A Case of Akathisia After Switching From Branded to Generic High-Dose Olanzapine

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As many established atypical antipsychotics lose patent exclusivity, use of generic atypical antipsychotics will expectably rise in light of cost. US Food and Drug Administration (FDA) approval of generic drugs requires demonstration of bioequivalence of a generic agent (specifically, a plasma C_{max} and area under the curve [AUC] falling within a 90% confidence interval of 80%–125% of that achieved with a branded formulation) but no required evaluation of efficacy or tolerability.[1] Limited data make it difficult for clinicians to advise patients on when less-expensive generic formulations differ from branded drugs in efficacy or adverse effects.

The FDA approved the first generic formulation of olanzapine on October 24, 2011. Herein is the case of new-onset severe akathisia arising within several days after switching from the branded to generic formulation in a bipolar I disorder patient previously maintained on a regimen including high-dose olanzapine, with resolution of symptoms soon after resuming the branded drug.

Case report. Mr A, a 33-year-old man, had a 17-year history of *DSM-IV* bipolar I disorder involving past auditory hallucinations; a remote history of comorbid *DSM-IV* alcohol, cannabis, and opiate abuse; and past year benzodiazepine and stimulant abuse. Past treatments, yielding intolerances or lack of efficacy, included adequate trials of lithium, divalproex, lamotrigine, aripiprazole, paliperidone, quetiapine, and ziprasidone. For several years, olanzapine 30 mg/d yielded the most enduring and reliable improvement in conjunction with sertraline 250 mg/d and gabapentin 1,800 mg/d. Shortly after generic olanzapine became available (Teva Pharmaceutical Industries, Ltd), it was substituted by the patient's pharmacy for branded drug without his immediate realization. Within 5 days, the patient called to report hand tremors and spasms in his upper extremities with difficulty holding a cup and clinically significant restlessness in his lower extremities that interfered with sleep. There was no increased muscle tone or rigidity. He described the sensation as "internalized uncontrollable twitching" and denied anticholinergic adverse effects or sedation. No other pharmacotherapy changes or illicit substance use occurred in the interim. A benzodiazepine for apparent akathisia was not begun given its recent abuse. Rather than try a β-blocker or risk a worsening of symptoms by lowering the olanzapine dose, the patient wished to retry branded olanzapine, which was resumed 9 days after the switch to generic. He reported full resolution of motor symptoms and stable mood within 48 hours of resuming the branded drug.

This case is noteworthy for the abrupt onset of a clinically significant new adverse motor effect, despite maintaining a constant high dose of olanzapine, in the context of changing from a branded to a generic formulation of olanzapine. The absence of any preexisting adverse motor effects on longstanding treatment with high-dose branded olanzapine, or akathisia with other atypical antipsychotics, makes the observed sequence of events particularly striking and unanticipated. It is thought that antipsychotics with relatively "loose" D_2 dopamine receptor binding in the basal ganglia may be less prone to cause akathisia or extrapyramidal adverse effects,[2] fostering expectations that high doses of an agent such as olanzapine may be motorically well-tolerated. In this case, sudden akathisia presumably reflected regionally greater D_2 dopamine extrapyramidal binding, perhaps due to increased bioavailability with the generic preparation. The patient's reluctance to lower his "usual" dose prevented examination of this hypothesis or exploration of related concerns about possible lesser efficacy at a lower dose.

While the present case depicted new adverse events after a stable high dose of branded Zyprexa was changed to the same dose of generic olanzapine, similar disruptions to homeostasis could arise for patients on stable low-dose regimens. In patients for whom branded atypical antipsychotic drugs are changed to generic formulations, clinicians should be alert to the possibility that pharmacokinetic variability may lead to pharmacodynamic unpredictability.

References

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