

# Letters to the Editor

## Lack of Desipramine Toxicity With Citalopram

**Sir:** Selective serotonin reuptake inhibitors (SSRIs) are known to inhibit specific human hepatic cytochrome P450 (CYP) isoenzymes, which are critical in the metabolism of most medications.<sup>1</sup> Paroxetine is thought to possess highly potent inhibiting properties for the CYP2D6 isoenzyme.<sup>2,3</sup> CYP2D6 is the major enzyme involved in catabolism of many commonly used agents, including neuroleptics, antidepressants, Type IC antiarrhythmics, codeine,  $\beta$ -blockers, and dextromethorphan.<sup>4</sup> Citalopram is thought to possess weak inhibition of this isoenzyme along with CYP1A2 and CYP2C19 and no inhibition of CYP3A4 (data on file, Forest Laboratories, Inc., 1997).

It is difficult to measure the clinical impact of this phenomenon outside of the laboratory. Hepatic isoenzyme inhibition can lead to adverse side effects in patients receiving combinations of medications that are metabolized through these pathways. I report such an interaction in a patient taking paroxetine that disappeared when she was switched to citalopram treatment.

**Case report.** Ms. A, a 45-year-old white woman, met DSM-IV criteria for major depressive disorder and dysthymia and failed several trials of antidepressants from all available drug classes in addition to electroconvulsive therapy. Many agents were used in combination, and antidepressants were usually pushed to maximal dosage. There was no decrease in depression after consultation at 2 nationally ranked depression treatment programs along with ongoing weekly psychotherapy over several years with 3 different therapists.

Ms. A had a total lack of antidepressant response to concomitant pindolol, 2.5 mg t.i.d.; desipramine, 300 mg/day in divided doses; clonazepam, 1 mg b.i.d. and 2 mg h.s.; and olanzapine, 10 mg h.s., although the 2 latter medicines helped with insomnia. Paroxetine augmentation was initiated, with titration to 40 mg/day achieved over 3 months. Ms. A developed lightheadedness, ataxia, and increased confusion. The serum desipramine level was 1810 ng/mL (therapeutic range, 75–300 ng/mL). The desipramine dose was decreased to 200 mg/day in divided doses; 8 days later, her serum desipramine level was still elevated at 1665 ng/mL. The dose of paroxetine was decreased to 30 mg/day, and desipramine was decreased to 150 mg/day with marked reduction of side effects. However, Ms. A's serum desipramine level remained elevated 13 days later at 1153 ng/mL. Paroxetine was tapered and discontinued, and desipramine was decreased to 100 mg/day in divided doses. Citalopram was begun and titrated to 40 mg/day. Ms. A's serum desipramine level dropped into the therapeutic range, to 195 ng/mL, over the next 2 months. Her mood also was improved on clinical examination during her citalopram trial, and she has maintained a reduction in depressive symptoms over several months to date.

This case reflects likely desipramine toxicity caused by hepatic CYP2D6 isoenzyme blockade from paroxetine. This blockade appears to have been minimized by switching to citalopram. It is possible that the lower serum desipramine level

still reflected mild inhibition by citalopram that was not clinically significant in this patient.

There are several alternative explanations to the lowered desipramine level described in this patient. It is possible that desipramine dosage reduction accounted for the dropping blood levels of desipramine, although the final 50-mg reduction would then have accounted for over an 80% decrease in desipramine concentration. It also is possible that the patient decreased desipramine on her own beyond my recommendations, although she denied noncompliance with her medication regimen. It would have been helpful to have obtained a blood desipramine level prior to paroxetine administration to more clearly illustrate the extent of inhibition. Further clinical examination of patients receiving combinations of tricyclic antidepressants and SSRIs may more clearly delineate the extent of these drug interactions.

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## Subtyping Micromanic Episodes

**Sir:** I read with great interest Dr. McElroy's conceptualization of the explosivity component in intermittent explosive disorder as containing the features of what she terms a "microdysphoric manic episode."<sup>1</sup> While the idea of re-visioning explosivity as a brief manic episode is, to me, a diagnostic breakthrough with important treatment implications, her categorization of these episodes as "dysphoric" seems imprecise.

The DSM-IV (1994) lists 3 synonyms to exemplify a dysphoric mood: sadness, anxiety, or irritability.<sup>2(p768)</sup> *Webster's Collegiate Thesaurus*, however, equates dysphoria with only depressive synonyms, e.g., dejection, gloom, melancholy.<sup>3(267)</sup> Psychiatric clinicians could increase diagnostic precision by aligning more with the colloquial usage offered in *Webster's*.

Therefore, I recommend that explosive attacks be included under the umbrella of mania rather than microdysphoria. McElroy herself provides theoretical support for this in her statement: "DSM implies that euphoria is a core feature of mania, but I would argue that irritability and aggression actually comprise the core feature of mania."<sup>4(p21)</sup> Empirical support is provided by her explosive subjects, 75% of whom "felt relieved

after they exploded,” and nearly half (48%) “said the acts were pleasurable.”<sup>1(p9)</sup>

Along these lines, then, the following subtypes for brief manic episodes are suggested. An explosive event for a patient diagnosed with intermittent explosive disorder could be better categorized as a “micromanic episode, explosive type.” Providing that other medical reasons are ruled out, events of agitation could be identified as “micromanic episodes, agitated type.” Likewise, brief remitting episodes of irritability could be termed “microhypomanic episodes, irritable type.” And although sexual addiction is not among the current DSM nomenclature, some forms of this condition could be conceptualized as a patient’s attempt to control the recurrence of “micromanic episodes, euphoric type.” Such a conceptualization could provide theoretical justification for pharmacotherapy for this condition under guidelines similar to those suggested by McElroy<sup>1</sup> for intermittent explosive disorder.

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### Clarifying the Safety of the MAOI Diet and Pizza

**Sir:** We appreciated Drs. Shulman and Walker’s study<sup>1</sup> attempting to clarify and extend our clinical experience<sup>2</sup> demonstrating the apparent safety of ingesting at least some types of pizza along with a monoamine oxidase inhibitor (MAOI). Their studies<sup>3,4</sup> clarifying the specifics of the MAOI diet have been an invaluable aid to all clinicians who prescribe these important antidepressant medications.

Our premise in noting the safety of MAOI-treated patients’ ingesting kosher pizza was based on the fact that kosher pizza establishments do not generally use aged cheeses as a topping. In contrast, at the time of our original letter, we contacted a number of local, nonkosher pizza establishments in our area, including a chain outlet noted in Shulman and Walker’s report.<sup>1</sup> Cheeses considered aged were sometimes routinely used as a topping by some of these establishments. While we have not been able to find any case reports of pizza-induced hypertensive crises in reviewing the literature, we have heard of anecdotal reports of hypertensive crises seemingly related to the ingestion of nonkosher pizza. Unfortunately, we do not know if these latter, unverified cases were related to eating gourmet pizza or pizza purchased from smaller establishments versus large chain outlets or perhaps to other factors such as the freshness of the ingredients. Parenthetically, if the authors or others are aware of verified cases, it would be interesting to hear about them.

With these facts in mind, it would be useful to know specifically what types and exact amounts of cheese were used in the pizzas Shulman and Walker studied. Were they aged cheeses, and if so, why was the tyramine content so low? If they were not

aged cheeses, can we safely say that their findings generalize to American pizza chain outlets? That is, do Canadian franchises of these chains use the same suppliers and same types of cheese as their American counterparts?

We hope Shulman and Walker can clarify these points, as minimizing dietary restrictions would enhance the acceptability of MAOIs to our patients. In the meantime, educating patients what to look for and ask about when ordering pizza in *any* setting may continue to be the safest approach.

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### Drs. Shulman and Walker Reply

**Sir:** Drs. Feinberg and Holzer have asked for clarification of the types of cheeses used by large pizza chain outlets. To the best of our knowledge, the cheese most commonly used is mozzarella cheese, which, strictly speaking, is an aged cheese. However, it appears to be one of the milder cheeses, and our previous analyses have shown relatively low tyramine levels in mozzarella. Our first study<sup>1</sup> found 2.4 mg of tyramine per serving of mozzarella, and in the article recently published in the *Journal*,<sup>2</sup> the tyramine content was even lower at 0.5 mg per serving. Some chains report the inclusion of Parmesan cheese as a common topping, but that is not an aged cheese, and in our 1989 study<sup>1</sup> we found a tyramine content of only 0.2 mg per serving for Parmesan cheese. Finally, one of the chains has used Romano cheese in their sauce for flavor, but in minute amounts. The tyramine content reported in our recent article<sup>2</sup> found a minuscule amount of tyramine in Romano cheese: 0.12 mg per 30-gram serving. To the best of our knowledge, the ingredients used in the Canadian chain outlets are identical to those used by American suppliers and counterparts. We also welcome any further clarification in that area.

We did not measure the exact amounts of cheese in each of the pizzas sampled. Liberally, we used half of a medium-sized pizza as a single serving, and our total tyramine content was consistently low in all 4 pizza chain outlets studied. Thus, on the basis of our tyramine analyses of both individual cheeses and the total tyramine content of pizzas themselves, we have consistently found low tyramine levels.

Like us, Feinberg and Holzer have not found any case reports of pizza-induced hypertensive crises, but they allude to “anecdotal” reports of such crises in nonkosher pizzas. We endorse their invitation to clinicians to report any documented cases of this nature. As in all clinical medicine, we have to make judgment calls in our recommendations based on the best available evidence.<sup>3</sup> In this particular situation, we are balancing realistic compliance concerns with quality of life and safety issues. Given all the available evidence, we believe that we can

stand by the recommendations in our article "Refining the MAOI Diet."<sup>2</sup>

We welcome further contributions to the discussion such as those from interested clinicians like Feinberg and Holzer who have taken the trouble to investigate concerns that are of great practical relevance.

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### A Case Report of Serotonin Syndrome Associated With Combined Nefazodone and Fluoxetine

**Sir:** Serotonin syndrome is a potentially lethal condition caused by excessive serotonergic activity and is diagnosed by the presence of at least 3 of 10 symptoms: mental status changes (confusion, hypomania), agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever.<sup>1</sup> It most frequently develops after coadministration of 2 serotomimetic agents, 1 of which is often (but not always) a monoamine oxidase inhibitor.<sup>2</sup> To our knowledge, the following is the first report of serotonin syndrome involving the combination of nefazodone, a 5-HT<sub>2</sub> antagonist, and fluoxetine, a selective serotonin reuptake inhibitor (SSRI).

**Case report.** Mr. A, a 50-year-old man with a history of major depressive disorder, developed sexual dysfunction after several months of treatment with fluoxetine, 60 mg/day, and requested a change in antidepressant medication. A decision was made to switch him to nefazodone. He was instructed to taper his dose of fluoxetine over 4 days and then begin nefazodone, 100 mg b.i.d. Mr. A. reduced his dose of fluoxetine to 40 mg for 2 days but then, for unknown reasons, added nefazodone at the above dose. He took the medications concurrently until he was admitted to the hospital 6 days later.

One day prior to admission, Mr. A developed lethargy, inattention, ataxia, disorientation, vomiting, and myoclonus. On the day of admission, he also experienced visual hallucinations of tiny elephants walking across his computer keyboard. Mr. A's medical history was significant for multiple myeloma in remission for 8 years. He had been taking alpha interferon, 5 million units 3 times a week, for several years. He was taking no other medications and had no history of antipsychotic use. He also had no history of alcohol or illicit substance use.

At admission, Mr. A was afebrile and had a normal pulse and blood pressure. His physical examination was remarkable for myoclonus, slightly increased muscle tone bilaterally, and hyperreflexia, which affected the lower extremities more severely than the upper extremities. His neck was supple. On examination of his mental status, Mr. A demonstrated inattention, word-finding difficulties, disorientation, and visual hallucinations. A complete blood count was normal. Urinalysis and urine toxicology screen results were negative. Blood and urine cultures were

negative. A comprehensive chemistry panel was remarkable only for potassium of 2.6 mEq/L. A lumbar puncture showed no evidence of infection. Serum fluoxetine level was 245 ng/mL (42-469) and norfluoxetine level was 177 ng/mL (52-446).

Mr. A was given a presumptive diagnosis of serotonin syndrome, and both antidepressants were discontinued. He received intravenous fluids, potassium replacement, and a total of 5 mg of haloperidol for agitation. On day 2, he remained afebrile; his potassium had normalized, but he was more agitated and confused, his hyperreflexia had worsened, and he had developed tremors. Although he had no history of alcohol use, he was placed on lorazepam, 1 mg t.i.d., and thiamine, 100 mg q.d. A consulting neurologist agreed that serotonin syndrome was still the most likely diagnosis, but recommended empiric treatment with phenytoin and acyclovir, which were both initiated. An electroencephalogram was consistent with mild, diffuse encephalopathy.

On day 3, Mr. A improved markedly with decreased myoclonus, tremors, and confusion. Phenytoin and acyclovir were discontinued, and lorazepam was tapered. On day 4, findings from neurologic and psychiatric examinations were normal. He was alert and fully oriented. He was discharged home on no antidepressant. Head magnetic resonance imaging (MRI) performed 1 week after discharge was normal.

The final diagnosis of serotonin syndrome in our patient was clear since the onset of his symptoms was coincident with the initiation of a second serotonergic antidepressant. He met at least 6 of the diagnostic criteria, and extensive medical and neurologic evaluations ruled out infectious, metabolic, and illicit substance-related etiologies. This case is remarkable both because it is one of the few reported in the absence of treatment with a monoamine oxidase inhibitor and because it is only the second report of serotonin syndrome involving nefazodone and an SSRI,<sup>3</sup> although there also has been a report involving the related compound trazodone in combination with an SSRI.<sup>4</sup>

A puzzling aspect of this case of serotonin syndrome is the length of time necessary for this patient to recover after discontinuation of the 2 antidepressants, given nefazodone's relatively short half-life. One possibility is that the patient's concurrent treatment with alpha interferon, which has poorly characterized effects on cytochrome P450 enzymes, decreased the clearance of nefazodone or one of its metabolites (such as *m*-CPP, a potent serotonin agonist itself). Another possibility is that the patient worsened on day 2 as a result of haloperidol-induced akathisia, rather than from progression of the serotonin syndrome.

This case indicates that clinicians should be aware of nefazodone's potential for contributing to serotonin syndrome and that they should be cautious of coadministering nefazodone and an SSRI.

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