

Supplementary Table 10. Clozapine in Japan

Delay in clozapine approval

- The first clozapine application in 1975 was retracted due to concern about agranulocytosis.¹⁴⁰
- During the 1990s several lawsuits against the Japanese drug agency concerning drug-related deaths led to slower approval of new drugs. Thus, many psychiatric drugs which had been approved in Western countries took many years to be approved in Japan.¹⁴⁰
- The clozapine application took from December 2007 to April 2009 for approval.¹⁴⁰
- The Japanese package insert states, “Start at 12.5 mg, increasing by 25 mg/day, with a target dose of 200 mg/day in 3 weeks. The maintenance dose is 200–400 mg/day, with a maximum dose of 600 mg.” This titration may be too fast for Japanese clozapine PMs.¹⁴¹

1/3 of Japanese patients may develop clozapine-induced fever (vs. 5% prevalence in initial German and US studies)

- In 2013, Kishi et al.¹⁴² published the first clozapine trial in Japan including 38 TRS inpatients treated in a 12-week, single-arm clinical trial under real-world conditions using raters masked for the type of antipsychotic. They targeted a dose of 200 mg/day within 3 weeks; the maximum dose was up to 600 mg/day and 34% (13/38) were taking valproate. The 29% (11/38) incidence of fever was described but not commented upon.
- In 152 patients following the standard Japanese titration, Tsukahara et al.¹⁴³ found a 38% (57/152) incidence of fever during the first 4 weeks.

Other clozapine-induced inflammations are also frequent with rapid Japanese titration

- In the first Japanese trial with 38 patients, Kishi et al.¹⁴² found no cases of myocarditis, but
 - 1 case of pneumonia and
 - 1 case of high fever with eosinophilia.
- In the 152 titrations during the first 4 weeks, Tsukahara et al.¹⁴³ also found:
 - 13% (20/152) incidence of pleuritis,
 - 5% (7/152) incidence of myocarditis and
 - 1% (2/152) incidence of interstitial nephritis.
- Japanese cases of myocarditis have been published.^{144,145}
- In VigiBase until 2021,⁶⁷ Japan accounted for 73% (30/41) of Asian reports of clozapine-induced myocarditis. During clozapine-induced myocarditis and compared with non-Asian countries, Asian countries had the highest risk of:
 - serious outcomes (adjusted OR=2.39, CI 1.11 to 5.17; p=0.02) and
 - fatal outcomes (adjusted OR=4.35, CI 1.25 to 15.19; p=0.021).
- A study in a pharmacovigilance database identified 51 clozapine-related DRESS¹⁰⁴ cases of which Japan was first, accounting for 24% (12/51), while UK was second with 18% (9/51).

1st article commenting on the role of rapid Japanese clozapine titrations in 2022

- In 2022, Kikuchi et al.¹⁴⁶ published a 43-yo male non-smoker Japanese patient:
 - He was started on 12.5 mg/day of clozapine and up-titrated to 150 mg/day on day 15.
 - A fever on day 17 led to suspicion of pneumonia and antibiotic treatment.
 - On day 22, they wisely diagnosed clozapine-induced acute eosinophilic pneumonia.
 - After clozapine discontinuation, they waited until after there were no signs of inflammation including a normal CRP and on day 81, they restarted 12.5 mg/day of clozapine. They only increased the dose by 25 mg/week up to 200 mg/day, which is much slower than the protocol issued by the Japanese package insert.

CRP, c-reactive protein; DRESS, drug reaction with eosinophilia and systemic symptoms; OR, odds ratio; CI, confidence interval; PM, poor metabolizer; TRS, treatment-resistant schizophrenia