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LETTER TO THE EDITOR

Revisiting clozapine-induced mania: When a case report informs clinical decisions

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Dear Editor,

We write to express our gratitude to Dusunen Adam Journal of Psychiatry and Neurological Sciences and, in particular, to Oğuz et al. (1) for their 2014 case report, "Mania Possibly Induced by Clozapine". Their report described a rare and clinically counterintuitive adverse reaction that subsequently proved directly relevant to our own clinical reasoning.

Our multidisciplinary team encountered a patient with schizophrenia who developed hypomanic symptoms shortly after clozapine was re-initiated. The patient had no previously documented history of mania or hypomania, and the temporal association between clozapine titration and symptom onset prompted a broad differential diagnostic evaluation. Available investigations did not identify a toxic-metabolic, neurological, or substance-induced explanation, and the phenomenology was more consistent with hypomania than with psychotic exacerbation or behavioral disinhibition. Faced with this unusual presentation, we searched the literature and identified the report by Oğuz et al. (1), which provided a valuable precedent for considering clozapine itself as a potential contributor. Further clinical details, diagnostic considerations, and treatment outcomes from our case have been described in our published Psychopharmacology for the Clinician column in the Journal of Psychiatry and Neuroscience (2).

Although second-generation antipsychotics are generally used to treat mania, they have occasionally been associated with manic or hypomanic switches, primarily in case reports and case series, possibly reflecting their complex neuropsychopharmacological properties (3). In our case, the report by Oğuz et al. (1) was clinically valuable because it highlighted a rare but plausible adverse drug reaction and proposed a potential receptor-level explanation involving serotonergic and dopaminergic mechanisms. Guided by this insight, we reconsidered our differential diagnosis and elected to continue clozapine uptitration to offset the dopamine binding profile observed at lower doses. The patient's condition subsequently stabilized, allowing clozapine treatment to continue at a higher dose.

Recognizing the educational value of this encounter, we subsequently published a detailed report examining the potential manicogenic properties of clozapine (2). Additional recent literature, although sparse, has also described mania-like symptoms temporally associated with clozapine initiation in patients with schizophrenia (4). These observations are clinically important because clozapine is widely regarded as the gold-standard treatment for treatment-resistant schizophrenia and, in selected cases, as a treatment option for severe or refractory bipolar disorder (5–8). This clinical reputation may lower suspicion of clozapine as a potential contributor when new-onset mood elevation occurs, particularly when

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the presentation is initially attributed to psychotic activation, behavioral disinhibition, substance use, or the natural course of the illness.

Mechanistically, this apparent paradox is plausible because clozapine has a complex pharmacodynamic profile whose clinical effects may vary across dose ranges (5, 9). At lower doses, serotonergic effects, including 5-HT2A and 5-HT2C antagonism, may enhance dopaminergic transmission in corticolimbic circuits. Oğuz et al. (1) also discussed possible contributions from D4 receptor dysregulation and downstream noradrenergic activation. In addition, norclozapine, clozapine's major metabolite, has pharmacological properties that may further complicate the net clinical effect, including partial agonism at D2/D3 receptors and activity at muscarinic receptors (10). These mechanisms remain hypothetical and should not be overinterpreted on the basis of individual cases. Nevertheless, they provide biological plausibility for the observation that a medication with established antipsychotic effects, and one that may be clinically useful in manic states, could in rare circumstances be associated with manic or hypomanic excitation.

Our experience highlights three points:

1. Case reports remain valuable when the phenomena in question are rare, paradoxical, and unlikely to be adequately characterized in randomized trials or meta-analyses. The 2014 Dusunen Adam case report (1) served precisely this purpose by alerting our multidisciplinary team to a plausible adverse drug reaction during a period of diagnostic uncertainty.
2. Clozapine's pharmacology should not be oversimplified or assumed to be uniformly protective against mood elevation. In patients who develop new-onset increased energy, decreased need for sleep, grandiosity, pressured thoughts, or increased goal-directed activity during clozapine initiation or re-initiation, medication-associated hypomania should be considered in the differential diagnosis after substance-induced, toxic-metabolic, neurological, and primary mood-disorder explanations have been reasonably assessed.
3. Management may differ from that of a first manic episode unrelated to medication exposure. Depending on the clinical context, options may include closer monitoring, dose adjustment, continued titration, augmentation with a mood stabilizer, or discontinuation of the suspected agent.

We therefore encourage colleagues worldwide to continue submitting well-documented reports of rare adverse effects associated with clozapine and other treatments. Such reports may not provide evidence of statistical association, but they can nevertheless inform clinical reasoning when similar cases are encountered.

We again thank the Editorial Board for maintaining an accessible archive that enabled our team to identify the 2014 report at a moment of clinical uncertainty. We hope that our own contribution (2) may, in turn, assist another team confronted with a similar diagnostic dilemma and promote the vigilant and reflective use of clozapine, which remains an essential treatment for treatment-resistant schizophrenia.

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