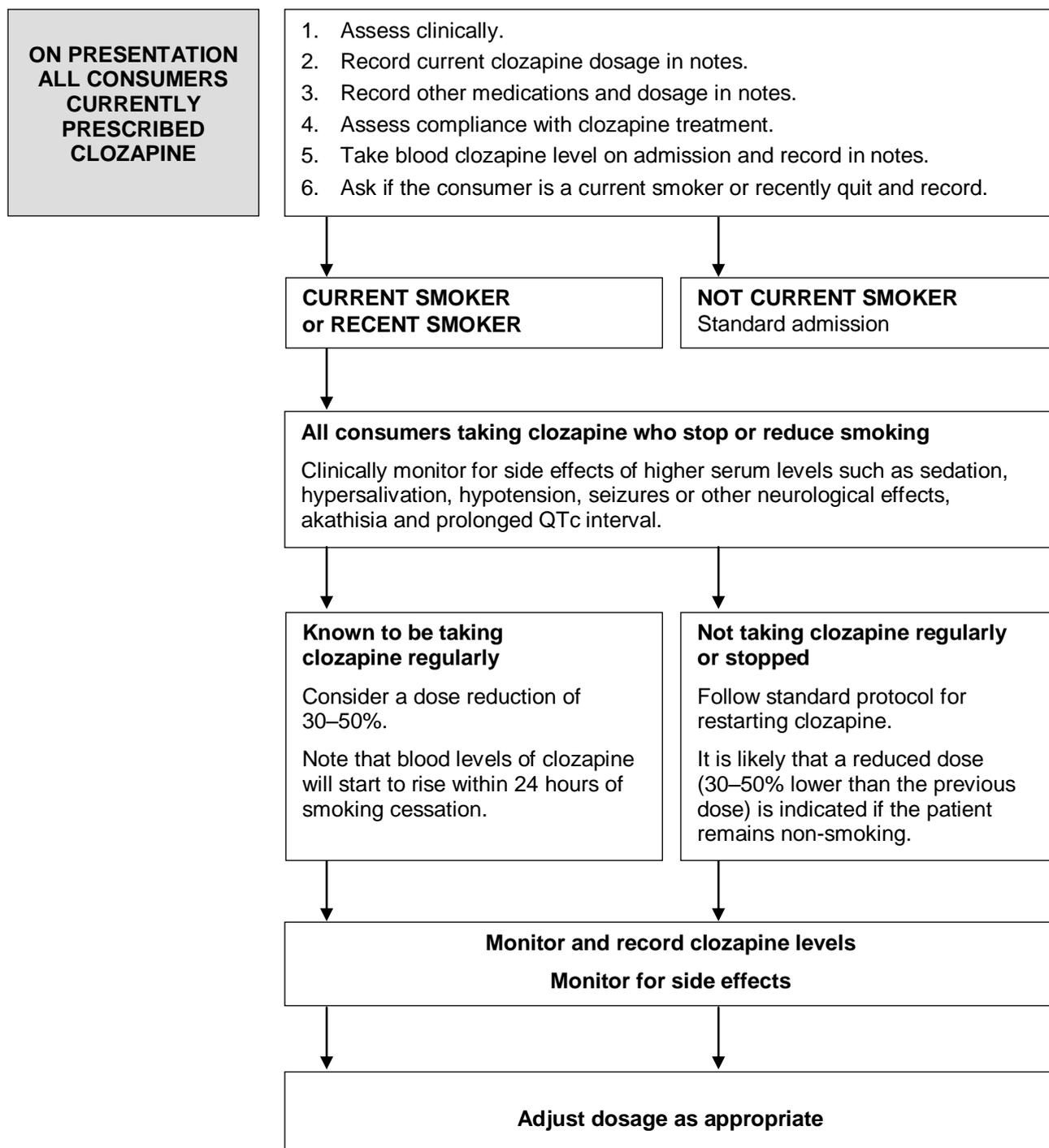


# Clozapine and smoking cessation

Smoking cessation can cause a rise in clozapine blood levels.

**NOTE: It is the TAR in cigarettes which affects clozapine metabolism NOT the nicotine.  
NRT use does not affect clozapine levels.**



**At all times, clinical assessment overrides suggestions made in this guide.**

**A separate guide deals with how to manage clozapine in a patient who resumes or may resume smoking.**

## Background

- Clozapine has a narrow therapeutic index and significant toxic side effects.
- Clozapine is metabolised in the liver by the cytochrome P450 system.
- The tar in cigarettes induces P450 1A2 activity, which affects the metabolism of clozapine.
- Other drugs are also affected including olanzapine, fluvoxamine and haloperidol. Caffeine and non-psychiatric drugs such as warfarin and insulin are affected by smoking through a different mechanism.
- Clozapine levels do not correlate well with efficacy or toxicity, and are simply a marker to allow for dose adjustment (1, 2). There is no 'right' blood level of clozapine; the aim is symptom control without toxicity.
- Higher blood levels of clozapine can cause sedation, hypotension and increased risk of neurological adverse effects including seizures. Other toxic effects of clozapine, including agranulocytosis, are not dose related.

## Smoking and clozapine

- To have equivalent blood levels, non-smokers need lower doses of clozapine than smokers (perhaps up to 50% lower) (1, 3).
- Many factors can affect blood levels of clozapine e.g. age, gender and other medications. There is significant individual variation (3, 4).
- Five cigarettes a day may be enough for enzyme system induction (1).

## Smoking cessation and clozapine levels

- Smoking cessation leads to a rapid exponential decrease in cytochrome P450 activity. A new steady state is reached in about 1 week (4, 5).
- When smokers taking clozapine quit smoking, their blood levels can rise and toxic effects can occur (1, 4, 6–9). It is not clear how common this is, but it appears to be uncommon<sup>†</sup>.

## Monitoring clozapine dosage in smoking cessation

- The evidence supports:
  - immediate decrease of clozapine dose on cessation of smoking (4, 6, 10).
  - a stepwise dose reduction of about 10 per cent daily for four days (4, 6).
- Therapeutic drug monitoring should occur to account for individual variation (4, 6).
- Blood and clinical monitoring should continue for up to six months.
- Consumers who restart smoking after discharge need ongoing monitoring.

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<sup>†</sup>. A literature search done in August 2011 of Embase + Medline and PsycInfo found 4 case reports of clozapine related adverse events associated with smoking cessation published between 2000 and 2011.