Zaponex Fact Sheet
Clozapine dosing

Important Information

The information provided in this fact sheet is intended for healthcare professionals and should not be used as a patient information leaflet.

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on information from scientific literature and previous successful experience. Each case should, of course, be considered individually.

Clozapine initiation

Titration/dosing schedule for treatment-resistant schizophrenic patients
The Zaponex SPC states on starting clozapine therapy in treatment-resistant schizophrenic patients: "12.5 mg once or twice on the first day, followed by 25 mg once or twice on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 to 100 mg at half-weekly or, preferably, weekly intervals."[1] A dosing schedule card featuring these recommendations can be found on the ZTAS website (www.ztas.co.uk).

A slower titration may sometimes be necessary; for elderly or very young patients, for those started in the community, for patients who are physically compromised or have poorly tolerated other antipsychotics, or in case dose-related side-effects would emerge. If a particular dose is not tolerated by the patient, decrease to one that was previously tolerated; if this leads to resolution of the adverse effect, a slower increase can be tried. [2]

"After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. Treatment should be maintained for at least 6 months. If the daily dose does not exceed 200 mg, once daily administration in the evening may be appropriate.[1]

Titration/dosing schedule in patients with Parkinson's disease psychosis
The Zaponex SPC states on starting clozapine therapy in patients with Parkinson's disease psychosis: "The starting dose must not exceed 12.5 mg/day, taken in the evening. Subsequent dose increases must be by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening.

The mean effective dose is usually between 25 and 37.5 mg/day. In the event that treatment for at least one week with a dose of 50 mg fails to provide a satisfactory therapeutic response, dosage may be cautiously increased by increments of 12.5 mg/week.

The dose of 50 mg/day should only be exceeded in exceptional cases, and the maximum dose of 100 mg/day must never be exceeded. Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment.

When there has been complete remission of psychotic symptoms for at least 2 weeks, an increase in anti-parkinsonian medication is possible if indicated on the basis of motor status. If this approach results in the recurrence of psychotic symptoms, clozapine dosage may be increased by increments of 12.5 mg/week up to a maximum of 100 mg/day, taken in one or two divided doses (see above)." [1]

Patients 60 years and older
Elderly patients are usually more vulnerable to certain clozapine-induced side effects such as sedation and orthostatic hypotension. Pharmacodynamics may be altered as control over reflex actions (such as blood pressure and temperature regulation) is reduced, and receptors may have become more sensitive. In addition, pharmacokinetics become affected at many levels, such as slower absorption, increased volume of distribution, and lower metabolism and clearance of drugs.[2,3]. Keeping patients on the lowest possible dose will reduce these risks.[4,5] Very slow titration may be needed in some patients, and a lower end dose (100-300 mg daily) is often appropriate.[6–9] As per the SmPC, "initiation of treatment is recommended at a particularly low dose (12.5 mg (half of one 25 mg tablet) given once on the first day), with subsequent dose increments restricted to 25 mg/day."[1] These should preferably be lower, especially in the beginning. It may even be considered to start titration at a quarter 25 mg tablet (6.25 mg) in elderly patients, especially if frail, as 12.5 mg may not always be tolerated.[3] For further information and advice on patient management see the fact sheet "Elderly patients".

Switching from a previous antipsychotic
The Zaponex Summary of Product Characteristics (SPC) states: "It is generally recommended that clozapine should not be used in combination with other antipsychotics. When clozapine therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the other antipsychotic should first be discontinued by tapering the dosage downwards.[1] In many cases though, to avoid mental relapse it is common practice to slowly reduce the dose of the previous antipsychotic drug while titrating clozapine up (cross-tapering).[10]

Clozapine therapy is contraindicated in combination with all long-acting depot antipsychotics.[1] When clozapine is initiated in a patient who is switched from a depot antipsychotic, it is usually acceptable that clozapine is started on the day that the next depot injection would be due, but there are a couple of exceptions of depots that have delayed clearance: olanzapine pamoate, paliperidone palmitate, risperidone depot (Risperdal Consta) and aripiprazole depot (Abilify Maintena) all require a longer wash-out period.[10,11] Please contact ZTAS for further information.

Zaponex orodispersible tablet (ODT)
Due to some patients having difficulties with taking clozapine in regular tablet or solution form, Leyden Delta B.V. registered the Zaponex ODT in June 2019. The ODT has been developed for patients with swallowing and compliance issues, and is available in the following strengths: 12.5 mg, 25 mg, 50 mg, 100 mg and 200 mg. Additional Zaponex ODT Product information (SPC and PIL) is available via the Electronic Medicines Compendium: https://www.medicines.org.uk/emc/product/10121/smpc.

The ODT is not meant to be a substitute for the regular tablet or solution; patients who are able to take these formulations are still encouraged to continue doing that. Clozapine is often crushed and dissolved in (cold/tepid) food or liquid for easier intake, but we would recommend to use the standard tablet for this, as the ODT has not been tested for this purpose. However, taking the ODT with some water is allowed as per the SmPC, and reports have officially stated that "in line with the guideline on the investigation of bioequivalence, bioequivalence of the orodispersible tablets taken with water can be assumed."

The ODT is bioequivalent to and has a comparable pharmacokinetic profile as the regular tablet, as well as the same titration requirements. Patients can thus be initiated or re-started on the tablet as usual, or switched from a regular tablet to the ODT without the need for dose adjustments.
The ODT is a brittle tablet and can therefore not be split in half; for splitting tablets we would recommend to use the standard tablets.

Monitoring tolerability during clozapine initiation
In order to assess whether clozapine can be introduced safely, a baseline review of the patient's physical health, clinical parameters, and personal/family history should be done. Measuring of baseline vital signs (see below), metabolic parameters (weight, BMI, waist circumference, fasting glucose and lipids), liver function tests (LFTs) as well as cardiac parameters (troponin, C-reactive protein (CRP) and ECG) is strongly recommended, as this will help interpreting any abnormal findings further on in treatment. In addition, consideration should be given to potential drug interactions with current medications (prescription, over the counter, and herbal products), smoking status (particularly if there is the intention to quit smoking), caffeine intake, and previous tolerability to other psychotropic medication.

To evaluate tolerability to clozapine, intensive monitoring of the vital signs* and for any emerging adverse effects is advised, at least daily during the titration phase and thereafter concurrent with mandatory blood testing. The vital signs include blood pressure (sitting and standing; to identify orthostatic hypotension, which is common during clozapine titration), pulse, temperature, and respiratory rate. Moreover, it is highly recommended to monitor troponin and CRP weekly during the first month, as well as liver and metabolic parameters after the first 1, 3, and 6 months. A plasma level assay may be taken halfway the titration phase and when steady state of the target dose has been reached (at least 5 days after the last dose change). A useful summary of all monitoring recommendations based on the medical and scientific literature is presented in table format in the "Monitoring guidelines for adults", and extensive advice on initiation of clozapine is also given in the "Out-patient initiation guidelines" (both available on the ZTAS website). The latter document, as well as "The Maudsley Prescribing Guidelines in Psychiatry"[2], may also be helpful for initiation in other settings.

Therapeutic range (treatment-resistant schizophrenia)

The Zaponex SPC states: "In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. The total daily dose may be divided unevenly, with the larger portion at bedtime. To obtain full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (not exceeding 100 mg) are permissible up to 900 mg/day." "Treatment should be maintained for at least 6 months."[1]

There are large differences in clozapine dosage between individuals, as serum clozapine levels between patients can vary as much as 45-fold for the same dose.[13,14] Plasma levels are more closely related to clinical efficacy and can therefore be used more accurately for defining therapeutic ranges.

* Monitoring of vital signs. Day 1: baseline; blood pressure also hourly for 6 hrs after dose (not if patient asleep); Day 2: before morning dose and 2 and 6 hrs after the dose; Day 3 through the rest of titration until stable dose has been achieved: before morning dose and 6 hrs after the dose.[12]

The fact sheet "Clozapine metabolism and plasma level monitoring", available on the ZTAS website, provides more information on this topic.

Each dose should be adjusted to the needs of the individual patient, with the objective of achieving maximum clinical benefit with minimal side effects.[2,15]

Estimating a target dose for an individual patient
During titration, it may be difficult to choose a target dose for an individual patient, as clinical response and tolerability vary greatly among patients on a similar dose, and not all patients show immediate clinical benefit. Female gender[16–18], non-smoking status[19–23], high caffeine intake[24–26], Asian ethnicity[14,27,28], high body weight[29] and older age[30,31] are reasons to aim for a lower target dose. As a rough guideline, a published nomogram[29] may be used to estimate the dose necessary to reach 0.35 mg/L, which is the lower threshold of the therapeutic plasma range (0.35-0.6 mg/L[12]). This predictive model takes age, gender, weight, metabolism and smoking status into account.[29] Of course, a target dose should only be used as a reference. Clinical benefit and low side effect burden are the main indicators of an adequate dose. We always advise plasma level monitoring to establish the actual clozapine level (see fact sheet "Clozapine metabolism and plasma level monitoring").

Following the nomogram (shown in Appendix A), based on only gender and smoking status, the target dose (by the end of titration) for a level of approximately 0.35 mg/L in a 40-year-old would be on average:[29]

	Smoker	**Non-smoker**
Male (80 kg)	525 mg	325 mg
Female (70 kg)	435 mg	265 mg

The following adjustments to dose may be anticipated (MR = metabolic ratio; clozapine/norclozapine):

+ 8% for every 0.1 lower MR (reference 1.32)
+ 4% for every 5 years below 40 years
+ 5% for every 10 kg bodyweight below 80 kg

- 8% for every 0.1 higher MR (reference 1.32)
- 4% for every 5 years above 40 years
- 5% for every 10 kg bodyweight above 80 kg

In addition, some (East-)Asians who have slower metabolism may only require half to two-thirds the daily dose of a Caucasian patient.[14,28,32–34] It may be considered to trial half the usual dose and/or monitor the plasma levels during titration to exclude slow metabolisers.[27]

Moreover, dose adjustments should be anticipated in case of co-medication and other substances that can influence clozapine's metabolism. Certain antibiotics, SSRI antidepressants (particularly fluvoxamine), caffeine etc., can increase clozapine plasma levels, meaning that patients can usually do with a lower dose. Infection and inflammation can also have a substantial effect on clozapine's metabolism; temporary dose reductions down to half of the normal dose may be necessary. More details can be found in the fact sheet "Clozapine metabolism and plasma level monitoring".

Dosing and side effects
Like other (antipsychotic) drugs, clozapine can cause side effects. Many of these can be minimised at the beginning of treatment by slowly titrating the dose upwards.[2,15]

Typical side effects associated with fast titration and high plasma levels are orthostatic hypotension, hypersalivation, sedation, tachycardia, nocturnal enuresis, constipation, and, more rarely, seizures, confusion[2,15] and neuroleptic malignant syndrome (NMS).[35] In addition, patients are at increased risk of developing myocarditis when clozapine is rapidly titrated.[36] The risk of developing clozapine-induced neutropenia/agranulocytosis does not seem to be substantially correlated to dose, plasma levels or rate of titration.[37–40]

Some of the side effects seen with Zaponex treatment can be disruptive or distressing for the patient and as a result may affect their compliance with therapy. Therefore, side effects should be managed carefully, with specific advice tailored to the individual patient. For further advice on managing clozapine-induced hypersalivation, tachycardia, nocturnal enuresis, seizures, NMS, etc. see the respective fact sheets on these side effects.

Dosing during therapy

Once daily versus twice daily dosing
The Zaponex SPC mentions: "Cautious titration and a divided dosage schedule are necessary to minimise the risks of hypotension, seizure and sedation. (…) If the daily dose does not exceed 200 mg, once daily administration in the evening may be appropriate."[1]

Reasons for prescribing twice daily instead of once daily are mainly theoretical. To our knowledge, there has never been a comparative study on once daily vs. twice daily dosing that evaluated effectiveness and tolerability. However, as clozapine elimination is relatively fast, theoretical modelling shows considerably smaller fluctuations with twice daily dosing compared to once daily (Figure 1).[41]

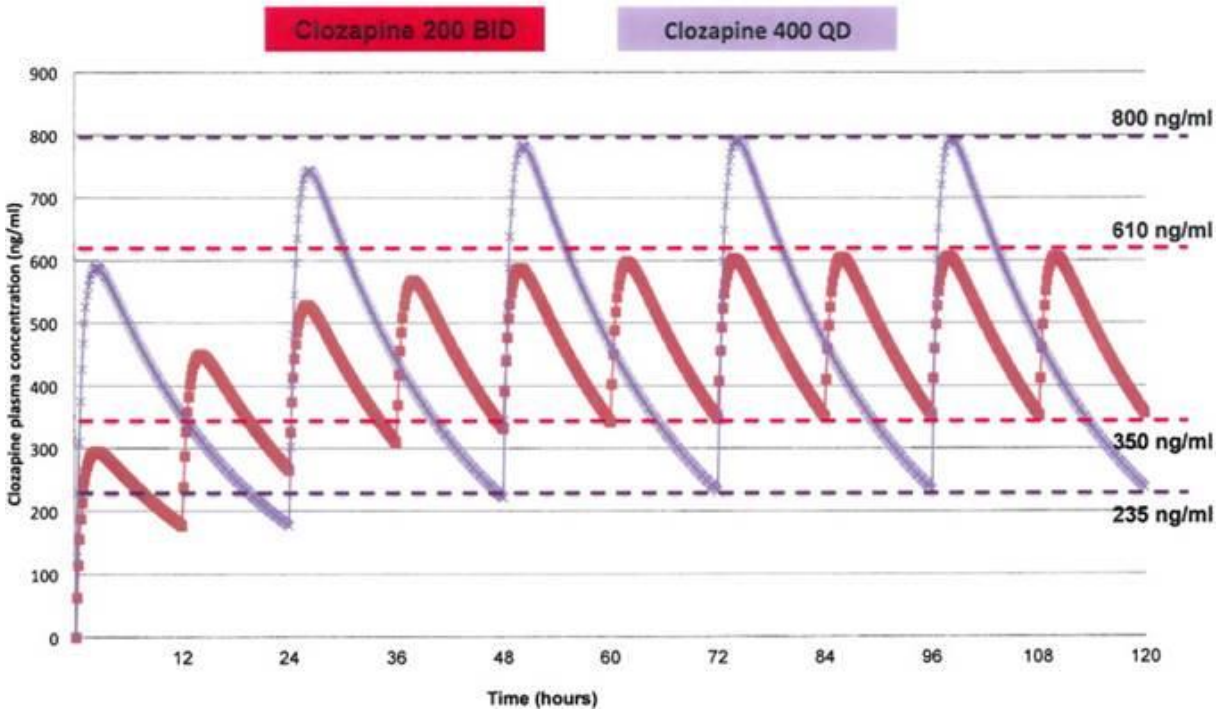


Figure 1: Differences in plasma level curves between once (purple) and twice daily dosing (red).

As visualized in figure 1, twice daily dosing (red line) with identical dosages taken mane (in the morning) and nocte (at night) is preferred over taking the full daily dose at once (purple line), in order for the plasma level to fluctuate less over the course of day. The advantage of this is that clozapine plasma levels are more likely to pulsate within the therapeutic range of 0.35 - 0.6 ng/mL. With once daily dosing, the plasma level peaks are higher and the trough levels are lower. In these circumstances, the peaks can periodically surpass the 0.6 level which increases the risk of side effects (hypotension, sedation, enuresis, hypersalivation, etc), and also frequently dip below the therapeutic threshold of 0.35, which could theoretically cause psychotic breakthrough symptoms. It is hypothesised that large fluctuations in clozapine levels may lead to low striatal dopamine D2-receptor occupancy at the end of the 24 hours dosing interval, possibly below what is necessary for sufficient antipsychotic effects.[41,42]

We are aware that many patients experience side effects from clozapine, and for this reason they take a larger portion or sometimes even the total daily clozapine dose at night. As said before, in these situations, plasma levels show much more variation between the troughs and the peaks, and a plasma assay level itself will also be much higher than the trough level because a larger proportion of the daily dosage is taken at night. Still, this may be preferable over experiencing debilitating side effects during daytime. For more details about how once-daily dosing affects the plasma level assay, please see the fact sheet “Clozapine metabolism and plasma level monitoring”.

A cross-sectional naturalistic study, performed at 2 large psychiatric institutes in North America involving a total of 984 clozapine patients, demonstrated that once daily dosing was common practice: around 75% of the patients received their clozapine dose once daily, even though doses exceeded 200 mg daily in the majority of them. In-patient status was related to a divided dosing regimen with clozapine. This finding may reflect the custom of using a divided dosing regimen during clozapine introduction to minimise the risk of specific side-effects such as hypotension, seizure, and sedation, as recommended in the SPC. Although this study was not positioned to establish differences in efficacy or tolerability, no differences in diagnosis of seizures or positive symptom remission were found among the groups.[43]

Fluvoxamine or cimetidine addition to reduce tablet load

Fluvoxamine is a strong inhibitor of clozapine’s main metabolising enzyme CYP1A2 and can increase plasma clozapine concentrations with a factor 2 to 12.[44–46] Addition of fluvoxamine has been proposed in case of high daily clozapine doses, in order to reduce the number of daily ingested clozapine tablets[44,45,47–49], along with its beneficial effect on negative and obsessive-compulsive symptoms. It has also been suggested that this approach may reduce certain side effects of clozapine[48], notably weight gain and metabolic derangement[50,51], although there is only limited evidence to corroborate this theory.[52] In a therapeutic drug monitoring study, the combined treatment with fluvoxamine and clozapine led to higher median concentration/dose (C/D) ratios in both non-smokers and smokers. In the latter group, the opposing effects of CYP1A2 induction by smoking and inhibition by fluvoxamine on clozapine serum concentrations balanced each other out.[53] Shymko et al. investigated which optimal combination of fluvoxamine and clozapine would be needed to achieve therapeutic clozapine plasma levels of >350 µg/L (with a clozapine: norclozapine (CZ/NCZ) ratio of ≥2). The result demonstrated that a combination of a daily minimum of 50 mg fluvoxamine together with ≤300 mg clozapine produced the optimal combination of therapeutic clozapine levels and high CZ/NCZ ratios in 90% of patients.[54] However, another literature study demonstrated an optimal combination of 300 mg fluvoxamine with 25 mg of clozapine in an adolescent to achieve a stable and tolerable treatment result.[55]

The more moderately potent multi-enzyme inhibitor cimetidine (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4[56,57]) has been suggested to be valuable for patients who are not suitable for treatment with an antidepressant, or when adding a potent CYP1A2 inhibitor would carry too much risk.[2,58] This antihistamine might also be a useful treatment for the gastro-oesophageal reflux sometimes seen with clozapine.[59]
This approach should probably only be considered in order to facilitate clozapine adherence in case of insufficient clozapine levels at high dosage.[45,52] Addition of potent CYP-inhibitors to clozapine therapy should be executed with great care and with strict plasma level monitoring, as clozapine toxicity can be imminent.

Missed doses
If one single dose of Zaponex is omitted or forgotten, the dose can be taken as soon as possible after this has been discovered.[60] However, we strongly advise not to take the forgotten tablets when the next dosing is almost due (approximately 6 hrs or less before the next dose). The patient should be instructed not to make up for a missed dose by doubling the number of tablets for the next dose.[60]

Re-titration after a treatment break
The Zaponex SPC states: "In patients in whom the interval since the last dose of clozapine exceeds 2 days (48 hours), clozapine should be re-titrated, increasing gradually from 12.5 mg (half of one 25 mg tablet) once or twice per day on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, in any patient who has previously experienced respiratory or cardiac arrest with initial dosing, but was then able to be successfully titrated to a therapeutic dose, re-titration should be carried out with extreme caution."[1]

The Maudsley Prescribing Guidelines in Psychiatry has a section devoted to re-starting clozapine after a treatment break: Table 1 "provides general advice on re-starting clozapine after gaps of various lengths. It takes account of the need to regain antipsychotic activity with clozapine while ensuring safety during titration. The key feature is **flexibility**: the dose prescribed for a patient depends upon their ability to tolerate previous doses."[2]

Table 1 Re-starting clozapine[2]

Time since last clozapine dose	Action to re-start
Up to 48 hours	Restart at previous dose – no re-titration required
48 – 72 hours	Begin rapid re-titration as soon as possible On day 1, re-start with half of the previously prescribed total daily dose given in divided doses 12 hours apart. Then give 75% of previous daily dose on day 2 and, if prior doses have been tolerated, the whole of the previous daily dose in the normal dosing schedule on day 3
72 hours – 1 week	Begin re-titration with 12.5 or 25 mg clozapine Try a second dose 12 hours later if the first is well tolerated. Increase to ´normal´ dose according to patient tolerability over at least 3 days
More than 1 week	Re-titrate as if new patient Aim to reach previously prescribed dose within 2-4 weeks. Increase according to tolerability

If a treatment break exceeds 3 days (72 hrs since the last dose administration), ZTAS needs to be notified of the treatment break and the blood monitoring frequency may need to be increased, depending on the current monitoring frequency and the length of the treatment break. More details can be found in the paragraph '*Monitoring during re-titration*' on the next page, as well as in the ZTAS Manual.[61]

Fast dose (re-)titration
Over the last years, several groups have published about fast clozapine titration. In a study with schizophrenic patients who had been previously exposed to clozapine (n=73), and in patients who received the drug for the first time (n=38), clozapine was started with a dose of 25 mg followed by additional doses of 25–50 mg administered as needed every 6 h in the first 24 hours. On subsequent days, the dose was increased by not more than 100 mg each day until satisfactory symptom control. The authors state that none of the patients had seizures, severe hypotension or other major adverse reactions.[62] A controlled study was performed by the same group with bipolar patients (rapid titration n=44; standard titration n=23), with similar results, although specific comparative data on side effects were not provided.[63]
The same rapid titration strategy was successful in a case published by Hammond *et al.*[64] A clozapine-naïve patient with acute psychosis with agitation and aggressive behaviour was started on an initial clozapine dose of 12.5 mg to test tolerability, followed by a 25 mg dose every 6 hours on the first day. Under close supervision and monitoring, they continued to rapidly escalate the total daily dose, while keeping individual dose increments small and repeating that same dose at the following dosing moments of a day.[†] When there was a substantial improvement in the patient´s acute symptoms, a normal titration schedule was resumed to minimise the risk of adverse effects. The patient tolerated the medication well, only experiencing initial sedation and tachycardia, which responded to propranolol started on day 7 of clozapine treatment. The patient continued to do well on clozapine, remaining stable as an outpatient 6 months later.[64]

A controlled study with schizophrenic patients (rapid titration n=25; standard titration n=26) from another group investigated an even faster dosing regimen, but one patient had suspected myocarditis, and hypotension was more common in the rapid titration group.[65] A case of a patient who developed NMS after rapid clozapine titration was reported by Lockhead *et al.*[66]

The issue has been raised whether rapid titration may lead to reduced treatment adherence due to an increased risk of side effects.[66,67] Clozapine is often viewed as the last hope for patients and therefore, it is crucial that factors impacting long-term adherence are examined.[66,67] Although the above studies also investigated fast dose titration in clozapine-naïve patients, they do not justify fast titration in patients taking clozapine for the first time, mainly because group sizes are too small to draw conclusions on the risks of (rare) side effects. Fast titration in clozapine-naïve patients should only be considered as a last resort in severe cases that cannot be managed otherwise.[67]

In two recent studies, the authors concluded that rapid titration could be very beneficial because it might shorten the duration of patient and family suffering associated with uncontrolled psychotic

[†] An initial clozapine dose of 12.5mg to test tolerability with subsequent 25mg doses administered every 6 hours on day 1; 50mg TID (every 8 hours) on day 2; 50mg QID (every 6 hours) on day 3; 62.5mg, 75mg, and 87.5mg with 7 hours interval on day 4; 75mg, 75mg, and 100mg with 7 hours interval on day 5; 125 mg mane and 150 mg nocte on day 6; and 150mg BID on day7. To monitor for adverse effects, they checked vital signs every 4 hours, physically examined the patient before every medication dose (assessing blood pressure, pulse, presence of myoclonus, chest pain, dizziness, and constipation), and obtained daily complete blood counts.

symptoms, reduce the need and risks associated with polypharmacy, and reduce the costs of health care services of prolonged hospitalization. Based on these findings, it can be argued that rapid titration might be specifically helpful in clozapine withdrawal psychosis (occurring within a few days of clozapine cessation), which, if not treated early or aggressively, can lead to prolonged and complicated psychotic relapses.[68,69]

In conclusion, for patients who need rapid re-titration after a treatment-break, the abovementioned reports may indicate that shortening the time interval between small dose increments may be an approach that is better tolerated than using larger dosing steps with more time in between (although this comparison was not made by these studies). A first dose of 12.5 or 25 mg can be seen as a pharmaceutical challenge test[62], and if this is well tolerated, then rapid titration is more likely to be successful. A subsequent strategy can be to administer the same dose at 3-4 dosing moments a day and repeat that after each small dose increment on the following day[64], hereby spreading the total daily dose and probably avoiding high peak plasma levels. We strongly advise against increasing the total dose by more than 100 mg daily.[1] Fast re-titration is more likely to be tolerated after a relatively short treatment break. We advise against fast titration in patients who are clozapine-naïve, who experienced severe side effects during initial clozapine titration, out-patients, elderly, people with Parkinson´s disease, or those vulnerable to seizures (due to medical history or co-medication). Fast titration remains a clinical decision that should take into account the need to quickly regain antipsychotic activity while ensuring safety during titration.[70]

Monitoring during re-titration
Re-titration after a treatment break should be accompanied by daily monitoring of the vital signs, before dose administration and repeated afterwards (timing as recommended on page 3 during initial monitoring, if feasible) until it is evident that the patient tolerates the dose well.
If a treatment break exceeds 3 days (72 hrs since the last dose administration), ZTAS needs to be notified of the treatment break and the blood monitoring frequency may need to be increased, depending on the current monitoring frequency and the length of the treatment break. Table 2 is an excerpt from the ZTAS Manual and lists the monitoring frequencies applicable for re-starting Zaponex treatment after a treatment break.[1]

Table 2 Monitoring frequency after treatment break[61]

Monitoring frequency	Duration treatment break	Monitoring frequency after treatment break
Weekly	≤ 3 days	Weekly, continue 18 weeks period
Weekly	> 3 days but ≤ 1 week	Weekly, continuing the 18 weeks period; patient must have at least 6 weeks of weekly monitoring prior to a decrease of the monitoring frequency to fortnightly
Weekly	> 1 week	Weekly, restart 18 weeks period
Fortnightly	≤ 3 days	Fortnightly, continue
Fortnightly	> 3 days but ≤ 4 weeks	Weekly monitoring for 6 weeks, then continue fortnightly
Fortnightly	> 4 weeks	Weekly, restart 18 weeks period
4-Weekly	≤ 3 days	4-Weekly, continue
4-Weekly	> 3 days but ≤ 4 weeks	Weekly monitoring for 6 weeks, then continue 4-weekly
4-Weekly	> 4 weeks	Weekly, restart 18 weeks period, after 18 weeks, switch to 4-weekly

Discontinuing clozapine

Withdrawal of Zaponex should be done gradually over a period of at least 1–2 weeks[1,2,12] but preferably 4[71], to decrease the risk of withdrawal symptoms and rebound psychosis. A slow withdrawal schedule facilitates homeostatic mechanisms. A general rule of thumb is to taper the dose by 25 mg every other day, but the rate and amount of dose reductions should be adjusted depending on the current daily dose.
ZTAS must be notified when treatment is ceased.[1] Blood monitoring must be continued for another 4 weeks after the last Zaponex dose, using the patient's established frequency of monitoring (*i.e.* if the patient's blood is monitored once a week, four additional tests would be required; two in case of fortnightly monitoring, and one for monthly).

Abrupt withdrawal
If abrupt discontinuation is necessary (*e.g.,* because of neutropenia), the patient should be carefully observed for the recurrence of psychotic symptoms and for withdrawal symptoms, mostly caused by cholinergic rebound.[1]

Clozapine seems to cause more pronounced problems upon withdrawal than other antipsychotics, which may arise from a variety of suggested mechanisms: serotonergic influence, enhanced dopaminergic sensitivity, involvement of D_4 receptors, cholinergic rebound, and possible gamma-aminobutyric acid (GABA)-ergic involvement.[72] The short half-life of clozapine (mean 14.2 hours)[1], resulting in a rapid decline of plasma levels, along with the fact that clozapine is often used for the most unwell patients, may also be contributing factors.[12])

Cholinergic rebound symptoms may vary in severity from mild, self-limiting symptoms of nausea and headache, to more pronounced vomiting, sweating, diarrhoea[1,73] and (rarely) severe extrapyramidal symptoms.[74] Most withdrawal symptoms occur within 24-48 hours of stopping and resolve after 3-7 days.[75] One case report described a male patient who developed rebound cholinergic syndrome and catatonia three days after abrupt discontinuation of as much as 50 mg of clozapine. Other reports described cholinergic rebound following cessation of high doses of clozapine. Evidence that cholinergic rebound is responsible for the majority of withdrawal issues comes from the observation that the use of anticholinergic agents, particularly trihexyphenidyl, can treat most of these problems.[73] As described in the first case report, low dosing of clozapine does not preclude severe manifestations of the phenomenon, so progressive tapering should therefore be adopted in any case whenever possible.[76]

Next to cholinergic rebound syndrome, it has been described that sudden clozapine withdrawal can result in quick and severe mental deterioration in some patients (rapid onset/rebound psychosis).[73,77–81] There have been reports that the severity of psychopathology after clozapine withdrawal exceeded that of what was recorded prior to clozapine initiation.[81,82]
This phenomenon is thought to involve a complex mechanism of (long-term) pharmacodynamic brain adaptations, resulting in receptor super-sensitivity to certain neurotransmitters. Enhanced dopamine and serotonin sensitivity is thought to be the main problem: their receptors, which clozapine blocks with high affinity (especially D_4 and 5-HT_{2A}), are upregulated after abrupt clozapine discontinuation. The ensuing increase in neurotransmitter signalling may lead to worsening severity of psychosis, with the appearance of new and more complex symptoms.[72,82] The incidence of rapid-onset psychosis appears to be around 20%, with a typical presentation of 24-48 hours following abrupt

discontinuation.[82] Those on a higher dose of clozapine appear to be at the highest risk of such withdrawal complications.[80]

Although seizures are more strongly associated with high clozapine plasma levels, they have been incidentally reported as a clozapine withdrawal reaction. Skelly et al. described a case of high dose clozapine withdrawal which led to possible seizure-like activity. The patient was on a clozapine dose of 1400 mg daily (plasma level 0.63 mg/L), but had to discontinue due to severe constipation. Approximately 72 hours later he experienced shaking of head and arms, urinary incontinence but no rigidity. CT scan showed a minor subdural haematoma, possibly from the patient hitting himself in the head.[72]
Although cholinergic rebound may have been involved, serotonin signalling could have been the underlying problem here as well.[72,82] Serotonin syndrome was suggested as a possible cause of seizure-like activity, where abrupt removal of clozapine, a strong 5-HT_{2A}-serotonin receptor antagonist, causes an upregulation and overstimulation of these receptor types. Symptoms of such serotonergic rebound indeed include motor symptoms like hyperreflexia, catatonia, agitation and restlessness.
Another candidate is lack of GABA-ergic activity. Withdrawal of GABA-ergic agents is known to cause seizures, and since clozapine is said to be a GABA-agonist, seizures may be caused in the same way by sudden clozapine discontinuation.[72]

Pharmacological treatment to counter rebound effects (symptomatically or prophylactically) may be appropriate with acute clozapine withdrawal.[83] As stated above, anticholinergics such as trihexylphenidyl may control many of the discontinuation symptoms (e.g. rebound diarrhoea) since cholinergic rebound seems to be responsible for the majority of these symptoms.[73,84] Sappälä *et al.* indeed showed that patients receiving concomitant anticholinergic drugs (such as antiparkinsonians, tricyclic antidepressants, and antipsychotics with anticholinergic properties) were significantly less likely to deteriorate than those not receiving these drugs (21.4% vs 71.4%, p = 0.008).[85]
Cyproheptadine, a non-selective 5-HT_2 receptor antagonists, may also be effective to prevent serotonergic rebound.[72,86–89]
A combination of cyproheptadine and low-dose loxapine has even been formulated to yield a similar pharmacological profile as seen with clozapine and other atypical antipsychotics (high occupancy of 5-HT_2 receptor blockade and relatively low blockade of D_2 receptors).[90] This combination has been used successfully as an alternative to clozapine following an episode of agranulocytosis in a case reported by Aboueid and McCarthy.[89]

Lastly, there have been several case reports of malignant catatonia after abrupt discontinuation of clozapine in patients with schizophrenia or schizoaffective disorder.[91–102] Consequences of catatonia vary, but can include increased mortality, therefore accurate diagnosis and prompt treatment is necessary. Yet, catatonia is often underrecognized by clinicians.[103] In addition to this, the clinical picture may overlap with NMS[104,105], so clinicians should be alerted if NMS-like symptoms arise (fever, altered mental state, autonomic instability, extrapyramidal syndrome, catatonia), and check if clozapine has recently been stopped (possibly due to non-compliance or medication error). Please see the ZTAS website for additional information about NMS during clozapine treatment.

The onset of catatonic symptoms in the published cases started 1.5 to 7 days after abrupt clozapine withdrawal, with the exception of a patient who suffered 3 catatonic episodes, 10–18 days after 3 instances of sudden clozapine withdrawal. Symptoms resolved between 4 days to 3 weeks, aided by various treatments of which re-initiation of clozapine was found to be the most effective, followed by electroconvulsive therapy, and oral/intramuscular lorazepam being effective in only a few cases.[103,106,107]

The mechanism of clozapine withdrawal catatonia is not completely understood, but as with withdrawal seizures, cholinergic rebound and GABA hypoactivity are proposed as possible causes. It has been suggested that clozapine may increase GABA activity by, for instance, blockade of various other receptor types on GABA interneurons, and that abrupt clozapine withdrawal results in GABA hypoactivity, contributing (probably together with multiple other receptor systems) to the development of catatonic symptoms in vulnerable patients.[102,107] Since serotonergic rebound has been suggested as an additional cause of catatonia, and no single treatment of withdrawal catatonia seems to be as effective as re-starting clozapine, this underlines clozapine's complex effects on multiple receptor types. This is also reflected in the wide diversity in symptoms that can appear after abrupt clozapine discontinuation, so this should be an additional incentive for gradual discontinuation of clozapine wherever possible.

Advice for daily practice:

- For most patients with treatment resistant schizophrenia, the standard titration scheme with a split dose is advised
- Patients with Parkinson's disease psychosis should follow another, much slower titration schedule, ending at a substantial lower dose
- Tolerability to clozapine needs to be monitored, especially during (re-)titration
- Carefully search for the lowest dose that exerts optimal efficacy with the least occurrence of side-effects for each patient; most patients respond to plasma levels between 0.35 and 0.6 mg/L
- Lower target dose is usually required in case of:
  - female gender
  - non-smoking
  - high caffeine intake
  - Asian ethnicity
  - high body weight
  - older age
  - co-medication that inhibits clozapine metabolism
- In order to establish adequate (maintenance) dosage, evaluating plasma clozapine levels can be a valuable tool (see fact sheet Clozapine metabolism and plasma level monitoring)
- In some cases, faster re-titration is feasible after dose omissions of <7 days; however, treatment breaks may have (temporary) consequences for blood monitoring frequency
- In case of termination of clozapine, gradual dose reduction is advised to decrease the risk of withdrawal symptoms or rebound psychosis. Blood monitoring should be continued for another 4 weeks after the last dose
- If abrupt discontinuation is necessary, the patient should be carefully monitored and pharmacological treatment for rebound symptoms may be considered.

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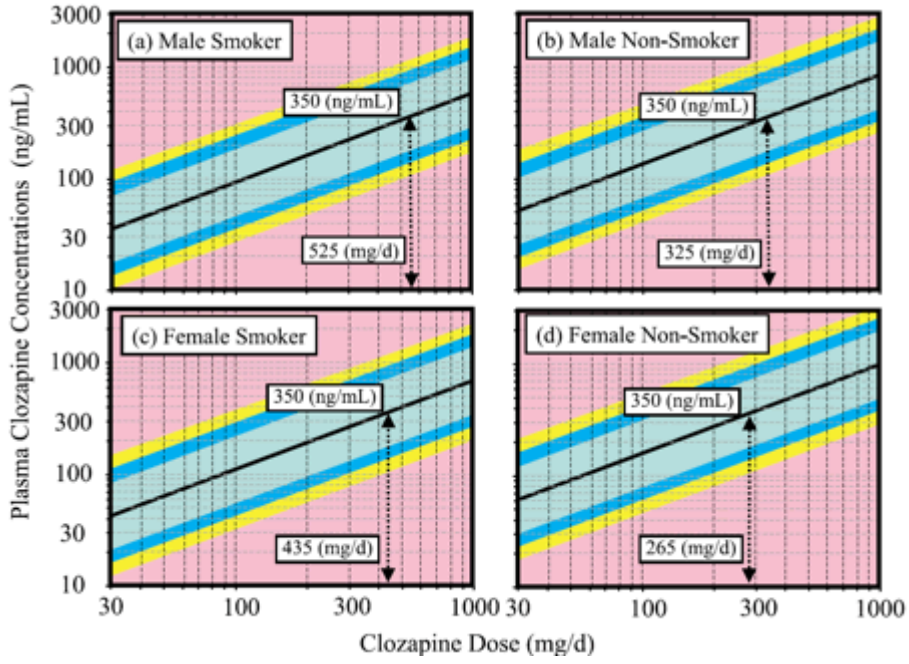
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Appendix A

Nomograms showing the likelihood of an observed plasma clozapine concentration for a given daily dose.[29]



Nomograms showing the likelihood of an observed plasma clozapine trough-concentration for a given daily dose in a 40 year old patient with an average weight of 80 kg (male) or 70 kg (female) and a clozapine/norclozapine MR of 1.32.

(a) Male Smoker; (b) Male Non-Smoker; (c) Female Smoker; (d) Female Non-Smoker.

The broken arrows show the highest likelihood that a given daily dose leads to a plasma clozapine concentration of 350 ng/mL.

NB: from this nomogram no likelihood can be estimated for other associated with a specific clozapine concentrations, i.e., the likelihood estimation works only in the vertical direction and not in the horizontal direction.

Key:
- Green area = 50% of patients;
- Green & Blue areas together = 75% of patients;
- Green, Blue & Yellow areas together = 95% of patients;
- Pink area = less than 5% of patients.