

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 the publication of the column.

Management of clozapine-induced fever: a case of continued therapy throughout fever

A 22-year-old, white, nonsmoking man was admitted to the psychiatric ward with symptoms of psychosis. In the previous year he had been experiencing auditory hallucinations. At the time of admission, he endorsed tactile hallucinations, somatic delusions and delusions of reference. He had been using marijuana daily and inhaling solvents frequently. He underwent a thorough psychiatric evaluation, including an electroencephalogram (EEG) and head computed tomography. Initially there was insufficient information to differentiate between schizophrenia and drug-induced psychosis; however, with time and sobriety, the diagnosis of schizophrenia became clear.

The patient was started on risperidone, but severe extrapyramidal symptoms developed. He then underwent trials of olanzapine and aripiprazole, but was unable to tolerate these owing to extrapyramidal symptoms and poor control of psychotic symptoms, respectively. A family meeting was held to discuss clozapine. The risks, side effects and benefits of the medication were explained, and the decision was made to initiate a trial. He was started at 12.5 mg daily and titrated to 100 mg twice daily over 10 days. On day 14, a fever of 39.1°C developed. The on-call psychiatrist stopped the clozapine, but the treating psychiatrist restarted it at a low dose (25 mg twice daily) the next day. A thorough medical workup was completed; his blood counts, blood cultures, urine culture, troponins, creatine kinase and chest radiograph were all normal. The patient felt unwell, and his blood indicated dehydration and elevated creatinine. The patient tolerated

the clozapine well, and was at a dose of 100 mg twice daily 10 days later, with good control of his psychotic symptoms. Clozapine and norclozapine levels at this dose were 1764 and 990, respectively. The fever persisted for 5 days after the initial spike and then dissipated along with his systemic symptoms. The highest recorded temperature was 40.1°C.

This case illustrates a difficult clinical decision when fever appears during clozapine treatment: continue clozapine while determining the source of the fever, as in this case, or stop clozapine while completing the workup and, if appropriate, rechallenge. Because fever is also an early sign of neuroleptic malignant syndrome, myocarditis or infection in the presence of agranulocytosis, all rare but potentially fatal side effects of clozapine, the latter choice is often made. However, this choice also creates the potential for emergent symptoms, a prolonged hospital stay and a rechallenge of reduced efficacy. As fever is also a common and benign side effect of clozapine,^{1,2} there are likely many instances when discontinuing clozapine strictly based on the presence of fever is ill serving. A solid understanding of clozapine-induced fevers and sound clinical judgment is required.

Clozapine-induced fever is a common side effect, with a reported incidence of 0.5%–55%, depending on study methodology and fever definition.^{1–5} Typical clozapine fevers spike to less than 40°C, average 2.5 days, and occur within the first month of therapy.^{1–4} They do not appear dose-related,¹ although 1 study found an association between fever and rate of clozapine titration in a Chinese population.⁶ Clozapine-induced fevers are also associated with gastrointestinal or res-

piratory complaints.⁷ The etiology of clozapine-induced fevers is unknown, but theories include mild neuroleptic malignant syndrome, allergic reaction, infection that evaded detection and immune modulation.^{1–3}

Clozapine-induced fevers are documented as a benign side effect.^{1,2,8} Tham and Dickson² examined the presence of clozapine-induced fever in 93 clozapine initiations and found no association between clozapine-induced fever and subsequent agranulocytosis or other adverse reactions within 1 year of initiating therapy. The presence of fever did not predict discontinuation of the therapy at 1 year.

Fever during clozapine treatment presents a clinical challenge. All cases of fever require evaluation with a complete physical exam, complete blood count, creatine kinase, troponins, chest radiograph, EEG, blood cultures and urinalysis. If the fever characteristics are typical of a clozapine-induced fever and there are no further concerns, we advocate for continued clozapine therapy. Numerous authors support this approach;^{1–4,9} however, to our knowledge, this is the first detailed case report demonstrating the safety of this practice.

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Psychopharmacology for the Clinician columns are usually based on a case report that illustrates a point of interest in clinical psychopharmacology. They are about 650 words long. Columns can include a bibliography which will be available only on the journal website.

References

1. Lowe CM, Grube RRA, Scates AC. Characterization and clinical management of clozapine-induced fever. *Ann Pharmacother* 2007;41:1700-4.
2. Tham JC, Dickson RA. Clozapine-induced fevers and 1-year clozapine discontinuation rate. *J Clin Psychiatry* 2002;63:880-4.
3. Jeong S-H, Ahn Y-M, Koo Y-J, et al. The characteristics of clozapine-induced fever. *Schizophr Res* 2002;56:191-3.
4. Nitenson NC, Kando JC, Frankenburg FR, et al. Fever associated with clozapine administration. *Am J Psychiatry* 1995;152:1102.
5. Lapierre YD, Ghadirian A, St Laurent J, et al. Clozapine in acute schizophrenia efficacy and toxicity. *Curr Ther Res* 1980; 27:391-400.
6. Pui-yin Chung J, Shiu-yin Chong C, Chung KF, et al. The incidence and characteristics of clozapine-induced fever in a local psychiatric unit in Hong Kong. *Can J Psychiatry* 2008;53:857-62.
7. Trémeau F, Clark SC, Printz D, et al. Spiking fevers with clozapine treatment. *Clin Neuropharmacol* 1997;20:168-70.
8. Miller DD. Review and management of clozapine side effects. *J Clin Psychiatry* 2000;61(Suppl 8):14-7.
9. Hinze-Selch D, Mullington J, Pollmächer T. Sleep during clozapine-induced fever in a schizophrenic patient. *Biol Psychiatry* 1995;38:690-3.