

# RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH

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## Factors influencing clozapine plasma concentrations

The use of therapeutic drug monitoring for clozapine is indicated in various situations, including poor compliance, inadequate response to treatment, presence of significant adverse effects, the presence of specific disease states (especially hepatic disease) and where there may be drug interactions. In clinical practice, the dose of clozapine is usually adjusted to provide plasma concentrations of 350 - 600 micrograms per litre. However some patients may respond to lower concentrations, or conversely may experience limiting adverse effects despite concentrations in the recommended range.

Clozapine undergoes significant hepatic metabolism via the cytochrome P450 system. The two principal metabolites are norclozapine (N-desmethylclozapine) and clozapine-N-oxide. CYP1A2 is responsible for the conversion of clozapine to norclozapine and CYP3A4 mediates metabolism to clozapine-N-oxide. Norclozapine is a weak active metabolite of clozapine and although reported in TDM, the clinical importance is not well established.

There is variability of clozapine plasma concentrations that is influenced by a range of factors including age, gender, smoking, and drug interactions. Males seem to metabolise clozapine faster than females and achieve lower average plasma concentrations. Patients aged between 45-54 years of age have been found to have higher clozapine plasma levels than 18 to 26 years old: this could be due to a decreased liver enzyme activity in the older age group.

Tobacco smoke, which contains aromatic hydrocarbons, can induce CYP1A2 resulting in clozapine levels up to 50% lower than those observed in non-smokers. Nicotine delivered in patches and other nicotine products used to assist with smoking cessation does not induce CYP1A2 (i.e. the interaction is mediated by inhaling the smoke itself). Smoking 7 - 12 cigarettes per day is probably sufficient to induce clozapine metabolism. Care must be taken to monitor patients closely after they cease smoking during clozapine treatment, as plasma levels may increase by up to 50%, leading to increased adverse effects, notably seizures.

Agents that induce the activity of CYP3A4 (e.g. phenytoin, carbamazepine, rifampicin and St John's wort) may reduce clozapine levels and cause a recurrence of psychotic symptoms. Caffeine is an inhibitor of CYP1A2 and may increase clozapine concentrations, but this effect may or may not be of clinical significance. Care should be exercised for patients consuming large doses of caffeine-containing products such as coffee, tea and cola drinks.

Concurrent treatment with clozapine and Selective Serotonin Reuptake Inhibitors (SSRIs) warrants specific consideration. Fluvoxamine is a potent inhibitor of CYP1A2 and has been shown to increase clozapine concentrations up to 10-fold in several studies and case reports. Other SSRIs such as paroxetine, sertraline, fluoxetine appear to cause a modest increase in clozapine concentrations, possibly through inhibition of CYP2D6. Citalopram appears less likely to interact with clozapine.

Other drugs that can potentially increase plasma clozapine concentrations include erythromycin, ciprofloxacin, and cimetidine. Only selected pharmacokinetic interactions are described above and this piece has not addressed not pharmacodynamic interactions. As clozapine can interact with many drugs, it is advisable to review reliable drug information resources to assess potential clinical significance so patient care can be individualized and optimized.

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**FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: [chris.alderman@rgh.sa.gov.au](mailto:chris.alderman@rgh.sa.gov.au)**  
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