Priapism Associated With Conventional and Atypical Antipsychotic Medications: A Review

Michael T. Compton, M.D., and Andrew H. Miller, M.D.

Background: Priapism is a prolonged, usually painful, and persistent penile erection not usually associated with sexual stimuli, resulting from a disturbance in the normal regulatory mechanisms that initiate and maintain penile flaccidity. This infrequent adverse event of antipsychotic medication use requires emergency evaluation and has potentially serious long-term sequelae including erectile dysfunction. Clinicians prescribing antipsychotic medications should be aware of this rare but serious adverse event.

Method: A computerized search, using the MEDLINE database (1966–summer 2000), located cases of priapism associated with most conventional antipsychotics as well as with clozapine, risperidone, and olanzapine. The search included no restrictions on languages. Keywords included *priapism* combined with *antipsychotic agents* and the names of the currently available atypical antipsychotics. Twenty-nine publications were located using these parameters. Additional publications were reviewed for general background on pathophysiology, evaluation, and management. The quality of the evidence reviewed is limited by the observational and uncontrolled nature of case reports, case series, and review articles.

Results: Psychotropic-induced priapism is currently believed to be caused by the α_1-adrenergic antagonism of these medications. Detumescence is sympathetically mediated, and α_1-adrenergic antagonism (within the corpora cavernosa) inhibits detumescence. The propensity of individual antipsychotics to induce priapism can presumably be estimated on the basis of α_1-adrenergic blockade affinities. Of the conventional antipsychotics, chlorpromazine and thioridazine have the greatest α_1-adrenergic affinity and have been most frequently reported to be associated with priapism. Of the atypical antipsychotics, risperidone has greater α_1-adrenergic affinity, although 3 of the 5 currently U.S. Food and Drug Administration (FDA)–approved atypicals have been reported to be associated with priapism.

Conclusion: Virtually all antipsychotic medications have been reported to rarely cause priapism due to their α-adrenergic antagonism. This adverse event should be considered a urologic emergency. Clinicians should be familiar with this infrequent serious adverse event of antipsychotic medications.

(J Clin Psychiatry 2001;62:362–366)

Received April 7, 2000; accepted Aug. 28, 2000. *From the Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Ga.*

Reprint requests to: Michael T. Compton, M.D., Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Emory-West Campus, 1256 Briarcliff Rd., Suite 165, Atlanta, GA 30306.

Priapism is an infrequent adverse event that requires emergency evaluation and has potentially serious long-term consequences, including erectile dysfunction due to ischemia and fibrosis of the corpora cavernosa. Defined as a prolonged, usually painful, and persistent penile erection not usually initiated by sexual stimuli, priapism results from a disturbance in the normal regulatory mechanisms that initiate and maintain penile flaccidity.[1] The persistent erection affects only the corpora cavernosa, sparing the corpus spongiosum and glans penis. Known causes include sickle cell disease, perineal trauma, leukemia and other neoplasms, substances of abuse,[2,3] and many medications including antihypertensives, anticoagulants, trazodone, and many antipsychotics, especially the phenothiazines[4] (Table 1). In recent years, an increasingly common cause of priapism has been intracavernous drug therapy for erectile dysfunction. Though infrequent, priapism is a serious adverse event that requires urgent urologic consultation within 4 to 6 hours of onset (for corporal aspiration of blood, irrigation, and injection of an a-adrenergic agonist, or for a surgical shunt procedure to promote venous egress from the corpora cavernosa) to decrease the chances of serious sequelae. Clinicians prescribing antipsychotics should be aware of this rare but serious adverse event.

To locate cases of priapism associated with antipsychotic medications, we undertook a computerized literature search using the MEDLINE database (1966–summer 2000). Our search included no language restrictions. Keywords included *priapism* combined with *antipsychotic agents* and the names of the currently available atypical antipsychotics. Twenty-nine publications were located using these parameters. We reviewed additional publications for general background on pathophysiology, evaluation, and management. The quality of the evidence reviewed is limited by the observational and uncontrolled nature of case reports, case series, and review articles.

Table 1. Causes of Priapism

Medications
Intracavernosal injection of vasoactive substances (phentolamine, papaverine, prostaglandin E_1)
Antihypertensives (prazosin, labetalol, nifedipine, guanethidine, hydralazine)
Anticoagulants (heparin, warfarin)
Trazodone
Conventional and atypical antipsychotics
Alcohol, marijuana, cocaine, other substances of abuse
Hematologic disorders (sickle cell anemia, leukemia, lymphoma, thrombocythemia)
Trauma to perineum, spinal cord injury
Malignant penile infiltration of tumors
Inflammatory disorders of the urogenital tract
Idiopathic causes

PATHOPHYSIOLOGY

During the flaccid state, the penile arterioles that supply blood inflow into the corpora cavernosa and the sinusoidal spaces within the corpora are in a tonic state of contraction mediated by α-adrenergic activity.[4] During erection, parasympathetic tone increases (mediated by fibers originating in the sacral plexus), and smooth muscle relaxation occurs via the pelvic nerve. Relaxation of cavernous and arteriolar smooth muscle leads to increased blood flow into the sinusoidal spaces and compression of the emissary veins against the tunica albuginea, with a consequent decrease in venous outflow.[5]

The mechanism of priapism associated with psychotropics is thought to be related to α-adrenergic blockade mediated by α receptors in the corpora cavernosa of the penis; the blockade favors parasympathetic-mediated erection and inhibits sympathetic-mediated detumescence[6] (Figure 1). The ratio of α-adrenergic blockade to anticholinergic activity may be a deciding factor.[7–9] Many psychotropic medications have some level of α-adrenergic antagonism, which likely upsets this regulatory balance (Table 2). The precise mechanisms of antipsychotic-induced priapism remain to be fully elucidated, and it is likely that a multifactorial physiologic mechanism accounts for many cases. Some have proposed possible roles for the histaminic system[11] and hypersensitization of β-adrenergic receptors,[12] in addition to notions of adrenergic-cholinergic balance.

Priapism is commonly classified into 2 categories.[1] High-flow priapism is rare and is not usually a true emergency. In high-flow priapism, well-oxygenated blood persists in the corpora. An example of high-flow priapism is that caused by a pudendal fistula between an artery and the cavernosa following a perineal trauma. Such a priapism is usually painless due to lack of ischemia, and prognosis is favorable. Low-flow priapism accounts for the majority of cases and is the type of priapism associated with antipsychotic medications. Venous drainage from emissary venules is blocked or decreased, which causes

Figure 1. Pathophysiology of Antipsychotic-Induced Priapism

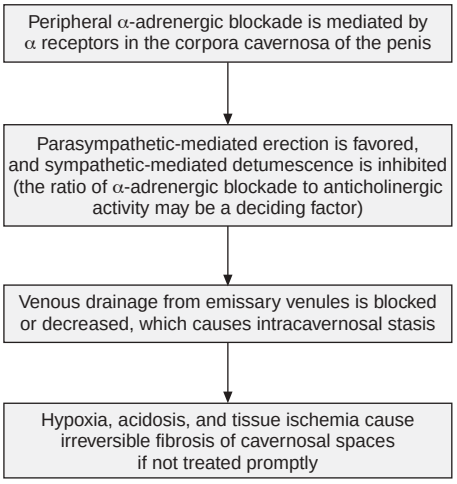

Table 2. α_1-Adrenergic Blockade Affinities of Antipsychotics in Order of Increasing Affinity, Compared With Prazosin[a]

Drug	Affinity[b]
Olanzapine	2.3
Loxapine	3.6
Haloperidol	5.9
Thiothixene	9.1
Fluphenazine	11
Quetiapine	12
Clozapine	15
Thioridazine	20
Risperidone	37
Ziprasidone	38
Chlorpromazine	38
Prazosin	250

[a]Data from Richelson.[10]
[b]$10^{-7} \times 1/K_d$, where K_d = equilibrium dissociation constant in molarity.

intracavernosal stasis. This leads to hypoxia, acidosis, and tissue ischemia, which can cause irreversible fibrosis of cavernosal spaces if not treated promptly. In low-flow priapism, the blood gases begin to show signs of ischemia and acidosis after 6 hours.[13] Since it is currently believed that psychotropic-induced priapism is correlated with α_1-adrenergic antagonism within or close to the cavernosal space[14,15] (causing inhibition of sympathetically controlled detumescence), the propensity of individual antipsychotics to induce priapism can be presumably estimated based on α_1-adrenergic blockade affinity (Table 2).

PRIAPISM CAUSED BY CONVENTIONAL ANTIPSYCHOTICS

Many conventional antipsychotics have been reported to cause priapism. In a retrospective study of all 207 priapism patients treated in Finnish hospitals from 1973

through 1990, compared with age- and time-matched controls, phenothiazines and trazodone were implicated in 28% of cases after excluding patients using intracavernous injections.[16] Abuse of alcohol, use of antihypertensives and anticoagulants, lumbar disc pain, and chronic prostatitis also increased the liability for priapism. The percentage of men taking both psychotropic medications and using alcohol was also quite high, at 18%. In another review of 34 cases of priapism, 9 patients (26%) had recently or currently used phenothiazines.[17] Clitoral priapism or clitoral engorgement in women is evidently very rare.[18]

Episodes of priapism have occurred after a change in medication to a different class, after increasing the dose of the same antipsychotic, and after restarting an antipsychotic after a period of noncompliance.[7,18] Various case reports have associated priapism with chlorpromazine, thioridazine, levomepromazine, mesoridazine, fluphenazine, perphenazine, pericyazine, promazine, molindone, haloperidol, and thiothixene,[6,7,18,19] all of which have varying degrees of α-adrenergic antagonism. Multiple cases have been documented with low-potency dopamine receptor (D_2) antagonists with higher α-adrenergic blockade, especially chlorpromazine and thioridazine,[18] whereas fewer cases have been reported with higher-potency D_2 antagonists such as haloperidol.[20] However, a variety of factors other than frequency of occurrence may influence the frequency of an event being reported (e.g., influence of previous case reports, physicians' attitudes about various antipsychotics). Patients who are prescribed potent α-blocking antipsychotics should be warned of the potential side effects and should be advised to notify their physician immediately for prolonged erections.[18] Although the incidence of priapism linked to trazodone has been estimated at between 1 in 1000 and 1 in 10,000, the incidence related to antipsychotics, although likely lower, has not been estimated in the literature.

PRIAPISM CAUSED BY ATYPICAL ANTIPSYCHOTICS

More recently, 3 of the 5 atypical antipsychotics approved by the U.S. Food and Drug Administration for treatment of psychosis have been associated with priapism in various case reports. The first case of priapism associated with clozapine appeared in the literature in 1992.[21] Since that time, 6 other cases have been published.[22–27] Three cases of priapism associated with risperidone have been published,[28–30] as well as a case describing unwanted, prolonged erections of 15 to 30 minutes in duration.[31] More recently, priapism has been reported to occur with the administration of olanzapine. One case report documents reversible episodes of priapism lasting up to 2 hours,[32] and the other 3 reports describe priapism requiring treatment.[27,33,34] Quetiapine and ziprasidone have not yet been reported to cause priapism.

EVALUATION AND MANAGEMENT

The main responsibility of the psychiatrist for the clinical evaluation and treatment of priapism induced by antipsychotics is immediate referral to a urologist. While urgent consultation is being obtained, the psychiatrist can perform a focused history and physical examination. The history should cover factors that may cause priapism singly or in combination with an antipsychotic. This includes a thorough medical history, prior history of priapism or prolonged erections, medication history, substance use history, and review of systems. The physical examination should include a genitourinary examination. In priapism, the corpora cavernosa are engorged while the corpus spongiosum and glans penis are spared due to their separate and more efficient venous drainage.[7] Inguinal lymphadenopathy or prostatic nodules may be a sign of malignancy. Splenomegaly discovered on abdominal examination may indicate leukemia or lymphoma. Basic laboratory tests indicated include a complete blood count with differential to rule out hematologic disorder or malignancy, a coagulation screen, a urine drug screen, urinalysis and urine culture if clinically indicated, and sickle cell preparation if indicated. History alone is not sufficient to differentiate high-flow and low-flow priapism. Urologists use cavernous blood gas determination, color duplex ultrasound scanning, cavernosography, and internal pudendal arteriography in differentiating the 2 types.[35]

Conservative measures can be initiated, including pain control, vigorous hydration,[36] and cold compresses,[7] while the patient awaits urologic consultation. Upon initial contact with the urologic service, they may recommend other medical management in the interim before their examination of the patient. Such consultation should be obtained within 4 to 6 hours to prevent long-term sequelae, such as erectile dysfunction. Prognosis is directly influenced by promptness of treatment to induce detumescence; early presentation and initiation of treatment may be the most important factors in a successful outcome.[37,38] Urologic management to restore venous egress from the corpora cavernosa commonly consists of aspiration of the corpora and intracavernous injection with an α-adrenergic agonist (e.g., with a 21-gauge butterfly needle).[13] A commonly used agent is phenylephrine, 250 to 500 μg every 5 minutes until detumescence takes place. Epinephrine, 10 to 20 μg, and ephedrine, 50 to 100 μg, may also be used.

Serious consequences include impotence in approximately 50% of patients with an episode of priapism,[39] which further emphasizes the importance of urgent urologic consultation for immediate treatment. The decision of whether to restart a patient on a specific antipsychotic agent after an episode of priapism is a difficult clinical decision and requires careful attention to the risk-benefit ratio. The clinician must consider both possible recurrence of priapism (which may be more likely with any

medication with α-adrenergic antagonism after an index episode) and recurrence or exacerbation of psychotic symptoms. An agent with low peripheral α-adrenergic blocking properties would be preferred.[40,41]

CONCLUSION

Considering the multitude of case reports in the literature, priapism appears to be associated with most antipsychotic medications, representing a small but definite risk. There is also a medicolegal risk associated with priapism and its sequela of impotence.[4] Physicians prescribing medications associated with priapism should inquire about a history of prolonged erections.[11] Any patient treated with antipsychotics with a prior history of priapism or other risk factors for priapism (such as sickle cell disease and the use of other α-adrenergic blocking medications) should be forewarned about priapism and educated on its grave sequela, permanent and total erectile dysfunction. Case reports quite likely tend to underestimate the importance of other factors contributing to the development of priapism, including concurrent medications and other risk factors. Although millions of men take medications associated with priapism, only a small number develop the problem, which may indicate that in some men, the corpora cavernosa are uniquely sensitive to α-blocking agents.[11,42] The infrequency of this adverse event may be related to the idea that priapism may be a complex and multifactorial disorder, with the interaction of several factors necessary for it to become manifest.[14] Clinicians should be cognizant of the theoretical increased risk when prescribing drugs with α-adrenergic antagonism in combination, such as trazodone and a phenothiazine.

Priapism seems to occur most frequently early in the morning, often first noticed at awakening. It is associated with other medications including many antihypertensives, anticoagulants, and trazodone, and outcome is poor in patients whose priapism is attributed to medications.[43] Three clinically relevant points made by Thompson et al.[18] are worth restating: first, a past history of prolonged erection linked to medication use is common before the onset of priapism; second, there seems to be no relationship between the length of treatment and the dosage of antipsychotic medication in relation to the onset of priapism; and third, decreased reporting of prolonged erections and delay in reporting priapism lead to increased morbidity.

In summary, priapism is a serious adverse event associated with antipsychotic medication use, which is presumably related to peripheral α-adrenergic antagonism. The psychological consequences of the event, its treatment, and its adverse sequelae are important considerations in patients who have experienced priapism, which may represent an additional humiliating and traumatic event.[44] If erectile dysfunction is the eventual outcome, the patient may require further psychiatric intervention to help deal with concerns over loss of masculinity and associated emotional reactions of guilt, anxiety, and depression.[40] Future compliance with antipsychotic medications can also be adversely affected by the experience of priapism. Clinicians should be familiar with this serious adverse event of antipsychotics. Cases should be reported to the manufacturers of medications and reported in the literature so that a fuller understanding of antipsychotic-induced priapism can be achieved.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), labetalol (Normodyne, Trandate), loxapine (Loxitane and others), mesoridazine (Serentil), molindone (Moban), nifedipine (Adalat, Procardia), olanzapine (Zyprexa), perphenazine (Trilafon and others), prazosin (Minipress and others), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), warfarin (Coumadin), ziprasidone (Geodon).

REFERENCES

1. Harmon WJ, Nehra A. Priapism: diagnosis and management. Mayo Clin Proc 1997;72:350–355
2. Fiorelli RL, Manfrey SJ, Belkoff LH, et al. Priapism associated with intranasal cocaine abuse. J Urol 1990;143:584–585
3. Altman AL, Seftel AD, Brown SL, et al. Cocaine associated priapism. J Urol 1999;161:1817–1818
4. O'Brien WM, O'Connor KP, Lynch JH. Priapism: current concepts. Ann Emerg Med 1989;18:980–983
5. Lue TF, Hellstrom WJG, McAninch JW, et al. Priapism: a refined approach to diagnosis and treatment. J Urol 1986;136:104–108
6. Segraves RT. Effects of psychotropic drugs on human erection and ejaculation. Arch Gen Psychiatry 1989;46:275–284
7. Patel AG, Mukherji K, Lee A. Priapism associated with psychotropic drugs. Br J Hosp Med 1996;55:315–319
8. Greenberg WM, Lee KK. Priapism treated with benztropine [letter]. Am J Psychiatry 1987;144:384–385
9. Fishbain DA. Priapism resulting from fluphenazine hydrochloride treatment reversed by diphenhydramine. Ann Emerg Med 1985;14:600–602
10. Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. J Clin Psychiatry 1999;60(suppl 10):5–14
11. Abber JC, Lue TF, Luo JA, et al. Priapism induced by chlorpromazine and trazodone: mechanism of action. J Urol 1987;137:1039–1042
12. Greenberg WM, Lee KK. Beta blockers for treatment of priapism associated with use of neuroleptics [letter]. Am J Psychiatry 1988;145:1480
13. Walsh PC, Retik AB, Vaughan ED, et al, eds. Campbell's Urology, vol 2. 7th ed. Philadelphia, Pa: WB Saunders Co; 1998:1172–1214
14. Kogeorgos J, De Alwis C. Priapism and psychotropic medication. Br J Psychiatry 1986;149:241–243
15. Dorman BW, Schmidt JD. Association of priapism in phenothiazine therapy. J Urol 1976;116:51–53
16. Kulmala R, Lehtonen T, Nieminen P, et al. Aetiology of priapism in 207 patients. Eur Urol 1995;28:241–245
17. Macaluso JN, Sullivan JW. Priapism: review of 34 cases. Urology 1985; 26:233–236
18. Thompson JW Jr, Ware MR, Blashfield RK. Psychotropic medication and priapism: a comprehensive review. J Clin Psychiatry 1990;51:430–433
19. Banos JE, Bosch F, Farré M. Drug-induced priapism: its aetiology, incidence, and treatment. Med Toxicol 1989;4:46–58
20. Gomez EA. Neuroleptic-induced priapism. Texas Med 1985;81:47–48
21. Seftel AD, DeTejada IS, Szetela B, et al. Clozapine-associated priapism: a case report. J Urol 1992;147:146–148
22. Ziegler J, Behar D. Clozapine-induced priapism [letter]. Am J Psychiatry 1992;149:272–273
23. Rosen SI, Hanno PM. Clozapine-induced priapism. J Urol 1992;148: 876–877
24. Barbieri NB, Dubé JM. Clozapine and priapism: an association to consider [in French]. Can J Psychiatry 1994;39:128

25. Moinfar N, Goad S, Brink DD, et al. Clozapine-related priapism. Hosp Community Psychiatry 1994;45:1044
26. Hovermann P, Nurnback-Ross B, Albrecht J. Priapism with clozapine therapy [in German]. Nervenarzt 1997;68:74–76
27. Compton MT, Saldivia A, Berry SA. Recurrent priapism during treatment with clozapine and olanzapine [letter]. Am J Psychiatry 2000;157:659
28. Emes CE, Millson RC. Risperidone-induced priapism. Can J Psychiatry 1994;39:315–316
29. Maizel S, Umansky L, Knobler HY. Risperidone-induced priapism [in Hebrew]. Harefuah 1996;130:744–745
30. Nicolson R, McCurley R. Risperidone-associated priapism [letter]. J Clin Psychopharmacol 1997;17:133–134
31. Tekell JL, Smith EA, Silva JA. Prolonged erection associated with risperidone treatment [letter]. Am J Psychiatry 1995;152:1097
32. Deirmenjian JM, Erhart SM, Wirshing DA, et al. Olanzapine-induced reversible priapism: a case report [letter]. J Clin Psychopharmacol 1998; 18:351–353
33. Heckers S, Anick D, Boyerman JF, et al. Priapism following olanzapine administration in a patient with multiple sclerosis. Psychosomatics 1998; 39:288–290
34. Gordon M, de Groot CM. Olanzapine-associated priapism [letter]. J Clin Psychopharmacol 1999;19:192
35. Goto T, Yagi S, Matsushita S, et al. Diagnosis and treatment of priapism: experience with 5 cases. Urology 1999;53:1019–1023
36. Pohl J, Pott B, Kleinhans G. Priapism: a three-phase concept of management according to aetiology and prognosis. Br J Urol 1986;58:113–118
37. Bertram RA, Webster GD, Carson CC. Priapism: etiology, treatment, and results in series of 35 presentations. Urology 1985;26:229–232
38. Pantaleo-Gandais M, Chalbaud R, Chacon O, et al. Priapism: evaluation and treatment. Urology 1984;24:345–346
39. Nelson JH, Winter CC. Priapism: evolution of management in 48 patients in a 22-year series. J Urol 1977;117:455–458
40. Griffith SR, Zil JS. Priapism in a patient receiving antipsychotic therapy. Psychosomatics 1984;25:629–631
41. Van Hemert AM, Meinhardt W, Moehadjir D, et al. Recurrent priapism as a side effect of zuclopenthixol decanoate. Int Clin Psychopharmacol 1995; 10:199–200
42. Lawrence JM, Stewart TD, Frankel FH. Alpha blockade and priapism [letter]. Am J Psychiatry 1984;141:825
43. Larocque MA, Cosgrove MD. Priapism: a review of 46 cases. J Urol 1974; 112:770–773
44. Chen EYH, Lee AS. Neuroleptic-Induced priapism, hepatotoxicity and subsequent impotence in a patient with depressive psychosis. Br J Psychiatry 1990;157:759–762