

# Safety of Trazodone as a Sleep Agent for Inpatients

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*Trazodone, an atypical antidepressant with relatively low anticholinergic and cardiac conduction effects, offers useful augmentation to classic antidepressant drugs, notably selective serotonin reuptake inhibitors. One rare but serious side effect of the drug is priapism, the urological emergency in which the cavernosa of the penis become painfully engorged in the absence of sexual stimulation. The authors present what appears to be the first published case of priapism requiring urologic intervention after a single 100-mg dose of trazodone. In addition to a discussion of the history and physiology of trazodone and priapism, the authors present a profile of patients who present a safety risk in treatment.*

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Trazodone is a triazolopyridine derivative that works as a selective inhibitor of neuronal serotonin uptake and also has peripheral serotonin antagonist and alpha-adrenergic antagonist effects.<sup>1</sup> The drug has been used in the United States since 1982 as an antidepressant with minimal anticholinergic effects as well as a relative paucity of the cardiac conduction effects found among tricyclic antidepressants; additionally, its neuropsychobiology has been well described.<sup>1–3</sup>

Since trazodone is structurally unrelated to tricyclics, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors, it can often be used to safely augment therapy with these classic antidepressant drugs.<sup>1</sup> Moreover, since its most common side effect is sedation, trazodone is commonly used as a sleep agent for patients taking first-line antidepressants, including SSRIs—many of which have activating properties.<sup>4</sup> Other common adverse effects include anorexia, blurred vision, sweating, weight changes, orthostasis, dizziness, headache, memory impairment, insomnia, and gastrointestinal effects, including nausea, vomiting, diarrhea, and dry mouth. Rare, serious side effects include arrhythmias, hyper- or hypotension, hemolytic anemia, leukocytosis, methemoglobinemia, and seizures. Patients with preexisting cardiac disease who are taking trazodone should be monitored for arrhythmias, and trazodone is not recom-

mended for use during initial recovery from myocardial infarction.<sup>5</sup>

In this article, we 1) limit our discussion to the serious complication of priapism and 2) present a profile of patients who present a safety risk in treatment.

In the following case history, we describe a patient in whom a single 100-mg dose of trazodone precipitated priapism that required emergency urologic consultation and treatment following failure to resolve spontaneously. To our knowledge, priapism following a single dose of trazodone and requiring urologic intervention has not been reported. This case was exempt from institutional review board review because it was part of a quality assurance review and presentation.

## Case Report

Mr. A, a 42-year-old African American man, presented to the emergency room with suicidal ideation and auditory

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## Case Reports

hallucinations. His family history was relevant for paternal ethanol and cocaine use and extensive ethanol use in his extended family. He had been functional in society, holding a management position in a restaurant. Although he had a history of arrests for various misdemeanors, he denied any history of imprisonment. He also denied any medical diagnoses. At intake, he reported bothersome nightmares with trazodone. He denied all allergies to medications.

His psychiatric history included many years of depressive episodes. These episodes were associated with psychotic symptoms when accompanied by concurrent cocaine usage. Three years prior to presentation, he had a 30-day admission in another hospital for depression, which was followed by treatment in an 8-month inpatient and outpatient substance abuse program. He had since relapsed repeatedly, with short periods of abstinence. His last cocaine use was within a week of presentation. He had been using 0.5 g per week for over a decade. He also had used marijuana and consumed alcohol within a week prior to admission. Although he reported that he once took an antidepressant in the past, he was not taking any medications at the time of his presentation. Upon admission, Mr. A had significant psychomotor retardation, decreased speech rate and tone, and poor eye contact. He reported suicidal ideation with thoughts of setting himself on fire or taking an overdose of pills, and he had second-person auditory pseudohallucinations telling him to execute these plans. He denied any symptoms of anxiety. The results of a physical examination and laboratory studies were unremarkable.

His condition was treated with fluoxetine, 20 mg orally each day, and olanzapine, 2.5 mg orally each night. Because of his difficulty sleeping, which was refractory to diphenhydramine, an on-call resident wrote an order for trazodone at bedtime because of its antidepressant and sedating properties, although this medication had not been ordered by the treatment team because of his complaint of nightmares. Four hours after his first dose of 100 mg of trazodone, Mr. A noticed a persistent, painful erection but declined to tell the nurse because of embarrassment. Seven hours after taking the trazodone, Mr. A experienced increasingly excruciating pain, and he notified his nurse. Intravenous fluids and analgesics were given, and the urology team was consulted expeditiously. The condition failed to resolve spontaneously, but it was successfully controlled by saline irrigation and phenylephrine under lidocaine local analgesia. The patient reported having normal morning tumescence by the next day.

### Discussion

Priapism is characterized by a persistent, painful erection due to isolated engorgement of the corpora cavernosa in the absence of sexual desire. Priapism is classified into the low-flow (ischemic) and the less common high-flow (non-ischemic) types. The latter of these is most often associated with arteriosinusoidal shunting after penile or perineal trauma and is not considered an emergency. Low-flow priapism is associated with many etiologies, including hematological diseases (sickle cell disease, leukemia), hypercoagulable states, fat emboli, and autonomic nervous dysfunction. While most cases are of unknown etiology, drugs are considered to be a common cause of priapism. Associations have been demonstrated between ischemic priapism and many medications with alpha-adrenergic blocking activity or central serotonin-like activity.<sup>4,6-11</sup>

The major complication of ischemic priapism is cavernosal fibrosis with resultant impotence or abnormal erectile function, which normally does not occur if the priapism is treated within 4 hours of onset. Thus, this condition comprises a urologic emergency, and it is important that patients with priapism seek immediate medical attention. Despite initiation of treatment, it has been estimated that 40%–50% of patients with priapism become impotent.<sup>7</sup> Among the most frequently seen iatrogenic causes of priapism is trazodone therapy for depression. It is likely that the sympatholytic activity of trazodone is responsible for local autonomic imbalance, which leads to priapism. Also, it has been postulated that nocturnal erections in REM sleep may help precipitate priapism by increasing blood flow and drug delivery to cavernosal tissue.<sup>1</sup>

### History of Trazodone-Induced Priapism

During the period from 1982 to 1988, at least 20 cases of priapism with trazodone therapy were reported. These occurred in patients ages 24 to 60 who were taking standard doses of 100–600 mg per day for a duration ranging from 6 days to 4 weeks.<sup>1</sup> While many cases of trazodone-induced priapism have been published in case reports, a majority of these cases involved patients who had taken trazodone for weeks or who had had recent increases in their trazodone doses. One study reported the occurrence of priapism with daily use of trazodone at doses of 50–400 mg between days 1 and 64 of treatment. Those data suggested that the condition was most likely to occur during the first

28 days of treatment, although no study indicated a dose that was most likely to cause priapism.<sup>12</sup>

In one case series, two patients were presented who suffered from priapism while receiving trazodone therapy. However, in those cases the priapism had occurred after recent increases in the trazodone doses.<sup>1</sup> In response to another case report, one physician wrote a letter reporting a patient who experienced priapism after a single 50-mg dose of trazodone.<sup>13</sup> In this patient, however, the condition subsided spontaneously over 15 minutes of observation. Isolated cases of priapism have been reported with the use of citalopram<sup>8</sup> and fluoxetine.<sup>11</sup>

We report here a case of ischemic priapism that occurred after administration of a single 100-mg dose of trazodone and that did not resolve spontaneously. One possibly pertinent characteristic of this atypical case is our patient's history of cocaine use. In one previously published case report, a patient suffered from priapism after taking an overdose of trazodone while actively abusing cocaine. Since cocaine has been associated with priapism in the past, the report suggested that combined trazodone and cocaine use might increase the risk of priapism.<sup>14</sup> It is of note, however, that our patient was not actively using cocaine at the time of his complication. As for the effects of chronic cocaine use on priapism occurrence, one recent urological publication suggested that chronic cocaine use might lead to priapism by depleting sympathetic nerve terminals, although this is not completely understood.<sup>15</sup> Also,

priapism has been reported with fluoxetine use,<sup>16</sup> and fluoxetine was prescribed for Mr. A's depression.

### Conclusion

As an atypical antidepressant, trazodone is an efficacious drug that is useful for its relative safety when used with other antidepressants and for its sedating properties, which can aid with insomnia caused by other antidepressants or the depressive condition itself. An important side effect of trazodone is priapism, a painful condition that may constitute a urological emergency, requiring rapid treatment to help prevent long-term erectile dysfunction. Unfortunately, patients with priapism are often embarrassed or hesitant to seek help, so it is important that patients beginning use of trazodone or other causative drugs are informed of this side effect and of the need for rapid discontinuation of the medication and treatment if priapism should occur.

Patients who are at high risk for developing priapism include patients with sickle cell anemia or sickle trait, leukemia, autonomic nervous system dysfunction, or hypercoagulable states. In addition, high-risk patients include those who are taking SSRIs and those who have used cocaine or overdosed on cocaine or trazodone. Because of their predisposition to this serious complication of trazodone, these patients should be treated cautiously, and alternative treatments should be considered for the treatment of insomnia or depression.

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