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LETTER TO THE EDITORS

A case of recurrent priapism during prolonged clozapine administration

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The atypical antipsychotic drug clozapine is the most effective labeled agent for treatment-resistant schizophrenia, and its use is rapidly expanding in other off-label psychiatric and neurological conditions.[1] Despite its proven efficacy, clozapine remains underutilized,[2] largely due to its association with numerous potentially lethal adverse drug reactions, such as pneumonia, agranulocytosis, eosinophilia, systemic symptoms, metabolic syndrome, hypotension, bradycardia, syncope, seizures, myocarditis, cardiomyopathy, mitral valve incompetence, hepatotoxicity, pancreatitis, sialorrhea, gastrointestinal hypomotility, priapism, and hematological and non-hematological cancer.[1] Hence, a key issue in current worldwide psychiatric education is training physicians to prevent or rapidly treat these adverse drug reactions.[1,2]

Here we report on a Venezuelan patient of mixed Asian, Indigenous, and African ethnicity with priapism that has recurred on at least three occasions during his lifetime, two of which were probably related to clozapine use. Currently 45 years of age, he was diagnosed with Paranoid schizophrenia at the age of 16, which is now in remission (DSM-5-TR code 295.9). After his mother's death, he remained homeless for many years, with no known relatives, and underwent irregular outpatient psychiatric control, receiving olanzapine, quetiapine, risperidone, and haloperidol in unspecified doses. He was admitted to the Zulia University Hospital as inpatient in the early months of 2023 for 470 consecutive days (until the present). His inpatient pharmacological treatment (mg/day) consisted of: clozapine 300 mg, carbamazepine 900 mg, trifluoperazine 5 mg, alprazolam 2 mg, biperiden 2 mg, and intramuscular fluphenazine 25 mg for 21 days, with good clinical response. His therapeutic regimen remained similar throughout inpatient treatment.

The patient reported an episode of priapism an undefined number of years ago, which was treated with penis irrigation/aspiration, although no further details about the treatment or its duration could be obtained.

On August 26, 2024, the patient reported another episode of priapism, which was resolved through similar methods 6 days later. On September 5, a slow dose reduction of clozapine was started, but after 3 days, at a dose of 200 mg/day, another episode of priapism occurred. The urologist decided to add clopidogrel 75 mg/day and dexamethasone 8mg/day. Clozapine was rapidly withdrawn, and there has been complete remission so far (November 30, 2024). Current treatment consists of quetiapine (400 mg/day), alprazolam (2 mg/day), carbamazepine (900 mg/day), and clopidogrel (75 mg/day).

In a PubMed search conducted on November 22, 2024, we found 14 published reports of clozapine-associated priapism, 10 in patients who were only receiving clozapine and 4 whose treatment also included other antipsychotic or psychotropic drugs. In four of the cases, priapism recurred more than twice. All of these case reports were authored by independent and unconnected researchers. Table 1 describes clozapine-associated priapism cases from two sources: the U.S. Food and Drug Administration data and worldwide data from the World Health Organization pharmacovigilance system.

Schifano et al.[3] reviewed the Food and Drug Administration's Adverse Event Reporting System between 2015 and 2020 to identify drugs associated with a minimum of 30 reports of priapism (as a parsimonious threshold) and computed the proportional reporting ratios and 95% CIs (Table 1, first two columns). The proportional reporting ratio is the ratio between the frequency at which a specific adverse event is reported for the drug of interest relative to all adverse events reported for that same drug, and the frequency with which the same adverse event is reported for the drug(s) in the comparison group relative to all adverse events for drugs in the comparison group.[4]

The authors identified 1233 reports of priapism, 933 of which (75.7%) were associated with 11 medications that had a minimum of 30 priapism reports each. Therefore, the proportional reporting ratio for each of the 11 identified drugs was compared with the remaining ten agents.[3] A proportional reporting ratio > 1 suggests that priapism is more commonly reported for individuals taking the drug of interest relative to the comparison drugs. Trazodone, olanzapine and tadalafil had disproportionate reporting levels, with proportional reporting ratios of 9.04 (95%CI 7.73-10.58), 1.55 (95%CI 1.27-1.89), and 1.42 (95%CI 1.10-1.43), respectively.[3] Clozapine was last among the 11 agents with > 30 priapism reports, with a proportional reporting ratio of 0.3 (95%CI 0.2-0.4).

The Food and Drug Administration report focused on episodes of clozapine-associated priapism from 2015 to 2020 in the USA. The other two columns in Table 1 present data from the World Health Organization's VigiAccess database, which was launched in 2015 to provide the public with information about the potential side effects of medications. Side effects, which are technically known as adverse drug reactions, are reported by all countries connected to the World Health Organization's pharmacovigilance system. We report here the number of clozapine-associated priapism episodes in relation to those reported for other commonly used antipsychotics. The number of reports for each antipsychotic was calculated as percentage of all adverse drug reactions for that specific agent. For clozapine, 271 cases of priapism were reported out of a total of 221407 adverse drug reactions (0.15%), which was lower than risperidone (0.25%) or quetiapine (0.18%) (Table 1). The reason that

Table 1 Frequency of clozapine-associated priapism compared to other drugs

Clozapine vs. other drugs (FDA-FAERS)			Clozapine vs. other antipsychotics (WHO VigiAccess)[†]		
Agent	n (%)[‡]	PPRs (95%CI)	Agent	n (N total reactions)[§]	% in relation to total reports[‖]
Trazodone	197 (15.9)	**9.0 (7.7-10.6)**	Risperidone	538 (130803)	0.29
Quetiapine	153 (12.5)	0.7 (0.63-0.75)	Quetiapine	323 (101267)	0.18
Risperidone	130 (10.5)	0.8 (0.7-0.9)	**Clozapine**	**271 (221407)**	**0.15**
Olanzapine	106 (8.6)	**1.6 (1.3-1.9)**	Olanzapine	211 (83277)	0.11
Aripiprazole	80 (6.5)	0.7 (0.6-1.3)	Aripiprazole	197 (82692)	0.11
Tadalafil	74 (6.0)	**1.4 (1.1-1.8)**	Paliperidone	127 (57073)	0.07
Sertraline	58 (4.7)	0.6 (0.5-0.8)	Ziprasidone	72 (15735)	0.04
Sildenafil	39 (3.2)	0.7 (0.5-1.0)	Haloperidol	65 (42660)	0.04
Methylphenidate	33 (2.7)	(0.8-1.6)	Lurasidone	10 (15923)	0.01
Alprostadil	32(2.6)	0.9 (0.6-1.3)	Iloperidone	23 (1124)	0.01
Clozapine	31 (2.5)	**0.3 (0.2-0.4)**	Asenapine	6 (7349)	0.00

Bold type denotes values significantly higher than clozapine values; $p < 0.05$.
FDA-FAERS = Food and Drug Administration Adverse Event Reporting System; PRR = proportional reporting ratio.
[†] World Health Organization database.
[‡] Number of cases (percentage of all cases of priapism).
[§] Number of cases of priapism (total of reported adverse drug reactions).
[‖] Percentage of cases of priapism in relation to the total of priapism reports.

clozapine has a higher incidence of priapism in the U.S. Adverse Event Reporting System than global VigiAccess database remains unclear. We could speculate that physicians and patients are more likely to report clozapine-associated priapism in the USA than worldwide, as well as that the same case could be reported several times in parallel, and/or that quetiapine and risperidone may be used in polypharmacy more often than clozapine. Hence, the latter antipsychotics might be overreported. However, this important issue requires further investigation. The prominent role of risperidone in the VigiAccess hierarchy agrees with its potent antagonistic effects on α_1 adrenergic receptor, which plays a key role in the development of priapism (see below). The effects of risperidone are among the highest in commonly used atypical antipsychotics.[5]

We could not determine the date of or the pharmacological treatment used in our patient's first priapism episode. During the second episode, which was well monitored, the patient was receiving clozapine (300 mg/day) and the following agents (VigiAccess priapism reports in parentheses): carbamazepine (17), trifluoperazine (1), alprazolam (13), biperiden (1), and fluphenazine (0). Only clozapine is in the Food and Drug Administration's 30-report list.[4] Thirteen days after the second priapism episode was resolved, a third episode occurred after the clozapine dose had been reduced to 200 mg. At that point clozapine was abruptly withdrawn and the patient was switched to quetiapine (400 mg) plus the previously prescribed medications. The priapism resolved rapidly following the administration of clopidogrel and dexamethasone, and the patient has remained without recurrence since November 24, 2024. This present case highlights the clinical importance of monitoring and managing rare but serious adverse drug reactions, such as priapism, in patients treated with clozapine. Priapism, a urological emergency characterized by prolonged penile erection, involves significant clinical and psychosocial implications. In patients with schizophrenia, a disorder already associated with substantial treatment challenges, priapism can exacerbate stigma, reduce treatment adherence, and lead to distressing physical consequences such as erectile dysfunction. There are two basic types of priapism: ischemic and non-ischemic. The former is more common and is related to adverse drug reactions and systemic diseases, while the latter is mainly due to penis trauma.[6] Hence, priapism associated with clozapine or other antipsychotics appears to belong to the ischemic type.

From a health care system perspective, priapism requires urgent and often invasive interventions, such as penile aspiration or intracavernosal injections, to avoid permanent complications. Untreated cases can lead to ischemic damage and long-term morbidity, resulting in a considerable burden on health care resources and the patient's quality of life.[3]

Given the well-established role of clozapine in managing treatment-resistant schizophrenia, early recognition and management of its adverse effects, including priapism, are crucial. This requires timely collaboration between psychiatrists, urologists, and primary care providers. Preventive measures, such as monitoring for predisposing factors like previous priapism episodes, polypharmacy with drugs that affect α_1 or α_2 adrenergic receptors, and several systemic diseases, should be incorporated into routine practice.[3,6] Educating clinicians to recognize the early signs of priapism, even mild cases, can reduce intervention delays and the risk of permanent erectile dysfunction.

The pharmacological basis of clozapine-induced priapism lies primarily in its antagonistic effects on α_1 and α_2 adrenergic receptors and a set of intracellular mechanisms involving cAMP, cGMP, nitric oxide, and ATP-sensitive potassium channel.[3,5] These receptors regulate penile detumescence by mediating smooth muscle contraction in the corpora cavernosa. Clozapine's inhibitory effects on these pathways can lead to sustained erections and obstructed venous outflow, as observed in the present case. The patient's heightened sensitivity to adrenergic blockade, coupled with clozapine's sedative properties, which delay symptom recognition, underscores the need for close monitoring during therapy.

Emerging evidence suggests that genetic polymorphisms in adrenergic receptor function and drug metabolism may predispose certain individuals to priapism. Clozapine's pharmacokinetics, influenced by variations in CYP1A2 and CYP3A4 enzyme activity, may increase susceptibility in slow metabolizers.[6-8] These findings highlight the potential utility of pharmacogenetic testing and therapeutic drug monitoring in identifying at-risk populations and optimizing clozapine therapy.

The reported case also raises important questions about the interplay of concomitant medications, such as carbamazepine, alprazolam, risperidone, and quetiapine, in amplifying priapism risk (Table 1). Although clozapine was implicated in this instance, polypharmacy should be carefully investigated to assess the contribution of other agents.[3,6]

In summary, this case report on a schizophrenia patient who experienced three episodes of priapism, two of which were associated with clozapine use. Other authors have reported that priapism ceased to recur after clozapine was completely withdrawn and reinstated.[9,10] This case underscores the importance of vigilantly monitoring rare adverse effects, particularly in the context of clozapine's growing global use. Future research should explore the molecular and genetic underpinnings of clozapine-induced priapism and evaluate preventive strategies to improve patient outcomes. Expanding pharmacovigilance systems to include rare adverse drug reactions like priapism can lead to safer prescription practices and optimize the therapeutic benefits of clozapine in vulnerable populations.

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The authors report no conflicts of interest.

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KAG: Investigation, Resources.
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TB: Writing – original draft, Writing – review & editing.
JL: Validation, Methodology.
CC: Validation, Methodology.
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