

Supplementary Table 3. Basic concepts in pharmacokinetics applied to clozapine

Clozapine as a narrow therapeutic index drug and its minimum therapeutic dose

- A TDM guideline²²⁻²⁴ proposed a therapeutic range from 350 to 600 ng/mL.²⁴
- Clozapine has a narrow therapeutic index of 1.7^a ($600/350=1.7$).²⁵
- The literature²⁶ agrees that a plasma clozapine concentration of 350 ng/mL is the minimum therapeutic concentration in serum/plasma required for therapeutic response.
- Individuals or groups can be compared using their minimum clozapine therapeutic dose.^{27,28}

Definition of clozapine PM

- A clozapine PM needs approximately half of the minimum therapeutic dose compared with their ancestry group and sex-smoking subgroup, the doses range from:²⁹⁻³¹
 - 75 (♀ non-smokers) to 150 mg/day (♂ smokers) in patients of Asian ancestry, and
 - 75 (♀ non-smokers) to 200 mg/day (♂ smokers) in patients of European ancestry.³¹

Limited^a knowledge³⁰ of clozapine genetic and non-genetic PMs

- Clozapine genetic PMs account for approximately <10% patients.^{29,30,33} The mutations associated with total or partial loss of CYP1A2 activity vary according to ancestry:³⁰
 - Asian ancestry. Based on Japanese data,^{34,35} in East Asians 4 alleles can result in lower metabolic activity (CYP1A2*8, CYP1A2*11, CYP1A2*15 and CYP1A2*16). In Japanese (and East Asians) clozapine patients <1% may have each of these alleles.
 - European ancestry. In 2003, a French woman was described with CYP1A2*7;³⁶ her minimum therapeutic dose was 81 mg/day.³⁰ This allele has not been described again, but 1% of Europeans have CYP1A2*6, with no or little activity.³⁷
- Clozapine non-genetic PMs. In clinical samples, clozapine non-genetic PMs may be more prevalent^{29,30,33} than genetic PMs and be explained by:
 - Inhibitors: potent (including amiodarone, fluvoxamine, or ciprofloxacin)^{27,28} or moderate (including oral contraceptives or high doses of caffeine intake).^{27,28}
 - Obesity. Clozapine deposits in the fat tissue; as the % of fat tissue ↑, clozapine metabolism ↓ within an individual patient.³⁸ In 586 Asians, <1% were PMs due to obesity.³³ Cross-sectional clozapine TDM studies^{39,40} also suggest that metabolism and obesity ↓ clozapine metabolism. Obesity ↓ metabolism of other CYP1A2 drugs.⁴¹
 - Inflammation. The cytokines released during systemic inflammation and associated with ↑ CRP elevations ↓ the synthesis and action of CYP1A2 and other CYPs metabolizing clozapine.⁴²⁻⁴⁴ Inflammation ↑ clozapine concentrations in case reports^{42,45} and cohort studies of infections,⁴⁶ including COVID-19.⁴⁷

Clozapine UM definition

- To establish that a patient is a clozapine UM through TDM, complete adherence is required (1/3 of outpatients with schizophrenia report not taking some of their oral medications).⁴⁸
- The clozapine UM literature started in 1998⁴⁹ and focuses on Western patients with minimum therapeutic doses >900 mg/day^c and includes a few male smokers of European ancestry.³⁰ An African-American male smoker taking valproate has also been described as UM.⁵⁰ These genetic UMs under induction are probably rare; around 1% of patients of European ancestry.
- There are no well documented UM cases in patients of Asian ancestry (in them a minimum therapeutic dose >600 mg/day during complete adherence may suggest an UM).

Limited^b knowledge³⁰ of clozapine genetic UMs during induction

- Unknown variants of CYP1A2 may explain clozapine UMs, according to published articles.
- Unknown variants of the nuclear receptors⁵¹ which control induction may be a possibility:
 - UMs during induction of CYP3A4⁵² and glucuronidation⁵³ have also been described.
 - Caffeine UMs^d have been described under induction by smoking and omeprazole.⁵⁴

^aThe therapeutic index is 1.7 (found by dividing upper range by lower range; $600/350=1.7$). This indicates a narrow therapeutic index; clozapine has the narrowest index among SGAPs;²⁵ ^bSeven years ago,³² the definitions of clozapine PMs and UMs by the author was much less developed. Even a review article from two years ago³⁰ does not have a version as comprehensive as the version in this Box. Thus, this information should be considered provisional and needing confirmation, since it is likely than in 2–3 years this information may need to be corrected and updated; ^cWhen plasma/serum clozapine concentrations are <150 ng/mL they cannot be used to accurately estimate the dose needed to reach 350 ng/mL. When concentrations are >150 ng/mL (and not very high) clozapine follows linear kinetics, which means that the relationship between the dose and the concentration is stable (the ratio between the concentration and the dose is a constant); ^dIn a study of 265 long-term psychiatric patients 3 (1% of 265) had extremely high caffeine intake ($\geq 1,499$ mg/day). All three patients were under the influence of two inducers since they were smokers taking another mild CYP1A2 inducer, omeprazole.⁵⁴ CRP, c-reactive protein; CYP1A2, cytochrome P450 1A2; CYP3A4, cytochrome P450 3A4; PM, poor metabolizer; SGAP, second-generation antipsychotic; TDM, therapeutic drug monitoring; UM, ultrarapid metabolizer; COVID-19, coronavirus disease-2019