

**GUIDELINE FOR THE USE OF CLOZAPINE**  
**19-11-2009 Version**

**I) PRESCRIBING CLOZAPINE**

la) Objective

Clozapine is a medication which occupies a special and irreplaceable position in psychopharmaceutic treatment. Most physicians treat only a few patients with clozapine and therefore do not acquire much experience with this medication. Moreover, clozapine is associated with uncommon and life-threatening risks. The present guideline aims to provide recommendations and instructions to support daily practice with regard to clozapine treatment. The information on which this guideline is based and answers to specific questions may be found in the explanatory supplement at the end of the guideline. In individual cases it may be permissible or necessary to depart from the guideline, provided there are good reasons to do so.

This guideline is based on the results of scientific research, our own experience and the views developed in the Netherlands Clozapine Collaboration Group, a working group of psychiatrists and other professionals such as internists, pharmacists or general practitioners who focus on treating patients with treatment-resistant psychotic disorders. The utmost care has been taken in the preparation of this publication. The authors do not accept liability for any incomplete or incorrect information which it may nevertheless contain. Any suggestions for corrections or improvements to the information in the guideline will be gratefully received.

Ib) Indications

1. Treatment-resistant positive and negative symptoms in schizophrenia, non-respondent to at least two different antipsychotics including a second-generation antipsychotic, administered in adequate dosage for sufficient duration (possibly previously in special cases).
2. Treatment-resistant schizophrenia in children and adolescents, non-respondent to at least two different antipsychotics including a second-generation antipsychotic, administered in adequate dosage for sufficient duration.
3. Untreatable extrapyramidal side effects of antipsychotics in patients, also with two second-generation agents (including quetiapine).
4. Psychotic disorders which arise during the course of Parkinson's disease when standard treatment has failed.
5. Untreatable tardive dyskinesia and tardive dystonia, in cases where antipsychotics are imperatively indicated.
6. Treatment-resistant schizoaffective disorder, bipolar disorder and depressive disorder with psychotic features.
7. Treatment-resistant aggression in schizophrenia or schizoaffective disorder.
8. Treatment-resistant medication abuse or dependency in schizophrenia or schizoaffective disorder.
9. Recurrent suicidal behaviour in treatment-resistant and non-resistant schizophrenia and schizoaffective disorder.
10. In exceptional cases: treatment-resistant aggression and/or self-mutilation in borderline personality disorder, autism or severe intellectual disability.

In the Netherlands clozapine is registered for indications 1, 3, 4 and 5, in the US for indication 9.

Clozapine is the most effective antipsychotic, also among non-treatment-resistant patient populations. However, because of its side effects clozapine is not suitable as a medication of first choice. Patients should be given adequate information about these side effects in advance. At the same time, mortality in patients treated with clozapine is in fact lower than in patients using other antipsychotics. If a patient is mentally incompetent when assessed as being eligible for clozapine treatment – that is, insufficiently capable of understanding the information and weighing up his or her interests –, the consent of the patient's legal representative is required. In special cases involuntary treatment with clozapine by intramuscular administration may be considered.

In the case of psychosis in Parkinson's disease a neurologist should assess eligibility for clozapine treatment and for the other indications a psychiatrist or a doctor with experience of clozapine treatment.

#### Ic) Contraindications

- History of agranulocytosis or granulocytopenia (unless due to chemotherapy)
- Myeloproliferative diseases
- Impaired bone marrow function
- Uncontrolled epilepsy
- Severe liver, kidney or heart disease (ASAT/ALAT 4 x the upper limit; clearance < 30 ml/min; myocarditis)
- Acute paralytic ileus
- Psychosis due to alcohol/intoxication/medication at the acute stage
- Coma, circulatory collapse, CNS depression.

Caution is advised regarding:

- Medications with a known higher risk of agranulocytosis such as carbamazepine, thyreostatics, metamizol, spironolactone
- Prostatic hypertrophy
- Glaucoma
- Duodenal ulcer
- Diabetes mellitus
- Constipation
- History of paralytic ileus
- Cardiomyopathy, heart failure, angina pectoris, recent heart attack, diseases related to heart rhythm disorders (ventricular tachycardia and ventricular fibrillation) and conduction disorders (prolonged QTc interval)

#### Id) Interactions

Clozapine is metabolized by the liver enzyme system cytochrome P450 (CYP1A2, to a lesser extent CYP3A4).

Clozapine plasma levels are **increased** by factors including:

- Many SSRI's (NB: fluvoxamine may increase the level tenfold!)
- Classic antidepressants (particularly nortriptyline)
- Cimetidine
- Caffeine

- Inflammatory reaction

Clozapine levels are **lowered** by factors including:

- Antiepileptics (specifically carbamazepine, to a lesser extent phenytoin)
- Smoking.

le) Before commencing treatment

- Psychiatric examination (question the patient explicitly about compulsive symptoms, because clozapine may cause obsessive compulsive complaints); define target symptoms for clozapine treatment
- Optional: heteroanamnesis and PANSS or some other assessment tool to evaluate the effect
- Somatic anamnesis: previous history and family history in relation to epilepsy, bone marrow and blood diseases, liver, kidney and heart diseases, glaucoma, prostatic hypertrophy, diabetes mellitus, gastrointestinal complaints, defecation pattern
- Medication and intoxications (smoking, coffee, drugs)
- Dizziness and sedation while on previous medication
- General physical examination (RR lying and standing, pulse, temperature, height, waist and weight)
- Laboratory tests: general blood screening including WBC and differential, liver and kidney functions, electrolytes, fasting glucose, fasting cholesterol, HDL cholesterol and triglycerides
- If the WBC count is below  $3.5 \times 10^9/l$  or the neutrophil granulocyte count is below  $2.0 \times 10^9/l$ , treatment should only be started in consultation with a haematologist (in the case of benign ethnic neutropenia or patients of African descent the lower limit may be lowered in consultation with a haematologist)
- Optional: EEG. (EEG abnormalities may lead to a more cautious titration). ECG (QTc interval) (antipsychotics increase the chance of sudden cardiac death)
- Before treatment begins and at regular intervals during treatment (SPC: at every consultation) the patient must be made aware that extra blood tests are needed if there are any signs of agranulocytosis (see below).

## II) MEDICATION SCHEDULE

- Initially the dose of clozapine given must be low and it must be increased gradually because of side effects (specifically hypotension and sedation). The speed of titration varies very widely among individuals. Because constipation often occurs it is recommended that in addition to the clozapine the patient should also immediately start on a laxative such as macrogol-electrolytes, 1 sachet daily. Initial dosage of clozapine: on the first day 12.5 mg once or twice, followed by 25 mg once or twice on the second day. In very rare cases even an initial dose of 12.5 mg may lead to severe sedation and orthostasis. It is therefore worth considering starting with 2 doses of 6.25 mg. If this is tolerated well, the dosage can be increased by 25-50 mg a day (this more rapid titration mainly in the case of hospitalized patients), but for the first 14 days no more than 300 mg should be given each day. If necessary, the dosage can then be further increased in increments of 50-100 mg once or twice a week. A single dose of 200 mg may be given in the evening. Higher quantities administered in one dose are usually also tolerated well. A more gradual titration schedule is recommended in the

case of orthostatic hypotension, tachycardia, age above 60, epilepsy, renal clearance <30 ml/min or use of metabolism-inhibiting medications.

If clozapine is interrupted for two days or longer, treatment should start again with a trial dose of 12.5 mg to test how much tolerance has been lost. Then – depending on the tolerance – the dose can be increased to the original level quite rapidly. In the case of patients with Parkinson’s disease and older patients the dose should be titrated even more cautiously: start with 6.25 mg or 12.5 mg before sleep. The dose should be raised by 12.5 mg twice a week at the most. For patients with Parkinson’s disease the effective dose is usually between 25 and 50 mg and should preferably be given in a single dose before sleep.

Example of titration schedule for inpatients			
1 <sup>st</sup> week		2 <sup>nd</sup> week	
Day 1	2 x 12.5 mg	Day 8	150 mg
Day 2	50 mg	Day 9	150 mg
Day 3	75 mg	Day 10	150 mg
Day 4	100 mg	Day 11	200 mg
Day 5	100 mg	Day 12	200 mg
Day 6	100 mg	Day 13	200 mg
Day 7	100 mg	Day 14	200 mg

  

Titration schedule for outpatients			
1 <sup>st</sup> week		2 <sup>nd</sup> week	
Day 1	2 x 12.5 mg	Day 8	75 mg
Day 2	25 mg	Day 9	100 mg
Day 3	25 mg	Day 10	100 mg
Day 4	50 mg	Day 11	100 mg
Day 5	50 mg	Day 12	100 mg
Day 6	50 mg	Day 13	100 mg
Day 7	75 mg	Day 14	100 mg

- Certain classic antipsychotics (particularly phenothiazines) also increase the chance of granulopenia. It is important to try to switch from a depot to the oral form so that in the event of agranulocytosis all medication can be stopped immediately.

Clozapine blood levels may vary 45-fold in patients given the same dose. Prescribing the same dose for every patient is not rational. Known predictors for clozapine levels are sex (women have higher levels), smoking (reduces level) and age. On the basis of these factors an initial estimate can be made of the dose required for an adequate level.

Target dose (by the end of initiation) for a level of approximately 400 ng/ml in adults (including young adults).

	Smoker	Non-smoker
Man (80kg)	525 mg	325 mg
Woman (70kg)	435 mg	265 mg

### III) MONITORING DURING INITIATION

Clozapine is a medication which is associated with more risks than other medications. This is why various routine checks are recommended, some of which are even compulsory. In spite of clozapine's special risks, the total mortality associated with clozapine treatment is lower than that associated with other first or second generation antipsychotics. Often outpatients can also start taking clozapine, provided the routine checks are carried out and there are sufficient opportunities for the patient to talk to the treating physician. The treating physician must be able to reach the patient immediately (for example via a mobile telephone number) if lab results make this necessary. It is recommended that the patient's GP and any other medical specialists involved be notified that the patient is starting on clozapine and that the patient be given a document which can provide information for an out-of-hours medical centre if agranulocytosis is suspected (see Appendices 1 and 2).

### IIIa) WBC counts

- First 18 weeks: weekly WBC and granulocyte counts (in connection with a 0.68% chance of agranulocytosis)
- After 18 weeks: WBC and granulocyte counts every four weeks. For possibly stopping these routine checks see 'haematology' in the explanatory supplement
- If clozapine treatment is stopped within the first 18 weeks for non-haematological reasons, the WBC and granulocyte counts are to be checked weekly for four weeks or until the first time the WBC count  $>3.5 \times 10^9/l$  and the neutrophil granulocyte count  $>2.0 \times 10^9/l$
- If after 18 weeks the treatment is stopped for more than 3 days but less than 4 weeks for non-haematological reasons, then if clozapine treatment is restarted the WBC and granulocyte counts must be checked weekly again for 6 weeks
- If treatment stops for more than 4 weeks, weekly checks must take place again for 18 weeks
- If there are any signs of infection (temperature  $\geq 38^\circ C$ , sore throat, flu symptoms) during the first 18 weeks: WBC and differential within 24 hours to exclude agranulocytosis (also during weekends). In the event of a temperature  $\geq 38^\circ C$ , sore throat or flu symptoms after the first 18 weeks, WBC and differential the next working day. If a fever is accompanied by ulcers in throat or anus, WBC and differential within 24 hours even after the first 18 weeks. In all cases assessment of the results by a doctor on the same day is recommended.
- If WBC count falls to between  $3.0$  and  $3.5 \times 10^9/l$  or neutrophil granulocytes to  $1.5$ - $2.0 \times 10^9/l$ : check twice weekly until the counts have stabilized or increased.
- If WBC count falls below  $3.0 \times 10^9/l$  or neutrophil granulocyte count falls below  $1.5 \times 10^9/l$ : consult supervisor and internist/haematologist about stopping clozapine and about somatic treatment policy (check blood and infection). Consider giving a haematopoietic growth factor (G-CSF). **Do not put the patient on clozapine again.** For exceptions see the section on haematology in the explanatory supplement.

### IIIb) Other recommended routine checks

During clozapine initiation the patient should be asked regularly (weekly) about any constipation (for treatment see below under side effects).

Weight (BMI and/or waist measurement), blood pressure and fasting glucose should be checked after 1, 2, 3 and 6 months and then annually. If there are practical problems with the fasting glucose test it can be replaced by HbA1c in combination with the non-fasting glucose level. Fasting cholesterol, HDL cholesterol and triglycerides should be checked after 3 months and then annually.

Clozapine is associated with an increased risk of myocarditis. Sixty-two per cent of cases occur during the first four weeks of treatment and 85% within two months. Myocarditis can lead to death. The symptoms sometimes initially resemble benign side effects which commonly occur during clozapine initiation, such as flu-like symptoms (unexplained fever, fatigue, lethargy), hypotension or tachycardia. Laboratory tests (hypereosinophilia, C-reactive protein (CRP), creatine kinase-MB (CK-MB), troponin) may help to differentiate. If dyspnoea, orthopnoea, increased central venous pressure, third or fourth sound, pericardial friction rub, souffle consistent with mitral or tricuspid insufficiency, peripheral oedema and/or crepitations over the lungs are observed, the patient must be referred to a cardiologist urgently.

### IIIc) Monitoring clozapine plasma levels

- Clozapine plasma levels vary widely with the same dose. Because of this, initiating clozapine without checking plasma levels not only entails high risks, but may also result in inadequate treatment
- Plasma levels can be checked six days after the last dose alteration; many patients reach a steady state even after three days, so that blood tests can be done after the fourth day
- Blood samples may be taken 11½ to 12½ hours after the last dose has been ingested
- Clozapine has a relatively narrow therapeutic margin. Side effects depend on plasma concentration, increasing rapidly with levels over 750 ng/ml and particularly above 1050 ng/ml. For patients with treatment-resistant schizophrenia the therapeutic threshold for clozapine plasma levels is approximately 400 ng/ml. The chance of response above this threshold is twice as high as with levels beneath it. If a patient shows a response at a low level, there is no need to increase that level. If the level is above 400 ng/ml, at least eight weeks should be taken to assess the effect
- If there is no response, levels of over 400 ng/ml to a maximum of 700 ng/ml can be tried
- For some patients, taking a large number of tablets a day is an insurmountable problem. A possibility worth considering is to make use of clozapine's interaction with fluvoxamine. An addition of 25 mg to 50 mg fluvoxamine can raise a low clozapine level by a factor of 3.5, but meticulous clinical and blood count monitoring are essential
- Fever resulting from an inflammatory reaction can more than double the clozapine level, sometimes leading to drowsiness, dizziness or other signs of intoxication. In this event, clozapine ingestion should be temporarily discontinued or the dose reduced or halved, possibly depending on the clozapine level.
- Summary of situations in which plasma levels should be checked: monitoring plasma levels is recommended throughout initiation, for example when the 100 mg dose is reached, if there are unexpectedly strong side effects, and when initiation is complete; after initiation, 14 days after increasing or reducing medication with a known

interaction effect; starting or stopping smoking or excessive caffeine intake; severe dose-dependent side effects or toxicity (particularly seizures, hypersalivation, sedation, hypotension); fever resulting from an inflammatory reaction; to check treatment compliance; psychotic decompensation (or imminent psychotic decompensation).

#### IV) SIDE EFFECTS

- Agranulocytosis: see WBC counts
- Convulsions: at the first seizure, check plasma level, possibly reduce the dose, and consult neurologist. During initiation, try to avoid reducing benzodiazepines. At second seizure possibly add valproate.
- Sedation: mainly when treatment starts, therefore increase dose gradually, biggest dose or single daily dose before the night, possibly reduce the dose if condition persists.
- Hypersalivation: mainly when treatment starts, but often persistent. At night place a towel on the pillow. If it also happens in the daytime and is unacceptable: swallow training or chewing gum, reduce dose or add anticholinergic (be aware of the possibility of delirium), for example a scopolamine patch. For further possibilities, see explanatory supplement.
- Orthostatic hypotension: mainly when treatment starts and when dosage is increased rapidly; dosage should be increased gradually.
- Constipation: be aware of the possibility of ileus. Macrogol-electrolytes, psyllium product, lactulose 15-30 ml, magnesium oxide 1-5 g, possibly in combination. Macrogol-electrolytes to a maximum of 3 daily doses of 1 sachet is the best choice because it can be taken with 125 ml of water. To take psyllium fibres, 3.6 g 1 to 2 daily doses of 1 sachet, the patient must drink at least 2 litres of water. For some patients this may be a problem and it requires proper instruction, because if not enough fluid is taken psyllium fibre exacerbates constipation. The drawback of lactulose (a maximum of 3 daily doses of 30 ml) is that it often leads to stomach cramps and flatulence.
- Tachycardia: reduce dose (possibly give metoprolol or if orthostasis is also present propranolol).
- Weight gain: give dietary rules, possibly refer to dietician. Recommend exercise.
- Hyperthermia/fever: particularly in the first three weeks temperature may rise to over 38°C, usually benign. Be aware of the possibility of agranulocytosis, myocarditis and neuroleptic malignant syndrome.
- Leukocytosis: mainly when treatment starts, sometimes persistent. Is benign.
- Eosinophilia: particularly in the second month, in about 5-50% of patients. Usually transient, rarely precedes complications (including myocarditis, agranulocytosis).
- Liver enzyme elevation: usually transient, no routine checks needed except in the case of pre-existing liver diseases.
- Gastrointestinal complaints: possibly acid reducers or antacids.
- Myocarditis/cardiomyopathy: If complaints such as fever, tachycardia and flu-like symptoms with dyspnoea, chest pain, heart failure or arrhythmia occur in the first few weeks – be aware of the possibility of myocarditis. To rule it out, check troponin and/or consider referral to cardiologist. If symptoms are severe, refer to cardiologist immediately.

- Diabetes mellitus: weight loss/ diet/ oral antidiabetics/ insulin/ possibly discontinue clozapine.
- Obsessive-compulsive symptoms: ensure levels are within the therapeutic margin, possibly discontinue clozapine. Otherwise behavioural therapy and/or SSRI supplement (watch interactions).
- Withdrawal psychosis: taper clozapine off slowly (olanzapine to bridge the gap if clozapine is suddenly discontinued).
- Hypercholesterolemia: Cholesterol lowering agents (statins).
- Hypertriglyceridemia: Fibrates.

#### V) OVERDOSING/ SYMPTOMS OF TOXICITY

Symptoms of toxicity usually occur if the dose is increased too rapidly or if there are unexpectedly high plasma levels (usually at or above 1000 ng/ml).

- Extreme hypersalivation, impaired swallow reflex
- Dysarthria, ataxia, balance disorders
- Sedation, attention disorder
- Tachycardia.

Severe symptoms of toxicity:

- Sedation, lethargy
- Hypotension, coma, acute death
- Delirium, hallucinations, disorientation, agitation, confusion
- Convulsions, tremor, fasciculations, myoclonus, hyporeflexia or areflexia
- ECG abnormalities (prolonged QTc interval), sinus tachycardia, myocarditis
- Acute liver failure
- Erosive haemorrhagic gastritis.

The treatment of toxicity consists of supportive measures. Complications (coma, ECG abnormalities, epileptic fits) are treated symptomatically by intubation and artificial respiration to prevent aspiration pneumonia, ECG monitoring /antiarrhythmics and benzodiazepines respectively. Flumazenil may be able to counteract the coma. For hypotension sympathomimetics are contraindicated, because clozapine has alpha-adrenolytic action.



**Supplement to the guideline for the use of clozapine: Side Effects Table.**

!	Agranulocytosis	Comment: dose-independent side effect	Action: see WBC counts
!	Constipation	Comment: Be aware of possible ileus.	Action: at least two litres of fluid, sufficient exercise, consult dietician, fibre-rich diet. Laxatives: macrogol/electrolytes 1-3 daily doses of 1 sachet, or psyllium fibre 3.6 g 1-2 daily doses of 1 packet (make sure fluid intake is sufficient)
!	Convulsions	Comment: clozapine lowers the convulsion threshold.	Action: at first seizure, halve clozapine dosage and check plasma levels. During initiation avoid reducing benzodiazepines. At second seizure, add valproate, possibly consult neurologist
	Diabetes mellitus	Comment:	Action: if fasting glucose and HbA1C are still too high when checked again, refer to a somatic physician for further treatment
	Dry mouth	Comment:	Action: oral balance
!	ECG abnormalities	Comment: usually clinically irrelevant and transient.	Action: assess prolonged QTc interval: if QTc interval is longer than 480 msec, clozapine is contraindicated! If possible assess whether other medication prolongs QTc interval. Low calcium also produces a longer QTc interval: in case of doubt, check calcium+albumin immediately and refer to or consult cardiologist.
	Eosinophilia	Comment: particularly in second month, in c. 5-50% of patients, usually transient, rarely precedes complications (including myocarditis, agranulocytosis).	
	Extrapyramidal disorders	Comment: a consequence of excessively rapid plasma level elevation.	Action: adjust dosage.
	Gastric complaints	Comment:	Action: treat with pantoprazol 40 mg. If not sufficiently effective, check amylase: irritation of the pancreas, pancreatitis. In severe cases discontinue clozapine.
	Hypercholesterolemia	Comment:	Action: refer to dietician for dietary advice, for further treatment refer to somatic physician (GP).
	Hypersalivation	Comment: mainly when starting, but often persistent.	Action: for night-time occurrence put a towel on the pillow. If also in the daytime and unacceptable: swallow training or chewing gum, reduce dose or add anticholinergic (be aware of possible delirium), for example a scopolamine patch. For other possibilities see explanatory supplement.
!	Hyperthermia/ Fever	Comment: specifically in the first three weeks temperature elevations to over 38°C, usually benign.	Action: exclude causes such as agranulocytosis, myocarditis and NMS. If the fever is accompanied by leukocytosis, left shift and an increased sedimentation rate, further examination is needed.
	Hypertriglyceridemia	Comment:	Action: refer to a dietician for dietary recommendations, for further treatment refer to GP.
	Leukocytosis	Comment: mainly when treatment starts, sometimes persistent. Usually benign, especially if there is no left shift.	Action:

	Liver enzyme elevation	Comment: usually transient, no routine checks required except in the case of pre-existing liver disorders. Hepatitis is rare, usually asymptomatic and transient. Cholestasis due to hypersensitivity may arise: reduce dose. Increased amylase may indicate irritation of the pancreas, pancreatitis.	
!	Myocarditis/ cardiomyopathy	Comment: if symptoms such as fever, tachycardia and flu-like symptoms with dyspnoea, chest pain or heart failure occur in the first few weeks after starting: be aware of possible myocarditis.	Action: to exclude myocarditis ECG + troponin + CK-MB and ASAT/ALAT checks <b>immediately</b> , and/or consider referral to cardiologist. If symptoms are severe refer to cardiologist immediately.
	Myoclonus	Comment: may be precursor of a seizure.	Action: Reduce dose and titrate more gradually. Possibly give valproate.
	Nausea, vomiting	Comment:	Action: treat with antacids, domperidone or ranitidine, see also under 'gastric complaints'.
!	Neuroleptic malignant syndrome	Comment: rare. Not an absolute contraindication for starting (or restarting) clozapine.	Action: distinguish from isolated CPK elevations or transient hyperthermia.
	Obsessive compulsive symptoms	Comment:	Action: ensure plasma levels are within therapeutic margin, possibly discontinue clozapine, otherwise behavioural therapy and/or SSRI add-on (be aware of interactions).
	Orthostatic hypotension	Comment: mainly during initiation and when dose is increased rapidly; increase dose gradually.	Action: Watch fluid balance, 2 litres of fluid a day, preferably also in the form of stock etc. Caution when rising from sitting or lying down.
!	Pulmonary thrombo-embolism	Comment:	Action: diagnostics and treatment of thrombosis
	Sedation	Comment: mainly due to co-medication with benzodiazepines!	Action: preferably cut back benzodiazepines before starting clozapine. During clozapine initiation be very cautious in reducing benzodiazepines while maintaining the same dose of clozapine. When increasing clozapine dose: increase dose slowly, give largest – or whole – dose before the night, possibly reduce dose if symptom persists.
	Tachycardia	Comment:	Action: reduce dose, reduce caffeine and nicotine (watch clozapine plasma levels). If tachycardia persists (longer than a week >120/min), consider consulting somatic physician. Reduce dose (possibly give metoprolol or propranolol if orthostasis is also present). Consider myocarditis.
	Urinary incontinence	Comment:	Action: treatment by pelvic floor training (refer to physiotherapist) or by medication (refer to somatic doctor/GP)
!	Urine retention	Comment:	Action: catheterize immediately. Possibly first perform additional diagnostic tests with echoscopy, if available. Exclude urine retention due to constipation, otherwise: discontinue clozapine.
!	Venous thrombo-embolism	Comment:	Action: diagnostic tests and treatment of thrombosis
	Weight gain	Comment:	Action: refer to dietician at an early stage, preferably as a preventive measure! Exercise, dietary advice.
	Withdrawal psychosis	Comment:	Action: Taper off clozapine slowly (olanzapine to bridge the gap if clozapine is discontinued acutely).

# **Clozapine – Explanatory supplement accompanying a guideline**

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## Introduction

Clozapine occupies a unique position among antipsychotics.<sup>1,2</sup> In the Netherlands it was first taken off the market because of its increased risk of agranulocytosis, but ultimately it was admitted again when it became clear that for some patients this drug was a last resort. In spite of this special status, many psychiatrists are wary of prescribing clozapine because of the known risks and other complications associated with it. These explanatory notes discuss the indications for clozapine, the risks and the side effects. Special emphasis is placed on information which may be relevant to practical issues involved in clozapine treatment. Essential steps have been set out in the guideline.

Often the treating physician will have to weigh up the advantages of clozapine (greater effect) and the drawbacks (higher risk of complications). The risks can be reduced by monitoring. It is also important to realize that mortality in the patient group treated with clozapine is *lower* than in the population which is prescribed second-generation antipsychotics or stops clozapine treatment.<sup>3,4</sup> This lower mortality can be partly explained by a reduced number of suicides.

## Indications

Clozapine has a place in the treatment of treatment-resistant psychiatric disorders:

- 1) Treatment-resistant positive and negative symptoms of schizophrenia, non-responsive to at least two different antipsychotics, including a second-generation antipsychotic, of adequate dose and duration (possibly earlier in special cases).
- 2) Treatment-resistant schizophrenia in children and adolescents, non-responsive to at least two different antipsychotics, including a second-generation antipsychotic, of adequate dose and duration
- 3) Untreatable extrapyramidal side effects of antipsychotics, including two second-generation antipsychotics (including quetiapine).
- 4) Psychotic disorders arising in the course of Parkinson's disease, when standard treatment has failed.
- 5) Untreatable tardive dyskinesia and tardive dystonia, if the use of antipsychotics is urgently indicated. Treatment of tardive movement disorder if alternatives fail.
- 6) Treatment-resistant schizoaffective disorder, bipolar disorder and depressive disorder with psychotic features.
- 7) Treatment-resistant aggression and substance abuse in schizophrenia or schizoaffective disorder.
- 8) Recurrent suicidal behaviour in treatment-resistant and non-resistant schizophrenia and schizoaffective disorder.
- 9) In exceptional cases: treatment-resistant aggression and/or self-mutilation in borderline personality disorder, autism or severe intellectual disability.

Clozapine is registered for indications 1, 3, 4 and 5 in the Netherlands, and for indication 8 in the US.

Clozapine is the most effective antipsychotic, even in non-treatment-resistant populations. However, because of its side effects clozapine is not suitable to be a medication of first choice. Patients should be given adequate information about these side effects in advance. If a patient is insufficiently capable of understanding this information and making an informed

decision when assessed to be eligible for clozapine treatment, a person who is able and qualified to represent the patient's interests must be consulted. In special cases involuntary treatment with clozapine by intramuscular administration may be considered.<sup>5</sup>

The decision that clozapine treatment is indicated must be made by a psychiatrist or a physician experienced with clozapine treatment.

### **1) Treatment-resistant schizophrenia and schizoaffective disorder**

Clozapine is the only antipsychotic which is more effective than standard antipsychotics, even in a non-treatment-resistant population.<sup>6,7</sup> It is only because of its side effects that clozapine is not suitable as a medication of first choice. Even after the introduction of second-generation antipsychotics clozapine has been regarded as the 'gold standard' for the treatment of treatment-resistant schizophrenia and schizoaffective disorder.<sup>8,9,10,11,12,13</sup>

In a study among first-psychosis patients it emerged that the chance of a response in these patients to treatment with a second (second-generation) antipsychotic after failure of a first (second-generation) antipsychotic was considerably reduced (76% chance of response to first antipsychotic, 23% to second antipsychotic).<sup>14</sup> It was not until clozapine was started (as the third antipsychotic) that a positive effect was observed again (77% responders). This study stresses that clozapine deserves a place at the top of the list of measures in the event of treatment failure, at the most after two unsuccessful treatments.

Because there is evidence that olanzapine (and amisulpiride, which is not registered in the Netherlands) is a little more effective than other second-generation antipsychotics, olanzapine might be tried before clozapine.<sup>15</sup> If non-compliance is suspected, a trial treatment with a depot antipsychotic may also be considered.

During the second stage of two big efficacy studies it emerged that in a treatment-resistant population clozapine was continued longer and also improved psychotic symptoms more effectively than second-generation antipsychotics.<sup>16,17</sup> In naturalistic studies patients have been found to stay on clozapine the longest in comparison with other antipsychotics and the risk of rehospitalization is lower with clozapine than with most other antipsychotics.<sup>18</sup> This is even more striking in view of the fact that patients put on clozapine are usually very severely ill. To date clozapine is the only antipsychotic which has been shown in a randomized study to work better – according to a depression scale – in patients with schizophrenia and comorbid depression than any other antipsychotic plus antidepressant.<sup>19</sup>

### **2) Treatment-resistant schizophrenia in children and adolescents**

For children and adolescents clozapine was first trialled in an open study of treatment-resistant schizophrenia. The results corresponded to those among adults. Blanz et al. (1993) examined 57 patients aged between 10 and 21 (average age 16.8).<sup>20</sup> The average age of 36 patients studied by Remschmidt et al. (1994) was 18.3.<sup>21</sup> A third open study was carried out among 11 children aged between 11 and 13.<sup>22</sup> Kumra et al. (1996) were able to show in a double-blind comparative study among 21 children with an average age of 14 that in this population with treatment-resistant schizophrenia clozapine was significantly more effective in relation to both positive and negative symptoms.<sup>23</sup> A comparison of clozapine and olanzapine showed that clozapine was significantly better with regard to negative symptoms and numerically better for response (only 25 patients were involved).<sup>24</sup> In a follow-up study 2 years later it turned out that in the patients who had been taken off olanzapine and put on

clozapine the positive symptoms had improved. A similar study found that clozapine was superior to olanzapine in terms of both response and positive and negative symptoms.<sup>25</sup> In a follow-up to this study, 10 of the 19 olanzapine non-responders did respond to clozapine.<sup>26</sup> In general, weight gain and metabolic abnormalities appear to be more severe in children and adolescents than in adults.

### **3) Untreatable extrapyramidal side effects of antipsychotics**

Because of the special risks associated with clozapine, it is prudent to try other second-generation antipsychotics first before deciding to prescribe clozapine because of untreatable extrapyramidal side effects of antipsychotics. Quetiapine would seem to be appropriate in this case, particularly for patients who did not tolerate a classic antipsychotic or perphenazine.<sup>27,28</sup> Clozapine is registered for this indication and in view of favourable experience with patients with Parkinson's disease would still seem to be an option.

### **4) Psychotic disorders accompanying Parkinson's disease**

Psychosis is a frequent complication in the treatment of Parkinson's disease. Delirium may also occur. First-generation antipsychotics are contraindicated because of the chance of aggravating the primary disease. Two randomized, placebo-controlled studies were conducted with clozapine which showed efficacy on final doses of around 25-35 mg without aggravation of the movement disorder.<sup>29</sup> To the extent that other second-generation antipsychotics have been studied properly, the results are disappointing:<sup>30,31</sup> no efficacy and/or aggravation of the parkinsonism. The treatment of delirium in Parkinson's disease has not been examined in a randomized study. However, there has been experience and the pharmacological considerations are the same as with psychosis.

The treatment of medication-induced psychosis in Parkinson's disease consists in the first place of reducing the dosage of some anti-Parkinson's drugs. Treatment with a cholinesterase inhibitor may also be considered. If psychosis persists in spite of reducing medication or if the movement disorder worsens so that medication reduction is problematic, antipsychotics are indicated. The treating physician then has to choose between two courses of action: on the one hand registered treatment with clozapine, which has been proved to be effective and demonstrably has very good clinical results but is also associated with dangerous side effects, including agranulocytosis, and on the other hand off-label treatment with second-generation antipsychotics which do not have as many dangerous side effects, but do not work as well. Faced with this dilemma it seems justified to use quetiapine as a first step and if this fails then to use clozapine. Risperidone and olanzapine remain as a third choice. If clozapine treatment is chosen, the compulsory WBC checks are necessary, because the chance of agranulocytosis is not dose dependent.

### **5) Tardive dyskinesia and tardive dystonia**

It has been established that with clozapine there is a very low, minimal chance of tardive dyskinesia, even after years of treatment.<sup>32,33</sup> In double-blind or cross-over studies of tardive dyskinesia and in open label studies of tardive dystonia, clozapine has been shown to have a beneficial effect.<sup>34,35</sup> This may be a reason to use clozapine in the case of tardive movement disorders, both to treat the movement disorder itself and to cause as little as possible harm if an antipsychotic continues to be needed to treat the psychiatric disorder.

## 6) Schizoaffective and mood disorders

As monotherapy or as augmentation of mood stabilizers clozapine is effective for treatment-resistant psychosis, psychotic, non-psychotic or dysphoric mania and also depression in the context of a bipolar or schizoaffective disorder.<sup>36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52</sup> In the bipolar and schizoaffective group it appears that the improvement is even significantly greater than in the group with schizophrenia.<sup>53,54</sup> The polarity of the mood dysregulation is an important factor: manic and compound psychotic conditions had a 71% chance of improving as opposed to 52 % for a depression. Whether or not in combination with mood stabilizers, clozapine also seems to have a mood stabilizing, prophylactic effect, even with rapid cycling.<sup>55,56,57,58,59,60</sup> There are also favourable reports of the effect of clozapine on treatment-resistant psychotic depressive disorders.<sup>61,62,63</sup> Since it has been shown that most second-generation antipsychotics are effective in the treatment and prevention of mania and some of them also for depression in the context of a bipolar I disorder, it is recommended that these should be tried first, before using clozapine.<sup>64</sup>

## 7). Treatment-resistant aggression in schizophrenia and schizoaffective disorder

In non-randomized, controlled studies clozapine was commonly found to have an anti-aggressive effect.<sup>65,66,67</sup> The antisuicidal and anti-aggressive effects appear to be *independent* of the improvement of positive, negative, depressive and general psychopathological symptoms.<sup>68</sup> A controlled study has indicated that clozapine reduces the number of arrests for delinquent behaviour.<sup>69</sup> This fits in with the finding of another study among forensic, mainly psychotic patients: among the group on clozapine conditional release was revoked significantly less frequently than among the group on haloperidol.<sup>70</sup> Two randomized studies showed that clozapine has a superior effect to haloperidol and second-generation antipsychotics on (physical) aggression and hostility in patients with schizophrenia and schizoaffective disorder.<sup>71,72,73</sup> The first study population consisted of patients who were moderately treatment-resistant and had not been specially selected for aggression, while the second consisted of patients without treatment resistance but with aggression. In principle the evidence produced by these studies to support the indication for treatment-resistant aggression is at least as convincing as that for recurrent suicidal behaviour in schizophrenia and schizoaffective disorder, for which clozapine is registered in the US.

## 8) Treatment-resistant substance abuse or dependency in schizophrenia or schizoaffective disorder

Clozapine has a beneficial effect on patients with a dual diagnosis of schizophrenia and alcohol or drugs abuse or dependency.<sup>74,75,76,77,78</sup> In a non-randomized controlled study it was found that patients who had been given clozapine because of a treatment-resistant psychosis or because of severe extrapyramidal side effects went into remission from their substance abuse or dependency more frequently than patients taking other antipsychotics. These patients also relapsed less frequently into substance abuse. Findings regarding decreased cigarette smoking are contradictory.<sup>79,80</sup> Double-blind randomized studies among patients with dual diagnosis are presently underway, but have not yet been completed. However, trial treatment with clozapine in the event that other treatments fail is justified in view of the severity of the consequences due to co-morbidity.

### **9) Recurrent suicidal behaviour in treatment-resistant and non-resistant schizophrenia and schizoaffective disorder**

In epidemiological and other non-randomized controlled studies clozapine has been shown to reduce the risk of suicide.<sup>81,82,83,84</sup> Some studies found a reduction of 80%. In a randomized comparison of clozapine with olanzapine in patients with schizophrenia or schizoaffective disorder and a high suicide risk clozapine was found to be clearly more beneficial than olanzapine with respect to several parameters of suicidality.<sup>85</sup> Most of the patients in these studies did not have treatment-resistant psychoses. In the US clozapine is registered for this indication.

### **10) Treatment-resistant aggression and/or self-mutilation in borderline personality disorder, autism or severe intellectual disability**

Sometimes clozapine is used as a last-resort medication for treatment-resistant aggression and/or self-mutilation in borderline personality disorder, autism or severe intellectual disability. However, there are no randomized studies in this area – only case descriptions. It is interesting that clozapine also seemed to be effective in aggressive or self-mutilating patients who were not psychotic.<sup>86,87,88,89,90,91</sup> For an overview see Schulte & Netherlands Clozapine Collaboration Group (2007).<sup>92</sup> Obviously, in view of the special risks associated with clozapine other treatment alternatives should be exhausted before clozapine is prescribed and the clinical picture must be grave enough to justify the risks of a trial treatment with clozapine.

### **11) Special patient populations**

Dev & Krupp (1995) describe 102 pregnancies during clozapine treatment, with eight non-elective and 13 elective abortions.<sup>93</sup> Fifty-nine births resulted in 61 babies, of whom 51 were healthy, five with deformations and five with health problems in the neonatal phase. Some mothers had been taking other drugs as well as clozapine which may have led to the deformations. For 22 pregnancies no information was available. Four babies were breastfed while the mother was on clozapine. One of these babies developed reversible agranulocytosis and another became extremely sleepy.

Clozapine has proved to be effective in elderly people with treatment-resistant primary psychotic disorders.<sup>94,95</sup> There are indications that the response among 55 to 65-year-olds is higher than among over-60s. If the dose is increased extra slowly, tolerance is reasonable. The chance of blood abnormalities may be higher in this age group than in younger patients.

Nine cases have been published of schizophrenia with psychogenic polydipsia and hyponatremia in which clozapine had a beneficial effect on the polydipsia and its physical consequences.<sup>96,97</sup>

### **Contraindications**

Patients who have previously reacted to clozapine with severe granulocytopenia or agranulocytosis, have a bone marrow disorder or are being treated with medication which suppresses the bone marrow function may not be treated or retreated with clozapine. For specific considerations regarding simultaneous treatment with cytostatics, see the Haematology section. There is a relative contraindication for patients who have reacted to other medications with the blood abnormalities referred to above.<sup>98</sup> If after due consideration



the decision is made to prescribe clozapine all the same, the WBC count must be monitored very carefully (for instance twice a week). Clozapine rechallenge may be considered even for patients who have suffered leukopenia in the past on clozapine, provided they have never had WBC counts of less than  $2.0 \times 10^9/l$  and provided they are monitored very strictly (see under granulocytopenia and agranulocytosis). Patients with alcoholic or toxic psychosis, with medication toxicity or in a comatose condition may never be treated with clozapine. The same applies to circulatory collapse and/or depression of the central nervous system, regardless of the cause. Severe liver, kidney or heart disease or a paralytic ileus are contraindications.

### **Modes of administration**

In the Netherlands 25, 50, 100 and 200 mg tablets are available. Unfortunately Novartis has stopped the production worldwide of 2 ml ampoules with 25 mg clozapine/ml. In the Netherlands these and also 125 mg/5 ml ampoules are now produced by the hospital pharmacy Ziekenhuis Apotheek en Laboratorium Venray (ZALV). Clozapine can be administered by intramuscular injection, **in which case the required oral dose can be halved**. Injections may be a solution if a patient needs clozapine, but cannot or will not swallow.<sup>99,100,101</sup> Amounts of injection fluid over 4 ml should be divided and administered at two injection sites.<sup>102</sup> Clozapine tablets can be crushed and mixed with water.<sup>103</sup> Oral ingestion must then take place quickly, as it is not known how long the suspension is stable.

## **Plasma levels and duration of an adequate trial**

### **Metabolization and the importance of monitoring clozapine plasma levels**

Plasma levels can be checked six days after the last dose change; many patients reach a steady state even after three days, so that blood samples can be taken from the fourth day onwards. If co-medication which may affect the clozapine plasma level is discontinued or added, the plasma level should be checked after 14 days. Except in the event of acute toxicity, the right time for blood sampling is always  $12 \pm 1/2$  hours after ingestion of the last dose. The benefit of monitoring clozapine plasma levels has sometimes been questioned.<sup>104</sup> However, a systematic review with meta-analysis has shown that the absolute difference in risk of non-response in the treatment of refractory schizophrenia or schizoaffective disorder is 43% dependent on a plasma level above or below 350 to 400  $\mu g/l$ .<sup>105,106</sup> There may be patients who need higher plasma levels than this threshold. In one study the effect decreased again when the plasma level rose above 700  $\mu g/l$ . Above this level the chance of side effects also increases.

Therefore if there is no response during the escalation phase at lower levels, the recommendation is to aim for a clozapine plasma level above 350 to 400  $\mu g/l$ . Levels above this threshold provide the greatest chance of response. If clozapine is administered once daily in the evening, the threshold should be increased by 23%.<sup>107</sup> If *serum* levels are determined, it should be taken into account that *plasma* levels are 10% higher.<sup>108</sup> It is important to realize that a quarter to a third of patients respond at levels below the threshold. They do not need higher levels and levels above the threshold would only mean burdening them unnecessarily with side effects.

However, there is another reason why it helpful to monitor clozapine plasma levels: clozapine has numerous side effects – such as anticholinergic effects or epileptic seizures – which depend on dosage and plasma levels.<sup>109,110,111</sup> Checking plasma levels prevents patients being prescribed higher doses than necessary. However, dosage offers little to go by. It is known

that with the same dose of clozapine, plasma levels can vary by a factor of 45 (Potkin et al. 1994). However, intra-individually the variability is small – 20%.<sup>112</sup> Connections between sex, time frame and plasma levels have also been found:<sup>113</sup> in the fourth and sixth week of clozapine treatment women reach a higher plasma level-dose quotient than men. In both sexes the level also rises slightly between week four and six; then the quotient increases in men and decreases in women. On the basis of various factors such as sex, weight, smoker or non-smoker, a prediction can be made about the dose which will result in the 350 to 400 µg/l threshold (see also the Table in the guideline under II) MEDICATION SCHEDULE).<sup>114</sup>

CYP1A2 is the main enzyme involved in breaking down clozapine.<sup>115</sup> This enzyme is induced by several kinds of cabbage, broccoli, chicory and char-grilled (barbecued) food. There has been no investigation of the extent to which these interactions are clinically relevant. Polycyclic aromatic hydrocarbons (PAHs) in cigarette smoke also inhibit CYP1A2, which is why smokers have lower clozapine levels. CYP2C19 poor metabolizers (\*2/\*2 genotype) have 2 to 3 times higher levels than extensive metabolizers. Normally CYP3A does not play a role in breaking down clozapine, but this pathway becomes important when CYP1A2 is inhibited, for example by fluvoxamine (see below). In that case only CYP3A5 and 3A7 play no role.

The level is increased by a factor of 1.6 in carriers of the ABCB1 gene, which encodes P-glycoprotein. CYP2B6, 2C9 and 2D6 do not affect clozapine levels. Inflammatory reactions such as infections of the upper respiratory tract or urinary tract may lead to sudden toxic clozapine concentration levels, sometimes with delirium.<sup>116,117,118</sup> (Moreover, a patient confined to bed or hospitalized will smoke less or not at all, which can also lead to increased clozapine levels). There is evidence that cytokines may inhibit CYP1A2 and CYP3A4.<sup>119,120,121,122</sup> Increased CRP is associated with very high clozapine levels.<sup>123</sup> In the event of infections patient or their carers should watch out for sedation or other signs of raised concentrations. In that case a temporary dose reduction is required, possibly while monitoring plasma levels.

Factors including sex, age and race play a role in the wide inter-individual variability.<sup>124</sup> Substances which have an impact on the cytochrome P450 oxidases (1A2, 3A4 and 2D6) will also affect clozapine plasma levels.<sup>125, 126</sup> Carbamazepine, phenytoin, smoking, rifampicin, aminoglutethimide, barbiturates and ritonavir may reduce levels,<sup>127</sup> while caffeine, cimetidine, ciprofloxacin, erythromycin and some SSRIs including nefazodone may increase them.<sup>128,129</sup> There are doubts as to whether or not erythromycin can in fact lower clozapine concentration.<sup>130</sup> Other studies involving citalopram, paroxetine and fluoxetine showed no significant increase in clozapine levels.<sup>131,132,133,134,135,136</sup> Nevertheless, on the basis of case reports the American SmPC text warns of possible interaction between clozapine and citalopram.<sup>137</sup> Fluvoxamine certainly has a strong inhibitory effect on clozapine clearance through inhibition of CYP1A2.<sup>138</sup> With a daily dose of 50 mg fluvoxamine the clozapine plasma becomes 2 or 3 times higher, to a maximum of as much as 5 times.<sup>139</sup> The combination of clozapine and fluvoxamine is safe provided the clozapine level is monitored, and this combination is sometimes used successfully to attain an effective plasma level if the level is too low in spite of a high dose.<sup>140,141,142</sup> If a patient refuses to take the number of tablets required to attain a therapeutic level, the addition of fluvoxamine may be a solution. However, pharmacologically speaking monotherapy with clozapine is the first choice, because it is easier to control. At the same plasma level the side effects of clozapine are just as strong regardless of whether the level has been attained by fewer clozapine tablets in combination with fluvoxamine or by many clozapine tablets without fluvoxamine. It is wise

to add only 25 or 50 mg of fluvoxamine in the first instance and to monitor the clozapine plasma level while increasing the dose of fluvoxamine in increments of 25 mg. Even after a week with the addition of 50 mg of fluvoxamine the clozapine level will have risen, but it will rise even further in the second week.<sup>143</sup> Increasing the fluvoxamine to 100 mg will again increase the clozapine level by about half.

Since the relation between clozapine dosage and plasma levels is linear in monotherapy,<sup>144</sup> it is possible to calculate the dose needed to attain the desired level on the basis of the steady-state trough level (for example after four days on a fixed dose).<sup>145</sup> If the desired level is twice as high, for example, the dose will have to be doubled. While the patient is on clozapine this may help to avoid excessively high plasma levels while still attaining the threshold quickly.

### **Duration of an adequate trial**

A systematic review came to the conclusion that the chance of a response after a patient has been on a fixed dose for four months without responding is very low.<sup>146</sup> It is better to make sure the clozapine plasma level is high enough. There is strong evidence that the definitive therapeutic effect at a certain level can be evaluated within eight weeks. A later response – without increasing the plasma level – is unlikely.

### **Strategies if clozapine does not help enough**

Very little is known about what to do if clozapine does not help even when the concentration is (well) above the threshold defined. Chong & Remington (2000) have summarized augmentation strategies.<sup>147</sup> They conclude that there is no convincing evidence to support these strategies. The treating physician must therefore weigh up various factors such the patient's suffering, the chance of a positive effect and the risks of a trial.

Several possibilities are listed below, in random order. Studies of the addition of a second antipsychotic with clozapine after clozapine monotherapy has proved insufficiently effective are contradictory. The systematic review with a meta-analysis comes to the conclusion that the evidence supporting this strategy is weak.<sup>148</sup> Positive results were found with sulpiride addition (600 mg/d) in an RCT and contradictory results (two negative and one positive RCT) with risperidone addition.<sup>149,150, 151,152</sup> Aripiprazole augmentation had only a slight positive effect on negative symptoms and triglycerides.<sup>153</sup> The Netherlands Clozapine Collaboration Group knows of cases in which the clozapine dose could be reduced successfully provided another antipsychotic was added.<sup>154</sup> This means that patients who do not respond to low clozapine levels and cannot tolerate high levels may be potential candidates for the addition of a second antipsychotic.

A strategy for which some evidence emerges from a meta-analysis is the addition of lamotrigine.<sup>155</sup> Considering the lack of good alternatives, there is enough evidence to justify offering clozapine non-responders a 24-week trial with the addition of 200 mg lamotrigine (incremented according to the standard rules).

Another strategy found effective in a randomized study is the addition of 20 mg of memantine.<sup>156</sup> In two trials indications were found that the addition of 2 and 3 gr respectively of EPA for 12 weeks had a positive effect on psychopathology as measured by the PANSS.<sup>157, 158</sup>

In an RCT the addition of 30 mg of mirtazapine for eight weeks was found to have a positive effect as measured by BPRS and SANS.<sup>159</sup> In a naturalistic study the addition of lithium (mean plasma level 0.50 mmol/l) for four weeks was found to have a positive effect as

measured by the CGI and the PANSS in the patient group with schizoaffective disorders, but not in the group with schizophrenia.<sup>160</sup> A systematic overview of case histories shows that ECT has a positive effect on the majority of clozapine non-responders.<sup>161</sup> These findings were later supported by a description of a cohort of 27 patients.<sup>162</sup>

If the desired response has not been attained by the end of the trial, the treating physician should consult with the patient as to whether he or she feels better on clozapine than on previous psychiatric drugs. Side effects and risks, such as tardive dyskinesia, may play a role in making a decision. For non-responders, stopping clozapine and continuing treatment with a classic or second-generation antipsychotic is an option.

## Interactions and side effects

### Interactions

All interactions of clozapine with other drugs published over a period of more than 20 years have been summarized by Edge et al. (1997).<sup>163</sup>

Because of the risk of agranulocytosis, other medications which also carry this risk are relatively contraindicated. Combination with carbamazepine is particularly suspect: it demonstrably leads to more granulocytopenia, though it has not been proved to lead to more agranulocytosis.<sup>164</sup>

Clozapine may enhance the central effects of alcohol, MAO inhibitors and drugs such as narcotics, antihistamines and benzodiazepines. Combination with benzodiazepines in particular should be treated with caution because of a possible higher chance of circulatory collapse and respiratory depression, which in rare cases may lead to cardiac and/or respiratory arrest. During clozapine initiation changes to benzodiazepine doses should therefore be avoided. Because of additive effects, caution should be observed in combining clozapine with drugs with anticholinergic, hypotensive or respiratory depressant properties. In rare cases combination with lithium may lead to neurotoxic symptoms.

Clozapine binds strongly to plasma proteins. This may lead to interactions with other drugs which are highly bound to plasma protein (such as coumarins).

Clozapine is metabolized mainly through cytochrome P450, which can lead to interactions with other medications (see above under plasma levels).

### The side effects of clozapine and how to deal with them

The side effects and risks of antipsychotics in general and clozapine in particular have been the subject of several overview articles.<sup>165,166,167,168</sup>

Clozapine has a strongly antagonistic effect on muscarine,  $\alpha_1$ ,  $\alpha_2$ ,  $\beta$ , histamine ( $H_1$ ), serotonin and GABA receptors. Many side effects are derived from this action. Table 1 gives an idea of the frequency.<sup>169</sup> Some side effects are not spontaneously mentioned by patients and only become evident when the patients are specifically asked.

Reaction	% (spontaneously mentioned plus when asked)	% (spontaneously mentioned)
Blurred vision	24	5
Constipation	34	8
Daytime drowsiness	52	10
Dysphoria	32	1
Energy loss	42	4
Headache	35	3
Hypersalivation	57	21
Lack of concentration	38	0
Memory problems	38	1
Nausea/Vomiting	24	8

Night-time sleep problems	32	1
Nocturnal enuresis	39	1
Orthostasis	27	4
Perspiration	21	4
Sedation	70	28
Sexual side effects	55	3
Tachycardia	30	0
Weight gain	31	7

Table 1 Common side effects in clozapine users (N=103)

### Central nervous system

#### Sedation

Many patients suffer from sedation when they start clozapine treatment, probably because of the drug's antihistaminergic and antiadrenergic effects. It is only in a small proportion of these patients that it is an ongoing problem. It may help to give most of the dose in the evening. A few cases have been described in which clozapine-induced sedation was treated with methylphenidate.<sup>170,171</sup> However, if methylphenidate is to be used the problem of sedation has to be weighed up against the risk of movement disorders and addiction associated with this drug.

#### Other effects on behaviour

Confusion and in rare cases delirium occur, particularly in elderly people and/or when the dose is increased rapidly. This is probably due to the anticholinergic effect. An overdose leads to coma.

#### Epileptic seizures

In comparison with many other antipsychotics clozapine significantly lowers the epileptic threshold.<sup>172</sup> This can lead to tonic-clonic seizures and – more rarely – to myoclonus or atonic seizures. Rapid dose increases, sudden substantial reduction in doses of benzodiazepines, a previous history of seizures, EEG abnormalities or skull injuries are risk factors. Clozapine concentration is a better predictor of a seizure than the dose. It is advisable to monitor clozapine plasma levels and possibly the EEG during clozapine initiation. As a rule a first seizure is not a reason to discontinue clozapine treatment. Often for patients without risk factors halving the clozapine dose and increasing it more gradually is an adequate solution. If a second seizure occurs, valproate can be added in order to continue clozapine treatment, but the EEG should be monitored.

#### Myoclonus

Patients with a higher risk of epileptic seizures also have an increased chance of myoclonus. Myoclonus may also foreshadow epileptic seizures. Dose reduction, more gradual titration or valproate are helpful.

#### Extrapyramidal symptoms, akathisia and tardive dyskinesia

These side effects are extremely rare with clozapine and are very probably at placebo level.

#### Neuroleptic malignant syndrome (NMS)

This dangerous complication has been reported in connection with clozapine in rare cases.<sup>173</sup> Of the 21 cases only one patient was also on lithium. The clinical picture is not essentially different from that associated with classic antipsychotics: autonomic dysregulation, extrapyramidal symptoms (in 71% of the NMS cases with clozapine), fever (37.5 – 40 °C), and mental changes. As a rule CPK is increased (on average 1500 U/L). No fatalities have been reported in connection with NMS and clozapine. Some patients were later still able to be put on clozapine safely. Clozapine has also been used successfully with patients who developed neuroleptic malignant syndrome on other antipsychotics.<sup>174</sup> NMS on clozapine must be differentiated from isolated CPK increases, which probably usually have no clinical significance (see below). When clozapine treatment starts, sometimes a benign transient hyperthermia occurs, which must also be distinguished from NMS (see below).

#### Withdrawal syndrome

Symptoms such as agitation, confusion, perspiration, diarrhoea, dyskinesia, headache, insomnia, nausea, restlessness and vomiting can be avoided if the dose is tapered off over a period of two weeks. However, to prevent a rebound psychosis a tapering off period of three to four months is recommended, also if a different (second-generation) antipsychotic is given to overlap. In comparison with other antipsychotics clozapine has a higher chance of a rapid relapse within 14 days, which can be explained by the fact that it is loosely bound to the D<sub>2</sub> receptor.<sup>175,176</sup> However, it is more likely that its strong anticholinergic effect leads to the relapse. Medication with an anticholinergic effect may reduce the chance of a psychotic relapse during clozapine withdrawal.<sup>177</sup> The same applies to olanzapine, which also has an anticholinergic effect.<sup>178</sup>

#### Increased creatine kinase (CK) and myopathy

Like other second-generation antipsychotics, clozapine is associated with increased CK and sometimes myopathy.<sup>179,180,181,182,183,184,185</sup> Usually it is not necessary to stop the clozapine and to date screening has not been recommended either. Rhabdomyolysis also occurs – very rarely – as a side effect, but the risk is even lower than with olanzapine.<sup>186</sup>

### Autonomic nervous system

#### Hypersalivation

Hypersalivation is a side effect which occurs in over half of patients, particularly during sleep. Some believe the cause is increased saliva production, others a reduced swallow reflex.<sup>187</sup> Some patients put towels on their pillows. Tolerance may develop, but not necessarily. Dose reduction or chewing gum may reduce this side effect. Swallow training as investigated and described among intellectually disabled people with hypersalivation may be considered.<sup>188, 189</sup> A systematic overview of the pharmacological treatment of clozapine-induced hypersalivation came to the conclusion that there is no clear-cut recommendation.<sup>190</sup> Anticholinergic seem to be effective, but it must be borne in mind that clozapine already has an intrinsic anticholinergic effect and that the anticholinergic block may lead to other side effects. In other medical conditions sometimes accompanied by hypersalivation (amyotrophic lateral sclerosis, Parkinson's disease) scopolamine patches are used.<sup>191</sup> A successful treatment with these patches for a patient on clozapine has been described.<sup>192</sup> Another alternative may be intranasal or sublingual administration of ipratropium bromide 0.03 mg/ml in a nasal spray or sublingual atropine (one drop 1% solution (0.5mg atropine)).<sup>193,194,195,196,197,198,199</sup> The advantage of these remedies is that they can be administered locally, but the drawback is possible overdosing by

the patient. For severe, treatment-resistant hypersalivation transdermal injection of botulinum toxin-A into the parotid gland by a doctor with experience with this drug may be considered. An initial response can be observed after 1-4 days, while the strongest effect can be seen at 1-2 weeks. The therapeutic effect remains up to 7-8 weeks with a gradual increase of saliva production towards 16 weeks. In elderly patients radiation of the parotid gland on both sides with a low dose of fast electrons (10-14 MeV) may be considered. This also leads to a reduction of salivation. The treatment requires one or two visits to a radiotherapeutic centre and does not take long. Side effects may be: some pain in the irradiated gland, transient redness or burning of the skin and a dry mouth. The duration of the effect is 4-6 months. Because the radiation may cause cancer after 10 to 15 years, this treatment is only an option for elderly patients. A last resort is surgical intervention.

### Hyperthermia

Benign transient hyperthermia sometimes occurs during the first three weeks of clozapine treatment. The temperature elevation is usually not more than 1.5 °C. If other causes such as infection resulting from agranulocytosis, dehydration or neuroleptic malignant syndrome have been ruled out, clozapine can be continued without any concerns. The temperature elevation disappears spontaneously within a few days and it is only rarely that antipyretics are needed. Sometimes fever is accompanied by leukocytosis and increased sedimentation.<sup>200</sup> In these cases further tests (physical, blood and urine tests, and possibly X-thorax and blood cultures) are advisable to rule out other causes.

### Other autonomic reactions

Perspiration and blurred vision have been reported in association with clozapine. Because of clozapine's strong anticholinergic effect, caution must be observed regarding patients with prostatic hyperplasia and narrow angle glaucoma.

## **Cardiovascular system**

If a patient has cardiovascular abnormalities (for example a previous history of heart attack or arrhythmia) a cardiologist must be consulted.

### Tachycardia

Tachycardia may occur in reaction to clozapine's effect of lowering the blood pressure, but notably also as a result of the drug's anticholinergic properties. This side effect is usually dose-dependent. Limiting caffeine and nicotine is recommended. If no tolerance for the side effect develops, an ECG is recommended to rule out heart disease. A cardioselective  $\beta$ -blocker (such as metoprolol) may be a solution for severe tachycardia if the patient's blood pressure permits it. Propranolol might also alleviate orthostasis. Tachycardia may be a symptom of myocarditis.

### Blood pressure

Hypotension and orthostatic complaints due to clozapine's  $\alpha$ -antiadrenergic effect often occur at the beginning of treatment, particularly in elderly patients or if the dose is increased rapidly. Dizziness and syncope may ensue. Usually tolerance develops. It is best to advise patients beforehand to rise slowly from a sitting or lying position, especially at night. If symptoms suggesting hypotension persist they should be objectified by measurements at various points in time. The symptoms are hypotensive if they are related to measured drops in



blood pressure (from  $\geq 20$  mm Hg systolic and/or 10 mm Hg diastolic). An initial measure is support stockings, possibly even thigh-high.<sup>201</sup> A second possibility is to raise the head of the bed 10 to 15 cm. However, the blood pressure should then be monitored for quite a long period because of the chance of hypertension when lying down. Fludrocortisone, starting with a low dose and with routine electrolyte and blood pressure monitoring, is the next possibility.<sup>202</sup> Dihydroergotamine (no longer available in the Netherlands) may also be used to raise the blood pressure.<sup>203</sup> Finally, co-treatment by a cardiologist may be considered.

Hypertension also sometimes occurs, particularly during the first six months.<sup>204</sup>

#### ECG changes and sudden cardiac death

Clozapine can lead to a repolarization disorder such as flattening or inversion of the T-waves. These changes are usually not clinically significant and often disappear if the medication is continued.<sup>205</sup> Like other antipsychotics, clozapine is associated with a higher risk of sudden cardiac death (3.67 times more frequently than people who do not take antipsychotics).<sup>206</sup> This risk is somewhat higher with clozapine than with classic antipsychotics (1.99 times higher) or other second-generation antipsychotics (2.26 times higher). The absolute risk of sudden cardiac death related to clozapine is 4 per 1000 patient years. It is generally assumed that sudden cardiac death results from torsade de pointes accompanied by prolonged QT intervals. ECG monitoring (QT interval) may reduce the risk. It is worth noting that Novartis's clozapine database does not contain any evidence of a higher risk of prolonged QT intervals or torsades de pointes.<sup>207</sup>

#### Myocarditis, pericarditis, cardiomyopathy

These are rare but dangerous side effects. The extent of the risk is controversial.<sup>208, 209</sup> The highest mortality found resulting from myocarditis was 0.6%. Nevertheless, clozapine treatment reduces total mortality among patients with treatment-resistant schizophrenia.<sup>210</sup> If myocarditis or cardiomyopathy occurs, in 80% of cases it is during the first month of clozapine treatment.<sup>211</sup> Cardiomyopathy can occur at any stage of clozapine treatment. Cardiomyopathy may manifest itself clinically as progressive heart failure, but may also remain completely asymptomatic.

The symptoms of myocarditis may consist of tachycardia (46% of clozapine-related myocarditis cases), exertional dyspnoea (27%), chest pain (32%), arrhythmia, fever (49%), leukocytosis (28%), weakening and dizziness.<sup>212, 213</sup> An ECG and a cardiological consultation must be considered if these symptoms occur during the first month of clozapine treatment. In two-thirds of these cases the ECG or ECHO shows abnormalities. Increased troponin (36% of cases) indicates heart injury.<sup>214</sup> Treatment of myocarditis consists of discontinuing clozapine and taking supportive measures. One successful and one unsuccessful case of clozapine rechallenge after myocarditis have been reported.<sup>215, 216, 217</sup> Just as after a severe clozapine-induced leukopenia, rechallenge is contraindicated. The decision to rechallenge can only be made in special circumstances and after careful consideration of the benefits and risks.

#### Respiratory system

Grohmann et al. (1989) have discussed apnoea as a very rare complication of the combination of clozapine and benzodiazepines.<sup>218</sup> If possible the combination should be avoided, especially during initiation and particularly in combination with parenteral administration of a benzodiazepine.

## **Gastrointestinal system**

Clozapine has several effects on the gastrointestinal system, not all of which can be predicted on the basis of its pharmacological properties.

### Constipation

Constipation and dry mouth occur in 14% and 6% respectively of patients and are due to clozapine's anticholinergic effect. Depending on the severity, there is a danger of intestinal obstruction and even ileus. Early observation of constipation and symptomatic treatment is therefore very important. The first step is at least two litres of fluid, sufficient exercise and a list of food intake (preferably by a dietician) with the recommendation of a fibre-rich diet. If this is not enough, bulk formers such as macrogol-electrolytes to a maximum of 3 daily doses of 1 sachet and/or psyllium fibre 3.6 gr 1 to 2 daily doses of 1 sachet can be prescribed. These are preferable to lactulose (maximum of 3 doses of 30 ml) because lactulose often leads to abdominal cramps and flatulence, and laxatives are required long-term. Macrogol-electrolytes are taken with 125ml of water. Psyllium fibre must be taken with at least 2 l of water. This may be problematic for some patients and it requires proper instruction, because if taken without enough fluid psyllium fibres will increase constipation. If response is insufficient, add magnesium sulphate, 3 500 mg tablets daily. Neostigmine/distigmine or oral carbachol are final possibilities, especially if there are several anticholinergic side effects.<sup>219</sup> Neostigmine is also indicated in the event of Ogilvie's syndrome (acute pseudo-obstruction due to an imbalance in the autonomic regulation of intestinal motility), a condition resembling ileus.<sup>220</sup>

### Nausea and vomiting

In spite of an expected anti-emetic effect due to the D<sub>2</sub> block, clozapine sometimes leads to these complaints. Metoclopramide, antacids or H<sub>2</sub> blockers may provide a solution. Swallowing problems have also been reported.

### Colitis

Very rare cases of colitis resulting from clozapine have been reported: eosinophilic and neutropenic colitis, pseudomembranous and necrotizing colitis or microscopic colitis.<sup>221, 222</sup> The colitis may lead to severe vomiting and diarrhoea.

### Hepatic system

Clozapine can lead to an elevation (usually transient) of liver enzymes. In rare cases hepatitis occurs, but it is usually reversible and asymptomatic. Cholestasis due to hypersensitivity must be ruled out. In this event dose reduction or discontinuation of clozapine is usually enough.<sup>223</sup>

## **Metabolism and endocrine system**

### Prolactin

Unlike many other antipsychotics, clozapine does not lead to elevated prolactin levels, which is why amenorrhoea, galactorrhoea and gynaecomastia have very rarely been observed. Vice versa, when women switch to clozapine they often start to menstruate again, also with the risk of unwanted pregnancy.

### Weight gain

Clozapine is an antipsychotic with a particularly high chance of weight gain.<sup>224</sup> Elevation of cortisol concentration, sedation and other mechanisms such as an impact on serotonin and histamine receptors have been held responsible for this. In a direct comparison with olanzapine, clozapine was found to lead to weight gain less frequently.<sup>225</sup> Type 2 diabetes

mellitus may occur. Dietary advice and exercise are recommended. The effect of dose reduction is uncertain. However, there are indications that a lower dose (100 mg vs. 300 mg vs. 600 mg) during the first 16 weeks of treatment causes less weight gain.<sup>226</sup> In this context, the lower the baseline weight is, the greater the weight gain will be, or in other words possibly obese patients do not gain more weight due to clozapine. There is also evidence that lower clozapine plasma levels cause less weight gain.<sup>227</sup> Clozapine often leads to higher levels of cholesterol and triglycerides, especially in men.<sup>228,229,230</sup> Treatment with clozapine in combination with fluvoxamine 50 mg leads to less weight gain and lower glucose and triglyceride than with clozapine alone.<sup>231</sup> Because this evidence comes from only one study among Chinese patients, for the time being it is not recommended that this strategy be used systematically.

#### Glucose metabolism

Like some other second-generation antipsychotics, clozapine has been associated with insulin-dependent diabetes and in rare cases with diabetic ketoacidosis.<sup>232,233</sup> If the fasting glucose is still too high in a repeated blood test, an oral glucose tolerance test must be carried out. The reference range varies depending on whether the glucose test is done using venous or capillary blood.

### Genito-urinary system

#### Interstitial nephritis

A few cases of interstitial nephritis have been reported. Since clozapine can give rise to allergic reactions, a connection cannot be ruled out.

#### Incontinence and urine retention

Like phenothiazines, clozapine sometimes leads to urinary incontinence, increased urge and increased frequency of urination. In one study incontinence turned out to be persistent in 25% of all patients on clozapine.<sup>234</sup> In just under half of patients incontinence improves spontaneously. Limiting fluid intake in the evening, imipramine, intranasal desmopressin (DDAVP) and ephedrine have been used incidentally to deal with this.<sup>235,236</sup> Because clozapine can also lead to urine retention, extreme caution should be observed in connection with benign prostatic hyperplasia and other bladder voiding disorders.

#### Priapism and retrograde ejaculation

Cases of both of these have been reported in connection with clozapine. Impotence occurs less frequently with clozapine than with haloperidol.

### Haematology

#### Granulocytopenia and agranulocytosis

Because of the risk of agranulocytosis (granulocyte count  $<0.5 \times 10^9/l$ ), in the Netherlands the prescription of clozapine is limited to the indications referred to above. In the case of benign ethnic neutropenia (for example in black people or Yemenite Jews), in consultation with a haematologist the lower limits for WBC and granulocytes can be reduced. In a small-scale study among a few dozen black people the reference range was found to be as follows: black men and women from Africa WBC count  $2.8-7.2 \times 10^9/l$  and  $3.0-7.4 \times 10^9/l$  respectively and granulocyte count  $0.9-4.2 \times 10^9/l$  and  $1.3-3.7 \times 10^9/l$  respectively. For black men and women

from the Caribbean region the reference range is  $3.1-9.4 \times 10^9/l$  and  $3.2-10.6 \times 10^9/l$  respectively and  $1.2-5.6 \times 10^9/l$  and  $1.3-7.1 \times 10^9/l$  respectively.<sup>237</sup>

WBC counts are usually done on venous blood, but they can also be done on capillary blood (finger prick) by collecting a few drops of blood in a tube such as the Becton Dickinson Microtainer.

In two studies the risk of agranulocytosis determined among a total of almost 25,000 patients was 0.68%.<sup>238, 239</sup> For the whole population the chance of dying from this complication was 0.016%. Eighty-five per cent of all cases of agranulocytosis occur during the first 18 weeks of treatment. The exact mechanism – toxic or allergic – is not clear. If the WBC and granulocyte counts drop below  $2.0 \times 10^9/l$  and  $1.0 \times 10^9/l$  respectively, a bone marrow biopsy is recommended.<sup>240</sup> In one case of clozapine-induced granulocytopenia a correlation was found between G-CSF levels and granulocyte counts.<sup>241</sup> Treatment with haematopoietic growth factors is recommended if the neutrophil count drops below  $1.0 \times 10^9/l$  (neutropenia). The growth factor is discontinued as soon as this level is reached again. Moreover, reverse isolation is required. As a rule patients recover within 14 to 24 days after clozapine treatment is discontinued.<sup>242</sup> If 75-150  $\mu g$  of granulocyte colony-stimulating factor (G-CSF) is administered subcutaneously twice a day, recovery can be effected within five to eight days.<sup>243, 244</sup> Two cases have been reported in which clozapine was successfully continued in spite of severe neutropenia when G-CSF was administered.<sup>245, 246</sup>

The risk of agranulocytosis decreases exponentially.<sup>247</sup> The US clozapine register of over 100,000 patients shows a risk of agranulocytosis per 1000 patient years of (figures in brackets are derived from a second, more recent cohort) 6.76 (3.25) to the 18<sup>th</sup> week, 0.40 (0.37) between weeks 19 and 52, and 0.39 (0.11) from week 52 onwards. The risk of death due to agranulocytosis if the four-weekly WBC count is discontinued after the first year of clozapine treatment is estimated to be 0.01 to 0.38/1000 patient years.<sup>248</sup> In the second six months of clozapine treatment these risks are approximately twice as high. In comparison, in 2003 inhabitants of the Netherlands had a risk of death due to a private accident, a traffic accident or an accident at work of 0.15, 0.06 and 0.07/1000 respectively. Therefore in the opinion of the Netherlands Clozapine Collaboration Group if a mentally competent and adequately informed patient explicitly wants to stop having routine blood tests, this can be permitted after the first six months of clozapine treatment. However, the WBC count must still be monitored immediately if there is any clinical suspicion of agranulocytosis. Even if the routine blood tests are stopped, low frequency tests, for example four times a year, are still advisable, because they may trace slow progressive drops in the WBC count.

For treatment-resistant patients who responded well to clozapine but had to stop the treatment because of low WBC or granulocyte counts, rechallenge can be considered in spite of the EMEA provisions, especially if no agranulocytosis has occurred.<sup>249</sup> The doctor will be even more inclined to take this risky step if the patient is a danger to himself or herself or to others (suicidality and/or aggression) and/or if the patient's suffering is greater without clozapine and there are no alternatives. The American SmPC text for clozapine keeps the option of restarting clozapine open, even with a WBC count  $<3.0 \times 10^9/l$  and granulocyte count  $<1.5 \times 10^9/l$ , provided these counts have never been lower than  $2.0 \times 10^9/l$  and  $1.0 \times 10^9/l$  respectively.<sup>250</sup> However, with an initial drop in the WBC count  $<3.0 \times 10^9/l$  the risk of agranulocytosis in rechallenge is 12 times higher. Weekly blood tests during the first year after restarting is recommended by the FDA. Add-on therapy with lithium or G-CSF may be considered.<sup>251, 252, 253, 254, 255, 256</sup> However, prolonged use of G-CSF may cause acute myeloid

leukaemia.<sup>257</sup> Because of the increased risk, clozapine rechallenge after stopping previously because of low WBC counts should only take place with the informed consent of the patient or the patient's legal representative and in collaboration with an experienced haematologist.

Nine cases have been reported of successful treatment by chemotherapy (because of malignancy) while clozapine treatment was continued.<sup>258</sup> Clozapine is not an absolute contraindication for treatment with cytostatics. The pros and cons must be carefully weighed up, taking specific factors into account: the risk of recurring psychosis if clozapine is discontinued (for example, the patient was a threat during a previous psychosis, impossibility of cancer treatment if the psychosis worsens), the purpose of the oncological treatment (curative or palliative), and the patient's life expectancy with or without oncological treatment.

#### Other haematological changes

Some other less important abnormalities are benign – but sometimes persistent – leukocytosis (0.6%) and eosinophilia (1%). In Europe it is recommended that clozapine be discontinued if the eosinophil count rises above  $3.0 \times 10^9/l$  and not restarted until it has dropped back below  $1.0 \times 10^9/l$ . In the US the limits referred to are  $4.0 \times 10^9/l$  and  $3.0 \times 10^9/l$  respectively. Thrombocytopenia and slight anaemia have also been reported.

#### Intoxication

The symptoms of an overdose depend on the dose the patient was accustomed to previously. Even for patients who have interrupted clozapine treatment only for three or more days the recommendation is to start with one or two daily doses of 12.5 mg. More rapid titration is only possible if this dosage is tolerated well. In patients who have not previously been treated with clozapine, 300-400 mg can lead to a life-threatening coma.<sup>259</sup> The symptoms are related to the central nervous system (extrapyramidal symptoms, agitation, hallucinations, convulsions, confusion, sedation and coma), the cardiovascular system (tachycardia, hypotension and cardiac arrhythmia) and the respiratory system (dyspnoea, respiratory depression, aspiration pneumonia). Most fatalities occur with doses above 2000 mg, mainly through heart failure, pneumonia and aspiration. However, even doses of 10,000 mg and more have been survived.

If a large quantity of clozapine is taken, the stomach should be pumped within 60 to a maximum of 120 minutes, and activated charcoal and laxatives should be given, in accordance with the standard protocol for overdose or poisoning of the hospital in question. If the clozapine was taken a longer period before, stomach pumping will not do any good, but laxatives and activated charcoal should always be given. The internist should be consulted. Dialysis is not helpful. Complications (coma, ECG abnormalities, epileptic fits) should be treated symptomatically with intubation and artificial respiration to prevent aspiration pneumonia, ECG monitoring/antiarrhythmics and benzodiazepines respectively. If hypotension occurs sympathicomimetics are contraindicated, because clozapine has alpha-adrenolytic action. Severe hypotension can be treated with angiotensin. If the patient is unconscious, flumazenil may be effective.<sup>260</sup> Late reactions sometimes occur up to five days after an overdose. Severe constipation can be treated with neostigmine.

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The Netherlands Clozapine Collaboration Group is a nation-wide collaborative group of doctors working in psychiatry, with the objective of knowledge acquisition and consultation regarding clozapine and the treatment of treatment-resistant psychotic patients. Executive Committee: D. van Dijk (psychiatrist), chair; Dr D. Cohen (psychiatrist), secretary; J. Bogers (psychiatrist), treasurer; Dr P.F.J. Schulte (psychiatrist), member; B. Bakker (internist), adviser.

Appendix 1  
Sample letter to GP before starting clozapine treatment

To the GP and any specialists involved

place, date

Re: prescription of clozapine

Dear colleague,

Your patient ..... will be treated with clozapine, a medication which can cause agranulocytosis. For this reason any other medication associated with the same risk should be avoided as much as possible. We will perform regular blood tests.

Policy after office hours: should there be any signs of infection (fever  $\geq 38^{\circ}\text{C}$ , sore throat, flu-like symptoms) during the first 18 weeks of the treatment, WBC count and differential should be checked within 24 hours to rule out agranulocytosis (including in the weekends). If fever  $\geq 38^{\circ}\text{C}$ , sore throat or flu-like symptoms occur after the first 18 weeks, WBC and differential the next working day. If a fever is accompanied by ulcers in throat or anus, WBC count and differential within 24 hours, even after the first 18 weeks. In all cases assessment of the results by a physician on the same day is recommended.

If WBC count falls to between  $3.0$  and  $3.5 \times 10^9/\text{l}$  or neutrophil granulocytes to  $1.5$ - $2.0 \times 10^9/\text{l}$ , check twice a week until the counts have stabilized or increased.

If WBC count falls below  $3.0 \times 10^9/\text{l}$  or neutrophil granulocyte count falls below  $1.5 \times 10^9/\text{l}$ , discontinue clozapine in consultation with the undersigned psychiatrist because of agranulocytosis or the risk of its development.

I hope I have provided you with sufficient information and otherwise I will be happy to discuss any issues.

Kind regards,

## Appendix 2

To assist the patient and others involved at an out-of-hours medical centre

Place, date

Mr/Ms....., born on ....., is being treated with clozapine. If there are any signs of infection (fever  $\geq 38^{\circ}\text{C}$ , sore throat, flu-like symptoms) during the first 18 weeks of clozapine treatment, WBC and differential must be checked within 24 (including in the weekends) to rule out agranulocytosis.

If fever  $\geq 38^{\circ}\text{C}$ , sore throat or flu-like symptoms occur after the first 18 weeks, WBC count and differential the next working day. If a fever is accompanied by ulcers in throat or anus, WBC count and differential within 24 hours, even after the first 18 weeks. In all cases assessment of the results by a physician on the same day is recommended.

If WBC count falls to between  $3.0$  and  $3.5 \times 10^9/\text{l}$  or neutrophil granulocytes to  $1.5$ - $2.0 \times 10^9/\text{l}$ , check twice a week until the counts have stabilized or risen.

If WBC count falls below  $3.0 \times 10^9/\text{l}$  or neutrophil granulocyte count falls below  $1.5 \times 10^9/\text{l}$ , discontinue clozapine in consultation with the undersigned psychiatrist because of agranulocytosis or the risk of its development.

Psychiatrist's signature



## References

- <sup>1</sup> Schulte PFJ. De plaats van clozapine bij de behandeling van schizofrenie. *Tijdschrift voor Psychiatrie* 2001; 43:715-720.
- <sup>2</sup> Chakos M, Lieberman J, Hoffman E, et al. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *Am J Psychiatry* 2001; 158: 518-526.
- <sup>3</sup> Tiihonen J, Lönnquist J, Wahlbeck K, Klaukka T, Niskanen A, Tanskanen A & Haukka J. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009; DOI: 10.1016/S0140-6736(09)60742-X.
- <sup>4</sup> Walker AM, Lanza LL, Arellano F, et al. Mortality in current and former users of clozapine. *Epidemiology* 1997; 8: 671-677.
- <sup>5</sup> Schulte PFJ, Stienen J. Involuntary treatment with clozapine in treatment resistant schizophrenia. *Schizophrenia Research* 2004;67(suppl.15):159.
- <sup>6</sup> Wahlbeck K, Cheine M, Essali MA. Clozapine versus typical neuroleptic medication for schizophrenia. *Cochrane Database Syst Rev.* 2000;(2):CD000059. Review. Update in: *Cochrane Database Syst Rev.* 2009;(1):CD000059.
- <sup>7</sup> Tuunainen A, Wahlbeck K, Gilbody SM. Newer atypical antipsychotic medication versus clozapine for schizophrenia. *Cochrane Database Syst Rev.* 2000;(2):CD000966. Review.
- <sup>8</sup> Schulte PFJ. De plaats van clozapine bij de behandeling van schizofrenie. *Tijdschrift voor Psychiatrie* 2001; 43: 715-720.
- <sup>9</sup> Breier AF, Malhotra AK, Su TP, et al. Clozapine and risperidone in chronic schizophrenia: effects on symptoms, parkinsonian side effects, and neuroendocrine response. *American Journal of Psychiatry* 1999; 156: 294-298.
- <sup>10</sup> Schooler N, Marder S, Kane J, et al. Clozapine and risperidone: a 29-week randomised clinical trial. Presentation at International Congress on Schizophrenia Research 1999, Santa Fe, USA.
- <sup>11</sup> Azorin JM, Spiegel R, Remington G, et al. A double-blind comparative study of clozapine and risperidone in the management of severe chronic schizophrenia. *Am J Psychiatry* 2001; 158: 1305-1313.
- <sup>12</sup> Conley RR, Tamminga CA, Bartko JJ, et al. Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. *American Journal of Psychiatry* 1998; 155: 914-920.
- <sup>13</sup> Conley RR, Tamminga CA, Kelly DL, et al. Treatment-resistant schizophrenia patients respond to clozapine after olanzapine non-response. *Biological Psychiatry* 1999; 46: 73-77.
- <sup>14</sup> Agid O, Remington G, Kapur S, Arenovich T, Zipursky RB. Early use of clozapine for poorly responding first-episode psychosis. *J Clin Psychopharmacol.* 2007 Aug;27(4):369-73.
- <sup>15</sup> Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, Asenjo Lobos C, Schwarz S, Davis JM. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry.* 2009 Feb;166(2):152-63.
- <sup>16</sup> McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, , et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry.* 2006 Apr;163(4):600-10.
- <sup>17</sup> Lewis SW, Barnes TRE, Davies, L, Murray RM, Dunn G, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophrenia Bull* 2006;32:715-23.
- <sup>18</sup> Tiihonen J, Wahlbeck K, Lönnquist J, Klaukka T, Ioannidis J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalization due to schizophrenia and schizoaffective disorder: observational follow-up study. *BMJ* 2006.doi: 10.1136/bmj.38881.382755.2F
- <sup>19</sup> Furtado V, Srihari V, Kumar A. Atypical antipsychotics for people with both schizophrenia and depression. *Schizophr Bull* 2009;35:297-8.
- <sup>20</sup> Blanz B, Schmidt MH. Clozapine for schizophrenia. *J Am Acad Child Adoles Psychiatry,* 1993; 32: 223-224.
- <sup>21</sup> Remschmidt H, Schulz E, Martin M. An open trial of clozapine in thirty-six adolescents with schizophrenia. *J Child Adoles Psychopharmacol* 1994; 4: 31-41.
- <sup>22</sup> Turetz M., Mozes T, Toren P, et al. An open trial of clozapine in neuroleptic-resistant childhood-onset schizophrenia. *Br J Psychiatry* 1997; 170: 507-510.
- <sup>23</sup> Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Arch Gen Psychiatry* 1996; 53: 1090-1097.
- <sup>24</sup> Shaw P, Sporn A, Gogtay N, Overman GP, Greenstein D, Gochman P, Tossell JW, Lenane M, Rapoport JL. Childhood-onset schizophrenia: A double-blind, randomized clozapine-olanzapine comparison. *Arch Gen Psychiatry.* 2006 Jul;63(7):721-30.
- <sup>25</sup> Kumra S, Kranzler H, Gerbino-Rosen G, Kester HM, De Thomas C, Kafantaris V, Correll CU, Kane JM.

- Clozapine and "high-dose" olanzapine in refractory early-onset schizophrenia: a 12-week randomized and double-blind comparison. *Biol Psychiatry*. 2008 Mar 1;63(5):524-9.
- <sup>26</sup> Kumra S, Kranzler H, Gerbino-Rosen G, Kester HM, DeThomas C, Cullen K, Regan J, Kane JM. Clozapine versus "high-dose" olanzapine in refractory early-onset schizophrenia: an open-label extension study. *J Child Adolesc Psychopharmacol*. 2008 Aug;18(4):307-16.
- <sup>27</sup> Miller del D, Caroff SN, Davis SM, Rosenheck RA, McEvoy JP, Saltz BL, Riggio S, Chakos MH, Swartz MS, Keefe RS, Stroup TS, Lieberman JA; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Extrapyramidal side-effects of antipsychotics in a randomised trial. *Br J Psychiatry*. 2008 Oct;193(4):279-88.
- <sup>28</sup> Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Capuano GA, Rosenheck RA, Keefe RS, Miller AL, Belz I, Hsiao JK; CATIE Investigators. Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: a CATIE study. *Am J Psychiatry*. 2007 Mar;164(3):415-27.
- <sup>29</sup> Schulte PFJ, van Laar T, van Gool WA, Bijl D, Leentjens AFG, Verhey FRJ. De ziekte van Parkinson II. Behandeling van neuropsychiatrische stoornissen. *Genesmiddelenbulletin* 2004;38:49-56.
- <sup>30</sup> Weintraub D & Hurtig HI. Presentation and management of psychosis in Parkinson's disease and dementia with Lewy bodies. *Am J psychiatry* 2007; 164: 1491-98.
- <sup>31</sup> Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis in Parkinson's disease: a review. *Drugs Aging*. 2008;25(8):665-82.
- <sup>32</sup> Juul Povlsen U, Noring U, Fog R et al. Tolerability and therapeutic effect of clozapine: a retrospective investigation of 216 patients treated with clozapine for up to 12 years. *Acta Psych Scand* 1985 ;71 :176-185.
- <sup>33</sup> Peacock L, Solgaard T, Lublin H et al. Clozapine versus typical antipsychotics: a retro- and prospective study of extrapyramidal side effects. *Psychopharmacology* 1996;124:188-196.
- <sup>34</sup> Egan MF, Apud J, Wyatt RJ. Treatment of tardive dyskinesia. *Schizophrenia Bulletin* 1997; 23: 583-609.
- <sup>35</sup> Van Harten PN, Kahn RS. Tardive dystonia. *Schizophrenia Bulletin* 1999; 25: 741-748.
- <sup>36</sup> Green AI, Tohen M, Patel JK, et al. Clozapine in the treatment of refractory psychotic mania. *Am J Psychiatry* 2000; 157: 982-986.
- <sup>37</sup> McElroy SL, Dessain EC, Pope HR, et al. Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry* 1991; 52: 411-414.
- <sup>38</sup> Suppes T, McElroy SL, Gilbert J, et al. Clozapine in the treatment of dysphoric mania. *Biol Psychiatry* 1992; 32: 270-280.
- <sup>39</sup> Tohen M, Zarate CA. Antipsychotic agents and bipolar disorder. *J Clin Psychiatry* 1998; 59 (suppl. 1): 38-48.
- <sup>40</sup> Suppes T, Webb A, Paul B, Carmody T, et al. Clinical outcome in a randomised 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. *Am J Psychiatry* 1999; 156: 1164-1169.
- <sup>41</sup> Frankenburg FR. Clozapine and bipolar disorder. *J Clin Psychopharmacol* 1993;13:289-290.
- <sup>42</sup> Suppes T, Phillips KA, Judd CR. Clozapine treatment of nonpsychotic rapid cycling bipolar disorder: a report of three cases. *Biol Psychiatry* 1994;36:338-340.
- <sup>43</sup> Antonacci DJ, Swartz CM. Clozapine treatment of euphoric mania. *Ann Clin Psychiatry* 1995;7:203-206.
- <sup>44</sup> Zarate JR Jr, Tohen M, Banov MD. Is clozapine a mood stabilizer? *J Clin Psychiatry* 1995;56:108-112.
- <sup>45</sup> Mahmood T, Vevlin M, silverstone T. Clozapine in the management of bipolar and schizoaffective manic episodes resistant to standard treatment. *Aust NZ J Psychiatry* 1997;31:424-426.
- <sup>46</sup> Shulman RW, Singh A, Shulman KI. Treatment of elderly institutionalized bipolar patients with clozapine. *Psychopharmacol Bull* 1997;33:113-118.
- <sup>47</sup> Degner D, Bleich S, Müller P, Hajak G, Adler L, Rüther E. Clozapine in the treatment of mania. *J Neuropsychiatry Clin Neurosci* 2000;12:283.
- <sup>48</sup> Calabrese JR, Gajwani P. Lamotrigine and clozapine for bipolar disorder. *Am J Psychiatry* 2000;157:1523.
- <sup>49</sup> Frankenburg FR, Zanarini MC. Uses of clozapine in non-schizophrenic patients. *Harvard Rev Psychiatry* 1994;2:142-150.
- <sup>50</sup> Calabrese JR, Kimmel SE, Woyshtville MJ et al. Clozapine for treatment-refractory mania. *Am J Psychiatry* 1996;153:759-764.
- <sup>51</sup> Bryous C, Ferrero F. Clinical observation of 11 patients under clozapine-lithium association. *Eur Psychiatry* 1993;8:213-218.
- <sup>52</sup> Moldavsky M, Stein D, Benatov R et al. Combined clozapine-lithium treatment for schizophrenia and schizoaffective disorder. *Eur Psychiatry* 1998;13:104-106.
- <sup>53</sup> Banov MD, Zarate CA Jr, Tohen M et al. Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. *J Clin Psychiatry* 1994;55:295-300.
- <sup>54</sup> Ciapparelli A, Dell'Osso L, Pini S, et al. Clozapine for treatment-refractory schizophrenia, schizoaffective disorder, and psychotic bipolar disorder: a 24-month naturalistic study. *J Clin Psychiatry* 2000; 61: 329-334.

- <sup>55</sup> Calabrese J, Meltzer HY, Markovitz PJ. Clozapine prophylaxis in rapid cycling bipolar disorder. *J Clin Psychopharmacol* 1991;11:396-397.
- <sup>56</sup> McElroy SL, Keck PE, Strakowski SM. Mania, psychosis, and antipsychotics. *J Clin Psychiatry* 1996; 57: 14-26.
- <sup>57</sup> Puri BK, Taylor DG, Alcock MEC. Low-dose maintenance clozapine treatment in the prophylaxis of bipolar affective disorder. *BJPC* 1995;49:333-334.
- <sup>58</sup> Fry MA, Altshuler LL, Bitran JA. Clozapine in rapid-cycling bipolar disorder. *J Clin Psychopharmacol* 1996 ;16 :87-89.
- <sup>59</sup> Hummel B, Dittmann S, Forsthoef A, Matzner N, Amann B, Grunze H. Clozapine as add-on medication in the maintenance treatment of bipolar and schizoaffective disorders. *Neuropsychobiology* 2002;45(suppl. 1):37-42.
- <sup>60</sup> Ciapparelli A, Dell'Osso L, Pini S, et al. Clozapine for treatment-refractory schizophrenia, schizoaffective disorder, and psychotic bipolar disorder: a 24-month naturalistic study. *J Clin Psychiatry* 2000; 61: 329-334.
- <sup>61</sup> Parsa MA, Ramirez LF, Loula EC, et al. Effect of clozapine on psychotic depression and parkinsonism. *J Clin Psychopharmacol* 1991; 11: 300-331.
- <sup>62</sup> Dassa D, Kaladjian A, Azorin JM, et al. Clozapine in the treatment of psychotic refractory depression. *Br J Psychiatry* 1993; 163: 822-824.
- <sup>63</sup> Ranjan R, Meltzer HY. Acute and long-term effectiveness of clozapine in treatment-resistant psychotic depression. *Biol Psychiatry* 1996; 40: 253-258.
- <sup>64</sup> Schulte R, Nolen WA. Antipsychotics. In: Kupka RW, Knoppert-van der Klein EAM, Nolen WA (red.). *Handboek Bipolaire Stoornissen. De Tijdstroom, Utrecht 2008, pag. 269-283.*
- <sup>65</sup> PFJ Schulte and the ClozapinePlusCollaborationGroup. Clozapine: anti-aggressive effect and compulsory treatment. *Proceedings of the 5th European Congress on Violence in Clinical Psychiatry* (eds. P. Callaghan, T. Palmstierna, H. Nijman, N. Oud), p. 303-307, Publisher Kavanah, Dwingeloo 2007.  
[http://www.oudconsultancy.nl/Resources/Violence\\_in\\_Clinical\\_Psycha.pdf](http://www.oudconsultancy.nl/Resources/Violence_in_Clinical_Psycha.pdf)
- <sup>66</sup> Glazer WM, Dickson RA. Clozapine reduces violence and persistent aggression in schizophrenia. *Journal of Clinical Psychiatry* 1998; 59 (suppl. 3): 8-14.
- <sup>67</sup> Volavka J. The effects of clozapine on aggression and substance abuse in schizophrenic patients. *Journal of Clinical Psychiatry* 1999; 60(suppl 12): 43-46.
- <sup>68</sup> Spivak B, Shabash E, Sheitman B, et al. The effects of clozapine versus haloperidol on measures of impulsive aggression and suicidality in chronic schizophrenia patients: an open, nonrandomized, 6-month study. *J Clin Psychiatry* 2003;64:755-760.
- <sup>69</sup> Frankle WG, Shera D, Berger-Herskowitz H, et al. Clozapine-associated reduction in arrest rates of psychotic patients with criminal histories. *American Journal of Psychiatry* 2001; 158: 270-274.
- <sup>70</sup> Stoner SC, Wehner Lea JS, Dubisar BM, et al. Impact of clozapine versus haloperidol on conditional release time and rates of revocation in a forensic psychiatric population. *J Pharm Technol* 2002;18:182-6.
- <sup>71</sup> Citrome L, Volavka J, Czobor P, Sheitman B, Lindenmayer JP, McEvoy J, Cooper TB, Chakos M, Lieberman JA. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. *Psychiatr Serv.* 2001 Nov;52(11):1510-4.
- <sup>72</sup> Volavka J, Czobor P, Nolan K, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, Cooper TB, Lieberman JA. Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychopharmacol.* 2004 Apr;24(2):225-8.
- <sup>73</sup> Krakowski MI, Czobor P, Citrome L, Bark N, Cooper TB. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry.* 2006 Jun;63(6):622-9.
- <sup>74</sup> Drake RE, Xie H, Mc Hugo GJ, et al. The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. *Schizophrenia Bulletin* 2000; 26: 441-449.
- <sup>75</sup> Ziedonis DM, Fisher W. Motivation-based assessment and treatment of substance abuse in patients with schizophrenia. *Directions in Psychiatry* 1996; 16: 1-8.
- <sup>76</sup> Zimmet SV, Strous RD, Burgess ES, et al. Effects of clozapine on substance use in patients with schizophrenia and schizoaffective disorder: a retrospective survey. *Journal of Clinical Psychopharmacology* 2000; 20: 94-98.
- <sup>77</sup> Green AI, Burgess ES, Dawson R, Zimmet SV, Strous RD. Alcohol and cannabis use in schizophrenia: effects of clozapine vs. risperidone. *Schizophr Res.* 2003 Mar 1;60(1):81-5.
- <sup>78</sup> Brunette MF, Drake RE, Xie H, McHugo GJ, Green AI. Clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. *Schizophr Bull.* 2006 Oct;32(4):637-43.
- <sup>79</sup> McEvoy J, Freudenreich O, McGee M, et al. Clozapine decreases smoking in patients with chronic schizophrenia. *Biological Psychiatry* 1995; 37: 550-552.
- <sup>80</sup> de Leon J, Diaz FJ, Josiassen RC, Cooper TB, Simpson GM. Does clozapine decrease smoking? *Prog Neuropsychopharmacol Biol Psychiatry* 2005;29(5):757-62.

- <sup>81</sup> Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. *American Journal of Psychiatry* 1995; 152: 183-190.
- <sup>82</sup> Reid WH, Mason M, Hogan T. Suicide prevention effects associated with clozapine therapy in schizophrenia and schizoaffective disorder. *Psychiatric Services* 1998; 49: 1029-1033.
- <sup>83</sup> Hennen J, & Baldessarini RJ. Suicidal risk during treatment with clozapine: a meta-analysis. *Schizophrenia Res* 2005;73:139-45.
- <sup>84</sup> Tiihonen J, Lönnquist J, Wahlbeck K, Klaukka T, Niskanen A, Tanskanen A & Haukka J. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009; DOI: 10.1016/S0140-6736(09)60742-X.
- <sup>85</sup> Meltzer HY, Alphas, L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry*.2003 Jul;60(7):735.
- <sup>86</sup> Balassa M, Deisenhammer E, Scherer H. Clozapine, ein nicht kataleptogenes Neuroleptikum, in der Behandlung von Verhaltensstörungen mit Erregungszuständen. *Wiener Medizinische Wochenschrift* 1971; 121: 90-92.
- <sup>87</sup> Chengappa KNR, Baker RW, Sirri C. The successful use of clozapine in ameliorating severe self mutilation in a patient with borderline personality disorder. *J Personality Dis* 1995; 9: 76-82.
- <sup>88</sup> Benedetti F, Sforzini L, Colombo C, et al. Low-dose clozapine in acute and continuation treatment of severe borderline personality disorder. *J Clin Psychiatry* 1998; 59:103-107.
- <sup>89</sup> Chengappa KNR, Ebeling T, Kang JS, et al. Clozapine reduces severe self-mutilation and aggression in psychotic patients with borderline disorder. *J Clin Psychiatry* 1999; 60: 477-484.
- <sup>90</sup> Frankenburg FR, Zanarini MC. Clozapine treatment of borderline patients: a preliminary study. *Compr Psychiatry*. 1993 Nov-Dec;34(6):402-5.
- <sup>91</sup> Wheatley M, Plant J, Reader H, et al. Clozapine treatment of adolescents with posttraumatic stress disorder and psychotic symptoms. *J Clin Psychopharmacology* 2004;24:167-173.
- <sup>92</sup> PFJ Schulte and the ClozapinePlusCollaborationGroup. Clozapine: anti-aggressive effect and compulsory treatment. *Proceedings of the 5th European Congress on Violence in Clinical Psychiatry* (eds. P. Callaghan, T. Palmstierna, H. Nijman, N. Oud), p. 303-307, Publisher Kavanah, Dwingeloo 2007.  
[http://www.oudconsultancy.nl/Resources/Violence\\_in\\_Clinical\\_Psycha.pdf](http://www.oudconsultancy.nl/Resources/Violence_in_Clinical_Psycha.pdf)
- <sup>93</sup> Dev VJ, Krupp P. Adverse event profile and safety of clozapine. *Rev Contemp Pharmacother* 1995; 6: 197-208.
- <sup>94</sup> Sajatovic M, Jaskiw G, Konicki PE, et al. Outcome of clozapine therapy for elderly patients with refractory primary psychosis. *Int J Ger Psychiatry* 1997; 12: 553-558.
- <sup>95</sup> Sajatovic M, Ramirez LF, Garver D, et al. Clozapine therapy for older veterans. *Psych Serv* 1998; 49: 340-344.
- <sup>96</sup> Lee HS, Kwon KY, Alphas LD, et al. Effect of clozapine on psychogenic polydipsia in chronic schizophrenia. *J Clin Psychopharmacol* 1991; 11: 222-223.
- <sup>97</sup> Canuso CM, Goldman MB. Clozapine restores water balance in schizophrenic patients with polydipsia-hyponatremia syndrome. *J Neuropsychiatry Clin Neurosci* 1999; 11: 86-90.
- <sup>98</sup> Mendelowitz AJ, Gerson SL, Alvir J, et al. Clozapine-induced agranulocytosis. Risk factors, monitoring and management. *CNS Drugs* 1995; 4: 412-421.
- <sup>99</sup> Lokshin P, Lerner V, Miodownik C, et al. Parenteral clozapine: five years of experience. (letter). *J Clin Psychopharmacology* 1999;19:479-480.
- <sup>100</sup> Schulte PFJ, Juan J. Stienen, Jan Bogers, Dan Cohen, Daniel van Dijk, Wendell H. Lionarons, Sophia L. Sanders, and Adolph H. Heck. Compulsory treatment with clozapine: a retrospective long-term cohort study. *Int J Law & Psychiatry* 2007; 30: 539-545.
- <sup>101</sup> McLean G, Juckes L. Parenteral clozapine (clozaril) (letter). *Australasian Psychiatry* 2001;9:371.
- <sup>102</sup> Mason AS, Granacher RP. Modes of Administration, in: *Clinical Handbook of Antipsychotic Drug Therapy*. Brunner/Mazel, New York, 1980.
- <sup>103</sup> Ramuth S, Flanagan RJ, Taylor DM. A liquid clozapine preparation for oral administration in hospital. *Pharmaceutical Journal* 1996; 257:190-191.
- <sup>104</sup> Olesen OV. Therapeutic drug monitoring of clozapine treatment. Therapeutic threshold value for serum clozapine concentrations. *Clin Pharmacology* 1998; 34: 497-502.
- <sup>105</sup> Schulte PFJ. Clozapin bei therapieresistenter Schizophrenie. Plasmaspiegel und Dauer eines ausreichenden Behandlungsversuchs. *Psychopharmakotherapie* 2003;10:102-111.
- <sup>106</sup> Schulte PFJ. What is an adequate trial with clozapine? Therapeutic drug monitoring and time to response in treatment-refractory schizophrenia. *Clinical Pharmacokinetics* 2003;42:607-618.

- <sup>107</sup> VanderZwaag C, McGee M, Mc Evoy JP, et al. Response of patients with treatment-resistant schizophrenia to clozapine within three serum level ranges. *Am J Psych* 1996; 153: 1579-1584.
- <sup>108</sup> Kaladjian A, Bery B, Deutmeny E, et al. Clozapine monitoring: plasma or serum levels? *The Drug Monitor* 1999; 21: 327-329.
- <sup>109</sup> de Leon J, Odom-White A, Josiassen RC, et al. Serum antimuscarinic activity during clozapine treatment. *J Clin Psychopharmacol* 2003;23:336-341.
- <sup>110</sup> Simpson G, Cooper T. Clozapine plasma-levels and convulsion. *Am J Psychiatry* 1978; 135: 99-100.
- <sup>111</sup> Yusufi B, Mukherjee S, Flangan R, et al. Prevalence and nature of side effects during clozapine maintenance treatment and the relationship with clozapine dose and plasma concentration. *Int Clin Psychopharmacol* 2007;22:238-243.
- <sup>112</sup> Oleson O, Thomsen K, Jensen P, et al. Clozapine serum levels and side-effects during steady-state treatment of schizophrenic patients: a cross-sectional study. *Psychopharmacology* 1995; 117: 371-378.
- <sup>113</sup> Fabrazzo M, Esposito G, Fusco R, et al. Effect of treatment duration on plasma levels of clozapine and N-desmethylclozapine in men and women. *Psychopharmacology* 1996; 124: 197-200.
- <sup>114</sup> Rostami-Hodjegan A, Amin AM, Spencer EP, et al. Influence of Dose, Cigarette Smoking, Age, Sex, and Metabolic Activity on Plasma Clozapine Concentrations: A Predictive Model and Nomograms to Aid Clozapine Dose Adjustment and to Assess Compliance in Individual Patients. *J Clin Psychopharmacol* 2004;24:70-78
- <sup>115</sup> Jacquenod Sirot E, Knezevic B, Perla Morena G, Harenberg S, Oneda B, et al. ABCB1 and cytochrome P450 polymorphisms. Clinical pharmacogenetics of clozapine. *J Clin Psychopharmacol* 2009;29:319-326.
- <sup>116</sup> Van der Molen-Eijgenraam M, Blanken-Meijs JTHM, Heeringa M, et al. Delirium door stijging van clozapinespiegels tijdens ontstekingsreactie. *Ned Tijdschr Geneesk* 2001; 145: 427-430.
- <sup>117</sup> De Leon J. Respiratory infections rather than antibiotics may increase clozapine levels: a critical review of the literature. *J Clin Psychiatry* 2004;65:1144-1145. *Eur J Clin Pharmacol* 2001;57:705-708.
- <sup>118</sup> Raaska K, Raitasuo V, Neuvonen PJ. Effect of influenza vaccination on serum clozapine and its main metabolite concentrations in patients with schizophrenia.
- <sup>119</sup> Raaska K, Raitasuo V, Arstila M, Neuvonen PJ. Bacterial pneumonia can increase serum-concentration of clozapine. *Eur J Clin Pharmacol* 2002;58:321-322.
- <sup>120</sup> Renton KW. Cytochrome P450 regulation and biotransformation during inflammation and infection. *Curr Drug Metab* 2004;6:235-243.
- <sup>121</sup> Aitken AE, Richardsen TA, Morgan ET. Regulation of drug-metabolizing enzymes. *Annu Rev Pharmacol toxicol* 2006;46:123-149.
- <sup>122</sup> Crawford JH, Yang S, Zhou M, Simms HH, Wang P. Down-regulation of hepatic CYP1A2 plays an important role in inflammatory responses in sepsis. *Crit Care Med*. 2004 Feb;32(2):502-8.
- <sup>123</sup> Pfuhlmann B, Hiemke C, Unterecker St, Burger R, Schmidtke P et al. Toxic clozapine serum levels during inflammatory reactions. *J Clin Psychopharmacol* 2009;29:302-394.
- <sup>124</sup> Touw D. Metabolisme van clozapine. Een analyse van de variabelen die het metabolisme van clozapine kwantitatief kunnen beïnvloeden. *Pharmaceutisch Weekblad* 1995; 130: 256-262.
- <sup>125</sup> Taylor D. Pharmacokinetic interactions involving clozapine. *Br J Psychiatry* 1997; 171: 109-112.
- <sup>126</sup> Eiermann B, Engel G, Johansson I, et al. The involvement of CYP1A2 and CYP3A4 in the metabolism of clozapine. *Br J Clin Pharmacol* 1997; 44: 439-446.
- <sup>127</sup> Jerling M, Lindström L, Bondesson U, et al. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. *Therapeutic Drug Monitoring* 1994; 16: 368-374.
- <sup>128</sup> Centorrino F, Baldessarini R, Frankenburg F., et al. Serum levels of clozapine and noreclozapine in patients treated with selective serotonin reuptake inhibitors. *Am J Psychiatry* 1996; 153: 820-822.
- <sup>129</sup> Khan AY, Preskorn SH. Increase in plasma levels of clozapine and noreclozapine after administration of nefazodone. *Journal of Clinical Psychiatry* 2001, 62:375-376.
- <sup>130</sup> Hägg S, Spigset O, Mjörndal T, Granberg K, Persbo-Lundqvist G, Dahlqvist R. Absence of interaction between erythromycin and a single dose of clozapine. *Eur J Clin Pharmacol* 1999; 55: 221-226
- <sup>131</sup> Taylor D, Ellison Z, Ementon Shaw L, et al. Co-administration of citalopram and clozapine: effect on plasma clozapine levels. *Int Clin Psychopharmacology*; 13: 19-21.
- <sup>132</sup> Eggert A, Crismon ML, Dorson PG. Lack of effect of fluoxetine on plasma-clozapine concentrations. *Journal of Clinical Psychiatry* 1994; 55: 454-455.
- <sup>133</sup> Brosen K, Naranjo CA. Review of pharmacokinetic and pharmacodynamic interaction studies with citalopram. *Eur Neuropsychopharmacol*. 2001 Aug;11(4):275-83.
- <sup>134</sup> Spina E, Scordo MG, D'Arrigo C. Metabolic drug interactions with new psychotropic agents. *Fundam Clin Pharmacol*. 2003 Oct;17(5):517-38.

- <sup>135</sup> Wetzel H, Angheliescu I, Szegedi A, et al. Pharmacokinetic interactions of clozapine with selective serotonin reuptake inhibitors: differential effects of fluvoxamine and paroxetine in a prospective study. *J Clin Psychopharmacol* 1998; 18: 2-9.
- <sup>136</sup> Avenoso A, Facciola G, Scordod MG, Gitto C, Drago Ferrante G, et al. No effect of citalopram on plasma levels of clozapine, risperidon and their active metabolites in patients with chronic schizophrenia. *Clin Durg Invest* 1998;16:393-98.
- <sup>137</sup> <http://www.pharma.us.novartis.com/product/pi/pdf/Clozaril.pdf> (accessed 19-2-2006)
- <sup>138</sup> Chang W, Augustin B, Lane H, et al. In-vitro and in-vivo evaluation of the drug-drug interactions between fluvoxamine and clozapine. *Psychopharmacology (Berl)* 1999; 145: 91-98.
- <sup>139</sup> Szegedi A, Angheliescu I, Wiesner J, et al. Addition of low-dose fluvoxamine to low-dose clozapine monotherapy in schizophrenia: drug monitoring and tolerability data from a prospective clinical trial. *Pharmacopsychiatry* 1999; 32: 148-153.
- <sup>140</sup> Lammern C, Deuschle M, Weigmann H, et al. Coadministration of clozapine and fluvoxamine in psychotic patients--clinical experience. *Pharmacopsychiatry* 1999; 32: 76-77.
- <sup>141</sup> Bender S, Eap C. Very high cytochrome P4501A2 activity and nonresponse to clozapine. *Arch Gen Psychiatry* 1998; 55: 1048-149.
- <sup>142</sup> Dequardo J, Roberts M. Elevated clozapine levels after fluvoxamine initiation. *Am J Psychiatry* 1996; 153: 840-841.
- <sup>143</sup> Fabrazzo M, La Pia S, Monteleone P, et al. Fluvoxamine increases plasma and urinary levels of clozapine and its major metabolites in a time- and dose-dependent manner. *J Clin Psychopharmacol* 2000; 20: 708-710.
- <sup>144</sup> Choc M, Lehr R, Hsuan F, et al. Multiple dose pharmacokinetics of clozapine in patients. *Pharm Res* 1987; 4: 402-405.
- <sup>145</sup> Oyewumi, L., Freeman, D., et al. (1995). Can low-dose clozapine pharmacokinetics predict steady-state plasma-concentration? *Therapeutic Drug Monitoring*, 17, 137-141.
- <sup>146</sup> Schulte PFJ. Clozapin bei therapieresistenter Schizophrenie. Plasmaspiegel und Dauer eines ausreichenden Behandlungsversuchs. *Psychopharmakotherapie* 2003;10:102-111.
- <sup>147</sup> Chong SA, Remington G. Clozapine augmentation: safety and efficacy. *Schizophrenia Bulletin* 2000; 26: 421-440.
- <sup>148</sup> Barbui C, Signoretti A, Mule S, Boso M, Cipiani A. Does the addition of a second antipsychotic drug improve clozapine treatment? *Schizophrenia Bull* 2009; 35: 458-68.
- <sup>149</sup> Shiloh R, Zemishlansky Z, Aizenberg D, et al. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. *Br J Psychiatry* 1997; 171: 569-573.
- <sup>150</sup> Honer WG, Thornton AE, Chen EY, et al. Clozapine alone versus clozapine and risperidon with refractory schizophrenia. *N Eng J Med* 2006;354:472-82.
- <sup>151</sup> Josiassen RC, Joseph A, Kohegyi E, et al. Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2005 Jan;162(1):130-6.
- <sup>152</sup> Anil Yagcioglu AE, Kivircik Akdede BB, Turgut TI, et al. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. *J Clin Psychiatry*. 2005 Jan;66(1):63-72.
- <sup>153</sup> Chang JS, Ahn YM, Park HJ, Lee KY, Kim SH, Kang UG, Kim YS. Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: an 8-week, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2008 May;69(5):720-31.
- <sup>154</sup> Wu G, Dias P, Wu Ch, Li G, Kumar Sh, et al. Hyperglycemia, hyperlipidemia and periodic paralysis; a case report of new side effects of clozapine. *Prog Neuro-Psychopharmacol & Biol. Psychiat* 2000; 24:1395-1400.
- <sup>155</sup> Tiihonen, J., Wahlbeck, K, & Kiviniemi, V. (2009). The efficacy of lamotrigine in clozapine-resistant schizophrenia: a systematic review and meta-analysis. *Schizophrenia Research*, doi:10.1016/j.schres.2009.01.002
- <sup>156</sup> Lucenaa, D, Fernandes B, Berke M, Dodde S, Medeiros DW, et al. Improvement of schizophrenia negative and positive symptoms with memantine as add-on therapy to clozapine: a double-blind, randomized, placebo-controlled trial. *Bipolar Disorders*, 11 (Suppl. 1), 57.
- <sup>157</sup> Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry*. 2002 Oct;59(10):913-9.
- <sup>158</sup> Emsley R, Myburgh C, Oosthuizen P, van Rensburg SJ. Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia. *Am J Psychiatry*. 2002 Sep;159(9):1596-8.
- <sup>159</sup> Zoccali R, Muscatello MR, Cedro C, Neri P, La Torre D, Spina E, Di Rosa AE, Meduri M. The effect of mirtazapine augmentation of clozapine in the treatment of negative symptoms of schizophrenia: a double-blind, placebo-controlled study. *Int Clin Psychopharmacol*. 2004 Mar;19(2):71-6.

- <sup>160</sup> Small JG, Klapper MH, Malloy FW, Steadman TM. Tolerability and efficacy of clozapine combined with lithium in schizophrenia and schizoaffective disorder. *J Clin Psychopharmacol*. 2003 Jun;23(3):223-8.
- <sup>161</sup> Kho KH, Blansjaar BA, de Vries S, Babuskova D, Zwinderman AH, Linszen DH. Electroconvulsive therapy for the treatment of clozapine nonresponders suffering from schizophrenia--an open label study. *Eur Arch Psychiatry Clin Neurosci*. 2004 Dec;254(6):372-9.
- <sup>162</sup> Hustig H, Onilov R. ECT rekindles pharmacological response in schizophrenia. *European Psychiatry* 2009. doi:10.1016/j.eurpsy.2009.04.005
- <sup>163</sup> Edge SC, Markowitz JS, Devane CL. Clozapine drug-drug interactions: a review of the literature. *Human Psychopharmacology* 1997; 12: 5-20.
- <sup>164</sup> Junghan U, Albers M, Woggan B. Increased risk of haematological side-effects in psychiatric patients treated with clozapine and carbamazepine? *Pharmacopsychiatry* 1993; 26: 262.
- <sup>165</sup> See under 78 Dev and Krupp
- <sup>166</sup> Hansen TE, Casey DE, Hoffman WF. Neuroleptic intolerance. *Schizophrenia Bull* 1997; 23: 567-582.
- <sup>167</sup> Lieberman JA, Kane JM, Johns CA. Clozapine: Guidelines for clinical management. *J Clin Psychiatry* 1989; 50: 329-338.
- <sup>168</sup> Lader, M. Some adverse effects of antipsychotics: prevention and treatment. *J Clin Psychiatry* 1999; 60 (suppl. 12): 18-21.
- <sup>169</sup> Yusufi B, Mukherjee S, Flanagan R, et al. Prevalence and nature of side effects during clozapine maintenance treatment and the relationship with clozapine dose and plasma concentration. *Int Clin Psychopharmacol* 2007;22:238-243.
- <sup>170</sup> Burke M, Sebastian CS. Treatment of clozapine sedation. *Am J Psychiatry* 1993; 150: 1900-1901.
- <sup>171</sup> Miller SC. Methylphenidate for clozapine sedation. *Am J Psychiatry* 1996; 153: 1231-1232.
- <sup>172</sup> Wong J, Delva N. Clozapine-induced seizures: recognition and treatment. *Can J Psychiatry*. 2007 Jul;52(7):457-63.
- <sup>173</sup> Ananth JA, Parameswaran S, Gunatilake S, et al. Neuroleptic malignant syndrome and atypical antipsychotic drugs. *J Clin psychiatry* 2004;65:464-470.
- <sup>174</sup> Weller M, Kornhuber J. Clozapine rechallenge after an episode of "neuroleptic malignant syndrome". *Br J Psychiatry* 1992; 161: 855-856.
- <sup>175</sup> Moncrieff J. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. *Acta Psychiatr Scand* 2006;114:3-13.
- <sup>176</sup> Seeman P, Tallerico T. Rapid release of antipsychotic drugs from dopamine D<sub>2</sub> receptors: an explanation for low receptor occupancy and early clinical relapse upon withdrawal of clozapine or quetiapine. *Am J Psychiatry* 1999; 156: 876-884.
- <sup>177</sup> Seppala N, Kivio C, Leinonen E. Effect of anticholinergics in preventing acute deterioration in patients undergoing abrupt clozapine withdrawal. *CNS Drugs*. 2005;19(12):1049-55.
- <sup>178</sup> Tollefson GD, Dellva MA, Mattler CA, Kane JM, Wirshing DA, Kinon BJ. Controlled, double-blind investigation of the clozapine discontinuation symptoms with conversion to either olanzapine or placebo. The Collaborative Crossover Study Group. *J Clin Psychopharmacol*. 1999 Oct;19(5):435-43.
- <sup>179</sup> Meltzer HY, Cola PA, & Parsa M. marked elevations of serum creatine kinase activity associated with antipsychotic drug treatment. *Neuropsychopharmacology* 1996;15:395-405.
- <sup>180</sup> Koren W, Koren E, Nacasch N, et al. Rhabdomyolysis associated with clozapine treatment in a patient with decreased calcium-dependent potassium permeability of cell membranes. *Clin Neuropharmacology* 1998;21:262-264.
- <sup>181</sup> Devarajan S, Dursun SM. Antipsychotic drugs, serum creatine kinase (CPK) and possible mechanisms. *Psychopharmacology* 2000;152:122.
- <sup>182</sup> Boot E, de Haan L. Massive increase in serum creatine kinase during olanzapine and quetiapine treatment, not during treatment with clozapine. *Psychopharmacology* 2000;150:347-348.
- <sup>183</sup> Meltzer HY. Massive serum creatine kinase increases with atypical antipsychotic drugs: what is the mechanism and the message? *Psychopharmacology* 2000;150:349-350.
- <sup>184</sup> Reznik I, Volchek L, Mester R, et al. Myotoxicity and neurotoxicity during clozapine treatment. *Clin Neuropharmacol* 2000;23:276-280.
- <sup>185</sup> Scelsa SN, Simpson DM, Mc Quiston HL, et al. Clozapine-induced myotoxicity in patients with chronic psychotic disorders. *Neurology* 1996;47:1518-1523.
- <sup>186</sup> Nederlands Bijwerkingen Centrum Lareb. Clozapine, olanzapine and rhabdomyolysis. September 2004.
- <sup>187</sup> Sleutjes FMAM, Hermens WAJJ. Een bijwerking van clozapine. *Speculaties over speekselvloed*. *Pharmaceutisch Weekblad* 2002; 28: 982-985.
- <sup>188</sup> Van der Burg JW, Didden R, Jongerius PH, & Rotteveel JJ. A descriptive analysis of studies on behavioural treatment of drooling (1970–2005). *Developmental Medicine & Child Neurology* 2007, 49: 390–394.

- <sup>189</sup> Van der Burg J JW, Didden R, Engbers N, Jongerius PH, & Rotteveel JJ. Self-management treatment of drooling: A case series. *J. Behav. Ther. & Exp. Psychiat.* 40 (2009) 106–119.
- <sup>190</sup> Syed R, Au K, Cahill C, Duggan L, He Y, et al. Pharmacological interventions for clozapine-induced hypersalivation. *Cochrane Database of Systematic Reviews*. 1, 2009.
- <sup>191</sup> Hockstein NG, Samadi DS, Gendron K, Handler SD. Sialorrhea: a management challenge. *Am Fam Physician*. 2004 Jun 1;69(11):2628-34. (binnenhalen bij: <http://www.aafp.org/afp/20040601/2628.pdf>)
- <sup>192</sup> Gaftanyuk O & Trestman RL. Scopolamine patch for clozapine-induced sialorrhea. *Psychiatr Serv* 2004; 55: 318.
- <sup>193</sup> Calderon J, Rubin E, Sobota W. Potential use of ipatropium bromide for the treatment of clozapine-induced hypersalivation: a preliminary report. *Int Clin Psychopharmacology* 2000;15:49-52.
- <sup>194</sup> Freudenreich O, Beebe M, Goff DC. Clozapine-induced sialorrhea treated with sublingual ipratropium spray: a case-series. *J Clin Psychopharmacology* 2004;24:98-100.
- <sup>195</sup> Hyson HC, Johnson AM, Jog MJ. Sublingual atropine for sialorrhea secondary to parkinsonism: a pilot study. *Movement disorders* 2002;17:1318-1320.
- <sup>196</sup> Comley C, Gallely C, Ash D. Use of atropine eye drops for clozapine induced hypersalivation. *Austr. New Zealand J Psychiatry* 2000;34:1033-1034.
- <sup>197</sup> Fischer RB, Eichrhon M. Was tun bei neuroleptikainduzierter Hypersalivation? *Psychiatrische Praxis* 2001;28:249-250.
- <sup>198</sup> Tessier P, Antonello C. Clozapine and sialorrhea: update. *J Psychiatry & Neuroscience* 2001;26:253.
- <sup>199</sup> Christiaens V, Pieters G. Hypersalivatie door clozapine: oorzaken en behandelmogelijkheden. *Tijdschrift voor Psychiatrie* 2005;47:39-44.
- <sup>200</sup> Vink J. Koorts en leukocytose als voorbijgaande bijwerkingen van clozapine. *Tijdschrift voor Psychiatrie* 2000; 42: 121-125.
- <sup>201</sup> Mathias CJ, Kimber JR. Treatment of postural hypotension. *J Neurol Neurosurg Psychiatry* 1998; 65: 285-289.
- <sup>202</sup> Lieberman JA, Kane JM, Johns CA. Clozapine: Guidelines for clinical management. *J Clin Psychiatry* 1989; 50: 329-338.
- <sup>203</sup> Whitworth AB, Fleischhacker WW. Adverse effects of antipsychotic drugs. *Int Clin Psychopharmacology* 1995; 9: 21-27.
- <sup>204</sup> Henderson DC, Daley TB, Kunkel L, et al. Clozapine and hypertension: a chart review of 82 patients. *J Clin Psychiatry* 2004;65:686-689.
- <sup>205</sup> Kang UG, Kwon JS, Ahn YM, et al. Electrocardiographic abnormalities in patients treated with clozapine. *J Clin Psychiatry* 2000; 61: 441-446.
- <sup>206</sup> Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009; 360: 225 – 235.
- <sup>207</sup> Warner B, Hoffmann P. Investigation of the potential of clozapine to cause torsade de pointes. *Adverse Drug React Toxicol Rev*. 2002;21(4):189-203.
- <sup>208</sup> Kilian JG, Kerr K, Lawrence C, et al. Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 1999; 354: 1841-1845.
- <sup>209</sup> Warner B, Alphas L, Schaedelin J, et al. Clozapine and sudden death. *Lancet* 2000; 355: 842.
- <sup>210</sup> Walker AM, Lanza LL, Arellano F, et al. Mortality in current and former users of clozapine. *Epidemiology* 1997; 8: 671-677.
- <sup>211</sup> Novartis (2000). Data on file.
- <sup>212</sup> Cooper LT. Myocarditis. *N Engl J Med* 2009; 360:1526-38.
- 213 Layland JJ, Liew D & Prior DL. Clozapine-induced cardiotoxicity: a clinical update. *MJA* 2009; 190: 190-2.
- 214 Van Bockel EAP, Tulleken JE, Ligtenberg JJM, et al. De betekenis van een verhoogde troponinewaarde zonder acute ischemische hartziekte. *Ned Tijdschr Geneesk* 2005;149:1879-83.
- 215 Reinders J, Parsonage W, Lange D et al. Clozapinerelated myocarditis and cardiomyopathy in an Australian metropolitan psychiatric service. *Australian and New Zealand Journal of Psychiatry* 2004; 38: 915-922.
- 216 Reid P. Clozapine rechallenge after myocarditis [letter]. *Australian and New Zealand Journal of Psychiatry* 2001; 35: 249.
- 217 Jayathilake I, Kumar Singh A. Clozapine rechallenge after myocarditis. *Australasian Psychiatry* 2009;17:421-422.
- 218 Grohmann R, R  ther E, Sassim N, et al. Adverse effects of clozapine. *Psychopharmacology* 1989; 99 (suppl.): S101-S104.
- <sup>219</sup> Smout AJP, Brummer RJ. Gastro-intestinale chirurgie en gastro-enterologie. X. Obstipatie: behandeling. *Ned Tijdschr Geneesk* 2000; 144: 884-886.
- <sup>220</sup> De Bruin GJ, Bac DJ, va Puijenbroek EP, van der Klooster JM. Syndroom van Ogilvie als bijwerking van clozapine. *Nederlands Tijdschrift voor Geneeskunde* 2009;153:1969-1972.



- <sup>221</sup> Pelizza, L & Melegari M. Clozapine-induced microscopic colitis. A case-report and review of the literature. *J Clin Psychopharmacol* 2007;27:571-74.
- <sup>222</sup> Hawe, R & Bolton, JM. Response to clozapine-induced microscopic colitis. A case-report and review of the literature. *J Clin Psychopharmacol* 2008; 28: 454-55.
- <sup>223</sup> Lieberman JA, Safferman AZ. Clinical profile of clozapine: adverse reactions and agranulocytosis. *Psychiatr Q* 1992; 62: 51-70.
- <sup>224</sup> Allison D, Mentore J, Moonseong H, et al. Antipsychotic induced weight gain: a comprehensive research synthesis. *Am J Psych* 1999; 156: 1686-1696.
- <sup>225</sup> Meltzer HY, Alphas, L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry*. 2003 Jan;60(1):82-91. Erratum in: *Arch Gen Psychiatry*. 2003 Jul;60(7):735.
- <sup>226</sup> De Leon J, Diaz FJ, Josiassen RC, et al. Weight gain during a double-blind multidosage clozapine study. *J Clin Psychopharmacology* 2007;27:22-27.
- <sup>227</sup> Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. *J Clin Psychiatry*. 2009 Jul;70(7):1041-50.
- <sup>228</sup> Gaulin BD, Markowitz JS, Caley CF, et al. Clozapine-associated elevation in serum triglycerides. *Am J Psychiatry* 1999; 156: 1270-1272.
- <sup>229</sup> Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry* 2000; 157: 975-981.
- <sup>230</sup> Dursun SM, Szemis A, Andrews H, et al. The effects of clozapine on levels of total cholesterol and related lipids in serum of patients with schizophrenia: a prospective study. *J psychiatry Neurosci* 1999; 24:453-355.
- <sup>231</sup> Lu ML, Lane HY, Lin SK, et al. Adjunctive fluvoxamine inhibits clozapine-related weight gain and metabolic disturbances. *J Clin Psychiatry* 2004;65:766-771.
- <sup>232</sup> American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; 27: 596-601.
- <sup>233</sup> Koller, E.A., Schneider, B., Bennett, K., Dubitsky, G. (2001). Clozapine-associated diabetes mellitus. *American Journal of Medicine*, 11, 716-723.
- <sup>234</sup> Lin CC, Bai YM, Lind, CY, et al. A retrospective study of clozapine and urinary incontinence in Chinese inpatients. *Acta Psych Scand* 1999; 100: 158-161.
- <sup>235</sup> Fuller MA, Borovicka MC, Jaskiw GE, et al. Clozapine-induced urinary incontinence: incidence and treatment with ephedrine. *J Clin Psychiatry* 1996; 57: 514-518.
- <sup>236</sup> Lieberman JA, Safferman AZ. Clinical profile of clozapine: adverse reactions and agranulocytosis. *Psychiatr Q* 1992; 62: 51-70.
- <sup>237</sup> Bain BJ. *Blood Cells. A practical guide*. Second edition. Blackwell Science, London 1995, p. 152.
- <sup>238</sup> Alvier JM, Lieberman JA, Safferman AZ, et al. Clozapine-induced risk factors in the United States. *The New England Journal of Medicine* 1993; 329: 162-167.
- <sup>239</sup> Munro J, O'Sullivan D, Andrews C, et al. Active monitoring of 12760 clozapine recipients in the UK and Ireland. *British Journal of Psychiatry* 1999; 175: 576-580.
- <sup>240</sup> FDA, schriftelijke mededeling, <http://www.fda.gov/cder/foi/label/2005/019758s054lbl.pdf>.
- <sup>241</sup> Schuld A, Kraus T, Hinze-Selch D et al. Granulocyte colony-stimulating factor plasma levels during clozapine- and olanzapine-induced granulocytopenia. *Acta psychiatr Scand* 2000; 102: 153-155.
- <sup>242</sup> Gerson SL, Meltzer H. Mechanisms of clozapine-induced agranulocytosis. *Drug Safety* 1992; 7 (suppl. 1): 17-25.
- <sup>243</sup> Barnas C, Zwierzina H, Hummer M, et al. Granulocyte-macrophage colonystimulating factor (GM-CSF) treatment of clozapine-induced agranulocytosis: a case report. *J Clin Psychiatry* 1992; 53: 245-225.
- <sup>244</sup> Lamberti JS, Bellnier TJ, Schwarkopf SB, et al. Filgrastim treatment of three patients with clozapine-induced agranulocytosis. *J Clin Psychiatry* 1995; 56: 256-259.
- <sup>245</sup> Sperner-Unterweger B, Czeipek I, Gaggl S, et al. Treatment of severe clozapine-induced neutropenia with granulocyte colony-stimulating factor (G-CSF). *Br J Psychiatry* 1998; 172: 82-84.
- <sup>246</sup> Conus P, Nanzer N, Baumann P. An alternative to interruption of treatment in recurrent clozapine-induced severe neutropenia. *Br J Psychiatry* 2001; 179: 180.
- <sup>247</sup> Kumar V. schriftelijke mededeling, [http://www.fda.gov/ohrms/dockets/ac/03/slides/3959S1\\_02\\_C-Novartis-Kumar.ppt](http://www.fda.gov/ohrms/dockets/ac/03/slides/3959S1_02_C-Novartis-Kumar.ppt).
- <sup>248</sup> Schulte PFJ. The risk of clozapine-associated agranulocytosis and mandatory white blood cell monitoring. *The Annals of Pharmacotherapy, Annals of Pharmacotherapy* 2006;40:683-688. DOI 10.1345/aph.1G396.
- <sup>249</sup> van der Bijl JR, Arends J, Slooff CJ, Schulte PFJ, Erjavec Z. Rechallenge met clozapine na granulocytopenie of agranulocytose; een verantwoorde interventie bij patiënten met een therapieresistente psychose? In:

---

Terugvalpreventie bij schizofrenie en verwante psychosen (C.J. Slooff, F. Withaar, M. van der Gaag, eds.). Kenniscentrum Schizofrenie Nederland. Assen, Den Haag, Groningen, Amersfoort, Utrecht, 2005.

<sup>250</sup> FDA, schriftelijke mededeling, <http://www.fda.gov/cder/foi/label/2005/019758s054lbl.pdf>

<sup>251</sup> Kanaan R, & Kerwin RW. Lithium and clozapine rechallenge: a retrospective case analysis. *J Clin Psychiatry* 2006;67:756-760.

<sup>252</sup> Whiskey E, & Taylor D. Restarting clozapine after neutropenia: evaluating the possibilities and practicalities. *CNS Drugs*. 2007;21(1):25-35.

<sup>253</sup> Conus P, Nanzer N, Baumann P. An alternative to interruption of treatment in recurrent clozapine-induced severe neutropenia. *Br J Psychiatry* 2001;179:180.

Rajagopal G, Graham JG, Haut FF. Prevention of clozapine-induced granulocytopenia/agranulocytosis with granulocyte-colony stimulating factor (G-CSF) in an intellectually disabled patient with schizophrenia. *J Intellect Disabil Res* 2007;51(part1): 82-85.

<sup>254</sup> Sperner-Unterweger B, Czeipek I, Gaggli S, Geissler D, Spiel G, et al. Treatment of severe clozapine-induced neutropenia with granulocyte colony-stimulating factor (G-CSF): remission despite continuous treatment with clozapine. *Br J Psychiatry* 1998;172:82-84.

<sup>255</sup> Hägg S, Rosenius S, Spigset O. Long-term combination with clozapine and filgrastim in patients with clozapine-induced agranulocytosis. *Int Clin Psychopharmacol* 2003;18:173-174.

<sup>256</sup> Ghaznavi S, Nakic M, Rao P, Hu J, Brewer JA, et al. Rechallenging with clozapine following neutropenia: treatment options for refractory schizophrenia. *Am J Psychiatry* 2008;165(7):813-8.

<sup>257</sup> Tigue CC, McKoy M, Evans AM, Trifilio SM, Tallman MS, et al. Granulocyte-colony stimulating factor administration to healthy individuals and persons with chronic neutropenia or cancer: an overview of safety considerations from the Research on Adverse Drug Events and Reports project. *Bone Marrow Transplant* 2007;40:185-192.

<sup>258</sup> A.R. van Gool, M.T. van der Velden, A.W. Oosten, E. van Meerten, W.M.A. Verhoeven, A.J.M. Loonen. Chemotherapie bij gebruik van clozapine: een verhoogde kans op agranulocytose? *Tijdschrift voor Psychiatrie* 50 (2008) 10, 673-678

<sup>259</sup> Le Blaye I, Donatini B. Acute overdose with clozapine: a review of the available clinical experience. *Pharmaceutical Medicine* 1992; 6: 169-178.

<sup>260</sup> Peetoom JJ, Schulte PFJ. Coma door clozapine met benzodiazepinen: de rol van flumazenil. *Tijdschrift voor Psychiatrie* 2004;46:185-190.