

Inability to Cry During SRI Treatment

Sir: It has been our clinical experience that serotonin reuptake inhibitors (SRIs) rapidly improve the symptom of excessive or inappropriate crying in depressed patients. This is consistent with reports in which SRIs improve pathologic crying in stroke patients.^{1,2} We, however, report three cases in which patients complained that they were unable to cry during SRI treatment. We know of no previous reports of this SRI-induced adverse effect.

Case 1. Ms. A is a healthy 42-year-old woman with a long history of obsessive-compulsive disorder with no comorbid depression. Results of a mental status examination were remarkable for her broad dramatic affect. She was taking no medications. She was treated with fluoxetine 60 mg/day, and over several months had a remarkable reduction of her obsessions and compulsions without suffering apathy or indifference. She reported that she had always been an emotional person and cried easily at church or while watching movies. During the first week of treatment, she noticed she could not cry. This was distressing to her, but she decided that fluoxetine had made such a difference in her life that she did not want to stop it. Loss of crying has persisted for 8 months with the exception that when she dropped a box on her toe, she was able to cry.

Case 2. Ms. B is a healthy 33-year-old woman who presented with new onset panic disorder with no depressive symptoms. She was treated with sertraline 50 mg/day and alprazolam 0.5 mg b.i.d. for 2 weeks, after which the alprazolam was discontinued. Before treatment, she was crying "all the time in fear," though she considered herself an emotional person who cried easily.

While she reported that her panic attacks and anticipatory anxiety stopped after 1 month of treatment, she noticed that she stopped crying after only several days of drug therapy. She did not like this. She was unable to cry while watching movies or during arguments with her husband. She experienced no other changes in affective responsivity, with the exception that she could no longer attain orgasm. She tolerated the inability to cry for 2 months but then asked to change medication. Her sertraline dose was lowered to 25 mg/day and after 1 week, she found she was able to cry normally. Her anxiety remained in remission.

Case 3. Ms. C is a healthy 35-year-old woman who presented with major depressive disorder. Among her symptoms, she reported crying frequently. She was taking no medication; treatment was begun with sertraline 50 mg/day. Her depressive symptoms gradually improved over several weeks without development of apathy or indifference. She noted that she stopped crying several days after beginning sertraline and wondered if this was abnormal as crying had always served as an "emotional release" for her. Several months into treatment, her pet dog died, and the patient was unable to cry in grief. She stopped taking the sertraline and 1 day later was able to cry when thinking about her dead pet. She subsequently resumed sertraline and again noticed she could not cry.

These cases illustrate that some women, independent of diagnosis, rapidly lose the emotional response of crying during treatment with sertraline or fluoxetine. Cessation of crying seems independent of apathy or indifference previously reported with fluoxetine and fluvoxamine.³ Two of the women did

not habituate to the effect, and one responded to dose reduction. These women all considered themselves highly emotional and were troubled by this change; patients with a propensity to cry may be at greater risk for this adverse effect, though the frequency of this effect is unstudied. Diminished crying ordinarily would be considered a therapeutic effect of SRIs. However, for a subset of patients, this may become an adverse effect and clinical dilemma. The presumed mechanism for this phenomenon may be related to changes in serotonergic neurotransmission as has been postulated in pathologic crying.^{1,2}

The views of the authors do not purpose to reflect the position of the Department of the Army or the Department of Defense (para 4-3, AR 360-5).

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Fluoxetine-Induced Akathisia Does Not Reappear After Switch to Paroxetine

Sir: The serotonin selective reuptake inhibitors (SSRIs), such as fluoxetine,^{1,2} sertraline,^{3,4} and paroxetine,⁵ have been repeatedly reported to produce akathisia that responded well to treatment with the β -adrenergic antagonist propranolol, dose reduction, or both. We report two cases of patients with refractory major depression who suffered from severe fluoxetine-induced akathisia that disappeared completely after fluoxetine withdrawal and did not reappear after administration of an equivalent dose of paroxetine, another SSRI antidepressant.

Case 1. Ms. A, a 47-year-old woman with a 5-year history of severe recurrent major depression with psychotic features, failed to respond to treatment with a combined trial of nortriptyline 200 mg/day, high-dose thyroxine 600 μ g/day, and thioridazine 200 mg/day. She was treated with fluoxetine up to 40 mg/day after nortriptyline was withdrawn. On Day 14 of fluoxetine treatment, she developed slight akathisia. Because she still suffered from depression, the fluoxetine dosage was gradually elevated to 80 mg/day within 2 weeks. Her depressive symptoms improved; however, akathisia and an unpleasant inner restlessness increased. The addition of propranolol 40 mg to her regimen led to an improvement of the akathisia within 6 hours, but also to a simultaneous recurrence of severe depressive symptoms. Decreasing the dosage of propranolol to 20 mg/day did not improve the depressive condition. However, discontinuation of the propranolol 7 days later led to a rapid improvement in depressive symptoms and to a recurrence of akathisia. Discontinuation of fluoxetine led to a complete disappearance of aka-

thisia 14 days after the last intake. One day after withdrawal of fluoxetine, paroxetine was administered in increasing dosages up to 80 mg/day within 3 weeks. During a 5-month observation period, no signs of akathisia and depression reappeared. Thioridazine and thyroxine were kept constant throughout the trial.

Case 2. Ms. B, a 54-year-old woman with a 3-year history of refractory depression, had been treated with various antidepressants and combinations (e.g., lithium, carbamazepine) without improvement. Finally, a combination of nortriptyline 300 mg/day, high-dose thyroxine 500 µg/day, and thioridazine 100 mg/day improved the condition, but Ms. B then suffered from an unpleasant dry mouth. Therefore, the dosage of nortriptyline was decreased to 200 mg/day, and fluoxetine was added to the regimen in increasing doses up to 80 mg/day. Four days after she began to receive 80 mg/day of fluoxetine, she experienced inner restlessness and akathisia. In addition, she reported frightening obsessive thoughts (fear of killing her grandchild) and marked anxiety. After reduction of the dose of fluoxetine to 40 mg/day, anxiety and obsessive thoughts disappeared; however, akathisia persisted during the following 3-week period. Akathisia completely disappeared a few days after the withdrawal of fluoxetine. Administration of paroxetine 40 mg/day was tolerated well without recurrence of akathisia during a 4-month follow-up. Nortriptyline, thyroxine, and thioridazine were kept constant during the paroxetine trial.

We would like to emphasize that both patients were extremely ill individuals and at the time were among the most refractory depressed inpatients in our department. Therefore, both patients received unusually high doses of antidepressants and even experimental drugs (high-dose thyroxine) that are part of our treatment procedure in refractory patients and may not be recommended for routine use.

The uncontrollable motor restlessness in both patients' hands and legs was indistinguishable from the akathisia seen in patients undergoing neuroleptic treatment. Both patients felt extremely distressed by the restlessness, which prevented them from sitting longer than a few minutes. The effectiveness of a β -blocker in treating the restlessness was confirmed in Case 1; however, the patient concomitantly became depressed. This is in line with suggestions that β -adrenergic receptor antagonists may trigger depression in predisposed individuals.⁶ It should be noted that both patients were taking high doses of fluoxetine (80 mg/day) and that reduction of fluoxetine dosage (20 mg/day) also may have been useful. In both cases, withdrawal of fluoxetine led to a complete disappearance of akathisia, which did not reappear after rechallenge with another SSRI antidepressant, paroxetine, at equivalent doses. This finding supports a recent study by Brown and Harrison suggesting that patients who discontinue one SSRI because of side effects can be treated successfully with another.⁷ However, immediate switching from fluoxetine to an alternate SSRI is sometimes associated with exacerbation of side effects characteristic of this drug class (e.g., nausea, tremor).

SSRI-induced akathisia was hypothesized to be the result of the inhibition of dopaminergic neurotransmission caused by increased serotonin activity.⁸ In vitro radioligand binding profiles indicated that paroxetine has a higher affinity for muscarinic cholinergic receptors compared with fluoxetine by at least one order of magnitude.⁹ Also, in our impression from clinical observation, paroxetine more often produces anticholinergic side effects than does fluoxetine. In some patients, anticholinergic drugs are effective in treating neuroleptic-induced akathisia. Therefore, one could speculate that the potentially reduced risk of paroxetine in producing akathisia may be due to its anticholinergic properties. We conclude from the case studies that

switching to paroxetine seems to offer a possible treatment option in depressed patients suffering from fluoxetine-induced akathisia.

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Response to Risperidone Addition in Fluvoxamine-Refractory Obsessive-Compulsive Disorder: Three Cases

Sir: We read with great interest the three cases reported by McDougle et al.,¹ in which patients with OCD refractory to fluvoxamine were treated with risperidone. We have also had a positive experience combining risperidone with an SSRI in a patient with compulsive tattooing (case report pending review). We assume the authors were not able to acknowledge the small open add-on trial of risperidone reported by Jacobsen² due to the lag time between submission and publication.

What is of interest in all three cases is that the patients suffered from various other psychopathology along with OCD, which put them somewhere along the obsessive-compulsive spectrum as described by Hollander and Wong.³ These patients probably represent a subset of patients who will very likely benefit from combination therapy as indicated by the authors. Their proposed double-blind study to ascertain what role risperidone may play in the pharmacologic treatment regimen of refractory OCD or the atypical case falling into a subtype of obsessive-compulsive psychopathology looks to be promising.

The opinions and assertions contained herein are the private view of their authors, and are not to be construed as official or as reflecting the views of the Department of the Army, Department of Defense, or the U.S. Government.

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Nefazodone and Symptoms Suggesting Neurotoxicity: A Case Report

Sir: We report a case of reversible neurotoxicity possibly induced by an increase in the dose of nefazodone.

Case report. Mr. A, a 43-year-old man with schizoaffective disorder, presented with complaints of paranoid ideation, auditory hallucinations, and suicidal ideation. One week prior to admission, he had discontinued his regularly prescribed medications, which included sertraline, risperidone, diazepam, cyclobenzaprine, and carbamazepine. The patient had no significant past medical history, and results of his admission physical examination and laboratory tests were within normal limits.

Upon admission, all of Mr. A's regular medications were reinitiated with the exception of diazepam, leading to rapid resolution of his psychotic symptoms. Sertraline was discontinued on Day 6 of hospitalization due to complaints of agitation. Since the patient had ongoing symptoms of depression, it was decided on Day 7 to initiate treatment with nefazodone 50 mg b.i.d. The dose of nefazodone was raised to 200 mg/day on Day 14 without complications, and raised again on Day 20 to 300 mg/day. On Day 22, the patient developed new-onset symptoms of ataxia, lethargy, confusion, and word-finding difficulties. Neurologic examination was significant for complete inability to perform heel-to-toe walking and bilateral dysmetria on finger-to-nose testing. Nefazodone was discontinued, resulting in the rapid resolution of the patient's symptoms with no significant cognitive or neurologic findings on examination by the following day. Treatment with nefazodone was then reinitiated at a lower dose of 200 mg/day, with no subsequent reemergence of the previous symptoms.

The reaction described above coincided with the dosage increase of nefazodone to 300 mg/day and resolved when nefazodone was discontinued, suggesting either a drug interaction or a direct dose-related neurotoxicity. Mr. A was taking several additional psychoactive medications, making it important to consider the question of inhibition of drug metabolism, particularly since nefazodone is a potent inhibitor of cytochrome P450 3A4 isoenzyme, is a weak inhibitor of P450 2D6 isoenzyme, and is highly protein bound.¹ Since carbamazepine is a substrate of cytochrome P450 3A4, the inhibition of carbamazepine metabolism by nefazodone with an associated progression to carbamazepine intoxication was possible. Carbamazepine toxicity is typically associated with drowsiness, disturbances of coordination, confusion, and ataxia, but the serum carbamazepine level on the day of the reaction was 7.5 µg/mL, making this an unlikely explanation. Mr. A, however, was also being treated with cyclobenzaprine, a muscle relaxant structurally related to the tricyclic antidepressants, which are demethylated by the cytochrome 3A4 isoenzyme. This raises the possibility that nefazodone was inhibiting the metabolism of cyclobenzaprine and thereby raising the serum level. Cyclobenzaprine toxicity is associated with ataxia, dysarthria, confusion, and disorientation,

providing one possible alternate explanation for the patient's symptoms. One additional issue is that cigarette smoking is known to be a cytochrome P450 inducer, and changes in smoking status can lead to changes in serum drug levels. Although Mr. A was a smoker, the absence of change in his smoking habit during the time period described in this case suggests that smoking was not a significant factor.

Nefazodone is a new antidepressant that blocks serotonin Type 2 (5-HT₂) receptors postsynaptically, inhibits 5-HT reuptake presynaptically, and blocks norepinephrine reuptake presynaptically.² The most commonly reported adverse effects are dry mouth, somnolence, nausea, dizziness, constipation, asthenia, light-headedness, and blurred vision.¹ It is not certain whether the symptoms experienced by Mr. A were related to a direct and reversible drug toxicity or a drug interaction. Nonetheless, this case report raises the possibility that dose-related neurotoxicity may exist with nefazodone and emphasizes the need to pay close attention to all possible drug interactions, particularly in patients being treated with multiple psychoactive agents.

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EPS With Fever Versus NMS

Sir: I would like to comment on the case report "Risperidone and Neuroleptic Malignant Syndrome" (November 1995 issue),¹ which details a patient who received 6 mg of risperidone and experienced severe parkinsonism 48 hours after discharge, which worsened to catatonia, mutism, etc., and a temperature of 100.2°F (38.1°C) after her medication was withdrawn. It is unusual for someone to develop severe extrapyramidal symptoms (EPS) 48 hours after discharge, and the possibility of overdose should be addressed.

When previously treated with high-potency neuroleptics, this patient developed marked EPS and received anticholinergics, benzodiazepines, and propranolol. No mention is made of concomitant medications when she was taking risperidone, but the sentence "All medications were discontinued" suggests that other medications were involved, probably anticholinergic agents. The abrupt discontinuation of all medications (i.e., risperidone plus anticholinergic) could worsen the patient's condition. A temperature of a 100°F (38°C) is no contraindication to the use of anticholinergics. The main point is that there is a tendency and, indeed, people recommend that when NMS is suspected, all medication be withdrawn. In a controlled study, we showed that simultaneous withdrawal of both a neuroleptic and anticholinergic produces an upsurge of EPS,² which is why we recommend that if neuroleptics are withdrawn, anticholinergics should be continued (if the temperature is below 102°F [39°C]). Even if the temperature is higher, one might consider a gradual decrease of anticholinergic with the concomitant addition of dopamine agonist to try to prevent EPS, which can be associated

with increased heat production at a time when the temperature control system may be malfunctioning because of dopamine blockade. "Extrapyramidal symptoms with fever" better describes this case and also directs attention to the need to avoid and treat EPS.

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Mandibular Dystonia Associated With the Combination of Sertraline and Metoclopramide

Sir: We report a case of mandibular dystonia that developed after sertraline, a serotonin reuptake inhibitor (SRI), was added to a chronic regimen of metoclopramide.

Case report. Ms. A, a 23-year-old white woman with no prior history of depression, presented to our inpatient crisis unit with a major depressive episode of 2 months' duration. Her only significant physical illness was gastroesophageal reflux, which had been well controlled for the prior 6 months with metoclopramide 15 mg q.i.d. The patient reported experiencing no side effects to this medication. She was taking no psychotropic medications at the time of admission. Results of physical examination, serum chemistries, and urine toxicology screen were unremarkable.

On Day 2 of hospitalization, Ms. A was started on sertraline 50 mg/day. After receiving two doses of sertraline during a 48-hour period, she complained of symptoms consistent with a mandibular dystonia: periauricular pain, jaw tightness, and the sensation of her teeth clenching and grinding. Oral administration of one dose of diphenhydramine 50 mg provided relief within 30 minutes. The following day, Ms. A reported a recurrence of these symptoms approximately 8 hours after receiving her third dose of sertraline. Oral administration of benzotropine mesylate 2 mg effectively relieved the symptoms. Sertraline was discontinued, and there was no recurrence of the extrapyramidal side effects (EPS). The following day, trazodone was initiated and titrated to 100 mg b.i.d. over the course of 1 week. No significant side effects were reported, and the patient was discharged to outpatient follow-up approximately 10 days after admission.

A number of case reports have described the development of EPS after the use of SRIs.^{1,2} Although the etiologic basis for the EPS is presently unclear, one hypothesis suggests that the underlying mechanism is mediated by the serotonergic inhibition of the dopamine pathways in the nigrostriatum.³ Metoclopramide is a gastrokinetic agent possessing significant dopamine receptor antagonistic properties.⁴ The development of EPS after the use of this agent has been widely reported in the literature.^{4,5}

At least three possible explanations might account for the development of mandibular dystonia in our patient. First, since the EPS occurred only after the addition of sertraline, it can be argued that this agent alone was responsible for inducing the dystonic reaction due to the inhibitory effects of serotonin on dopaminergic neurotransmission. However, although there have

been reports of an association of sertraline with akathisia,⁶ a MEDLINE computer search has revealed no previous reports that this SRI causes an acute dystonic reaction. It was not clinically feasible to attempt a trial of sertraline in the absence of metoclopramide, otherwise this approach could have helped clarify a causal relationship.

A second possible mechanism for the mandibular dystonia is the potential pharmacokinetic interaction between sertraline and metoclopramide. However, this is unlikely based on findings that most of metoclopramide is excreted as unchanged drug.⁷

A third and highly plausible explanation for the dystonia is the potential additive pharmacodynamic effect of sertraline with metoclopramide. It is theoretically possible that facilitation of the serotonin system with sertraline, combined with the dopamine antagonism produced by metoclopramide, synergistically produced a level of dopaminergic inhibition sufficient to produce dystonia in our patient. At the very least, this case ought to alert clinicians to the possibility that patients receiving the combination of sertraline and medications possessing dopamine-blocking properties (e.g., antiemetics, antipsychotics) may be at increased risk for experiencing EPS. The use of anticholinergic medications may be both a practical and an effective treatment modality in these particular situations of drug-induced EPS.

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Exercise-Induced Orgasms Associated With Fluoxetine Treatment of Depression

Sir: Paradoxically, fluoxetine has been reported both to delay or abolish orgasms¹ and also to induce spontaneous orgasms.²⁻⁴ Fluoxetine-associated exercise-induced orgasms represent an additional orgasmic disturbance that, to my knowledge, has not previously been reported. This letter reports a woman whose fluoxetine treatment for depression was accompanied by the development of orgasms arising unintentionally during vigorous exercise. The co-occurrence of these exercise-induced orgasms with the development of delayed orgasms during purposeful sexual activity may shed light on the relationship of serotonergic medications to sexual function.

Case report. Ms. A, a 50-year-old woman, sought treatment for symptoms of depressed mood, tearfulness, low energy, loss

of interest, intermittent awakening, passive suicidal ideation, and mood reactivity that had begun 2 years previously. Her appetite was undisturbed. She gave no history of prior unipolar or bipolar illness, psychosis, or significant anxiety symptoms. She denied substance abuse, had been in apparently good physical health, and was taking no medications prior to her antidepressant treatment. Prior to antidepressant treatment, she had enjoyed regular intercourse with her husband and had not experienced difficulty in achieving arousal and orgasm.

She was started on fluoxetine 20 mg/day but within days developed headaches and bruxism. These side effects subsided and her depressive symptoms improved substantially following a decrease in dosage to 10 mg/day. After several months at 10 mg/day, her mood worsened and her mood reactivity was exacerbated following the death of a friend. After her fluoxetine dosage was again increased to 20 mg/day, she experienced an improvement in mood unaccompanied by headaches or bruxism. Associated with this dose increase, however, she noted the dramatic presence of two symptoms of sexual dysfunction: one was an increased difficulty achieving orgasm during sexual intercourse and the other was the development of unintended exercise-induced orgasms that occurred with predictable regularity and ease.

The exercise-induced orgasms occurred while Ms. A walked vigorously on a treadmill. They soon began to occur during every exercise session (three times per week) after an interval of approximately 10 minutes. They were not associated with sexual fantasies nor with yawning. They were not associated with genital friction from tight exercise clothing. The patient described them as differing from orgasms related to intentional sexual activity in that there was less fantasy or sexual interest and less physiologic arousal, i.e., vascular engorgement of the external genitalia and lubrication. She found these experiences disturbing because she wondered whether they signified a loss of interest in her husband, with whom she had previously enjoyed a passionate sexual relationship. This concern was enhanced by her increased difficulty in achieving orgasm during sexual relations with her husband. The time and effort required had greatly increased, and the intensity of the experience had diminished since the increase in her fluoxetine dosage.

Ms. A found that cyproheptadine 4 mg taken orally prior to sexual intercourse partially alleviated the anorgasmia but was associated with sedation. Several months after resolution of her depressive symptoms, she tapered and discontinued fluoxetine and experienced return to her baseline sexual functioning.

The predominant effect of serotonergic antidepressants on sexual function is to reduce desire, arousal, and capacity for orgasm.⁵ Two serotonergic antidepressants, fluoxetine and clomipramine, have nevertheless been reported to induce spontaneous orgasms.²⁻⁶ In addition, increased sexual interest,⁷ even to the point of obsession,⁸ has been reported during fluoxetine treatment. Though not a strong peripheral α_1 antagonist, fluoxe-

tine has also been implicated in a case of prolonged erection.⁹ In this author's experience, another patient's spontaneous erections and orgasms have been associated with another serotonergic antidepressant, venlafaxine.

Animal and human studies of serotonergic effects on sexual behavior are complicated by the heterogeneity of serotonin receptors and the presence of multiple sites of action¹⁰ as well as interactions between serotonergic and other neurotransmitter systems. The mechanisms by which serotonergic antidepressants might enhance sexual desire, arousal, or orgasm remain far from clear. In this patient, the co-occurrence of delayed intentional orgasms with exercise-induced orgasms might cast doubt on an explanation that invokes the existence of a subpopulation of orgasm-enhancing serotonin receptors. Another hypothesis for the infrequent but significant increases in desire, arousal, or orgasm observed with serotonergic agents might be a central nervous system homeostatic response leading to down-regulation of serotonergic receptors or their sensitivity. Perhaps "adventitious orgasms" may occur in such patients, much as adventitious dyskinesic movements may develop in patients treated with dopamine antagonists. The emergence of such orgasms need not be associated with a recurrence of depressive mood, just as tardive dyskinesia can emerge in a patient still experiencing antipsychotic effects from neuroleptic treatment.

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