

Supplementary Table 5. Clozapine-induced fever

First description in German studies

- Clozapine-induced fever in the absence of any concomitant infection was first described by German researchers in a 1972 article in German.⁷⁸
- The next major step was a 1989 monographic number supported by the pharmaceutical company that marketed clozapine which reviewed experience with clozapine in continental Europe and the US in order to support the US marketing of clozapine. In this monographic number, several German clinicians summarize their clinical experience. Two groups proposed that fever in the absence of another cause developed in approximately 5% of the patients.^{79,80}
- More importantly, Helmchen⁸¹ described it as a transient phenomenon in which fever occurred between the 5th and 20th treatment days and was frequently associated with an increase in the erythrocyte sedimentation rate. This is the first article associating clozapine-induced fever with inflammation.

Understanding at the time of US clozapine marketing

- When clozapine was introduced in the US, the US clozapine experts called this fever “benign hyperthermia.” They considered a prevalence of 5% normal during the first 3 weeks of clozapine titration.⁸² They recommended stopping the clozapine titration when high fever develops (38.3°C) and ruling out infections. When a second titration was offered, it should be slower.⁸²

Later developments

- Pui-yin Chung et al.⁸³ compiled a retrospective chart of 227 inpatients started on clozapine in Hong Kong with a fever incidence of 14% (31/227). After comparing 31 cases with fever versus 196 controls, the significant multivariate ORs and their CIs were 18.9 (5.3 to 66.7) for a rate of titration >50 mg/week, 3.6 (CI 1.5 to 8.9) for valproate and 3.2 (1.2 to 8.3) for the presence of physical illness.
- In 2020, a case from a double-blind RCT using 3 different clozapine dosages was published.⁸⁴ This was a clozapine PM due to the co-prescription of oral contraceptives. She could not tolerate the standard titration and developed fever in the absence of infection which led to almost doubling her clozapine concentrations corrected by the dose. The inflammation associated with clozapine-induced fever has positive feedback by further increasing clozapine concentrations that further increased clozapine-induced inflammation.

CI, confidence interval; OR, odds ratios; RCT, randomized clinical trial; PM, poor metabolizer