

Supplementary Table 13. Clozapine in the UK

Guidelines for clozapine use

- The NICE guideline for schizophrenia¹⁵⁹ and the internationally recognized Maudsley psychopharmacology textbooks¹⁶⁰ do not mention ancestry in reference to clozapine dosing.
- Using TDM data from the UK/Ireland, Rostami-Hodjegan et al.³⁹ recommended, for reaching a concentration of 350 ng/mL, doses ranging from 265 mg/day in female non-smokers to 525 mg/day in male smokers. This study is contaminated by including 1) concentrations that were not trough or steady-state, 2) multiple measures of the same individual analyzed as independent samples, and 3) ignoring the possibility of non-adherence.
- Ignoring non-adherence provides higher recommended doses. In 6 well-controlled samples of patients of European ancestry,¹²⁷ the proposed range was 236 to 360 mg/day, lower than the UK recommendation of 265 to 525 mg/day.

Contributions from the UK in the area of clozapine-induced agranulocytosis

- Since 2005 (10 years earlier than the FDA⁷⁰) the UK has considered the role of benign ethnic neutropenia for prescribing clozapine.¹⁶¹
- Of 23 episodes recorded as agranulocytosis in clozapine patients, Taylor et al.¹⁶² proposed that 14 were not life-threatening and may not even be clozapine-related.
- The same group¹⁶³ has proposed implementing the revised FDA monitoring criteria in the UK.

Clozapine-induced myocarditis in the UK

- Until 2021, in Vigibase cases⁶⁷ of clozapine-induced myocarditis, the UK ranked 2nd after Australia in:
 - cases: with 590 (16.5% of 3752 myocarditis cases) and
 - fatal outcomes: with 25 fatal outcomes (providing a relative lethality of 4.2% of 590).
- In the 51 clozapine-related DRESS cases for a pharmacovigilance study,¹⁰⁴ the UK ranked second with 18% (9/51), this time after Japan.
- Segev et al.¹⁶⁴ proposed that only 11% (29/228) who had myocarditis diagnosed by UK clinicians were confirmed as probable for myocarditis but did not discuss their lethality.

Clozapine-induced CIGH in the UK

- Handley et al.¹⁶⁵ found GI ADRs explained 16% of UK clozapine fatal outcomes (718/4,572).
- They reviewed in detail reports of CIGH from 1992 to 2017 in UK.¹⁶⁵
 - 169 within the first 4 years of clozapine treatment, of which 3% (n=5) were fatal
 - 63 at 10–14 years of treatment, of which 25% (n=16) were fatal

Contributions in the area of clozapine-associated pneumonia

- In 2009, Taylor et al.¹⁶⁶ studied discontinuations and found:
 - 5 pneumonia deaths among 169 discontinuers out of 529 patients receiving clozapine
 - no pneumonia deaths in 250 controls receiving long-acting risperidone.

Clozapine prescriptions in the UK are average when compared with other European countries

- Whiskey et al.¹⁶⁹ estimated 69.3 clozapine prescriptions per 100,000 adults. This is intermediate among 10 other European countries (189 in Finland to 42 in Italy per 100,000 adults).

Clozapine in the UK is prescribed across all ancestry groups

- Iqbal et al.¹⁷⁰ reviewed the electronic medical records of 2,835 clozapine patients from 3 areas. Black patients accounted for 21% to 40% of the patients in the two London areas and 4% in the Oxford area. Asian patients ranged from 5%–7% in the London areas to 8% in Oxford.
- de Freitas et al.¹⁷¹ reviewed 1,837 clozapine patients in London. Patients considered of Black ancestry were 866 or 47% of 1,837 and those of Asian ancestry 123 or 7% of 1,837.
- In a 2002 review of charts at a London hospital,¹⁷² Taylor found 188 patients on clozapine; the mean doses ranged from 487 mg/day in 73 patients of Black ancestry, 473 mg/day in 104 of European ancestry and 391 in 11 of Asian ancestry.

ADRs, adverse drug reactions; CIGH, clozapine-induced gastrointestinal hypomotility; DRESS, drug reaction with eosinophilia and systemic symptoms; FDA, Food and Drug Administration; GI, gastrointestinal; NICE, National Institute for Health and Care Excellence; TDM, therapeutic drug monitoring