

## Priapism and renal colic in a patient treated with duloxetine

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### Abstract

Antidepressant medications are associated with a variety of genitourinary and adverse sexual effects, such as urinary hesitation, priapism, and delayed ejaculation. Here, we report a case of priapism and renal colic following initiation of duloxetine in a patient with history of tolerated selective serotonin reuptake inhibitor treatment. To our knowledge, this represents the first report of priapism and renal colic associated with duloxetine use. This case contributes to the current body of evidence describing adverse genitourinary and sexual effects associated with antidepressant medications.

**Keywords:** adverse drug reactions, sexual side effects, antidepressants, serotonin-norepinephrine reuptake inhibitor

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### Background

Sexual side effects, including delayed ejaculation, decreased libido, priapism, and anorgasmia, are associated with the use of antidepressant medications and untreated psychiatric illness.<sup>1</sup> While sexual side effects are relatively common, their exact incidence remains unclear as they are hypothesized to be underreported by patients unless asked about them specifically.<sup>2</sup> The rates of individual sexual side effects among different classes of antidepressants are variable. Studies have shown that duloxetine, a serotonin-norepinephrine reuptake inhibitor, possesses a

similar sexual side-effect profile to that of the selective serotonin reuptake inhibitors (SSRIs).<sup>3</sup> Specifically, priapism has been associated with the use of citalopram, fluoxetine, paroxetine, and sertraline.<sup>4-7</sup> Priapism is defined as an erection that is painful and persists beyond or is unrelated to sexual stimulation<sup>8,9</sup>; it is thought that roughly 30% of cases are medication induced.<sup>10</sup> Despite similarities in adverse sexual effect profiles, a PubMed literature search using the Medical Subject Heading terms *priapism*, *duloxetine*, and *antidepressive agents* conducted in April 2015 yielded no results reporting priapism associated with duloxetine use. Additionally, priapism is not listed as a potential adverse effect within the duloxetine prescribing information.<sup>11</sup>

Other genitourinary (GU) side effects, such as erectile dysfunction or urinary hesitancy, are also reported to occur with antidepressant treatment. Renal colic is a severe unilateral flank pain that radiates to the groin and occurs most frequently with the passage of a kidney stone through the ureter or by obstruction of the urinary tract.<sup>12</sup> Although urethral resistance and urinary hesitation have been reported as adverse GU effects of duloxetine,<sup>11</sup> a PubMed literature search in April 2015 using the Medical Subject Heading terms *renal colic* and *antidepressive*

agents yielded no results. Thus, the following report outlines a case of priapism and renal colic observed after initiation of duloxetine in a patient who previously tolerated treatment with an SSRI. To our knowledge, this represents the first publication reporting this occurrence.

## Case Report

Mr C is a 39-year-old white man with a past psychiatric history of depressive disorder (not otherwise specified), opioid dependence, and benzodiazepine dependence who was admitted to an inpatient psychiatric facility after a suicide attempt. Psychiatric diagnoses were assigned by the treating psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria. On admission, the urine drug screen was positive for barbiturates (prescribed phenobarbital for maintenance of seizure disorder), benzodiazepines (alprazolam abuse 2 days before admission), opioids (heroin use day before admission), and cocaine (last use the day before admission). He denied history of complicated withdrawal or withdrawal seizures. His past medical history was significant for nephrolithiasis as a young adult (last episode 20 years ago), chronic low back pain, and a baseline seizure disorder secondary to repeated concussions. On admission, Mr C reported taking gabapentin 600 mg orally 4 times daily, phenobarbital 162 mg orally twice a day, escitalopram 20 mg orally daily, and aripiprazole 10 mg orally daily. He reported medication nonadherence to escitalopram and aripiprazole for 4 months before admission.

Mr C was admitted and reinitiated on home medications. Escitalopram and aripiprazole were ordered for treatment of depressive symptoms but initiated at lower doses because of medication nonadherence. For benzodiazepine and heroin dependence, he was initiated on inpatient withdrawal assessment protocols on day 1 of admission and continued for 8 days on diazepam and 7 days on buprenorphine/naloxone, respectively. The patient denied any history of taking alternative antidepressants to treat chronic low back pain and depression, and expressed interest in this treatment approach. Therefore, escitalopram and aripiprazole were discontinued on day 5 of admission, and duloxetine was initiated on day 6 to target chronic low back pain and depression. The next day, Mr C reported pain in his scrotum and a persistent, painful erection that occurred within hours of his first dose of duloxetine 30 mg.

Per patient report, the erection persisted for over 2.5 hours and subsequently subsided without treatment. He also reported that during this time he was unable to urinate and experienced testicular swelling and unilateral flank pain. The patient denied any history of priapism in

the past, including while taking escitalopram as an outpatient. After the priapism resolved, physical examination by an internal medicine physician revealed no evidence of urethral discharge or lesions. He was noted to have marked scrotal erythema and warmth as well as tenderness to light palpation diffusely. Testes appeared to be normal size, and the penis was flaccid. There was presence of tender right-sided flank pain to deep palpation and percussion, and his range of motion was limited by pain in his back and scrotum. A urinalysis was done at the time of symptoms, which revealed 3+ urine blood, 1 squamous epithelial cell, and 540 red blood cells. Duloxetine was discontinued after 1 dose, and the patient had near complete resolution of adverse effect symptomatology by the following day, with the exception of unilateral flank pain, which decreased over the course of 3 days. Given the rapid improvement in GU symptoms after discontinuation of duloxetine, further workup to rule out nephrolithiasis was not performed. The patient was restarted on escitalopram and had no further complications during his hospitalization.

## Discussion

Priapism has been previously estimated to have an incidence of 1.5 per 100 000 person years<sup>13</sup> and may arise secondary to several causes.<sup>10</sup> Priapism is thought to occur via 2 distinct mechanisms, specifically, low-flow and high-flow priapism.<sup>8</sup> Low-flow priapism, also known as ischemic priapism, is thought to arise from decreased penile venous outflow, resulting in stasis of blood and priapism. High-flow priapism has been characterized by increased arterial inflow into the penis and resultant priapism secondary to excess venous outflow.<sup>8</sup> Typically, high-flow priapism is related to trauma or is idiopathic. Low-flow priapism has more diverse causes and is often due to medications, sickle cell disease, or leukemia, or it may also be idiopathic.<sup>8,13</sup> Duloxetine's mechanism of action involves inhibition of neuronal serotonin and norepinephrine reuptake without significant affinity for histaminergic, cholinergic, or adrenergic receptors.<sup>11</sup> Previous reports of SSRI-induced priapism have hypothesized serotonergic mechanisms involving specific serotonin receptors,<sup>14</sup> while reviews of other psychotropic mechanisms, such as trazodone and certain neuroleptics, have suggested the role of alpha-adrenergic blockade resulting in priapism.<sup>15</sup> In terms of serotonin receptor involvement, it has been shown that a penile erection is caused by 5-hydroxytryptamine (HT)<sub>1B</sub> and 5-HT<sub>1c/1d</sub> receptor stimulation, while 5-HT<sub>1a</sub> or 5-HT<sub>2</sub> receptor stimulation inhibits penile erection.<sup>7,16</sup> Previous reports have implicated cocaine abuse as a cause of priapism through its effect on norepinephrine reuptake and persistent systemic vasoconstriction.<sup>17</sup> A case report of the serotonin-norepinephrine reuptake inhibitor venlafax-

ine, associated with priapism in a young man with history of alcohol and cannabis abuse, has also been published.<sup>18</sup> When postulating a mechanism for duloxetine-induced priapism, involvement of serotonin, norepinephrine, or a combination of the two is plausible. Given our patient's history of SSRI tolerance, it stands to reason that noradrenergic activity may have been involved in our patient. Trials aimed specifically at evaluating the sexual side-effect profile of duloxetine found that men treated with duloxetine had a significant increase in difficulty reaching orgasm compared with those treated with placebo.<sup>11</sup> In contrast, priapism was not reported.

Renal colic is characterized as acute radiating flank pain associated with obstruction of the ureter, and it is often accompanied with hematuria, dysuria, nausea, and vomiting.<sup>12</sup> Previous studies have found that more than 1 million patients visiting the emergency department each year are diagnosed with renal colic or renal calculus.<sup>19</sup> To our knowledge, no case reports exist describing the occurrence of renal colic associated with antidepressant agents, and the exact mechanism by which such an adverse effect might occur is unclear. However, a plausible explanation may exist when considering duloxetine's role in the treatment of stress urinary incontinence. Studies have shown that duloxetine's inhibitory effects on the presynaptic reuptake of serotonin and norepinephrine result in increased contractility of the urethral sphincter, the musculature that regulates the flow of urine from the bladder.<sup>20</sup> Further, duloxetine has been approved in Europe as a treatment for stress urinary incontinence in females for over a decade.<sup>21</sup>

Our case presents novel information regarding potential GU and adverse sexual effects of duloxetine. However, several limitations should be discussed, primarily, the patient's history of nephrolithiasis as a young adult. Although nephrolithiasis cannot be completely ruled out by the workup presented, other symptoms consistent with nephrolithiasis and renal colic, such as polyuria, nausea, vomiting, fever, and ileus were not present in our patient. Additionally, the patient noted that his previous courses of nephrolithiasis persisted for longer durations of time compared with this episode. Nevertheless, nephrolithiasis should be considered as a potential alternative cause of renal colic in this report. Second, cocaine use may confound the identifiable etiology of priapism in some patient presentations, as this phenomenon has been reported previously.<sup>17</sup> However, given the time of our patient's last use of cocaine to the time of priapism (1 week), the authors concluded that this mechanism was unlikely. Lastly, the development of adverse effects after a single, initial dose of duloxetine also warrants discussion. Certain adverse sexual effects associated with antidepressants, such as anorgasmia and delayed ejaculation, are thought to be dose- and accumulation-related phenom-

ena.<sup>22</sup> Conversely, priapism appears to be a potential risk at any time during treatment with psychotropics, with a timeline ranging from initiation of treatment up to 2 years after initiation being reported in the literature.<sup>23</sup> Therefore, the priapism experienced by our patient falls within the range of timelines previously reported.

Both adverse events experienced by our patient were rated individually using the Naranjo adverse drug reaction likelihood scoring system.<sup>24</sup> Priapism was graded as a Naranjo score 6 (*probable*) based on answers to each of the following questions: did the adverse event appear after suspected drug was given (yes, 2 points); did the adverse reaction improve when the drug was discontinued (yes, 1 point); could alternative causes have produced the reaction (no, 2 points); was the event confirmed by objective evidence (yes—physical exam findings, 1 point). Renal colic was scored as a 3 (*possible*) by answers to the following: did the adverse event appear after suspected drug was given (yes, 2 points); did the adverse reaction improve when the drug was discontinued (yes, 1 point); could alternative causes have produced the reaction (yes, 1 point); was the adverse event confirmed by objective evidence (yes, 1 point). These adverse events were reported to the US Food and Drug Administration Event Reporting System as well as the adverse event review board at our institution.

## Conclusion

Patients who tolerate treatment with SSRIs, such as escitalopram, may still be at risk for adverse GU and sexual side effects associated with duloxetine treatment.

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