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Foreword

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. This leads to unwarranted reservations about prescribing clozapine, to the disadvantage of many patients. Because there is no evidence-based alternative for clozapine, it must be taken orally for a long period. This puts extra demands on the therapeutic relationship and degree of cooperation between the prescribing doctor and the patient.

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.

GUIDELINE FOR THE USE OF CLOZAPINE
by the Netherlands Clozapine Collaboration Group
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I) PRESCRIBING CLOZAPINE

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. Untreatable extrapyramidal side effects of antipsychotics in patients, even with two second-generation agents (including quetiapine).
3. Untreatable tardive dyskinesia and tardive dystonia, in cases where antipsychotics are imperatively indicated.
4. Psychotic disorders which arise during the course of Parkinson's disease when standard treatment has failed.
5. Recurrent suicidal behaviour in treatment-resistant and non-resistant schizophrenia and schizoaffective disorder.
6. 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.
7. Treatment-resistant schizoaffective disorder, bipolar disorder and depressive disorder with psychotic features.
8. Treatment-resistant aggression in schizophrenia or schizoaffective disorder.
9. Treatment-resistant medication abuse or dependency in schizophrenia or schizoaffective disorder.
10. In exceptional cases: treatment-resistant aggression and/or self-mutilation in borderline personality disorder, autism, severe intellectual disability or behavioural disorders in young people.

Clozapine is registered for indications 1, 2, 3 and 4 in the European Union and for indication 5 in the US.

In controlled studies – the majority randomized - clozapine has been shown to be the most effective antipsychotic for the indications referred to. The sole indication for which only case series are available as evidence is indication 10 and depressive disorder with psychotic features. 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 (see section on modes of administration).

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
- Reflux symptoms
- 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, particularly CYP1A2. Other enzymes such as CYP2C19, CYP3A4 and CYP2D6 usually do not play a major clinical role. For interactions see also Flockhart's cytochrome table (<http://medicine.iupui.edu/clinpharm/ddis/>).

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

- Many SSRIs (particularly fluvoxamine and to a lesser extent sertraline and fluoxetine)
- Classic antidepressants (particularly nortriptyline)
- Ciprofloxacin
- Risperidone (to a limited extent)
- Caffeine
- Inflammatory reactions

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

- Enzyme inducers (phenytoin and rifampicin lower the clozapine level by 65-85%; exacerbation of psychosis has been reported; carbamazepine, phenobarbital and omeprazol lower the clozapine level by 20-60%; however, no deterioration of symptoms has been reported)
- Smoking.

Ie) Before commencing treatment

- Psychiatric examination (question the patient explicitly about obsessive-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
- Physical history: past 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, due to benign (ethnic or familial) neutropenia (for example in people of African descent), the baseline WBC count is below $3.5 \times 10^9/l$ or the neutrophil granulocyte count is below $2.0 \times 10^9/l$, then – whether or not after consulting a haematologist – the lower limits may be lowered (see haematology section in the explanatory supplement)
- Before treatment begins and at regular intervals during treatment (Summary of Product Characteristics : at every consultation) the patient must be made aware that extra blood tests are needed if there are any signs of agranulocytosis (see below).
- Optional: EEG and ECG

II) MEDICATION SCHEDULE

- Preferably clozapine should be given once daily, before sleep. Initially the dose of clozapine given must be low and it must be increased gradually because of side effects (specifically hypotension and sedation). The tolerability 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 one 12.5 mg dose, followed by one 25 mg dose on the second day. In very rare cases (but definitely in elderly patients or patients with Parkinson's, see below) 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 may 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 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. Slow titration is usually preferable because then fewer side effects occur than with fast titration; side effects increase the chance of dropout, and in most cases there is no good alternative for clozapine.

If clozapine is interrupted for more than two days, 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 st week		2 nd 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 st week		2 nd 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 first generation 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. However, clozapine responders are also found among patients with clozapine levels significantly lower than 400ng/ml.

Nomograms have been published which predict dose depending on age, gender, weight and smoker/non-smoker (see section on plasma levels and duration of an adequate treatment). Target dose (by the end of initiation) for a level of approximately 350 ng/ml in a 40-year-old:

	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, the patient is able to cooperate and there are sufficient opportunities for consultations with 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 (in the European Union)

- 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 the haematology section 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 $\geq 38^{\circ}\text{C}$, 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 $\geq 38^{\circ}\text{C}$, 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. In the event of inflammatory reactions, the risk of elevated clozapine plasma levels or intoxication must be taken into account (see under ‘Monitoring clozapine plasma levels’).
- 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 weekly 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 $1.5 \times 10^9/\text{l}$: consult supervisor and internist/haematologist about stopping clozapine and about somatic treatment policy (further blood tests). Repeat WBC and granulocyte tests as soon as possible, and also at the end of the afternoon to exclude fluctuations throughout the day. If the test shows normal counts again it is not necessary to stop clozapine treatment. The risk of infection only starts to increase if the neutrophil granulocyte count falls below $1.0 \times 10^9/\text{l}$. Consultation with an internist-haematologist is recommended to decide on future treatment. With a neutrophil granulocyte count of below $0.5 \times 10^9/\text{l}$ the risk of infection is significant and there are nearly always clinical symptoms. 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. The clinical picture of myocarditis varies from asymptomatic to very severe symptoms, ultimately leading 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, soufflé 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.

Table: mandatory and recommended checks for patients on clozapine (guideline)

M = mandatory (summary of clozapine product characteristics); R = recommended (guideline); target symptoms: usually the range of indications (in addition to treatment-resistant psychosis, aggression, agitation, addiction)

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 risks (overdose), but may also result in inadequate treatment (underdose)
- 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 1000 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 clozapine plasma level monitoring are essential
- Inflammatory reactions (for example in the case of infection of the upper airways or urinary tract infections, but also decubitus or post-operative wound healing) 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; plasma levels should also be checked (sometimes immediately) in the event of 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 (in the case of prolonged tachycardia >120/min, consider 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 alert to the possibility of agranulocytosis, myocarditis (or other inflammatory reactions in organs or serous membranes 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 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 eosinophils, C-reactive protein (CRP), creatine kinase-MB (CK-MB) and troponin and/or consider referral to cardiologist. If symptoms are severe, refer to cardiologist immediately.
- Diabetes mellitus: weight loss/ diet/ oral antidiabetics/ insulin. Sometimes the diabetes disappears again once clozapine has been discontinued.

- 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, <i>or</i> 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: mouth gel
!	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.	Extrapyramidal disorders
	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.
	Hypertriglyce- ridemia	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 check eosinophils, troponin + CK-MB and ASAT/ALAT immediately , 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, if (and only if) the patient also has orthostasis, propranolol)). 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.^{1,2} 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.^{3,4} 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.

For first-episode psychosis associated with schizophrenia, clozapine works faster than chlorpromazine,⁵ but after a year clozapine is superior only in its effect on negative symptoms. Because of its side effects and the risks involved, clozapine is not suitable to be a medication of first choice, which is why it is only used if other treatment strategies fail. Patients should be given adequate information in advance about these side effects and risks. Without the patient's consent, as a rule clozapine treatment is unethical and legally impermissible. 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.⁶

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 clearly effective after non-response to other antipsychotics.^{7,8} 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.^{9,10,11,12,13,14}

Before starting clozapine it is useful to check carefully whether in previous treatments with antipsychotics dosage and duration were adequate. If non-compliance is suspected, a trial with depot antipsychotic therapy may also be considered.

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).¹⁵ It was not until clozapine was started (as the third antipsychotic) that a positive effect was observed again (77% responders). These findings were replicated by the researchers in a larger group of patients; the first and second antipsychotic were each trialled for a maximum of three months in three escalating doses.¹⁶ 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 amisulpride, which is not registered in the Netherlands) is a little more effective than other second-generation antipsychotics, olanzapine might be tried before clozapine.¹⁷

Four randomized studies compared olanzapine with clozapine in adults with treatment-resistant schizophrenia.¹⁸ Three of the four found that clozapine was numerically better with regard to positive and total symptom scores. These studies had methodological shortcomings which undermined the evidence of clozapine's superiority: low doses without checking clozapine plasma levels, small samples, inclusion of non-treatment-resistant patients and lack of a third group treated with a conventional antipsychotic (to test for assay sensitivity).

Nevertheless, it is still assumed that for treatment-resistant patients clozapine is superior to olanzapine, particularly since there is no evidence that olanzapine is effective for treatment-resistant schizophrenia.

During the second stage of two major 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.^{19,20} 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.²¹ 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.²² In some cases obsessive-compulsive symptoms improve with clozapine treatment, but in others they get worse or appear for the first time.²³

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).²⁴ The average age of 36 patients studied by Remschmidt et al. (1994) was 18.3.²⁵ A third open study was carried out among 11 children aged between 11 and 13.²⁶ 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.²⁷ A comparison of clozapine and olanzapine showed that clozapine was significantly better with regard to negative symptoms.²⁸ Moreover, the clozapine group – unlike the olanzapine group – also showed a clear improvement with regard to the total and positive symptom scores; however, the difference was not significant, possibly because the patient numbers were too small. 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.²⁹ In a follow-up to this study, 10 of the 19 olanzapine non-responders did respond to clozapine.³⁰ 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 conventional antipsychotic or

perphenazine.^{31,32} 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.³³ To the extent that other second-generation antipsychotics have been studied properly, the results are disappointing:^{34,35} 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. If the patient is unable or unwilling to take clozapine orally or may not do so (stomach pump), IM administration may be considered.

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.^{36,37} 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.^{38,39} 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

Naturalistic studies have shown that 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.^{40, 41, 42, 43,44,45,46,47,48,49,50,51,52,53,54,55,56}

A randomized study showed that clozapine had a more rapid antimanic effect than chlorpromazine.⁵⁷ In another randomized, open study among patients with bipolar I disorder or schizoaffective disorder, bipolar type, who had failed to stabilize at least on lithium plus carbamazepine (and in many cases also on antipsychotics), it emerged that treatment with clozapine as opposed to treatment as usual significantly improved manic and psychotic symptoms. It also showed a trend towards improvement in depressive symptoms.⁵⁸ There was no difference in side effects between the two groups, possibly due to a reduction in the number of psychiatric drugs in the clozapine group. In Denmark a mirror-image study of all patients with a bipolar I disorder who were put on clozapine between 1996 and 2007 showed that after commencement of clozapine there was a significant reduction in the numbers of admissions, admission days, psychiatric drugs and patients who had hospital contacts relating to intentional self-harm or overdose, while somatic medication did not increase.⁵⁹

In the bipolar and schizoaffective group it appears that the improvement is even significantly greater than in the group with schizophrenia.^{60,61} There is also evidence that for patients with bipolar disorder the clozapine dose does not have to be as high as for patients with schizophrenia.^{62, 63} The polarity of the mood dysregulation is an important factor: manic and mixed-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.^{64,65,66,67,68,69} There are also favourable reports of the effect of clozapine on treatment-resistant psychotic depressive disorders.^{70,71,72} 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 for treatment-resistant bipolar disorder, before using clozapine.⁷³

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

In non-randomized, controlled studies clozapine was commonly found to have an anti-aggressive effect.^{74,75,76} The antisuicidal and anti-aggressive effects appear to be *independent* of the improvement of positive, negative, depressive and general psychopathological symptoms.⁷⁷ A controlled study has indicated that clozapine reduces the number of arrests for delinquent behaviour.⁷⁸ 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.⁷⁹ 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.^{80,81,82} 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.^{83,84,85,86,87} 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 and were hospitalized less often. A Dutch study showed that in patients with a non-affective psychosis and cannabis dependency clozapine was associated with less craving than olanzapine or risperidone.⁸⁸

Despite the lack of a positive randomized study, a trial with clozapine seems justifiable for patients with schizophrenia /schizoaffective disorder and alcohol/drug abuse or dependency if other treatments fail, given the severity of the consequences due to co-morbidity.

Naturalistic studies and an RCT found that clozapine treatment is associated with significantly less smoking behaviour compared with other antipsychotics.^{89,90,91,92,93} In the Dutch study referred to above, 19.09% fewer smokers were found among clozapine users than among olanzapine or risperidone users (95% CI 0.46 - 37.72).⁹⁴ However, a second randomized, short-term study found no positive effect in a post hoc analysis.⁹⁵

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.^{96,97,98,99,100,101,102,103,104} 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.¹⁰⁵ 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, severe intellectual disability or behavioural disorders in young people

Sometimes clozapine is used as a last-resort medication for treatment-resistant aggression and/or self-mutilation in borderline personality disorder, autism, severe intellectual disability or behavioural disorders in young people. 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.^{106,107,108,109,110,111,112} For an overview see Schulte & Netherlands Clozapine Collaboration Group (2007).^{113,114} 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. When assessing whether a patient is

eligible for clozapine treatment, the following points must be considered: 1) the small, but not absent threat to the patient's life caused by clozapine, 2) the threat to the patient's life or the prospect of extreme suffering for the patient (or his or her carers) if clozapine treatment is not given, and 3) the relatively low level of proof of the effectiveness of clozapine for these disorders.

11) Special patient populations

Dev & Krupp (1995) describe 102 pregnancies during clozapine treatment, with eight non-elective and 13 elective abortions.¹¹⁵ Fifty-nine deliveries 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.^{116,117} 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.¹¹⁸ 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.^{119,120}

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.¹²¹ 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. Orodispersible clozapine tablets are produced in the US by Azurpharma (www.azurpharma.com) under the name Fazaclo®.

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). Provided they are stored in the dark and at room temperature, the clozapine ampoules can be kept for two years. There is also a company in Syria which produces the ampoules (www.elsaad.com). 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 it.^{122,123,124} Amounts of injection fluid over 4 ml should be divided and administered at two injection sites.¹²⁵ A liquid clozapine preparation can also be made, but it tastes bad.¹²⁶ Clozapine tablets can also be crushed and mixed with pudding. In water the tablets disintegrate within a few minutes. However, the tablets do not dissolve; it remains a suspension. Oral ingestion must take place soon after the mixture is stirred, since it is not known how long the suspension remains stable.

Patients who refuse or do not comply with treatment

Sometimes clozapine is very strongly indicated, but treatment with medication is fraught with problems because of patient-specific characteristics. Patients who are eminently eligible for clozapine treatment are, for example those with

- a) treatment-resistant schizophrenia
- b) recurrent physically aggressive behaviour towards people
- c) who for that reason have to stay in a closed ward continuously
- d) without prospects of improvement.

Patient-specific characteristics of refusal or non-compliance are:

- a) the patient refuses to take the clozapine offered
- b) the patient pretends to take the pills, but does not swallow them or vomits them out
- c) the patient does not realize that clozapine might be a useful medication that is worth trying.

What options are available to the treating doctor at that point?

1. Bribe the patient with a reward
2. Crushed tablets in pudding (CTP)
3. Involuntary treatment.

Re 1. The doctor can try to induce the patient to take the clozapine by promising a reward that is highly valued by the patient and of course also giving the reward once the clozapine has been taken.

Re 2. The 'CTP' option consists of crushing the standard dose of clozapine and mixing it with pudding, yoghurt or apple sauce. The medication is given every day under supervision. The reason for this is that treatment non-compliance is practically impossible provided the patient eats all of the custard or yoghurt.

With patients who are suspected of vomiting up their medication, it may be necessary to supervise them personally for 45 minutes. After this period the clozapine can usually no longer be vomited up. During the 45 minutes the nurse can undertake an activity which the patient enjoys, which may make taking the medication more appealing. The 45-minute period could be used to keep the patient company and hold a conversation, do some household chores, personal grooming, etc.

For the sake of convenience, CTP also includes taking clozapine in liquid form. However, there is a major drawback to this: the taste is too unpleasant for it to be an appealing option.

Re 3. Involuntary treatment is possible because there is an injectable form of clozapine. A major drawback is that the injection has to be given daily. There is no injectable clozapine with sustained release over a few days or weeks, nor can this be expected in the future. Another problem is that injection is painful (see also section on modes of administration).

Faced with the ultimate choice – the doctor holding the syringe in one hand and the tablet in the other – the patient often opts for oral ingestion of the clozapine after all.¹²⁷ Others only opt for oral ingestion after the first injection; the pain of the injection makes these patients change their minds.

A third possibility is that the patient only decides to take clozapine orally after the onset of the antipsychotic effect, for example because of improvement as regards delusions, anxiety or insight into the illness. However, sometimes it is impossible to continue the injections because infiltrates develop at the injection site.

Quite often patients only become treatment-compliant after successful compulsory treatment with clozapine.¹²⁸ Unfortunately this is not the case with everyone, and some patients want to stop taking clozapine again at a later point. Treatment non-compliance can be identified in several ways:

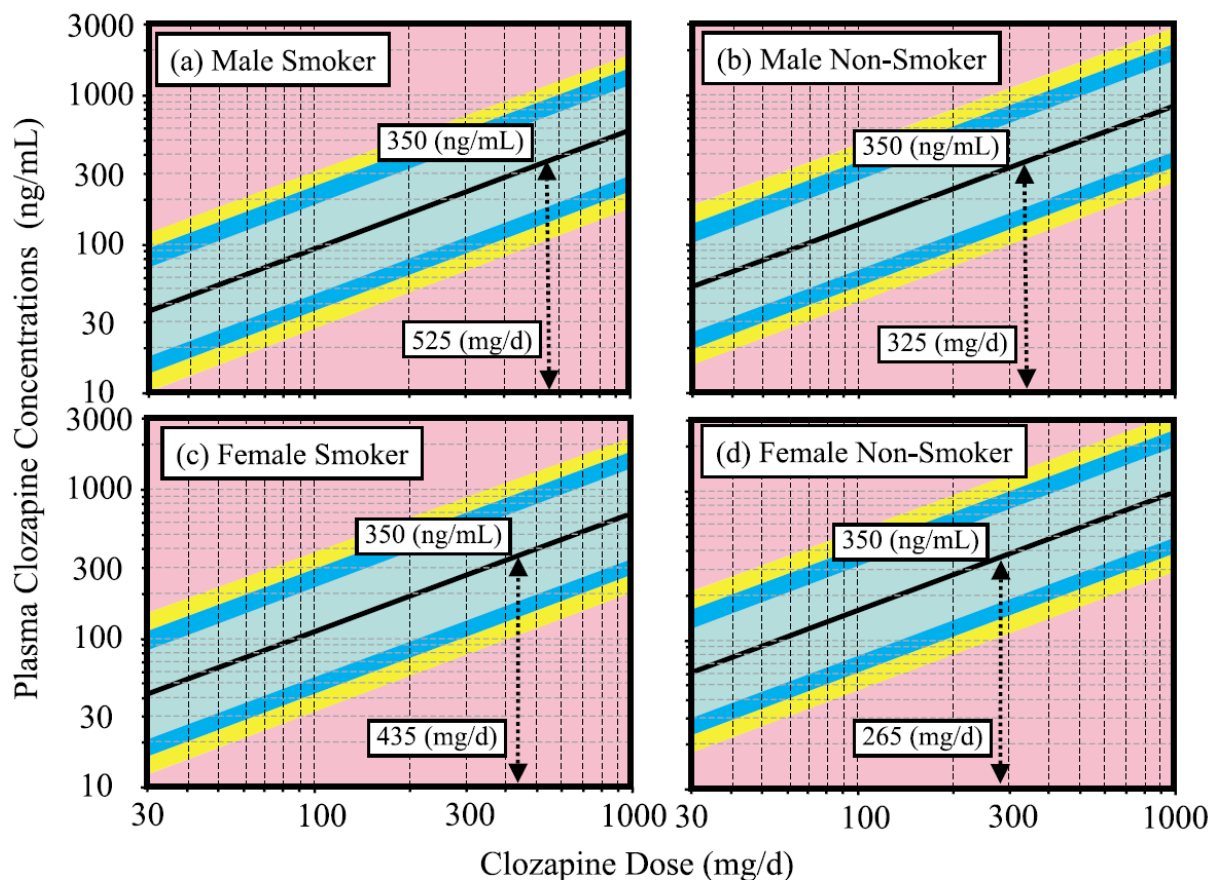
- 12 hours after the agreed ingestion time no clozapine can be found in the serum: the plasma level is below the detection limit
- clozapine levels – 12 hours after ingestion – fluctuate significantly although the dose remains the same
- the levels are not proportionate to the dose; in particular, high levels after a low (initial) dose suggests that the medication has been taken once, just before the blood test, in an attempt to mask treatment non-compliance
- unusual drowsiness when blood tests are taken also suggests sudden ingestion of a higher dose than otherwise
- unusual ratio between the clozapine and norclozapine levels (norclozapine = desmethylclozapine, a metabolite of clozapine). In a ‘normal’ non-smoking user the ratio of clozapine to norclozapine should be around 1.33:1 (within a range of 2:1 to 1:1). If the ratio of clozapine to norclozapine is higher than 3, the result is unreliable (wrong time for blood test, patient has taken wrong dose / tried to mask non-compliance) or CYP1A2 is inhibited (for example by ciprofloxacin, fluvoxamine or fever/infections) or N-demethylation is inhibited. If the ratio < 0.5 (norclozapine is more than twice as high as clozapine), this also suggests poor compliance in the preceding days .

If compulsory treatment is still on the cards, sometimes holding out the prospect of intramuscular administration and if necessary actually carrying out an intramuscular injection – usually just one – makes it possible to continue oral clozapine treatment. NB: before proceeding, always check that the criteria for compulsory treatment are met and report that coercion was used for the treatment.

Plasma levels and duration of an adequate treatment

Metabolization and the importance of monitoring clozapine plasma levels

Plasma levels can be checked three to five 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 patient is instructed to postpone the morning does until after the blood dose. Nomograms to predict the dose depending on age, gender, weight and smoking or non-smoking have been published.¹²⁹



The benefit of monitoring clozapine plasma levels has sometimes been questioned.¹³⁰ 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 the threshold of 350 to 400 µg/l.^{131,132} There is some evidence that with levels above 600 µg/l, 700µg/l or 838µg/l the chance of response decreases again.^{133,134,135} There may be patients who need higher plasma levels than those referred to. 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 µg/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%.¹³⁶ If *serum* levels are determined, it should be taken into account that *plasma* levels would be 7-10% higher.^{137,138} 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.

Norclozapine probably plays no role as regards effectiveness for treatment-resistance. In itself it is not an antipsychotic. However, there is evidence that the higher the ratio of norclozapine to clozapine blood levels, the better the effect is on cognition.^{139,140} This may be related to the fact that norclozapine has an agonistic effect on the M1 receptor, whereas clozapine is an antagonist of this receptor. Extremely low norclozapine levels combined with adequate clozapine levels suggest non-compliance.

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.^{141,142,143} Serum clozapine levels above 750 µg/l increase the chance of epileptic seizures by a factor of five.¹⁴⁴ Checking plasma levels may help to prevent 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 inter-individually by a factor of 45.¹⁴⁵ However, intra-individual variability is small in comparison: 20%.¹⁴⁶ Connections between sex, time frame and plasma levels have also been found:¹⁴⁷ 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).¹⁴⁸

Many side effects of clozapine depend on the doses and plasma levels. Often 1000 µg/l is regarded as an upper limit above which there is a greater chance of side effects, but this limit has not been well researched.^{149,150} However, the occurrence of side effects also relates strongly to the rate of increase in plasma levels. Case histories provide evidence that in some patients if the dose of clozapine is reduced, but a second antipsychotic is added, the effect can be maintained and the side effects reduced.^{151,152,153, 154}

CYP1A2 is the main enzyme involved in breaking down clozapine.^{155,156} Polycyclic aromatic hydrocarbons (PAHs) in cigarette smoke induce CYP1A2, which is why smokers have lower

clozapine levels. Patients who were smokers when they started taking clozapine but then stop smoking must be monitored carefully both as regards their general condition and their clozapine plasma levels, since those levels are likely to rise (see above). For example, in a series of 14 patients the average rise in plasma levels after stopping smoking was 46%, and the inter-individual variation ranged from -9.8% to +244.4%.¹⁵⁷ Evidently it is impossible to predict with any certainty how great the effect of stopping smoking will be on an individual's clozapine levels. This is why it is recommended that the patient and/or the patient's carers should monitor for symptoms caused by increased levels of clozapine (such as sedation or dizziness). A rule of thumb is that if a patient stops smoking and is taking CYP1A2 substrates with a narrow therapeutic margin, it is recommended that the dose be reduced by 10% each day for the first four days after cessation of smoking.¹⁵⁸ There is evidence that in slow metabolizers omeprazol induces CYP1A2, which might reduce the clozapine level.^{159,160} CYP1A2 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.

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.^{161,162,163} (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.^{164,165,166,167} Increased CRP is associated with very high clozapine levels.¹⁶⁸ 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, for example by half, possibly while monitoring plasma levels.

Oral contraceptives can also elevate clozapine levels, probably mainly by inhibiting CYP1A2.¹⁶⁹ Oral contraceptives also inhibit CYP3A4 and 2C19, which may contribute to the rise in plasma levels. If oral contraceptives are stopped, clozapine levels can be expected to fall.

Factors including sex, age and race play a role in the wide inter-individual variability.¹⁷⁰ Substances which have an impact on the cytochrome P450 oxidases (1A2, 3A4 and according to some authors 2D6) will also affect clozapine plasma levels.^{171,172} Carbamazepine, phenytoin, smoking, rifampicin, aminoglutethimide, barbiturates, St John's wort (*hypericum perforatum*) and ritonavir may reduce levels.¹⁷³ Caffeine (coffee, cola, energy drinks), cimetidine, ciprofloxacin, erythromycin, some SSRIs, nefazodone and gaseous anaesthetics can elevate the plasma levels.^{174,175} There is in fact some doubt as to whether erythromycin can really elevate the clozapine level.¹⁷⁶ Research shows that only a dose of over 400mg/day of caffeine affects the plasma level.¹⁷⁷ However, some cases have been reported which

suggest that a dose as low as 150 to 200mg/day can cause a significant increase (by a factor of 2, for example) of the clozapine level.^{178,179}

As regards SSRIs, other studies than that referred to above found no significant increase in plasma clozapine levels in response to citalopram, paroxetine or fluoxetine.^{180,181,182,183,184,185} Nevertheless, on the basis of case reports the American SmPC text warns of possible interaction between clozapine and citalopram.¹⁸⁶ Fluvoxamine certainly has a strong inhibitory effect on clozapine clearance through inhibition of CYP1A2.¹⁸⁷ With a daily dose of 50 mg fluvoxamine the clozapine plasma level becomes 2 or 3 times higher, to a maximum of as much as 5 times.¹⁸⁸ 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.^{189,190,191} 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.¹⁹² 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,¹⁹³ 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).¹⁹⁴ If the desired level is twice as high, for example, the dose will have to be doubled. During the clozapine initiation phase 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.¹⁹⁵ 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

The medication steps leading up to a first treatment with clozapine can be regarded as basic steps in a programme of care for psychotic disorders. There is a chance that none of these steps will be sufficiently effective. A group of patients who need long-term care will probably have psychotic symptoms for a long time and will not go into remission.

For the basic steps there is clear scientific evidence. This is not so much the case for the steps *after* starting clozapine treatment, including increasing the dose of clozapine until a higher blood level has been reached, about which only incidental reports are available.

A considerable number of articles have been published about trials of various substances and combinations to treat schizophrenia. These trials are often small in scale and often there are conflicting findings. In this guideline we have limited ourselves to randomized, controlled studies and meta-analyses, unless these have not been published and other results are in fact relevant. Moreover, we do not mention all the substances which have been trialled, because most of these trials are very limited and the findings do not lead to rational application in practice. Several studies examined drugs as augmentation of clozapine, a reasonable step if clozapine as monotherapy is insufficiently effective. In addition, certain drugs have been trialled as monotherapy for psychotic disorders or as add-ons to other antipsychotics than clozapine. We do make reference to Electroconvulsive Therapy (ECT) as an effective option.

All in all, the following strategies can be considered in the event of clozapine resistance or if clozapine is contraindicated.

- Combination of antipsychotics: 4 meta-analyses have been published, mostly, but not only, about studies of combinations with clozapine.^{196,197,198,199} The results show that combinations are more effective than monotherapy, but the differences, while statistically significantly, are small and of limited relevance to clinical practice. The studies are very heterogeneous and have a high chance of publication bias. The superiority of combinations disappears if studies from China or studies researching clozapine are excluded. Therefore for patients outside China and patients who do not use clozapine there is no proof that the combination of two antipsychotics is more effective than a monotherapy.

There is evidence that longer trials produce more favourable results; the same applies to trials in which the total dose equivalence is not increased when another drug is added. A general recommendation regarding combinations is to choose substances which are pharmacologically different.

- Mood stabilizers: as a monotherapy, lithium is not effective in treating psychotic disorders. Lithium is effective as an augmentation if there is a mood component in the psychiatric picture (schizoaffective).^{200,201,202} A meta-analysis showed that topiramate was beneficial for positive symptoms and also in a more general sense (PANSS total score) as an augmentation of clozapine, but this is controversial because the significance disappears if one particularly favourable study is excluded.²⁰³ The same applies to lamotrigine.^{204,205}

- Electroconvulsive Therapy: ECT is more effective than a placebo or 'sham ECT'. As monotherapy antipsychotics are more effective. There is some evidence that a combination of ECT and antipsychotics is more effective than antipsychotics alone. This treatment is therefore only an option if antipsychotics are not having the desired effect.²⁰⁶ The effectiveness is between 50 and 75%, which can be regarded as high, but the duration of the effect is limited, so that often maintenance treatment with ECT is needed.

ECT combined with clozapine proved to be effective in 90% of cases (9 publications).²⁰⁷ The follow-up period of these studies – most of which were case-based – was short (weeks) in some cases, but in most reasonably long (up to 3 years). In a small-scale trial of their own,

Kho et al. found a success rate of 74% and a recurrence rate of 62%; maintenance treatment proved successful in 60% of the patients whose symptoms had recurred.²⁰⁸ A retrospective study of adolescents found no difference between ECT combined with clozapine or with other antipsychotics, and a response rate of almost 70%.²⁰⁹

- Antidepressants may reduce negative symptoms and they are effective for depressive symptoms.²¹⁰ Mirtazapine as an add-on to first-generation antipsychotics and risperidone proved to be effective against negative symptoms and sometimes against positive symptoms. As an add-on to clozapine, in an initial trial mirtazapine proved to be effective against negative symptoms. A subsequent trial failed to confirm this.^{211,212,213,214} Mirtazapine as an add-on to clozapine therefore cannot be regarded as an effective intervention.

- In one small trial, memantine as an augmentation of clozapine proved to be effective against both positive and negative symptoms.²¹⁵ In a larger trial it was not found to be more effective as an add-on to a variety of new antipsychotics than a placebo.²¹⁶

- There is also evidence that omega-3 fatty acids as an add-on to antipsychotics have a beneficial effect on the PANSS, sometimes on its subscales, and on the BPRS. There have been a few studies of this for sub-groups using clozapine, but no clear conclusion could be drawn.^{217,218,219}

- Oestrogens as an add-on to antipsychotics were also shown to be effective, particularly with women, but they were studied mainly as an add-on to haloperidol or risperidone, not as an add-on to clozapine.^{220,221,222}

- Celecoxib and acetylsalicylic acid proved effective in trials, to varying degrees against positive or negative symptoms or on the PANSS Total Score. These were trials of add-ons to various antipsychotics.^{223,224,225} The addition of other drugs to clozapine specifically was not examined. Moreover, the research is still so limited that treatment with these substances cannot yet be included in treatment guidelines.

Providing care for patients with long-term treatment resistance can be demotivating for both patients and treating doctors and can lead to a certain degree of hopelessness. Doctors must therefore always be careful to provide rational treatment and to have sound reasons for any further medication steps, in order to avoid unnecessary polypharmacy. At the same time, patients must be offered every reasonable chance of improvement, which means that in the course of long-term care there may be good reasons to offer unconventional medication treatments. The way through the maze of insufficiently evidence-based possibilities is sometimes guided by the patient's suffering, and the decisions must be made step by step for each individual by the patient, the patient's representative and the treating doctor. However, it is recommended that such steps should be taken at, or with advice from, a centre with expertise in this treatment, and that the treatment should be evaluated meticulously so that any ineffective medication can be discontinued.

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).²²⁶

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.²²⁷

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 the clozapine initiation phase it is therefore best to avoid changing benzodiazepine doses or to do so cautiously, in small steps. 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.^{228,229,230,231}

Clozapine has a strongly antagonistic effect on muscarinic, α_1 , α_2 , β , histamine (H_1), serotonin and GABA receptors. Many side effects are derived from this action. Table 1 gives an idea of the frequency.²³² 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.^{233,234} 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.²³⁵ 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 traumatic brain injury 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.²³⁶ 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.²³⁷ 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 D₂ receptor.^{238,239} 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.²⁴⁰ The same applies to olanzapine, which also has an anticholinergic effect.²⁴¹

Increased creatine kinase (CK) and myopathy

Like other second-generation antipsychotics, clozapine is associated with increased CK and sometimes myopathy.^{242,243,244,245,246,247,248} 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.²⁴⁹

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.²⁵⁰ 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.^{251, 252} A systematic overview of the pharmacological treatment of clozapine-induced hypersalivation came to the conclusion that there is no clear-cut recommendation.²⁵³ Anticholinergics 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.²⁵⁴ A successful treatment with these patches for a patient on clozapine has been described.²⁵⁵ 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 per drop, a maximum of 2 drops a day).^{256,257,258,259,260,261,262} Another possibility is oral glycopyrrolate 1 mg once or twice daily.^{263,264} Glycopyrrolate has the advantage of having no central effect, because it does not pass the blood-brain barrier. The advantage of all 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, or – even better – the submandibular gland by a doctor with experience with this drug may be considered.²⁶⁵ 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.²⁶⁶ In these

cases further tests (physical, blood and urine tests, and possibly chest x-ray 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 β -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 α -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 ≥ 20 mmHg systolic and/or 10 mmHg diastolic). An initial measure is support stockings, possibly even thigh-high.²⁶⁷ 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 blood pressure monitoring, is a possible next step.²⁶⁸ If fludrocortisone is used, extra monitoring is required: a month after commencement and then every three months, check Creat, Na, K; blood pressure lying and standing twice a year; DEXA scan once every two years. Dihydroergotamine (no longer available in the Netherlands) may also be used to raise the blood pressure.²⁶⁹ Finally, co-treatment by a cardiologist may be considered.

Hypertension also sometimes occurs, particularly during the first six months.²⁷⁰ In a Korean study hypertension was found in 16.6% of patients 8 weeks after starting clozapine.²⁷¹

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.²⁷² 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).²⁷³ This risk is somewhat higher with clozapine than with conventional 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.²⁷⁴ A cross-sectional study did find a longer QT interval associated with clozapine than with some other antipsychotics.²⁷⁵

Myocarditis, pericarditis, cardiomyopathy

These are rare but dangerous side effects. The extent of the risk is controversial.^{276,277,278} It seems that in Australia myocarditis occurs with clozapine use ten times more frequently than elsewhere in the world: 0.7-1.2% of clozapine users in Australia as opposed to 0.15 to 0.6% in other countries. The highest mortality found resulting from myocarditis in clozapine users outside Australia was 0.2%. In spite of this risk of myocarditis (and other risks such as agranulocytosis), clozapine treatment reduces total mortality among patients with treatment-resistant schizophrenia.²⁷⁹ If myocarditis or cardiomyopathy occurs, in 80% of cases it is during the first month of clozapine treatment.²⁸⁰ 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.^{281,282} 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.²⁸³ 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.^{284, 285, 286} 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.²⁸⁷ If possible the combination should be avoided, especially during initiation and particularly in combination with parenteral administration of a benzodiazepine. Pleurisy, sometimes in the form of polyserositis or in combination with peripheral eosinophilia, has been reported as a rare side effect of clozapine.²⁸⁸

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.²⁸⁹ A large-scale study found this complication in 0.3% of all clozapine users, a smaller study in 2.2% (95% CI 95% 1.1 – 4.1).²⁹⁰ 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.²⁹¹ 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.²⁹²

Nausea, reflux symptoms and vomiting

In spite of an expected anti-emetic effect due to the D₂ block, clozapine sometimes leads to these complaints.²⁹³ Metoclopramide, antacids, proton-pump inhibitors or H₂ blockers may provide a solution.²⁹⁴ 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.^{295, 296,297} 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.²⁹⁸

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 associated with a particularly high risk of weight gain.²⁹⁹ Elevation of cortisol concentration, sedation and other mechanisms such as an impact on serotonin and histamine receptors may be responsible for this. In a direct comparison with olanzapine, it was found that after two years clozapine led less frequently to weight gain.³⁰⁰ Another small comparative study found a trend towards more patients with increased cravings for sweet or fatty foods in the olanzapine group (49% vs 23%), and numerically more patients in the olanzapine group with eating binges (17% vs 9%).³⁰¹

Partly because of the weight gain, type 2 diabetes mellitus may occur. Combining clozapine treatment with fluvoxamine 50 mg leads to less weight gain and lower glucose and triglycerides than clozapine monotherapy.³⁰² However, since this evidence comes from only one study among Chinese patients, for the time being it is not recommended that this strategy be used systematically.

Two treatment strategies are helpful for unwanted weight gain. The usual recommendations about a healthy lifestyle are very worthwhile as an intervention for these clozapine-induced problems, namely a) a healthy, varied diet and b) more, longer and more intensive exercise. In addition, a cautious reduction of the dose can be considered, accompanied by careful observation of the patient's psychiatric condition. There is evidence that a lower initial dose, that is 100 mg compared with 300 mg or 600 mg respectively during the first 16 weeks of initiation, causes less weight gain.³⁰³ Another finding is that the lower the baseline weight is, the greater the weight gain will be; in other words, possibly obese patients do not gain a lot more weight due to clozapine. There is also evidence that lower clozapine plasma levels cause less weight gain.³⁰⁴

Dyslipidaemia

The lipid spectrum consists of the following components: LDL-cholesterol (N < 4.5 mmol/l) (known as 'bad' cholesterol), HDL-cholesterol (N > 1.0 mmol/l (men) or 1.3 mmol/l (women) (known as 'good' cholesterol), total cholesterol (N < 6.5 mmol/l; total cholesterol/HDL-ratio: N < 5) and triglycerides (N < 1.7 mmol/l). Clozapine often leads to increased cholesterol and triglycerides, especially in men.^{305,306,307} If diabetes mellitus type 2 occurs or the total cholesterol > 8 mmol/l, treatment with statines is always necessary, regardless of other cardiovascular risk factors. With other dyslipidaemias the decision is made on the basis of the presence of other cardiovascular risk factors (for Europe see the risk table of 10-year mortality due to CVD for patients without CVD, in European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)).³⁰⁸ Since patients with severe psychiatric disorders have a 15 to 20-year shorter life expectancy than the general population, when using the risk table, consider adding 15 to 20 years to these patients' calendar age.

Hyperglycaemia and Diabetes Mellitus (DM)

Initial phase: diabetic ketoacidosis (DKA)

In rare cases, even during the initial phase severe disruption of the glucose metabolism may

occur; if it remains unnoticed, it can lead to potentially lethal diabetic ketoacidosis.³⁰⁹ This is why it is recommended that before starting clozapine treatment and every month during the first 3 months fasting glucose should be checked.

Maintenance phase

Clozapine, like some other second-generation antipsychotics, has been associated with type 2 DM.³¹⁰ A Dutch retrospective cohort study found that 22.3% (95% CI: 15.0-31.8%) of patients developed diabetes mellitus within 13.2 years (median observation period) of starting clozapine.³¹¹ It is uncertain whether this risk is greater than that of a control group using other antipsychotics.

The reference range for glucose depends on a) how the test is done (using venous or capillary blood) and b) whether the individual had fasted (or was supposed to have fasted) or not. Venous blood is most commonly used to check glucose levels. To check the treatment of known DM, often glucose levels of capillary blood are used.

Venous blood glucose levels	Fasting	Non-fasting
Normoglycaemia	< 6.0 mmol/l	< 7.8 mmol/l
Impaired glucose tolerance	6.0-6.9 mmol/l	7.8-10.9 mmol/l
Diabetes mellitus	≥ 7.0 mmol/l	≥ 11.0 mmol/l.

NB: In view of the major impact of the patient's fasting or non-fasting status on the interpretation of the result, it is important to explain carefully to the patient what 'fasting' means.

Because of the high incidence of diabetes, it is recommended that fasting glucose be checked annually during maintenance treatment. A rule of thumb applies to an increased glucose level: one abnormality is not abnormal. If this occurs the patient needs to be asked if he or she really had fasted. Then the test should be repeated and HbA1c, a test that shows the average blood glucose level over the previous 3 months, added. It is recommended that the doctor prescribing the clozapine should assume responsibility not only for WBC monitoring, but also for monitoring weight (BMI and/or waist circumference), blood pressure and metabolic parameters (fasting glucose, fasting cholesterol, HDL-cholesterol and triglycerides), since these can also show clozapine-induced abnormalities. Hyperglycaemia is associated with an increased chance of developing DM. Apart from the importance of other interventions (eating less, eating a healthier diet, more and more intensive exercise), blood glucose levels should then be checked more frequently, that is, at least twice a year. The treatment of DM depends on the local situation. It can be provided by a GP associated with the mental health care facility or possibly by an appropriately qualified nurse practitioner. However, in most cases the patient's GP will treat the DM.

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.³¹² A British study found nocturnal enuresis in 20.7% of clozapine users, 9.6% of olanzapine users, 6.7% of quetiapine users and 6.2% of risperidone users.³¹³ In just under half of patients incontinence improves spontaneously. Limiting fluid intake in the evening, oxybutinin, flavoxate, desmopressin (DDAVP, intranasal or oral; be aware of the possibility of hyponatraemia), imipramine, ephedrine and other medications have been used incidentally to deal with this.^{314,315,316}

Because clozapine can also lead to urine retention, extreme caution should be observed in connection with benign prostatic hyperplasia and other bladder voiding disorders.

Sexual function

Impotence does not occur more frequently with clozapine than with many other antipsychotics. Cases of priapism and retrograde ejaculation have been reported.

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 restricted to the indications referred to above and blood tests are compulsory, with the stipulation that if counts fall below certain threshold levels the blood tests must be performed more frequently or clozapine treatment must be stopped. In the case of benign ethnic neutropenia (for example in people of African descent or Yemenite Jews), the lower limits for WBC and neutrophil granulocytes can be reduced, possibly after consulting a haematologist.³¹⁷ Otherwise these groups of patients have a higher risk of being excluded from further clozapine treatment on the basis of WBC counts that are normal for them. Obviously this is very undesirable, since clozapine is the only registered medication for treatment-resistant schizophrenia and also has other unique indications.

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.³¹⁸ In Great Britain the service responsible for monitoring blood levels uses the following cut off points for patient with benign ethnic neutropenia:³¹⁹ if the white blood cell count is $2.5-3.0 \times 10^9/l$ or the neutrophil count $1.0-1.5 \times 10^9/l$, the WBC testing frequency is increased to twice a week until the counts stabilize or increase. If the white blood cell count $< 2.5 \times 10^9/l$ or the neutrophil count $< 1.0 \times 10^9/l$, clozapine treatment must be stopped.

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. There are also mobile point-of-care devices which can perform WBC tests with 5-part differential (lymphocytes, neutrophils, monocytes, eosinophils and basophils) at the patient's place of residence using only 10 µl of capillary or venous blood (for example from a finger prick) in less than 4 minutes.^{320,321}

In two studies among a total of almost 25,000 patients the risk of agranulocytosis was found to be 0.68%.^{322,323} For the population as a whole the chance of dying from this complication was put at 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.³²⁴ If the WBC and granulocyte counts drop below $2.0 \times 10^9/l$ and $1.0 \times 10^9/l$ respectively, consultation with a haematologist/internist is recommended. The diagnosis of agranulocytosis is definite if the neutrophil count drops below $0.5 \times 10^9/l$ or if an 'empty' bone marrow is found. A bone marrow biopsy is sometimes difficult to perform, but can be helpful if rechallenge is considered at a later point. If the neutrophil count drops below $0.5 \times 10^9/l$, the diagnosis of agranulocytosis is clear even without a biopsy. So long as the neutrophil count remains above $1.0 \times 10^9/l$, there is no increased risk of infection. With neutrophil counts between 0.5 and $1.0 \times 10^9/l$ the risk of infection is slightly elevated. In most cases fever can be treated as it is for regular outpatients. With neutrophil counts below $0.5 \times 10^9/l$ the risk of infection is significantly increased and there are nearly always clinical symptoms. The patient should be given parenteral antibiotics.

There seems to be a correlation between G-CSF levels and granulocyte counts in patients on clozapine.³²⁵ 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. As a rule patients recover from agranulocytosis within 14 to 24 days after clozapine treatment is discontinued.³²⁶ If 75-150 µg of granulocyte colony-stimulating factor (G-CSF) is administered subcutaneously twice a day, recovery can be effected within five to eight days.^{327,328} Two cases have been reported in which clozapine was successfully continued in spite of severe neutropenia when G-CSF was administered.^{329,330}

The risk of agranulocytosis decreases exponentially from the commencement of clozapine onwards.³³¹ 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 18th 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.³³² 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 person-years respectively. The risk of agranulocytosis (usually drug-induced) for the general population is between 2.4 and 15.4 per million person-years.³³³

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 European Medicine Agency or Food And Drug Administration provisions, especially if no agranulocytosis has occurred.³³⁴ 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.³³⁵ 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 must be considered.^{336,337,338,339,340,341,342} There is evidence that lithium elevates G-CSF and strengthens its effect.³⁴³ However, prolonged use of G-CSF may cause acute myeloid leukaemia.³⁴⁴ 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.³⁴⁵ 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

Clozapine, like other antipsychotics, elevates the risk of deep venous thromboembolism.³⁴⁶ It is uncertain whether this risk is higher with clozapine than with other antipsychotics. In a study among hospitalized psychiatric patients, a deep venous thromboembolism was found in 4 of 13,081 clozapine users (3.1 per 10,000), in 17 of 59,637 users of other antipsychotics (2.9 per 10,000) and in 8 of 30,282 patients not using antipsychotics (2.6 per 10,000).³⁴⁷ 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 chance of intoxication symptoms increases with higher blood levels and rapid elevation of blood levels. In patients who have not previously been treated with clozapine, 300-400 mg can lead to a life-threatening coma.³⁴⁸ 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.³⁴⁹ Late reactions sometimes occur up to five days after an overdose. Severe constipation can be treated with neostigmine.

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 in rare cases 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.

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 $1.5\text{-}2.0 \times 10^9/\text{l}$, 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 $1.5\text{-}2.0 \times 10^9/\text{l}$, 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

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