

Supplementary Table 8. Clozapine dosing in Asians

Limited TDM studies

- In 1997 in 162 Taiwanese patients, Chang et al.¹⁰⁹ calculated that each their patients had 30%–50% higher plasma clozapine concentrations than in Western studies.^a
- In 1997, in 12 Chinese Singaporean patients, Chong et al.¹¹⁰ found much higher mean plasma clozapine concentrations than in the US clozapine RCT. They proposed the higher clozapine concentration was due to: 1) other factors (lower body weight, female preponderance, and absence of smoking and alcohol use), and/or 2) ethnic differences.^b
- In 2005, Ng et al.¹¹¹ compared 20 Asian Singaporean patients (13 Chinese, 4 Indians and 3 Malaysians) and 20 Caucasian patients from Australia. Asian patients received a significantly lower mean clozapine dose (176 mg/day) than the Caucasian group (433 mg/day), but plasma clozapine levels were similar. Asian patients had higher clozapine concentration-to-dose ratios. The study was limited, as patients were not matched for sex or smoking status.

Clinician experience with dosing in Asian countries

- In 1998 in the *British Journal of Psychiatry*, Farooq¹¹² suggested that Pakistani patients may need lower clozapine doses than Western patients and are similar to Chinese patients.
- In a 2000 chart review of stable outpatients from 45 Singaporean patients (43 Chinese, 1 Malay, and 1 Indian) and 42 Canadian patients (36 Caucasians, 2 African-Americans, and 4 of Asian ancestry) Chong et al.¹¹³ found the mean clozapine doses were 169 vs. 408 mg/day.
- In 2008, Tang et al.¹¹⁴ reported that in China clozapine usual doses ranged from 200 to 400 mg/day.
- In a 2009 survey of 117 Indian psychiatrists, Shrivastava and Shah¹¹⁵ indicated that most (86%) of their patients were stabilized on clozapine doses lower than 300 mg/day.
- In 2012 Wang and Li,¹¹⁶ in an editorial in a Chinese psychiatric journal, stated that the mean dose reported in Chinese studies was 216 mg/day, which was much lower than the 431 mg/day reported in the non-Chinese literature, but they acknowledge that in China clozapine was used in the context of antipsychotic polypharmacy. Two US experts^{117,118} commented on this editorial but did not appear to be aware that Asians need lower clozapine doses.
- A 2016 survey of 15 Asian sites published in 2020¹¹⁹ reported mean clozapine doses of 198 mg/day, but clozapine was frequently prescribed with other antipsychotics.
- In a study of the national Japanese database for prescribing clozapine from 2009 to 2020, Toyoda et al.¹²⁰ found a mean dose had decreased in the last 4 years to 248 mg/day (4,567 patients) from 309 mg/day (3,696 patients) in the first 6.5 years.
- In a Taiwanese study in 2 hospitals from 2006 to 2017,¹²¹ 2,874 patients on monotherapy (2/3 of total clozapine patients) had a mean dose of 372 mg/day.

Lower CYP1A2 activity in Asians

- Ghotbi et al.¹²² used caffeine TDM as a probe for CYP1A2 activity and demonstrated, when compared with 190 Swedes, that 140 Koreans had approximately a 1.54-times higher caffeine index which is inversely related to CYP1A2 activity. Importantly in this study, they demonstrated that Koreans having the same CYP1A2 genotype, smoking habit and oral contraceptive use displayed significantly lower CYP1A2 activity than Swedes.

Cause of lower CYP1A2 activity in Asians

Currently,²⁹ it is unknown whether differences in CYP1A2 activity between Asians and Europeans may be related to differences at:

- the CYP1A2 gene, or
- another gene/s controlling CYP1A2 function.

^aThey calculated that each 100 mg/day dose results in 150 ng/mL plasma clozapine concentrations (30%–50% higher than that in Caucasian studies);¹⁰⁹ ^bChong et al.¹¹⁰ found a mean daily dosage at week 12 was 373±90 mg/day, which was lower than that reported in a US clozapine RCT (444 mg/day), but produced much higher mean plasma clozapine concentrations (1,078±385 ng/mL). CYP1A2, cytochrome P450 1A2; RCT, randomized clinical trial; TDM, therapeutic drug monitoring