

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 gave informed consent for its publication.

Successful management of clozapine adverse effects with extended (alternate day) antipsychotic dosing in a patient with schizophrenia

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A 57-year-old woman with treatment-resistant schizophrenia was started on clozapine as augmentation to her ongoing treatment with olanzapine (15 mg/d). Her psychotic symptoms started improving, as the dose of clozapine was gradually increased to 300 mg/d over a period of 4 weeks (average increase of 10 mg/d). An attempt to decrease the dose of olanzapine to 12.5 mg/d led to worsening of psychotic symptoms and hence, it was again increased to 15 mg/d. The patient's psychotic symptoms resolved completely after 2 months of regular treatment; however, she had significant adverse effects, such as hypersalivation throughout the day, constipation (passing stools once in 4–5 days despite dietary modification, exercise and taking ispaghula husk and lactulose syrup) and sedation lasting up to 12–14 hours/d. After discussion with the patient and caregivers, the treating team decided to continue the medications at the same dose despite the disabling adverse effects to prevent relapse of psychotic symptoms. A month later the caregivers changed the medication regimen without consulting the physicians. The patient was given 15 mg of olanzapine and 300 mg of clozapine on alternate days (i.e., 1 agent/d, alternating between the 2 agents instead of daily administration of both agents). The adverse effects started decreasing in severity in a week and completely subsided 2–3 weeks after starting the new regimen. A month later, during a visit to the physician, the patient was

free of psychotic symptoms as well as of adverse effects of the medications. The caregivers had also stopped giving lactulose syrup and ispaghula husk. The alternate day regimen was continued after educating the caregivers about the early warning signs of relapse. The dose of olanzapine was gradually decreased to 10 mg every alternate day over the next 9 months, and the dose of clozapine continued at 300 mg every alternate day. After 10 months the patient remained largely asymptomatic on the new regimen without any adverse effects of medications. Her fasting glucose levels and lipid profile have also remained largely unchanged.

Higher doses of antipsychotics are associated with greater adverse effects, emphasizing the need for lower therapeutic doses in maintenance treatment.^{1,2} Advances in psychotropic formulations have helped to decrease some of the adverse effects.³ Extended (alternate day) antipsychotic dosing is one of the strategies for preventing exposure to higher doses of antipsychotics.⁴

The peripheral pharmacokinetics of medications remain an important factor when deciding dosing for antipsychotics.⁵ But preliminary evidence suggests that central receptor occupancy half-life of a drug may be different from and longer than the peripheral terminal half-life.⁶ In addition, fast dissociation of clozapine and quetiapine from dopamine D2 receptors suggests receptor blockade need not be sustained over 24 hours in order for them to be effective.^{7,8} Studies with depot antipsychotics also have indicated that they would be effective even if D2 receptor occupancy level is less than 65% before the next administration.⁹ A randomized trial with extended antipsychotic dosing in stabilized patients with schizophrenia showed extended dosing to be just as effective as daily dosing in the prevention of relapse.¹⁰ Transient exposure to antipsychotics

in rodents has been shown to be associated with less risk for vacuous chewing movements (proxy for tardive dyskinesia in humans) than continuous exposure.¹¹ Continuous antipsychotic exposure has been associated with increased tolerance to antipsychotics, loss of antipsychotic response and supersensitivity psychosis.^{12–14} On the other hand, nondaily dosing for patients with a chronic illness like schizophrenia may pose adherence-related problems.¹⁵

For some patients, extended antipsychotic dosing may be a beneficial alternative to conventional antipsychotic dosing. Systematic research should address various aspects of extended antipsychotic dosing, including the impact of interindividual variability in pharmacokinetics of antipsychotics.

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