Priapism: Trazodone Versus Nefazodone

Sir: The incidence of sexual dysfunction with antidepressant drugs varies from a low of 1.9% to a high of 91%.[1] Such dysfunctions are believed to result from interactions with various neurotransmitter systems.[1–3] One of the most dramatic and potentially disabling is priapism, which is a prolonged, dysfunctional penile erection that is painful and impairs sexual desire. It is associated with venous drainage obstruction from the corpora cavernosa[4] but not from the glans penis and corpus spongiosum. Although 50% of all reported cases are idiopathic, drug-induced priapism comprises about 30% of all cases.[5] Antipsychotic medications account for 15% to 26% of cases, and antihypertensive medications account for 11% to 14%.[6] It is estimated[7] that the incidence of priapism linked to trazodone is 1 in 1000 to 1 in 10,000 and occurs at dosage levels of 50 to 400 mg/day, but mostly at 150 mg. Priapism is most likely to occur within 28 days after initiation of trazodone. Nefazodone, a triazolophenylpiperazine antidepressant, is an analogue of trazodone; however, several receptor systems differ from those of trazodone or of other antidepressants. It is a potent 5-HT_2 antagonist and a serotonin reuptake inhibitor. Comparative placebo-controlled studies have shown that nefazodone is an effective antidepressant.[8,9] During the premarketing development of nefazodone as an antidepressant, of the 3500 human subjects who received the drug (as of April 15, 1993) in various clinical trials, no priapism was reported (data on file, Oct. 28, 1993, Bristol-Myers Squibb).

Case report. A 51-year-old married man was admitted with aggressivity, destructiveness, and a 2-month history of anxiety, depressed mood, insomnia in all three phases (initial, middle, and terminal), and a lack of sex drive. He had no history of drug or alcohol abuse and had his first depressive episode at age 27, had another at age 33, and was hospitalized at age 47 for a major depressive episode. During his episodes of depression, he had an unsatisfactory response to several antidepressants including clomipramine and amitriptyline.

The patient met DSM-III-R criteria for major depressive disorder and signed informed consent to start the experimental medication nefazodone 200 mg b.i.d. for a period of 6 weeks. The medication was well tolerated with the only adverse complaints being muscle cramps and headache. Chloral hydrate was given for insomnia. On termination of the experimental protocol with nefazodone and in view of the patient's continued anxiety and insomnia, the decision was made to start trazodone 300 mg/day. The patient complained of some dizziness only. After 2 weeks on the same dosage of trazodone, the patient had an episode of gout and was given allopurinol; after 3 days on allopurinol and 17 days on trazodone therapy, the patient began to notice priapism. He was hospitalized for 2 days, his medication was discontinued, and the priapism subsided with conservative management. There have been no sequelae, and the patient has had subsequent normal sexual function over several years of follow-up. Because the patient was poorly responsive to antidepressant treatment with trimipramine and because of his previous favorable response to nefazodone, the latter was administered for 14 weeks and then discontinued as the depression was in remission. Subsequent medical investigation discovered that the hyperuricemia was caused by early polycythemia vera. This was a continuous variable during administration of trazodone and nefazodone.

The link between priapism and α_1-adrenergic blockage is well recognized.[10] Taylor et al.[11] extensively studied nefazodone and trazodone for their α_1-adrenergic antagonistic activity. Nefazodone was 5% as potent as the α_1-adrenergic agent phentolamine in the attenuation of the pressor response to phenylephrine in rats.[12] Similar data were obtained for the pressor response to norepinephrine. Intraarterial administration of nefazodone in the perfused hindlimb of the dog had 0.38 to 0.56 of the α_1-adrenolytic potency of phentolamine and 7% to 11% that of trazodone.

Polysomnographic studies of sleep architecture and nocturnal penile tumescence indicated that nefazodone increased REM sleep while trazodone, like other antidepressants, suppressed REM sleep.[13] Also, nefazodone at doses of 200 mg and 400 mg demonstrated differential effects on penile nocturnal tumescence in healthy volunteers; there was increased total tumescence time only to the extent that REM sleep was increased. Trazodone at a single dose of 100 mg and 200 mg increased total tumescence time by delaying the onset of detumescence; therefore, tumescence with trazodone continued well after the end of REM sleep.

We present the case of a man who developed priapism with trazodone administration but not with a prior and a subsequent course of nefazodone treatment. It is suggested[14] that although α_1-adrenergic blockade is a common property of psychotropic drugs, priapism itself is rare.

Priapism, therefore, is more likely to be manifest owing to an interaction among several factors. This report appears to confirm that observation. It appears that early polycythemia vera may have contributed to the priapism[15] as it does in cases of leukemia[16] and sickle cell anemia.[17] This mechanism may be mediated by peripheral α receptors in the corpora cavernosa.[18] The difference between nefazodone and trazodone in the development of priapism has thus far been evidenced in the animal studies showing α_1-adrenergic blockade, in REM studies of nocturnal penile tumescence in humans, and in this clinical experience with a depressed patient.

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Methylphenidate and SSRI-Induced Sexual Side Effects

Sir: We were interested to read "Methylphenidate Augmentation of Serotonin Selective Reuptake Inhibitors: A Case Series" and would like to raise the issue of the role of sexual functioning in the treatment of depression.[1] Not only can the addition of methylphenidate to an SSRI boost the antidepressant action, but it may also relieve sexual dysfunction caused by SSRI therapy. Sexual dysfunction due to SSRIs is a common, well-described side effect that can lead to noncompliance. Drug holidays, dose adjustment, and antidotes such as yohimbine, amantadine, bupropion, cyproheptadine, and buspirone have been suggested.[2–8] Success has been mixed, and disadvantages include loss of antidepressant effect and uncomfortable side effects.

Recently, several cases were reported in which psychostimulants were used to treat sexual dysfunction caused by SSRIs.[9,10] Psychostimulants resulted in augmentation of libido, heightened levels of excitement, improved quality of erection, enhanced orgasmic sensation, and lowered orgasmic threshold with greater potential for repeated experience.

In Case 1, the authors note that the patient had "diminished sex drive" on fluoxetine treatment; however, sexual function during paroxetine treatment before and after the addition of methylphenidate is not described. In Case 3, the sexual side effects were so severe as to result in discontinuation of sertraline. However, when sertraline was subsequently combined with methylphenidate, the sexual side effects were described as mild. The patient in Case 4 experienced "loss of libido" and "ejaculatory delay" on fluoxetine therapy and discontinued the medication. His treatment with paroxetine, clonazepam, and methylphenidate was "successful," but sexual function during this combination was not detailed.

Lastly, it would have been interesting to know the specific effects of the stimulants used in this study on all phases of the sexual response cycle—desire, excitement, orgasm, and resolution. If their experience was similar to our own, they might have noted an improvement in SSRI-induced sexual side effects with psychostimulant treatment. Further investigation in this area could lead to treatments for depression that are both more effective and better tolerated.

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Dr. Stoll and Colleagues Reply

Sir: The suggestion that psychostimulants, particularly methylphenidate, could reverse the sexual side effects associated with serotonin selective reuptake inhibitors (SSRIs) is intriguing. Empirically, since other dopamine agonists (such as amantadine) may be effective for relieving sexual dysfunction associated with SSRIs, it seems reasonable to assume that methylphenidate would be effective as well.

However, in our case series we were using methylphenidate primarily to augment the antidepressant response to SSRIs. Unfortunately, we did not systematically collect data on sexual functioning before and after methylphenidate was added to the ongoing SSRI therapy. The authors of the above letter suggest that sexual dysfunction could lead to noncompliance, which could lead to a worsening of depressive symptoms. We would add only that perhaps restoration of orgasm function and enhancement of libido is "antidepressant" in itself. We agree that psychostimulants merit further study both as adjuncts for the treatment of major depression and as a remedy for SSRI-associated sexual dysfunction.

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Cardiorespiratory Problems With Clozapine

Sir: In your May 1995 issue, Pitner et al. described the use of clozapine in four elderly psychotic patients and commented on a dearth of articles on this topic.[1] However, in 1994, we pub-

lished an article "Clozapine in the Elderly" in the *Journal of Geriatric Psychiatry and Neurology*.[2] Our article described the use of clozapine in eight patients, aged 68 to 80 years, who had a variety of diagnoses, including one patient with Parkinson's dementia and patients with schizophrenia, depression, and dementia with depression.

Pitner et al. also note the finding of bradycardia in two patients. Bredbacka and colleagues[3] described "severe cardiorespiratory dysregulation" in a 29-year-old man who developed severe orthostatic hypotension with no increase in pulse rate. Cardiovascular problems in patients treated with clozapine are rare, but as described by Pitner et al.[1] and Bredbacka et al.[3] may lead to significant morbidity. Clozapine is a useful drug for psychotic patients, but it needs to be started at a very low dose and titrated up slowly.

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Drs. Mintzer and Pitner Reply

Sir: We were delighted to read about the experience of Drs. Frankenburg and Kalunian with clozapine in elderly patients. We share their ideas about both the risks and benefits of clozapine in this population. In our opinion, however, any definitive judgment about this matter is premature. Appropriately designed studies are necessary before a final decision is made about the safety and efficacy of clozapine in the elderly population.

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Risperidone-Induced Ejaculatory and Urinary Dysfunction

Sir: Risperidone is a benzisoxazole derivative antipsychotic agent with serotonin 5-HT_2 and dopamine D_2 antagonistic properties. During premarketing evaluation of this compound, diminished sexual desire, erectile dysfunction, and orgasmic dysfunction were noted in at least 5% of patients.[1] In addition, product information[1] lists dysuria and other urinary difficulties among risperidone's adverse events. Complaints of sexual and urinary dysfunction were also reported during risperidone efficacy studies.[2,3] No cause-and-effect relationship was established for risperidone and sexual and urinary dysfunction, however. We describe a case in which ejaculatory dysfunction and dysuria developed during treatment with risperidone, remitted after the drug was discontinued, then recurred after rechallenge with risperidone.

Case report. The patient, a 38-year-old man with acute exacerbation of schizoaffective disorder, had been taking haloperidol decanoate (injection) 100 mg every month (last dose, 2 months prior to admission) and lorazepam 0.5 mg four times daily for 3 years. At admission, he was prescribed a regimen of risperidone 1 mg twice daily, benztropine mesylate 1 mg twice daily, and lorazepam 0.5 mg four times daily. The lorazepam was tapered and discontinued in the first week. One week after risperidone treatment was initiated, the patient complained that he had experienced ejaculatory problems while masturbating (retarded ejaculation and inability to ejaculate) and difficulty in urinating (urinary hesitancy) since he was started on the risperidone. He had no history of similar symptoms. Lithium carbonate 300 mg three times daily was added to the regimen. Benztropine mesylate was discontinued, but the urinary and ejaculatory symptoms continued. Physical examination, surgical consultation, and laboratory tests revealed no significant abnormalities. Risperidone was discontinued on Day 12 of treatment. Four days later, the ejaculatory and urinary symptoms resolved. After the patient had been symptom-free for 3 days, we obtained his informed consent and reinstituted risperidone treatment (1 mg twice daily). Two days later, the ejaculatory difficulties and dysuria recurred. Risperidone was again discontinued, and the symptoms cleared within 2 days.

Risperidone appeared to cause ejaculatory and urinary symptoms in our patient. Sexual function is a complex interaction of neurogenic, hormonal, and vascular mechanisms. Erection and ejaculation appear to be related to the stimulation of α-adrenergic neurons, while inhibition of orgasm function is associated with stimulation of serotonergic neurotransmission.[4] Anticholinergic action would impair erection and/or ejaculation, and α-adrenergic blockade would interfere with ejaculation.[5] With typical antipsychotic agents, urinary problems may be secondary to anticholinergic side effects, and ejaculatory problems may be secondary to dopamine and norepinephrine blockade. Prolactin secretion is tonically inhibited by dopamine. Blockade of dopaminergic activity elevates prolactin levels, which may lower testosterone and luteinizing hormone levels. Low levels of gonadal hormones diminish libido in both sexes. Hyperprolactinemia is thought to contribute to sexual dysfunction that develops during treatment with neuroleptics,[6] and hyperprolactinemia does occur during risperidone treatment. Plasma prolactin levels were found to increase sevenfold after the first risperidone dose.[7]

Risperidone has no peripheral or central anticholinergic activity,[8,9] yet urinary retention, transient dry mouth, and blurred vision have been reported with its use.[7] These anticholinergic-like effects may result from the indirect effects of either serotonin, norepinephrine, or dopamine on the cholinergic system. Thus, it appears that the dopamine blocking effect, the adrenolytic effect, and the anticholinergic-like effect may be responsible for both the ejaculatory and urinary dysfunction in our patient. These possible side effects may be correlated with the use of risperidone and can potentially affect patient compliance and quality of life.

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Coadministration of Isoniazid and Antidepressant Drugs

Sir: Isonicotinylhydrazide, also known as isoniazid, is a well-known agent for treatment of mycobacterial infections. It is also used for prevention of tuberculosis, given 300 mg/day for a period of at least 6 months.[1] In vivo studies, using benzylamine as substrate, have demonstrated that isoniazid in therapeutic doses inhibits plasma monoamine oxidase (MAO) with no significant effect on platelet MAO.[2] Perhaps this is the reason that the possibility of interaction with tyramine-containing food has been raised in patients taking isoniazid.[3] In fact, there are isolated cases of adverse interaction of isoniazid with food items such as cheese and with meperidine.[3–6] Furthermore, isoniazid inhibits hepatic metabolism of a number of drugs, including diazepam, chlordiazepoxide, prazepam, flurazepam, triazolam, phenytoin, carbamazepine, and ethosuximide.[3]

It is now known that serotonergic antidepressant drugs in combination with MAO inhibitors can cause serotonin syndrome, a potentially serious condition resulting from a central hyperserotonergic state.[7] In a brief report from Australia, Judd and associates[8] have described the concurrent use of isoniazid and antidepressant drugs in three HIV-positive male patients, two of whom were taking fluoxetine up to 20 mg/day. Although one of the fluoxetine-treated patients tolerated the combination, the second patient experienced vomiting and diarrhea, and after 10 days, the antidepressant was discontinued. The third patient was taking moclobemide (a reversible MAO-A inhibitor) and isoniazid. Two days after the dose of moclobemide was increased, he experienced nausea and vomiting, and the antidepressant had to be discontinued. The patient subsequently was started on fluoxetine and tolerated the isoniazid-fluoxetine combination without adverse effects. The authors, however, concluded that isoniazid-antidepressant drug interaction was not a definite cause of the above described effects.[8] While this report alerts us to a potential interaction between isoniazid and antidepressant drugs, we would like to report two patients who tolerated the combination of isoniazid and antidepressants without adverse effects.

Case 1. A 19-year-old white woman, after employment screening, was found to have a positive Mantoux test. She had been placed on isoniazid 300 mg/day. When presenting to our clinic, she met the criteria for major depression, single episode without psychotic features (DSM-IV, 296.23).[9] Sertraline 50 mg/day was added to her ongoing regimen of isoniazid. The sertraline was eventually increased to 150 mg/day. She responded to antidepressant and supportive therapies and has taken the combination for 8 months without adverse effects.

Case 2. A 43-year-old white woman with major depression (DSM-IV, 296.33), diabetes mellitus, and hepatitis C was admitted to our inpatient facility for recurrence of her depressive symptoms, which had resulted in a suicide attempt. She was started on nefazodone 300 mg/day. A few days later, she was transferred to an inpatient state facility where she was found to have a positive Mantoux test. Subsequently, she was started on isoniazid 300 mg/day and pyridoxine 50 mg/day. She gradually improved and was discharged on nefazodone 400 mg/day and buspirone 10 mg/day. No dietary restrictions were recommended. She has been on the four-drug combination for 5 months without adverse effects.

Our experience is limited to only these antidepressants in combination with isoniazid, and we propose that the absence of adverse effect in our patients is likely due to the substrate preference of plasma MAO. It has been suggested that plasma MAO is not similar to that of platelet MAO.[2] Lewinsohn and associates[10] have described plasma MAO from healthy human subjects. This enzyme, which is inhibited by isoniazid, utilizes benzylamine as its preferred substrate.

Our case reports suggest that isoniazid and antidepressant drugs are not always dangerous when coadministered. However, given pharmacodynamic and pharmacokinetic factors, this combination may at least require regular monitoring for symptoms of serotonin syndrome and hypertensive crisis. The incidence of tuberculosis is on the increase in the United States.[11] We are likely to encounter patients with depression and tuberculosis at a higher rate.

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