

*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.*

## Prescribing differently for women with first-episode psychosis

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A 32-year-old woman was referred to an early intervention clinic for multiple auditory hallucinations and delusions. She had had 2 prior episodes of depression: the first occurred 6 years earlier when her mother passed away from breast cancer at the age of 52. The second episode occurred 1 year ago, but the patient had been on 40mg of citalopram and free of depressive symptoms for the last 6 months. For the 2 months preceding the referral, she was increasingly becoming convinced that her ex-husband was poisoning her food, and she started hearing his mother's voice making elaborate comments about her clothes and food. She stopped going to work as a hairdresser after calling sick on many occasions because of "poisoned food." She had no family history of psychosis or mood disorders and did not use recreational substances.

On examination, the patient described being upset about not being able to work, but denied symptoms of depression or mania. She appeared perplexed but made good eye contact, and there was no hesitancy in her responses. She was convinced about the poisoning and argued that her ex-husband was able to poison her food via his mother's ability to control her mind from afar. She had no suicidal thoughts, had limited insight and was keen to return to her job.

The patient agreed to take aripiprazole 5mg, but she developed notable akathisia and refused further dose increase. Consequently, she was switched to olanzapine, titrated to a dose of 10 mg/d before sufficient response occurred. During the next

2 months, to her great distress, she gained 12 kg of weight. She was reluctant to continue her treatment but agreed to dietary interventions. She lost 5 kg of weight with intermittent fasting and exercise over 6 months, but took the prescribed olanzapine less than 50% of the time, despite taking citalopram regularly. When she later returned to part-time work, the hallucinations recurred. She deteriorated rapidly and began repeatedly calling her ex-husband's family and persistently asking her colleagues to taste food samples. She restricted herself to eat only fresh salads and drink tap water, for the fear of being killed.

Despite agreeing to be hospitalized, the patient refused to restart olanzapine for fear of weight gain. She settled on paliperidone 3 mg; this was increased to 9 mg over the next 10 days. Unfortunately, her prolactin level increased to about double her baseline values, though her symptoms improved; she no longer had concerns about poisoning or voices by the third week of admission. She agreed to take a long-acting injectable (LAI) and was given 2 loading doses of paliperidone palmitate (150 mg and 100 mg) before her discharge.

When the patient presented after 4 weeks to receive her first monthly injection, she reported lengthening of her menstrual cycle and had tremors and rigidity on examination. The scheduled injection was postponed by 10 days, and benzotropine 2 mg twice daily was prescribed. Currently, she is maintained on a reduced dose of 75 mg of paliperidone LAI every 4 weeks (to address hyperprolactinemia) and 40 mg citalopram, with no further requirement for benzotropine as her tremors subsided. Her weight gain was limited to 3 kg over the last 6 months, her prolactin levels were about 1.3 times above her baseline, and her menstrual cycles became regular but longer by 2–3 days. She

has received educational sessions on clozapine and is willing to consider a switch if symptomatic hyperprolactinemia persists.

This patient's case raises several important issues regarding the treatment of psychosis in women. While the patient's sex frequently influences diagnostic decisions, choice of medications and dose-related decisions are not always tailored to women. Most guidelines on antipsychotic use are not sex-specific, but a large body of evidence now suggests that psychotic symptoms generally respond at lower doses of antipsychotics in women than in men.<sup>1</sup> Antidepressant coprescriptions are also more likely in women<sup>2</sup> (as in our patient's case), and some may also dictate dose selection for certain antipsychotics. The serum concentration to dose ratio is generally higher for women for most antipsychotics.<sup>3</sup> Finally, the sensitivity to dose-related adverse effects is also higher in women;<sup>4</sup> this is a major reason for reduced treatment compliance.

Women are more likely to be prescribed aripiprazole, given its favourable profile especially on prolactin.<sup>5</sup> Along with lurasidone, aripiprazole is recommended as a first-choice antipsychotic in premenopausal women who are not pregnant or lactating.<sup>1</sup> This recommendation comes from expert opinion based on physiology; sufficient evidence from randomized controlled trials (RCTs) on sex differences regarding long-term tolerance are not yet available.<sup>6</sup> In a recently published RCT with a modest sample (93 men and 51 women), dose-corrected serum levels in women on aripiprazole were 56% higher than men,<sup>7</sup> indirectly supporting the use of lower doses in women.

Therapeutic response from olanzapine appears to be higher in women than men,<sup>8,9</sup> but the risk of overmedicating women is greater owing to multiple sex-related pharmacokinetic

differences (P-glycoprotein, lower cytochrome P450 enzyme CYP1A2).<sup>10</sup> This in turn increases the frequency of dose-related metabolic adverse effects, as in our patient's case. In a receptor occupancy study, women achieved ideal dopamine D2 receptor occupancy at significantly smaller doses of olanzapine than men.<sup>11</sup>

Antipsychotics with higher propensity to increase prolactin are generally best avoided as first-choice drugs or used in lower doses in women. In addition to near-term effects of increased prolactin on the menstrual cycle, the risk of breast cancer also appears to be higher in patients taking prolactin-elevating drugs.<sup>12</sup> Data from more than 30 000 women with schizophrenia indicate that patients with breast cancer are 1.56 times more likely to have had 5 or more years of exposure to prolactin-elevating antipsychotics than patients with schizophrenia without breast cancer.<sup>12</sup> This risk is especially relevant when there is a family history of breast cancer, as in our patient's case, supporting both a trial of a lower maintenance dose of paliperidone and a timely switch to clozapine.

The use of LAIs as well as clozapine is generally less frequent in women than men.<sup>1</sup> There are many reasons for this discrepancy, including a disproportionate inclusion of men in clinical trials<sup>13</sup> and a lack of sex-based analyses.<sup>14</sup> Recent data indicate that women may lose their advantage over men on clinical outcomes around the menopausal period (around 10 years after the first episode).<sup>15</sup> While dosing recommendations for LAIs are generally not sex-specific, lipophilic drugs such as paliperidone may sustain longer dosing intervals in the presence of higher adiposity.<sup>4</sup>

Sex potentially modifies the tolerance and, consequently, the long-term effectiveness of antipsychotics. Given the lack of sex-specific guidelines at present, re-evaluating our practices based on the emerging sex-stratified data from clinical trials is essential.<sup>16</sup> Genetic or receptor occupancy data are not routinely available for tailoring treatment decisions; on the other hand, sex is immediately available and valuable biological information on which

to personalize treatments. Prescribing differently for women, with sex-specific drug selection and dose determination, has the potential to reduce the overall adverse effects of antipsychotics in clinical practice.

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## References

- Brand BA, Haveman YRA, de Beer F, et al. Antipsychotic medication for women with schizophrenia spectrum disorders. *Psychol Med* 2021;1-15.
- Robinson DG, Schooler NR, John M, et al. Medication prescription practices for the treatment of first episode schizophrenia-spectrum disorders: data from the National RAISE-ETP Study. *Am J Psychiatry* 2015;172:237-48.

- Jönsson AK, Spigset O, Reis M. A compilation of serum concentrations of 12 antipsychotic drugs in a therapeutic drug monitoring setting. *Ther Drug Monit* 2019;41:348-56.
- Seeman MV. Men and women respond differently to antipsychotic drugs. *Neuropharmacology* 2020;163:107631.
- Sommer IE, Tiihonen J, van Mourik A, et al. The clinical course of schizophrenia in women and men — a nation-wide cohort study. *NPJ Schizophr* 2020;6:12.
- Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 2019;394:939-51.
- Hoekstra S, Bartz-Johannessen C, Sinkeviciute I, et al. Sex differences in antipsychotic efficacy and side effects in schizophrenia spectrum disorder: results from the BeSt InTro study. *NPJ Schizophr* 2021;7:39.
- Usall J, Suarez D, Haro JM. Gender differences in response to antipsychotic treatment in outpatients with schizophrenia. *Psychiatry Res* 2007;153:225-31.
- Ceskova E, Prikryl R, Libiger J, et al. Gender differences in the treatment of first-episode schizophrenia: results from the European First Episode Schizophrenia Trial. *Schizophr Res* 2015;169:303-7.
- Madla CM, Gavins FKH, Merchant HA, et al. Let's talk about sex: differences in drug therapy in males and females. *Adv Drug Deliv Rev* 2021;175:113804.
- Eugene AR, Masiak J. A pharmacodynamic modelling and simulation study identifying gender differences of daily olanzapine dose and dopamine D2-receptor occupancy. *Nord J Psychiatry* 2017;71:417-24.
- Taipale H, Solmi M, Lähteenvuo M, et al. Antipsychotic use and risk of breast cancer in women with schizophrenia: a nationwide nested case-control study in Finland. *Lancet* 2021;8:883-91.
- Kane JM, Schooler NR, Marcy P, et al. Effect of long-acting injectable antipsychotics vs usual care on time to first hospitalization in early-phase schizophrenia: a randomized clinical trial. *JAMA Psychiatry* 2020;77:1217-24.
- Santos-Casado M, García-Avello A. Systematic review of gender bias in the clinical trials of new long-acting antipsychotic drugs. *J Clin Psychopharmacol* 2019;39:264-72.
- Ayasa-Arriola R, Ortíz-García de la Foz V, Setién-Suero E, et al. Understanding sex differences in long-term outcomes after a first episode of psychosis. *NPJ Schizophr* 2020;6:33.
- Fernando P, Sommer IEC, Hasan A. Do we need sex-oriented clinical practice guidelines for the treatment of schizophrenia? *Curr Opin Psychiatry* 2020;33:192-9.