The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Management of sexual adverse effects induced by atypical antipsychotic medication

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A 28-year-old man recently diagnosed with schizophrenia was discharged from hospital on long-acting injectable risperidone (37.5 mg given every 2 weeks). At an outpatient visit 2 months later, his psychotic symptoms were well controlled, but he reported reduced libido and anorgasmia. The occurrence of those symptoms coincided with risperidone initiation. The patient had no previous history of sexual dysfunction, was not taking any other medications and denied any forms of substance use.

As risperidone was thought to be the cause of the patient's sexual dysfunction, the dose was reduced to 25 mg every 2 weeks. Unfortunately, his auditory hallucinations re-emerged, and there was no appreciable change in his sexual function. The serum prolactin level obtained at this time was 180 ng/mL (reference range for men:[1] 3–15 ng/mL). After discussion with the patient, we decided to cross-titrate to 15 mg/d of aripiprazole over a period of 4 weeks, which reduced his prolactin to 7 ng/mL. On this regimen, the psychosis stabilized and sexual adverse effects abated. The patient was later switched to long-acting injectable aripiprazole.

Sexual dysfunction is a common adverse event in patients treated with antipsychotics. The prevalence of reduced libido and problems with orgasm in patients treated with antipsychotics, regardless of sex, is 54.2% and 41.7%, respectively.[2] A widely accepted mechanism underlying antipsychotic-associated sexual dysfunction is dopamine D2 receptor antagonism.[3] Antagonism of D2 receptors in the mesolimbic pathway can lead to reduced libido through inhibition of motivation and reward.[3] Furthermore, antagonism of D2 receptors in the tuberoinfundibular pathway can lead to elevated prolactin levels, which can subsequently lead to a variety of sexual problems, including erectile dysfunction, ejaculatory disturbances and gynecomastia in men; amenorrhea and vaginal dryness in women; and reduced libido, anorgasmia and galactorrhea in both sexes.[3,4]

Generally, second-generation antipsychotics (SGAs) are associated with a lower risk of prolactin-associated sexual adverse effects than first-generation antipsychotics (FGAs) owing to their higher 5-HT_{2A}:D2 receptor antagonism ratios.[5] However, some SGAs (e.g., risperidone, paliperidone, amisulpride) are stronger D2 antagonists than others (e.g., aripiprazole, clozapine, olanzapine, quetiapine) and thus can markedly elevate prolactin levels.[5] Some studies found that prolactin elevations were greater with risperidone than haloperidol (an FGA),[6] despite risperidone having a higher 5-HT_{2A}:D2 receptor antagonism ratio than haloperidol.[7] This suggests that risperidone's activity at other receptors may also contribute to elevating prolactin levels. A significant dose–response relationship between oral risperidone and impaired orgasm has been reported in men.[8] Male sexual dysfunction associated with risperidone may also be mediated by decreased testosterone levels due to hyperprolactinemia.[8]

Antipsychotics can further impair sexual function through antagonism of peripheral α1-adrenergic and muscarinic receptors, which can disrupt normal blood flow and lead to erectile dysfunction.[3,4] Antagonism of α1-adrenergic receptors can also lead to abnormal ejaculation and priapism in men.[3,4] Sedative effects via H1 antagonism may lead to impaired arousal.[3,4]

Strategies to treat antipsychotic-induced sexual dysfunction include dose reduction,[9] switching to a prolactin-sparing antipsychotic (e.g., aripiprazole, olanzapine, quetiapine),[9,10] augmenting with aripiprazole,[9] or adding phosphodiesterase inhibitors specifically to treat erectile dysfunction.[9] In our patient's case, switching to aripiprazole substantially improved sexual function and stabilized psychosis. The likely mechanism explaining the improved sexual function is the elimination of significant D2 antagonism of the lactotrophs on the anterior pituitary that likely resulted from use of risperidone.[5] Since a dose reduction or a switch could lead to psychotic exacerbation, aripiprazole augmentation is an alternative strategy that can reduce prolactin levels (via partial D2 receptor agonism in the tuberoinfundibular pathway) in patients treated with risperidone.[9,11]

Some SGAs, including risperidone and paliperidone, can often induce sexual dysfunction in both male and female patients via prolactin elevation and other mechanisms. Clinicians need to be more vigilant about antipsychotic-associated sexual dysfunction and available treatment options because these adverse effects can affect a patient's quality of life and adherence to antipsychotic medication. More high-quality studies on the management of antipsychotic-associated sexual dysfunction are required.

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References

1. Fischbach FT, Dunning MB III, eds. *Manual of Laboratory and Diagnostic Tests, 8th ed*. Philadelphia (PA): Lippincott Williams and Wilkins; 2009.
2. Uçok A, Incesu C, Aker T, et al. Sexual dysfunction in patients with schizophrenia on antipsychotic medication. *Eur Psychiatry* 2007;22:328-33.
3. Bains S, Shah AA. Sexual side effects of antipsychotic drugs. *Adv Pharmacoepidem Drug Safety* 2012;1:109. doi:10.4172/2167-1052.1000109.
4. Just MJ. The influence of atypical antipsychotic drugs on sexual function. *Neuropsychiatr Dis Treat* 2015;11:1655-61.
5. Peuskens J, Pani L, Detraux J, et al. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. *CNS Drugs* 2014;28:421-53.
6. David SR, Taylor CC, Kinon BJ, et al. The effects of olanzapine, risperidone, and haloperidol on plasma prolactin levels in patients with schizophrenia. *Clin Ther* 2000;22:1085-96.
7. Seeman P. Clozapine, a fast-off-D2 antipsychotic. *ACS Chem Neurosci* 2014;5:24-9.
8. Liu-Seifert H, Kinon BJ, Tennant CJ, et al. Sexual dysfunction in patients with schizophrenia treated with conventional antipsychotics or risperidone. *Neuropsychiatr Dis Treat* 2009;5:47-54.
9. Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. *World Psychiatry* 2018;17:341-56.
10. Kirino E. Serum prolactin levels and sexual dysfunction in patients with schizophrenia treated with antipsychotics: comparison between aripiprazole and other atypical antipsychotics. *Ann Gen Psychiatry* 2017;16:43.
11. Kane JM, Correll CU, Goff DC, et al. A multicenter, randomized, double-blind, placebo-controlled, 16-week study of adjunctive aripiprazole for schizophrenia or schizoaffective disorder inadequately treated with quetiapine or risperidone monotherapy. *J Clin Psychiatry* 2009;70:1348-57.