of 15 consecutively hospitalized depressed patients who received MRI brain scans. The cohort included 7 men and 8 women. They ranged in age from 29 to 89 years. Twelve (80%) of these 15 patients had at least one identifiable cardiovascular risk factor. Six patients had two or more risk factors. Five patients (33%) had hypertension. Five (33%) were obese. Five (33%) had hyperlipidemia. Five (33%) smoked cigarettes. Two patients (13%) had diabetes. Evidence of leukoariosis was present in 9 patients (60%): 20% of those with obesity, 80% of those with hypertension, 80% of those with hyperlipidemia, 80% of the smokers, and 100% of those with diabetes. Hence comorbid diabetes was associated with a higher rate of subcortical hyperintensity lesions than were the other cardiovascular risk factors.

Despite the small sample size, the present study adds to the accumulating evidence relating cardiovascular risk factors and the development of subcortical white matter hyperintensity lesions in patients with depressive illness. The magnitude of the contribution of various cardiovascular risk factors does not appear to be equal.

The presence of leukoariosis is associated with the onset of depression in the elderly and with poor response to treatment. Hence, cardiovascular risk factors may have relevance in both the etiology and outcome of depressive illness. Just as comorbid depression has a negative influence on the outcome of patients with cardiovascular disease,[7,8] it is conceivable that comorbid hypertension, hyperlipidemia, cigarette smoking, and diabetes may adversely influence the outcome of depression. Hence, rigorous control of hypertension, hyperlipidemia, and hyperglycemia may prevent or improve the outcome of depressive illness.

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Reversible Parkinsonism in a 90-Year-Old Man Taking Sertraline

Sir: Since 1979, there have been reports of extrapyramidal effects, including dystonia, akathisia, and parkinsonism, associated with the use of serotonin selective reuptake inhibitors (SSRIs) in young, healthy patients.[1–7] There are few reports of SSRI-related extrapyramidal effects in the elderly or neurologically impaired, although such individuals might be more vulnerable. French physicians reported deterioration of parkinsonian patients taking SSRIs.[5] Fluoxetine was associated with the development of parkinsonism in a middle-aged woman with cerebral palsy.[6]

Because of their relatively low side effect profile, SSRIs are frequently prescribed for depression in geriatric and brain-injured patients. Here, we report a case of a geriatric patient with depression who developed florid, reversible parkinsonism associated with an increase in sertraline dosage.

Case report: Mr. A, a 90-year-old married white man without previous psychiatric history, presented with major depressive disorder, with melancholic features, which had had a gradual onset after his retirement 8 years earlier. He had a cardiac pacemaker (placed 10 years earlier for sinus node degeneration) and cervical spondylosis and was taking furosemide 40 mg and enalapril 5 mg/day for hypertension. Findings of mental status and neurologic examinations were unremarkable. He was started on sertraline 50 mg/day. After 4 months, his depressive symptoms had partially improved and his insomnia had lessened. However, irritability, loneliness, and somatic preoccupation were initially unchanged, then seemed to worsen. Sertraline was then increased over 6 weeks to 150 mg/day.

Within 2 weeks of the dosage increase to 150 mg/day, Mr. A developed a pill-roll tremor, masked facies, bradykinesia, micrographia, and a festinating gait with tendency to retropulse. He fell twice. Depressive symptoms also worsened. The sertraline dose was rapidly tapered, and after 2 weeks on the 50-mg dose, all signs of parkinsonism had resolved, and depression returned to the partially impaired level previously achieved on 50 mg. The onset of parkinsonian symptoms after a dose increase and their rapid resolution after dose reduction are consistent with a medication-induced syndrome. It could represent a side effect in a rare susceptible individual or an unmasking of subclinical Parkinson's disease. A drug interaction, while unlikely, given Mr. A's regimen, cannot be ruled out completely.

This case is the first report, to our knowledge, associating sertraline with parkinsonism and the first report of any SSRI-related extrapyramidal effect in a geriatric patient. A hypothesis explaining this phenomenon is that SSRIs trigger an increase in the presence of serotonin in the raphe nuclei, which then inhibits the production and release of dopamine in the basal ganglia.[5–7] Geriatric and brain-injured patients (or those with subclinical parkinsonism) may have less dopamine available in their nigrostriatal tract at baseline and might therefore be more susceptible to deleterious extrapyramidal effects of SSRIs, including sertraline.

SSRIs should remain a first-line treatment of choice for elderly depressed patients because of their overall superior side effect profile. Although undoubtedly rare, SSRI-induced parkinsonism may worsen depressive symptoms of anhedonia and social isolation, as it may have in this case, or produce incoordination and falls and risk of fractures in elderly individuals. Clinicians should, therefore, remain alert to the possibility of SSRI-induced parkinsonism, particularly after dosage increases.

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Corrections

Symbols dropped out of four articles in the May 1997 issue. They should be as follows:

In the Gillin et al. article "A Comparison of Nefazodone and Fluoxetine on Mood and on Objective, Subjective, and Clinician-Rated Measures of Sleep in Depressed Patients: A Double-Blind, 8-Week Clinical Trial" (1997;58:185–192), the corrected phrases should read "($r \geq .85$)" (p. 186, last paragraph, right column), "≥ 30 seconds" (p. 187, first paragraph, left column and p. 188, Table 3), and "≥ 10% of patients" (p. 188, second paragraph, left column). All p values in tables, figures, and text (pp. 188–191) should be followed by "≤" unless otherwise stated.

In the Sernyak et al. article "Chronic Neuroleptic Exposure in Bipolar Outpatients" (1997;58:193–195), the abstract should state "≤ 200 mg/day CPZ equivalents" (line 7, Results).

In the Tran et al. article "Extrapyramidal Symptoms and Tolerability of Olanzapine Versus Haloperidol in the Acute Treatment of Schizophrenia" (1997;58:205–211), the corrected phrases should read "a baseline total score of ≤ 3" (p. 209, first paragraph, left column) and "≥ 2 at any postbaseline visit" (p. 209, paragraph 3, left column).

In the Swartz et al. article "Frontotemporal Dementia: Treatment Response to Serotonin Selective Reuptake Inhibitors" (1997;58:212–216), the abstract should state "($.07 \leq p \leq 1.00$)" (last line, Results).

The staff regrets the errors.