Zaponex Fact Sheet
Agranulocytosis and neutropenia

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.

This fact sheet covers the following subjects (click to jump to the corresponding section):

Summary of Product Characteristics (SPC) statements

Section 4.4 Special warnings and precautions for use
"Clozapine can cause agranulocytosis. The incidence of agranulocytosis and the fatality rate in those developing agranulocytosis have decreased markedly since the institution of white blood cell (WBC) counts and absolute neutrophil count (ANC) monitoring. The following precautionary measures are therefore mandatory and should be carried out in accordance with official recommendations."[1]

Section 1
"In the UK, a white cell count with a differential count must be monitored:

- At least weekly for the first 18 weeks of treatment
- At least at 2-week intervals between weeks 18 and 52
- After 1 year of treatment with stable neutrophil counts, patients may be monitored at least at 4 week intervals
- Monitoring must continue throughout treatment and for at least 4 weeks after discontinuation"[1]

Section 4.4 Special warnings and precautions for use
"Prescribing physicians must comply fully with the required safety measures.

Prior to treatment initiation, physicians must ensure, to the best of their knowledge, that the patient has not previously experienced an adverse haematological reaction to clozapine that necessitated its discontinuation. Prescriptions should not be issued for periods longer than the interval between two blood counts.

Immediate discontinuation of clozapine is mandatory if either the white blood cell (WBC) count is less than 3000/mm^3 (3.0x10^9/L) or the absolute neutrophil count (ANC) is less than 1500/mm^3 (1.5x10^9/L)

at any time during clozapine treatment. Patients in whom clozapine has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to clozapine.

At each consultation, a patient receiving clozapine should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia. Patients and their caregivers must be informed that, in the event of any of these symptoms, they must have a blood cell count performed immediately. Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent these patients from accidentally being rechallenged in the future.

Patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a Consultant Haematology prior to starting clozapine.

Patients who have low WBC counts because of benign ethnic neutropenia should be given special consideration and may only be started on clozapine with the agreement of a Consultant Haematology."[1]

Section 4.3 Contraindications:

- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- History of clozapine-induced agranulocytosis.
- Impaired bone marrow function.
- Clozapine treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged.[1]

Background

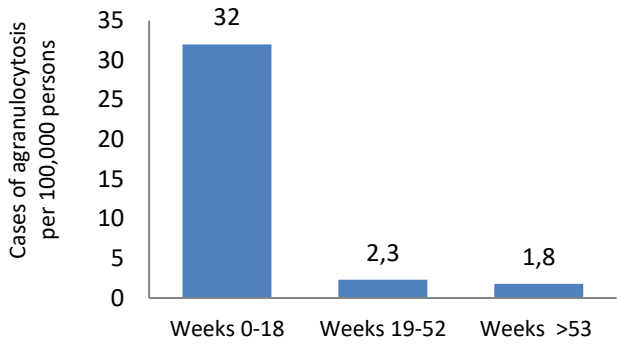
Definitions of agranulocytosis and neutropenia
Definitions of agranulocytosis and neutropenia often vary. In this document, we refer to agranulocytosis as having neutrophil counts below $0.5x10^9$/L. We define neutropenia as neutrophil counts between $0.5x10^9$/L and $1.5x10^9$/L. Technically, this classification is not correct, as all counts under $1.5x10^9$/L qualify as neutropenia,[2] and the term agranulocytosis is somewhat obsolete. But in the context of clozapine, these terms still are often used in the classification as described above,[3–6] probably to be able to distinguish between mild and severe neutropenia.

Incidence and prevalence of clozapine-induced agranulocytosis and neutropenia
The initial evaluation of the monitoring system in the United States has indicated that the cumulative incidence of agranulocytosis was 0.8% at 12 months and 0.9% at 18 months after clozapine initiation.[7] A later study reported an incidence of 0.38% within a 5-year study period.[8,9] These data are roughly comparable to results from the UK, where monitoring following the reintroduction of clozapine in 1990 demonstrated a cumulative incidence of agranulocytosis at 0.8% within a study period of 4.5 years.[4] The cumulative incidence of neutropenia (neutrophil counts between $0.5x10^9$/L and $1.5x10^9$/L) in clozapine-treated patients was reported to be around 2.7%[3] to 2.9%[4] in the UK and Ireland. Several studies estimate the prevalence of neutropenia (ANC < $1.5x10^9$/L; WBC < $3.0x10^9$/L) in clozapine users

to be 2-3%, and agranulocytosis (ANC < 0.5x10^9/L) to be 0.4-0.7%, although there are marked differences between different ethnicities, genders and age groups.[10]
The reported mortality rate of clozapine-induced agranulocytosis varies between 0.01 and 0.03% and the case-fatality is estimated to be 2.2-4.2%.[11] In a large meta-analysis of thirty-six studies with 260.948 clozapine-treated patients, the overall prevalence of agranulocytosis and related death were 0.4% and 0.05%, respectively.[12]

The incidence of both agranulocytosis and neutropenia is highest between week 6 and 18 after starting clozapine treatment. Figure 1 demonstrates that the incidence of agranulocytosis is drastically reduced after 18 weeks of treatment.[13] By the end of the first year of therapy, the risk of agranulocytosis is considered to be comparable to other antipsychotics.[14,15]

Figure 1. Incidence of agranulocytosis per 100,000 persons, categorised by weeks after initiation



Although most cases (85-90%) of clozapine-induced neutropenia occur during the first year,[14] there have been several reports of neutropenia or agranulocytosis later in treatment. In most of these cases, patients either had underlying infections,[16] or they received comedication that may have contributed.[15,17,18] Only incidentally did neutropenia or agranulocytosis develop after multiple years on clozapine monotherapy.[15,17]

Because of the clear association between the incidence of neutropenia and the duration of clozapine treatment, in the United Kingdom and Ireland, weekly full blood count monitoring is mandatory for the first 18 weeks, after which it is done fortnightly until the end of the first year, and every four weeks thereafter.

Interestingly, one meta-analysis of controlled studies comparing the association between clozapine and other antipsychotics and the development of neutropenia does not support the belief that clozapine has a stronger association with neutropenia than other antipsychotic medications.[19] The authors note that one large cross-sectional epidemiological study of healthy participants reported a point prevalence of neutropenia at an absolute neutrophil count threshold of <1.5x10^9/L between 0.38% and 4.5%, and at an absolute neutrophil count threshold of <1.0x10^9/L between 0.08% and 0.57%[20] and that, as a result, it is plausible that repeated haematological monitoring over time might result in the observation of events that are not necessarily aetiologically related to the medication of interest. Furthermore, a retrospective cohort study found no significant difference in incidence rates of neutropenia during clozapine exposure and non-clozapine exposure.[21] Clozapine-associated neutropenia is particularly prone to observation bias compared to other antipsychotics because of mandated haematological monitoring, potentially inflating the reported rates of clozapine-associated

neutropenia.[19] However, further research with larger samples is needed to replicate and support this finding.

Risk factors
Risk factors for neutropenia/agranulocytosis include non-white ethnicity,[22] the presence of a severe medical condition,[22] a low baseline neutrophil count[21,22] and a history of neutropenia.[21] Remarkably, epidemiological data suggest that some risk factors for clozapine-induced neutropenia are different from those of clozapine-induced agranulocytosis. In adults, the risk of agranulocytosis increases with age,[3,4,7,23] while the risk of neutropenia decreases with age.[3,4] Agranulocytosis seems to be more common in women,[7] although this finding could not be significantly confirmed by others.[4,21,22]

Depending on the underlying mechanism (see section *Mechanism*), the risk of neutropenia and agranulocytosis may[24] or may not[4,7,25,26] be dose-/plasma level-related. Most studies from the past decades found no, or only a very weak, correlation between clozapine plasma levels and neutrophil/WBC counts.[26–31] Although a few studies did find a significant correlation, they reported conflicting results, with one study showing a positive correlation[32] and another study showing a negative correlation.[33]
Furthermore, there have been some studies that examined the correlation between neutrophil counts and the plasma levels of norclozapine, the main metabolite of clozapine. Of these studies, some found no correlation[31,33] while others reported a positive correlation.[26,32,34] Smith et al. hypothesize that this positive correlation (that was also found for the norclozapine:clozapine ratio) might reflect reduced clozapine availability for the formation of reactive metabolites, i.e. nitrenium ions, that have the potential to negatively affect neutrophil levels.[34]

It has been suggested that a leukocyte count of 15% or more above the previous value could predict the occurrence of agranulocytosis within the next 75 days, as an increase in the count is sometimes seen before a precipitous fall.[35] A more recent, but much smaller study also reported a spike in neutrophils preceding the onset of neutropenia in three of five cases.[36] In another study, of 4 patients unsuccessfully rechallenged after previous neutropenia, 3 demonstrated a profile of a spike in neutrophils within a fortnight prior to neutropenia onset.[37]

Taylor et al. studied the pattern of neutrophil counts in nine episodes of clozapine-induced, life-threatening agranulocytosis.[38] The aim was to characterise the reaction and to distinguish it from benign and coincidental episodes of neutropenia. The nine episodes exhibited a distinct pattern of continuous and rapid neutrophil count decline to zero or near zero, followed by a prolonged nadir and delayed recovery. The mean time for neutrophils to fall from >2 x 10^9/L to <0.5 x 10^9/L was 8.4 days, and in five out of nine events the reduction occurred within 7 days. When agranulocytosis was established, the neutrophil counts remained below 0.5 x 10^9/L for several days until natural recovery or G-CSF treatment took effect. The observation from other studies that neutrophil counts initially rise before falling[35–37] was only observed in two or three cases. In a different study, the mean time for neutrophil counts to fall from > 2 x 10^9/L to < 0.5 x 10^9/L was 1 week.[23] On recovery, the median time to obtain counts above 0.5 x 10^9/L was 4 days and the time to achieve normal counts was 10 days. Because a substantial fraction of apparent clozapine-related neutropenia might be brief and benign, it is argued that neutrophil count patterns in patients may be a useful, additional indicator for the identification of potentially life-threatening agranulocytosis.[38]

Genetics and ethnicity
The genetic aetiology of clozapine-associated neutropenia is complex and likely involves variants from several genes, with the most evidence existing for *HLA-B*[39–42], *HLA-DQB1*[24,40,43,44], *HLA-DRB1*[45] and

SLCO1B3/*SLCO1B7*.[24,46] Human leukocyte antigen (HLA) genes located in the major histocompatibility complex (MHC) on chromosome 6 encode proteins that are responsible for regulating the immune system and are expected to be involved in clozapine-induced agranulocytosis,[47,48] although the causal variants and biological mechanisms are yet to be resolved.[46] Genetic variants at the liver-specific organic anion transporter polypeptides SLCO1B3 (and/or SLCO1B1) have been suggested to increase the risk of clozapine-associated neutropenia through a pharmacokinetic mechanism.[24]
One of the best-supported hypotheses to explain clozapine's association with agranulocytosis relates to the bioactivation of clozapine, or a stable metabolite, to a chemically reactive nitrenium ion.[49] The propensity for nitrenium ions to cause apoptosis to neutrophils, or be toxic to neutrophil precursors, is dose-dependent, lending support to the hypothesis that clozapine pharmacokinetics and bioavailability may be related to its potential to cause neutropenia.[24,50,51] Finally, *TNF* genes encode tumour necrosis factor (TNF) proteins, which are highly involved in the regulation of immune cells. Several *TNF* microsatellite alleles have been associated with clozapine-induced agranulocytosis; and whereas *TNFd3* (OR = 4.61) and *TNFb4* (OR = 7.69) were associated with increased susceptibility, *TNFb5* (OR = 0.08) showed a protective effect.[45]

Differences in the prevalence of clozapine-induced neutropenia and agranulocytosis may be partly explained by ancestry-based differences in alleles.[42] For example, *HLA-DQB1* 6672G>C is associated with neutropenia (OR = 6.20) and agranulocytosis (OR = 10.49) in individuals of European ancestry.[44] In a genome-wide association study (GWAS), individuals of African ancestry with the Duffy-null genotype were significantly more likely to develop neutropenia and have to stop clozapine treatment (OR = 20.4).[52] Neutropenia, but not agranulocytosis, is indeed more common in Africans and Afro-Caribbeans,[3,4] and these observations may be largely explained by the fact that these ethnic groups are more likely to have low baseline counts due to benign ethnic neutropenia (BEN). This hereditary condition is characterised by mild, chronic neutropenia, causally unrelated to clozapine, and nearly always associated with the Duffy-null genotype.[46] Information about adjusted monitoring of BEN patients is detailed further below.
A low baseline WBC count may also increase the risk of neutropenia in Caucasians.[3] However, in none of these ethnicities, low WBC or ANC counts seem correlated with an increased risk of agranulocytosis.[3,53–56]

Munro *et al*. reported that clozapine-induced agranulocytosis is more than twice as frequent in Asians compared to Caucasians, whereas the incidence of neutropenia is not significantly different.[3] A study among 980 Chinese patients, however, reported a neutropenia rate of 1.3% and an agranulocytosis rate of 0.3%.[57] These numbers are in fact lower than the numbers reported in the UK and the USA.[3,4] In a study among 3746 patients in Japan, neutropenia/leukopenia and agranulocytosis were observed in 4.9% and 1.0% of patients, respectively.[23] These numbers are more in line with the numbers reported elsewhere in the world.[3,4]
In individuals of Chinese ancestry, several loci were associated with clozapine-induced leukopenia and neutropenia and, due to their proximity to coding regions, two T-cell-related genes were implicated: *TRAC* (T cell receptor alpha constant) and *TRAT1* (T cell receptor-associated transmembrane adapter 1).[42] The involvement of these two genes provides further evidence that an immune mechanism may be involved in clozapine-induced neutropenia and agranulocytosis.

Testing for genes that may predispose to clozapine-associated neutropenia would be a useful tool to identify those with the highest risk. To be of clinical use, a predictive pharmacogenetic test should reliably identify individuals for whom the risk of developing neutropenia/agranulocytosis is low enough to make blood monitoring either unnecessary or reduce the frequency with which it is performed.[44] The key factor for a useful predictive variant is high sensitivity, which implies that the

number of people falsely classified as being not at risk is low. According to Girardin et al., a sensitivity of approximately 50% is required for allele testing to be clinically applicable.[58] Konte et al. argue that a risk of 0.13% for developing agranulocytosis is acceptable, because it corresponds with the risk of another antipsychotic for which no blood monitoring system is required.[44] As the risk of clozapine-induced agranulocytosis is currently estimated at 0.9%, the sensitivity of a predictive variant must be at least 85.7%. Unfortunately, according to these criteria, all of the previously-mentioned allelic variants have too low sensitivity to be reliable biomarkers in a clinical setting.[59,60]

Other causes of neutropenia
When neutropenia or agranulocytosis develops in a patient on clozapine, clozapine is often regarded as the causative factor of the condition. However, clinicians should always consider other causes of blood dyscrasias (blood cell count anomalies), as there are many. For instance, active or chronic infection with viruses (*e.g.* EBV, CMV), bacteria, mycobacteria or rickettsia, autoimmune neutropenia, several congenital syndromes, and malnutrition (*e.g.* vitamin B12, folate, copper, protein deficiencies) can all affect WBC and ANC counts.[61,62] Excessive alcohol ingestion can also cause bone marrow suppression, which can result in mildly reduced numbers and function of WBCs, especially neutrophils.[63] There may also be risks from unexpected sources such as the use of illicit cocaine adulterated with levamisole.[64]

Neutropenia risk of concomitant medication
In addition, several medicinal drugs have been implicated to cause neutropenia and/or agranulocytosis. Drugs with a medium potency to cause neutropenia and/or agranulocytosis should be avoided as much as possible in patients on clozapine.[56] For instance, many antipsychotics, antidepressants and antibiotics[65] can cause neutropenia or leukopenia.

The SPC of sodium valproate lists leukopenia and agranulocytosis as undesirable effects (with uncommon and rare frequencies respectively), and only warns for neutropenia in combination with quetiapine and olanzapine.[66] However, the concurrent use of valproate as a (prophylactic) anticonvulsive or mood stabiliser in clozapine patients was notably found to be associated with a substantially increased incidence of neutropenia.[10,67] This was not only confirmed in a case-control study of 136 cases and 136 controls of clozapine-treated patients, but a dose-response effect was also found, with greater associations for higher doses.[67] A retrospective study in 1084 patients calculated an odds ratio of 3.49 for the development of neutropenia in clozapine users with valproate co-administration, although the dose-response effect was not observed.[10] These results, taken in combination with the results from previous case series, suggest that the risk of clozapine-associated neutropenia could be reduced by avoiding concurrent valproate treatment.[67]

Drugs with a high potency to cause neutropenia, agranulocytosis and/or bone marrow depression are contraindicated in patients on clozapine (see Zaponex SPC section ‘Contraindications’, also shown on page 2 of this document). Table 1 includes examples of such medicines, but the list is neither exhaustive nor indisputable. For instance, different routes of administration can affect the risk of certain medication. Please contact Leyden Delta Medical Information at ZTAS (020 7365 5842) when in doubt about the use of co-medication.

If the use of a contraindicated medication cannot be circumvented and the benefits outweigh the potential risks, clozapine treatment can only be continued or commenced off-licence, requiring an off-licence agreement signed by the ZTAS-registered consultant. In an off-licence situation, it is usually advised to develop a treatment plan, preferably together with a relevant specialist doctor. A treatment plan may include altered blood monitoring criteria and/or increased monitoring. In some situations,

the use of granulocyte colony-stimulating factor (G-CSF) may also be anticipated. In the absence of a treatment plan, normal blood monitoring procedures will be employed and clozapine has to be stopped in case of a red result.

Table 1. Drugs with high potency to cause bone marrow suppression/agranulocytosis, which are contraindicated in patients on clozapine[13,68,69]	
Analgesics and non-steroidal anti-inflammatory drugs	Dipyrone, pyrazolone analgesics; phenylbutazone, piroxicam, fentanyl
Immunosuppressants	5-ASA agents (sulfasalazine, mesalazine), azathioprine, ciclosporin, leflunomide, mycophenolic acid, penicillamine, sirolimus, tacrolimus
Antibiotics and anti-infective drugs	Chloramphenicol*, ceftriaxone, sulfonamides (*e.g.* sulfamethoxazole and sulfadiazine); co-trimoxazole, dapsone**, norfloxacin, (benzyl) penicillin G**, rifabutin, voriconazol
Anticonvulsives	Carbamazepine, gabapentin
Antithyroid drugs	Carbimazole[70], methimazole, propylthiouracil
Antivirals	Interferon, HIV medication; emtricitabine, lopinavir/ritonavir, nevirapine, zidovudine, *etc.*
Cardiovascular drugs	Captopril***, enalapril, procainamide, ticlopidine
Chemotherapeutics, monoclonal antibodies and other anti-cancer treatment	Alkylating agents, antimetabolites, anthracyclines, cytotoxic antibiotics, antihormones, plant alkaloids and terpenoids, immunomodulators, methotrexate, nitrosoureas, protein kinase inhibitors, topoisomerase inhibitors, ofatumumab, rituximab, etc.
Depot antipsychotics	All****
Psychotropic drugs	Chlorpromazine, imipramine, pyrithyldione
Other	Adalimumab, belatacept, calcium dobesilate, deferiprone, dexrazoxane, hydroxycarbamide, levamisole (in adulterated cocaine), penicillamine, procainamide, oral isotretinoin
* long-term, high dose ** especially when dapsone has been used with other agents in the prophylaxis of malaria *** especially in patients with renal dysfunction **** although **myelosuppressive potencies vary among depots**, they **should be avoided since they cannot be withdrawn** when blood dyscrasias occur	
This list is not exhaustive. Please contact us at info@ztas.co.uk in case of doubt	

Benign ethnic neutropenia (BEN)

Up to half of the individuals from some ethnic groups (especially those of African descent and some ethnic groups in the Middle East) may have neutrophil counts that would be considered below normal in the Caucasian population, yet appearing quite healthy and with no apparent infections.[71] This condition is called benign ethnic neutropenia (BEN), caused by a genetic variant.[46] Patients with BEN are not at increased risk of developing clozapine-induced agranulocytosis.[3,54,55]

Patients who have low neutrophil counts as a result of BEN should be given special consideration and may be started on clozapine with the agreement of a haematologist. These patients will be monitored according to adjusted blood monitoring criteria.[1] The BEN confirmation form can be found at www.ztas.com (accessible on the ZTAS database for ZTAS-registered healthcare providers). It is

important that ZTAS receives the required documents to register a patient with BEN, so that this will be taken into consideration when analysing blood test results.[72]

More information on BEN can be found in the Zaponex fact sheet 'Benign ethnic neutropenia'.

Mechanism
The mechanism of clozapine-induced neutropenia and agranulocytosis is still not completely clear. As already explained in section *Genetics and ethnicity,* one of the proposed mechanisms is related to the direct toxicity of clozapine metabolites to the bone marrow stromal cells, in particular the immature neutrophil subpopulation.[73] The metabolism of clozapine forms at least three different metabolites with distinct cytotoxicity levels. Clozapine N-oxide and N-desmethylclozapine (norclozapine), for example, are relatively non-toxic products of cytochrome P450 enzyme metabolism, particularly CYP1A2 and CYP3A4.
However, clozapine can also be metabolised to highly toxic nitrenium ions by the action of myeloperoxidase (MPO), a peroxidase enzyme most abundantly expressed in neutrophils.[74] MPO produces hypohalous acids, such as hypochlorous acid (HOCl), for their antimicrobial activity in activated neutrophils. When HOCl interacts with clozapine or a stable metabolite of clozapine, the drug compound is presumably oxidised to a reactive nitrenium cation.[49,75,76] The formation of nitrenium ions can also be catalysed by a combination of horseradish peroxidase and hydrogen peroxide (H_2O_2), as well as a combination of MPO, H_2O_2 and chloride ion.[73]

The toxic effect of clozapine and its reactive metabolites on immune cells may lead to induction of pro-inflammatory cytokines that are also implicated to play a role in the development of eosinophilia, hyperthermia or myocarditis.[77] When MPO is inhibited *in vitro* and in rat models, the clozapine-induced release of certain pro-inflammatory mediators (e.g., IL-1β, CXCL1, and C-reactive protein) and neutrophil mobilisation is markedly reduced.[48] The pivotal role and presence of MPO in this process could therefore explain why clozapine and its metabolites affect almost exclusively granulocytes and their precursors.[78]
Through covalent bond formation and tyrosine kinase activation, reactive nitrenium ions are thought to induce apoptosis of both neutrophils and their precursors in the bone marrow in a dose-dependent manner.[48,50,51,73,79] Because of this dose-dependent effect, it is hypothesised that a pharmacokinetic mechanism may be involved; this is further strengthened by the aforementioned association found between variants in the liver-specific organic anion transporter gene *SLCO1B3* (and/or *SLCO1B7*) and an increased risk of clozapine-induced neutropenia.[24,46] However, negative correlations between clozapine dose or plasma level and decreases in neutrophil count have also been reported.[31,46]

An adaptive immune mechanism has also been hypothesised to play a role in clozapine-induced agranulocytosis, because of specific characteristics that have been observed with the condition, such as the initial timing and the more rapid onset and higher severity upon rechallenge. This hypothesis is further supported by the association of the condition with the aforementioned human leukocyte antigen (HLA) variants HLA-B and HLA-DQB1, involved in lymphocyte-mediated immune responses.[24,40,43,46] The immune mechanism itself has been proposed to be due to the irreversible binding of nitrenium ions to granulocytes, with consequent alterations of granulocyte membranes, leading to a formation of neo-antigens that elicit an immune response.[78]

Although clozapine-induced agranulocytosis is believed to be an idiosyncratic, adaptive immune-mediated reaction, the adaptive response must be preceded by innate immune activation; an early response that does not appear to be idiosyncratic.[48,80] Upon exposure of rats to a single dose of clozapine, an increase in circulating neutrophils and a decrease in lymphocytes was found within hours

of drug administration, along with transient spikes in the proinflammatory mediators IL-1β, CXCL1 and TNF-α in the blood, spleen and bone marrow. These observations are indicative of a rapid, highly coordinated multiorgan immune response.[81] In humans, even small subtherapeutic dosages, less than one-tenth of what corresponds to therapeutic blood levels in a rat model, still induce a detectable inflammatory response.[48]
Recently, Sernoskie et al. found that this clozapine-induced immune response requires the activation of inflammasomes, which are a class of multimeric protein complexes within the innate immune system; blocking inflammasome activation attenuated the proinflammatory response to clozapine *in vivo*. Clozapine induces inflammasome-dependent caspase-1 activation, which leads to IL-1β release *in vitro*: co-treatment of rats with a caspase-1 inhibitor or an IL-1 receptor antagonist also reduced the inflammatory response, suggesting that caspase-1-dependent IL-1β production is fundamental (although alone insufficient) for the induction of the early immune response to clozapine.[81]

Sernoskie et al. integrated their findings in the updated theorised model in Figure 1, of how clozapine bioactivation and clozapine-induced inflammation may lead to idiosyncratic drug-induced agranulocytosis (IDIAG):

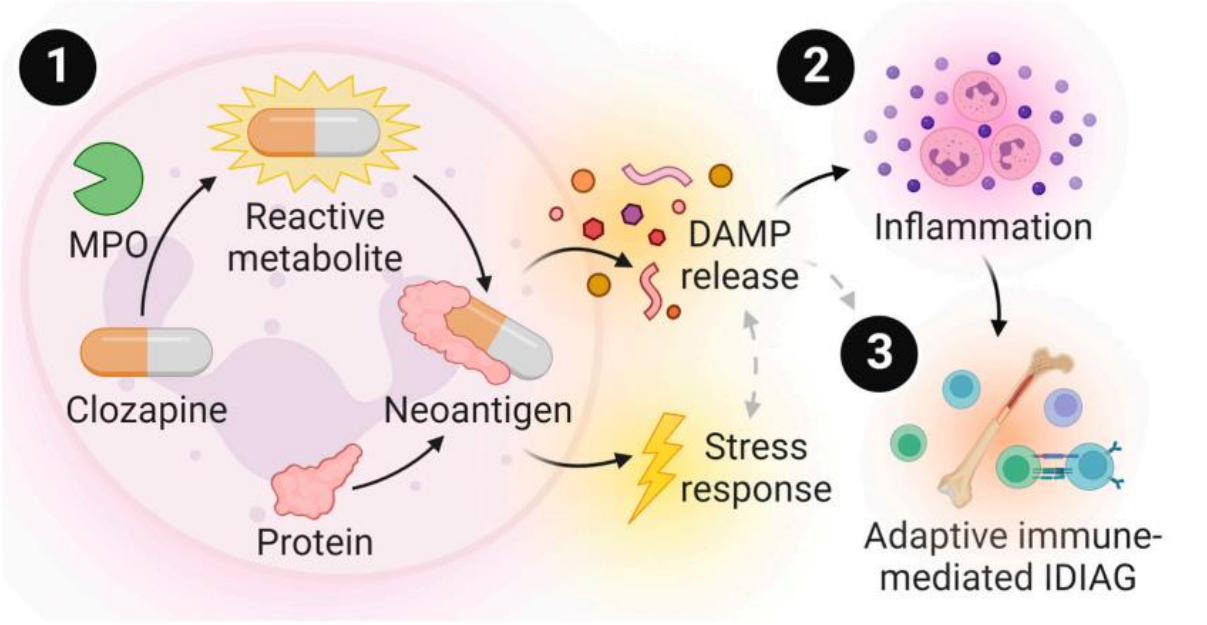


Figure 1: Updated model linking clozapine bioactivation and its induction of inflammation to IDIAG.[48]

1) Clozapine is oxidated by MPO-expressing cells into a reactive nitrenium ion that covalently modifies endogenous proteins, creating neo-antigens; depending on the affected proteins, this causes cellular dysfunction, release of damage-associated molecular patterns (DAMPs) and other proinflammatory mediators, and a self-reinforcing activation of the stress-response;
2) This creates a signalling cascade that chemically attracts (chemotaxis) and activates immune cells such as other neutrophils, leading to inflammasome activation; their signalling propagates a proinflammatory response through the increased release of proinflammatory cytokines (e.g., IL-1β, CXCL1) and acute phase proteins (e.g., α1AGP, CRP), and mobilises peripheral immune cells;
3) Specific haplotypes of HLA proteins on antigen-presenting cells offer the clozapine neo-antigens to certain T-cells; in the presence of appropriate co-stimulatory signals, an adaptive immune response is initiated that, if unresolved through tolerance, leads to targeted destruction of granulocyte precursors and onset of agranulocytosis.[48]

Since inhibition of MPO significantly dampens the clozapine-triggered release of IL-1β, several other inflammatory mediators and neutrophil mobilisation, this is believed to be a vital step in the adaptive immune response and progression to IDIAG.[48] Sodium valproate is believed to add to the neutropenia risk because it may intensify clozapine-associated oxidative stress by reducing glutathione production, which results in further toxicity to neutrophils and cell apoptosis.[67] Valproate in itself may also induce blood dyscrasias by affecting the differentiation of normal multipotent haematopoietic progenitors.[10]

Future studies should examine whether inhibition of inflammasome signalling during the initiation of clozapine treatment reduces the risk of agranulocytosis, as this could potentially enable the safer and more frequent use of clozapine in patients.

In vivo, clozapine-treated patients have been shown to have fewer nuclear lobes in their neutrophils, indicative of more immature neutrophils.[82] In addition, Löffler *et al*. found that numbers of haematopoietic stem and progenitor cells were raised during the initial weeks of clozapine treatment.[83] In an animal model, clozapine decreased neutrophil half-life, which was compensated by an increased rate of release from bone marrow.[84]

These data are in line with the hypothesis that increased bone marrow production compensates for a loss of neutrophils due to direct or indirect toxic effects. This theory may further be substantiated by the common observation of leukocytosis during the first weeks of clozapine therapy, which may be a sign of overcompensation. Subsequently, agranulocytosis may occur in some patients in whom the compensation of the bone marrow is not adequate or becomes exhausted. In addition, it is thought that an additional immune mechanism could also be involved in this.

Neutropenia vs. agranulocytosis
As mentioned previously, the risk factors for developing neutropenia or agranulocytosis do not always overlap, suggesting that agranulocytosis may not merely be a case of aggravated neutropenia. It is hypothesised that in neutropenia, only the peripheral mature neutrophils are affected, while in agranulocytosis, the bone marrow is affected as well.[85–87] In addition, it has been hypothesised that neutropenia is the result from direct toxic effects of clozapine and its metabolites, whereas agranulocytosis may be related to immunological reactions.[77] This would also explain why the success rate of a rechallenge after agranulocytosis is much lower than after neutropenia, which is 20% vs 69.6% respectively in a review by Manu *et al*.[5] In support of an immune (hapten)-related mechanism; low concentrations of clozapine significantly increased lymphocyte proliferation *in vitro* when using blood-derived mononuclear cells from patients with a history of clozapine-induced agranulocytosis. Cells from clozapine-users who did not develop agranulocytosis, and cells from healthy controls, did not show this proliferation.[88]

Factors increasing WBC and neutrophil counts

Circadian rhythm/diurnal variation of white blood cells
Some patients may exhibit a pronounced circadian rhythm in their leukocyte count.[89–91] The counts may show more than twice the amount of neutrophils in the afternoon compared to a morning sample.[91] A study performed in patients on clozapine found an increase in neutrophil counts after a minimum of 2 hours of wakefulness/mobility in 8 out of 10 patients, when compared to sampling immediately upon awakening.[92] This indicates that this phenomenon is not rare: if a patient's blood drawn in the morning displays a low count, it is worthwhile to try sampling at a later time point.

Exercise
Moderate[93] and heavy[94] exercise has been shown to substantially increase peripheral leukocyte counts, including neutrophils numbers.[95]

Lithium
Lithium is known to cause leucocytosis; the odds ratio in clozapine-treated patients is 3.39[10]). Lithium is therefore sometimes used adjunctive to clozapine therapy to raise neutrophil levels. Lithium-induced leucocytosis is not merely a redistribution of neutrophils that are marginated or are in the marrow reserves, but seems to involve a true proliferative response.[96]

There have been several case reports describing successful clozapine continuation or rechallenge after the co-prescription of lithium[97–105]

However, the use of adjunctive lithium to raise neutrophil levels is somewhat controversial.[37,55,106,107] Although lithium may effectively increase the neutrophil counts in cases of mild neutropenia, lithium does not seem to protect against deep clozapine-induced agranulocytosis,[37,87] and it may even mask an impending agranulocytosis.[87] One case of fatal agranulocytosis has been reported with the combined use of clozapine and lithium.[106,108] In addition, it has been suggested that lithium may negatively influence neutrophil function.[37,96]
One study showed increasing risks of leucocytosis with increasing lithium dosages and plasma levels, suggesting a dose-response effect.[10] Obtaining the neutrophil-boosting effects requires dosages of lithium in the range of those used to treat bipolar disorders (>0.4 mmol/L),[98,104] which in itself can be accompanied by adverse effects. When combined with clozapine, there is concern for an increased risk of neuroleptic malignant syndrome, seizures, (neuro)toxicity, renal injury, hypothyroidism, or metabolic side effects,[1,109] so it warrants close monitoring.

Lithium addition should probably only be considered in patients who have a history of recurrent mild amber results and low baseline counts, but not in those with true clozapine-induced neutropenia.[37,107] Particular vigilance is required in patients known to be at increased risk of agranulocytosis, notably older adults and those of Asian origin, and patients who are still within the high-risk period for clozapine-induced agranulocytosis (the first 18 weeks of treatment).[106,107]

If lithium is stopped in a patient on clozapine, it may be considered to monitor the WBC more frequently, as one case report described neutropenia following lithium discontinuation.[110]

Granulocyte colony-stimulating factor (G-CSF)
The chemokine G-CSF is a potent stimulator of the bone marrow, where it induces proliferation, differentiation, and release of neutrophils in the blood stream. It also positively acts on neutrophils that are already in the blood, by enhancing functional activation and preventing apoptosis.[2,111] (Long-term) G-CSF use is associated with musculoskeletal pain, bone pain, splenomegaly, hepatomegaly, and, uncommonly, splenic rupture.[112] Neutrophil dysplasia has been reported with G-CSF use,[113] and there is a theoretical increased risk of myeloid malignancy with long-term exposure.[112]

G-CSF can be used to support haematopoietic cell production, thereby allowing clozapine to be re-introduced or continued. In literature, there have been several reports documenting G-CSF allowing the continuation of clozapine in spite of neutropenia, or G-CSF use during the re-introduction of clozapine after (clozapine-induced) neutropenia.[114–135] In these reports, G-CSF has been used with varying success.

According to two systematic reviews, around 75% of patients (described in 17 articles) rechallenged on clozapine with G-CSF support were able to continue clozapine at a median follow-up of 12 months.[136,137] Also see section 'Off-licence rechallenge after neutropenia or agranulocytosis' for more information.

Like lithium, however, G-CSF use could mask a developing clozapine-induced agranulocytosis and potentially result in a precipitous drop in neutrophils when the bone marrow becomes exhausted. In addition, there are no treatment options remaining if G-CSF is administered prophylactically and agranulocytosis occurs.[87] In general, it is probably best to only consider using G-CSF in case of agranulocytosis or febrile neutropenia, not as a prophylactic measure. But in some off-licence situations, G-CSF may be able to allow clozapine continuation in patients for whom clozapine cannot or should not be stopped. For instance, in patients who receive concurrent chemotherapy, or to prevent recurrent clozapine-induced agranulocytosis in severe schizophrenia unresponsive to any other treatment.[115,121,126] Please call ZTAS Medical Information for further information if needed.

For further information on the use of G-CSF, see the ZTAS document 'G-CSFs During Severe Clozapine Induced Neutropenia', available on the secure area of the ZTAS website.

Management of amber and red results

Amber results
In case of amber results, ZTAS advises twice weekly FBC testing until the counts are back within green ranges. Some patients have (frequent) amber results and/or consequently low neutrophils counts, which may threaten the continuation of clozapine therapy. If such a patient uses concomitant medication known to cause neutropenia or leukopenia, it should be considered to withdraw these drugs, if possible. If the patient is of Afro-Caribbean or Middle Eastern ethnicity, a BEN status may be appropriate (see Zaponex Fact sheet 'Benign Ethnic Neutropenia').

Patients with low baseline counts and generally low WBC
If a patient's baseline WBC counts are too low to start clozapine therapy, we would advise to first repeat the test. The low count may be a temporary situation, possibly resulting from an infection. However, if the counts seem consistently low, it may be considered to investigate the causes (also see paragraph '*Other causes of agranulocytosis'* in this document). Co-medication may also contribute. If the patient has an ethnic background associated with BEN (see Zaponex fact sheet 'Benign Ethnic Neutropenia'), he or she may have this confirmed by a haematologist. If there seems to be no explanation for low WBC counts, and the patient is not suffering from recurrent infections, it may be assumed that the patient has naturally low WBC counts, in line with idiopathic benign neutropenia.[2,138,139] These patients are at increased risk of developing mild neutropenia during clozapine treatment, but not of developing agranulocytosis.[3,55]

A patient with naturally low WBC counts may run into frequent ambers and incidental red results when starting on clozapine. Continuous ambers may lead to a patient's decision to stop clozapine, and a red result will result in -essentially unnecessary- clozapine discontinuation. These patients are sometimes started on medications (e.g. lithium and G-CSF) in order to augment their WBC and ANC values and meet the criteria for use of Zaponex.[37,55] It may be questionable whether exposure to unnecessary, potentially harmful medications is the right strategy.[37,55] In such situations – in which the low neutrophil counts are considered benign, but a BEN diagnosis cannot be made – clinicians

sometimes treat a patient off-licence with adjusted cut-off values similar to the BEN criteria.[37] For more information on this possibility, please contact ZTAS Medical Information.

Red results
If a blood result for an 'On-Treatment' patient is classified as 'red', Zaponex must be stopped immediately. Upon receipt of a red result, ZTAS will immediately contact the consultant to notify him/her about the red result, to discuss the further management of the patient and to initiate the '*Red Alert procedure'*. The clozapine pharmacist and, if applicable, the general practitioner, will be contacted to notify that clozapine treatment must be stopped immediately. The 'Red Alert Guidelines', which include advice on patient management and preventive measures that should be taken, are sent out by fax or email.[140] In summary of these guidelines: daily blood testing and temperature measurement should be performed. The possible contribution of co-medication should be assessed, and discontinuation of suspect drugs should be considered. If the neutrophil count falls below $0.5x10^9$/L, or if a patient with neutrophil count below $1.0x10^9$/L develops a fever, it is strongly advised to contact a haematologist for an appropriate assessment and treatment regimen for the patient. In case of febrile neutropenia, urine and blood cultures should be taken. Broad spectrum antibiotics should be started and the patient's vital signs should be frequently monitored.[140]

The 'Red Alert Guidelines' advise to start antibiotics to mitigate the risk of infection, but some life style adaptations may also be appropriate. Simple soap and- water hygiene and hand-washing may help. Extreme disinfectant measures are probably ineffective, because the source of most infections in neutropenic patients are their own skin and gut flora. Avoidance of very crowded areas or close contact with infected individuals (especially during pandemics like COVID-19 and influenza) may decrease the likelihood of a precautionary admission for febrile neutropenia or for virus-induced mucosal breach to provide entry for a secondary bacterial infection. To avoid invasive fungal infection, neutropenic patients should also avoid highly contaminated sources such as mulch, dusty construction or demolition sites, and bird or animal waste.[62]

Although a neutrophil count below $1.5x10^9$/L warrants the discontinuation of clozapine, it does not necessarily lead to an increased risk of infection. ANC counts between $1.0x10^9$/L and $1.5x10^9$/L do not predispose the patient for developing infections. Patients with ANC counts between $0.5x10^9$/L and $1.0x10^9$/L are only at slightly increased risk of developing infections, but probably only if other arms of the immune system are impaired.[62] Patients with a neutrophil count below $0.5x10^9$/L are at significantly increased risk for major pyogenic infections and life-threatening infections, and when the neutrophil count falls below $0.2x10^9$/L the risks become very serious.[2,61]

Recovery
Typically, mild to moderate clozapine-induced neutropenia (neutrophil count between $0.5x10^9$/L and $1.5x10^9$/L) recovers rapidly (2–8 days) when clozapine is discontinued. A true agranulocytosis with a neutrophil count below $0.5x10^9$/L is more severe and for these patients, it was reported that the median time to obtain a count above $0.5x10^9$/L was 4 days; the time to achieve a normal count was 10 days.[38] Even if clozapine is stopped when the neutrophil count is just below $1.5x10^9$/L, agranulocytosis nonetheless develops in some patients, usually within 2–5 days and generally has a duration of 14–21 days.[141] However, the majority of neutropenia cases do not progress into these agranulocytosis ranges.[38]

Granulocyte colony-stimulating factor (G-CSF)
In clozapine-induced neutropenia, cessation of clozapine and close monitoring of the patient (ANC, blood pressure, pulse and temperature) are pivotal. In certain situations, neutropenia progresses into

prolonged or deep neutropenia, in spite of clozapine discontinuation. There are some reports indicating that the use of G-CSF may shorten the duration of agranulocytosis and hospitalisation, and that it probably reduces the morbidity of the disorder.[142–149] These reports were reviewed by Lally *et al*., who concluded that G-CSF may shorten the duration of agranulocytosis by half.[150] However, the evidence supporting the use of haematological growth factors in clozapine-induced agranulocytosis remains confined to anecdotal reports.[150]

ZTAS would recommend considering the use of G-CSF:

- In patients with neutrophil counts below $0.5x10^9$/L, who are at increased risk of complications and/or would benefit from a shorter disease period (*e.g.* age >65 years; HIV-infection; previous febrile neutropenia period; poor nutritional status and/or co-morbidity/co-medication associated with impaired immune function)
- In cases of protracted neutropenia (>7 days) with neutrophil counts below $0.5x10^9$/L
- When neutrophil counts drop below $1.0x10^9$/L with concurrent fever and/or signs of infection

A Consultant Haematology should be consulted before taking any decision regarding the use of G-CSF.

For further information on the use of G-CSF, see the ZTAS document: 'G-CSFs During Severe Clozapine Induced Neutropenia', available on the secure area of the ZTAS website.

Alternative antipsychotic treatment after clozapine discontinuation

The preferential option is to avoid all antipsychotics after clozapine discontinuation due to a confirmed (second consecutive) red result, as they all may induce blood dyscrasias. Our general advice is not to start another antipsychotic until two "green" results have been obtained on consecutive days. Especially depot antipsychotics are considered contra-indicated, since these can prolong an existing blood dyscrasia, but cannot be quickly withdrawn. However, clozapine withdrawal can result in quick and severe deterioration of the mental status,[151–153] so in clinical practice, schizophrenia treatment is often continued using another antipsychotic agent, one with a lower risk of haematological events.

Olanzapine
Olanzapine has been associated with agranulocytosis, neutropenia and leukopenia in many case reports.[154–164] Importantly, olanzapine has been reported to induce neutropenia in patients with a history of clozapine-induced neutropenia.[161,165–168] Moreover, olanzapine also has been frequently reported to prolong clozapine-induced neutropenia or agranulocytosis.[166,169–174] It has been hypothesised that close structural similarities of olanzapine to clozapine form the basis of this effect.[174]

Quetiapine
Quetiapine also shares structural similarities with clozapine[174] and it can also form reactive metabolites upon bioactivation.[175] In 2 case studies, quetiapine prolonged clozapine-induced neutropenia.[174] In addition, quetiapine has been linked to neutropenia in various case reports.[163,176–184] One case describes quetiapine-induced neutropenia in a patient with a history of clozapine-induced neutropenia.[185] In another case, neutropenia developed when quetiapine was added to clozapine treatment. Clozapine cessation did not resolve the problem.[186]

Risperidone
Risperidone has been implicated to cause leukopenia and neutropenia in numerous case reports[187–197] and has also been reported to cause neutropenia after being added to clozapine treatment.[198] Risperidone rechallenge appeared unsuccessful in a patient with a history of clozapine-induced neutropenia and resulted in recurring neutropenia.[199]

Aripiprazole
Aripiprazole alone is rarely implicated in causing neutropenia or agranulocytosis in case reports. Leukopenia has been described after aripiprazole was started in a patient on phenytoin.[200] Another case of aripiprazole-associated neutropenia was described in a patient who was also on fluoxetine.[201] In another report, aripiprazole was associated with low neutrophil counts in a patient who stopped risperidone due to neutropenia.[191] However, as this patient was African American, the low counts may also be explained by benign ethnic neutropenia.[191] Aripiprazole is also mentioned in the context of drug-induced neutropenia in a couple of other reports, but in these cases, the patients had a history of (drug-related) neutropenia.[163,179,202] A clear causative role for aripiprazole could not be established. There are no cases that describe prolonged clozapine-induced neutropenia with aripiprazole.

Amisulpride
So far, there is only one case report on amisulpride-induced neutropenia[178] and two case reports on amisulpride-induced agranulocytosis[203,204].
Yalcin *et al.* mention a possible role for amisulpride in sustaining neutropenia in a patient who developed neutropenia on quetiapine.[178] But due to the short exposure (2 days), a causative role for amisulpride is unlikely.[64] Although there are few case reports on amisulpride-induced neutropenia, the risk of neutropenia is listed as “uncommon” in the SPC of amisulpride,[205] and therefore the risk is similar as for some other antipsychotics like quetiapine and risperidone (see Table 2).

Haloperidol
We are aware that some trusts advise haloperidol as an alternative to clozapine after neutropenia. The SPC of haloperidol states that leukopenia is an uncommon (>1/1,000, <1/100) side effect of haloperidol. Agranulocytosis, neutropenia and pancytopenia are mentioned at unknown frequencies.[206] In literature, there are no clear case reports of neutropenia or agranulocytosis caused by haloperidol monotherapy, nor is there evidence that haloperidol could prolong clozapine-induced neutropenia or agranulocytosis. One case report describes neutropenia occurring after the addition of haloperidol to clozapine and sodium valproate.[207] Haloperidol also seems to be a relatively safe alternative antipsychotic agent after clozapine-induced neutropenia, although a small risk of leukopenia should be taken into account.

In conclusion, among the commonly used atypical antipsychotics, aripiprazole and amisulpride seem to be the safest substitutes for clozapine following clozapine-induced neutropenia or agranulocytosis. Decent alternatives to aripiprazole include haloperidol and risperidone. An overview of the risks of commonly used antipsychotics is provided in Table 2.

Table 2. Risks of commonly used atypical antipsychotics after clozapine cessation

Antipsychotic	Risk of neutropenia by SPC	(Case) reports of neutropenia associated with antipsychotic	(Case) reports of prolonged clozapine-induced neutropenia
Olanzapine	**Common**: leukopenia and neutropenia[208]	10+	Yes
Quetiapine	**Common**: leukopenia, decreased neutrophil count **Uncommon**: neutropenia **Rare**: agranulocytosis[209]	10+	Yes
Risperidone	**Uncommon**: neutropenia, white blood cell count decreased **Rare**: agranulocytosis[210]	10+	No
Aripiprazole	**Not known**: leukopenia and neutropenia[205]	6+	No
Amisulpride	**Uncommon**: leukopenia and neutropenia **Rare:** agranulocytosis[211]	3+	No
Haloperidol	**Uncommon:** leukopenia **Not known:** neutropenia and agranulocytosis[206]	0	No

Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, < 1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Mitigating the risk of clozapine withdrawal/rebound symptoms

Abrupt discontinuation of clozapine, as is necessary in case of a red result, can result in withdrawal symptoms, with cholinergic rebound as a major underlying mechanism.[212] Symptoms may vary in severity from mild, self-limiting symptoms of nausea and headache, to more pronounced vomiting, sweating, diarrhoea[1,213] and (rarely) severe extrapyramidal symptoms.[214] Most withdrawal symptoms occur within 24-48 hours of stopping and resolve after 3-7 days.[215]

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).[151–153,213,216,217] There have been reports that the severity of psychopathology after clozapine withdrawal exceeded that of what was recorded prior to clozapine initiation.[153,218]

There is no standardised protocol for the management of clozapine withdrawal syndrome following a red result. Pharmacological treatment to counter rebound effects (symptomatically or prophylactically) may be appropriate with acute clozapine withdrawal.[219] Anticholinergics such as trihexyphenidyl may control many of the discontinuation symptoms (e.g. rebound diarrhoea) since cholinergic rebound seems to be responsible for the majority of these symptoms.[213,220] Sappälä *et al.* 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).[221] Cyproheptadine, a

non-selective 5-HT2 receptor antagonists, may also be effective to prevent serotonergic rebound.[222–225] A combination of cyproheptadine and low-dose loxapine has even been formulated to yield a similar pharmacological profile seen with clozapine, as well as other atypical antipsychotics (high occupancy of 5-HT_2 receptor blockade and relatively low blockade of D_2 receptors).[226] This combination has been used successfully as an alternative to clozapine following an episode of agranulocytosis in a case reported by Aboueid and McCarthy.[225]

There have been several case reports of malignant catatonia after abrupt discontinuation of clozapine in patients with schizophrenia or schizoaffective disorder.[227–238] The clinical picture may overlap with neuroleptic malignant syndrome (NMS; see also Zaponex Fact Sheet 'Neuroleptic malignant syndrome' for the differences).[239,240]
The onset of catatonic symptoms in the majority of these cases started 1.5 to 7 days after abrupt 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.[241–243] Restarting clozapine after a clozapine-induced neutropenia is only possible under off-license conditions, and should only be considered when the original blood dyscrasia has resolved, and the benefits of rechallenge outweigh the potential risks.
It has been suggested that clozapine may increase GABA activity by, for instance, blocking 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.[238,243]

The wide diversity in withdrawal symptoms, combined with the fact that no single treatment of withdrawal catatonia seems to be as effective as re-starting clozapine, underline clozapine's complex effects on multiple receptor types. So wherever possible, a gradual discontinuation of clozapine is always preferable over an abrupt one.
For more information on abrupt clozapine withdrawal symptoms, please see the Zaponex fact sheet 'Clozapine dosing'.

Off-licence rechallenge after neutropenia or agranulocytosis

If a patient has had a confirmed (second consecutive) red result, the patient should not be restarted again in the future with any brand of clozapine. The patient's details are entered onto the Central Non Rechallenge Database (CNRD), which is a shared database of all clozapine brands in the UK.[72]

However, many clinicians feel they run out of options in cases where alternative therapy is unsuccessful and the mental status of their patient deteriorates. As a last resort, they consider rechallenge with clozapine. Rechallenge after a confirmed neutropenia/agranulocytosis would be considered off-licence treatment and requires an off-licence agreement, signed by the ZTAS registered consultant.

Before restarting clozapine in a patient who has previously experienced neutropenia/agranulocytosis, an extensive risk-benefit analysis should be made. Patients with a severe condition as the indication for clozapine, with a previously good response to clozapine and with dramatic deteriorations upon clozapine withdrawal are likely to benefit the most from a rechallenge with clozapine.[244] For analysis of the risks, the likeliness that the first neutropenia/agranulocytosis was a true and typical clozapine-

induced dyscrasia should be determined. If the first dyscrasia had the following characteristics, it is thought that the chances of a successful rechallenge are low:

- The drop in neutrophils was inconsistent with previous counts and was not merely a slight drop in a patient with a pattern of repeated low WBC counts[107]
- The neutropenia/agranulocytosis occurred in the first 18 weeks of treatment[107]
- The drop in ANC was severe and fell below $0.5x10^9$ cells/L[107,244]
- The blood dyscrasia was prolonged (>10 days)[87,107]
- There were no alternative explanations apart from clozapine for the first neutropenia/agranulocytosis, such as other medication, an infection or unrecognised BEN status[141,244]

In line with the above, Manu *et al.* reported that the success rate of clozapine rechallenge is indeed much higher after neutropenia (128 out of 203 patients; 63%) than after agranulocytosis (3 out of 17 patients; 18%).[245] In a previous study by the same main author, 46 out of 112 patients who experienced neutropenia (41%) were provided with treatments that have been shown to elevate neutrophil counts, *e.g.* lithium or G-CSF.[5] Interestingly, Béchard *et al.* investigated the clinical outcomes of 4 patients rechallenged after agranulocytosis, and rechallenge was found to be successful in all 4 cases (100%) without the use of G-CSF.[246]
In a study by Dunk *et al.*, 29 out of 46 patients who previously experienced neutropenia (63%) were successfully rechallenged. In most patients who did experience a second blood dyscrasia, the dyscrasia was more severe, lasted longer and reoccurred more quickly on rechallenge (median 5.5 weeks).[141] The use of prophylactic lithium or G-CSF was not reported in this study, but 5 patients received G-CSF as treatment for the second blood dyscrasia.[141] Prokopez *et al.* analysed the clozapine rechallenge of 19 patients after a clozapine-associated leukopenia or neutropenia (counts 0.5-$1.5x10^9$ cells/L). They conclude that 6 of the patients re-exposed to clozapine developed a new haematological adverse reaction, but actually only one patient developed mild neutropenia ($1.2x10^9$ cells/L).[247] Meyer *et al.* studied 19 patients who were rechallenged on clozapine following a previous neutropenia (counts 0.5-$1.5x10^9$ cells/L) in the UK. Four patients (21%) experienced further neutropenia, 2 of which developed agranulocytosis. Compared to successfully rechallenged patients, unsuccessfully rechallenged patients were significantly older, experienced onset of neutropenia sooner, and were more commonly co-prescribed valproate. All of the patients who developed neutropenia on rechallenge were prescribed lithium, re-affirming that lithium does not necessarily protect against clozapine-induced neutropenia.[37]

From these data, it seems that the risk of a fast re-occurring and deep agranulocytosis is mostly limited to patients who developed a true agranulocytosis with counts below $0.5x10^9$ cells/L on first exposure. In patients with a neutropenia upon first exposure, especially when the first neutropenia was outside of the high-risk period, the success rate seems considerably higher and the recurring neutropenia is usually not life-threatening. With these data in mind, rechallenge may be considered for any patient who responded well to clozapine, but developed a neutropenia with counts between 0.5 and $1.5x10^9$ cells/L.

A study by Silva *et al.* suggested that G-CSF may increase the success rate of clozapine (re-)initiation in patients with a history of neutropenia, either caused by clozapine or not.[134] Out of 14 (re)challenges with clozapine, 10 were successful (71%) and in 6 of the successful cases, G-CSF was co-prescribed; either on regular base (n=4) or only when neutropenia developed (n=2). In multiple other case reports, the use of G-CSF was found to be successful in preventing or managing episodes of neutropenia during clozapine treatment.[129–133]
In contrast, results from another study by Béchard *et al.* were less promising: only 3 out of 8 patients

(38%) were successfully rechallenged with clozapine, while all patients had received GCS-F.[135] Silva e*t al.* recommend that the use of G-CSF (or lithium) can be considered if neutrophil counts cannot be sustained at adequate levels, *and* if the risk of a dyscrasia and managing a rebound psychosis is considered too great.[244]

In case of rechallenge, it is probably wise to avoid co-medication that can also cause neutropenia and leukopenia, specifically sodium valproate.[37,67,244] If an anticonvulsant is indispensable, lamotrigine or topiramate may be safer alternatives,[248,249] but note that these agents need several weeks of titration. Interestingly, Yang et al. noted that patients who were co-prescribed valproate and lithium on top of clozapine did not have higher rates of either neutropenia nor leucocytosis when compared to patients using only one of them with clozapine. In fact, none of these patients developed neutropenia, although the authors point out that follow-up studies with a larger sample size are necessary to replicate this finding.[10] See also Zaponex fact sheet 'Seizures' for more information.

Only a handful of publications have provided information on the clozapine dosing schedule during re-challenge; three-quarters had adopted a more cautious rate than the normal recommended titration schedule. Nevertheless, there is currently not enough evidence to draw conclusions about the effect of titration rate on rechallenge success.[244,250]
It is advised to increase the monitoring frequency in the first 12 weeks of rechallenge to twice-weekly.[37] This is because recurring neutropenia is often faster and deeper than the first episode.[141] Thereafter, weekly monitoring can be continued from week 12 to 18. During weeks 18 to 52 the patient can be monitored fortnightly, as normal, after which, either fortnightly or 4-weekly monitoring would be proposed during year 2 according to further evaluation of risk.

Revision of clozapine monitoring guidelines
Recently, there have been some calls to action in literature concerning the revision of clozapine monitoring guidelines in the UK.[251–253] As mentioned in paragraph '*Incidence and prevalence of clozapine-induced agranulocytosis and neutropenia'*, one of the reasons for this is that some studies have questioned the association between clozapine use and neutropenia.[19,21] A meta-analysis of 20 studies found that the risks of both neutropenia and agranulocytosis were not significantly increased in patients exposed to clozapine compared to patients using other antipsychotics.[19] Furthermore, clozapine discontinuation for haematological reasons is often done unnecessarily, since the appearance of neutropenia during clozapine treatment is often related to other causes, such as undiagnosed BEN, vitamin deficiencies and viral infections; the prevalence of clozapine-induced neutropenia may therefore be an overestimation.[254] Another reason is that premature discontinuation of clozapine has significant adverse effects on patient outcomes. One study measured clinical outcomes with the Clinical Global Impression – Severity scale (CGI-S), and found that median scores increased from 4 ("moderately ill") before stopping clozapine to 5 ("markedly ill") 3 months after clozapine discontinuation.[251]

The final argument in favour of revision of monitoring guidelines is based on clinical and scientific knowledge of immunology. Neutrophil counts above $1.0x10^9$/L are generally sufficient to provide phagocytic defence, while counts below $0.5x10^9$/L increase the risk of infections in most patients and counts below $0.2x10^9$/L increase the risk of severe, life-threatening infections.[62] For (some of) these reasons, the US Food and Drug Administration (FDA) updated its clozapine regulations in 2015, by lowering the neutrophil cut-off value for clozapine cessation from $<1.5x10^9$/L to $<1.0x10^9$/L and removing the requirement for monitoring WBC counts.[251] A modelling study found that only 15% of the patients currently on the UK CNRD would meet the equivalent criteria for clozapine discontinuation under the FDA guidelines.[252] Success rates of clozapine rechallenge were also found to

be high (up to 81%) for patients on the CNRD. Therefore, implementation of the revised FDA monitoring criteria in the UK could possibly improve clozapine utilisation and the mental health of patients without putting them at major risks associated with haematological adverse events.

Lastly, Ingimarsson *et al.* argued that continued blood monitoring beyond the first 6 months of clozapine treatment may unnecessarily discourage a proportion of patients with TRS from receiving the treatment.[253] Because the risk of dying from agranulocytosis during clozapine treatment is relatively low, they believe that patients' values regarding long-term blood monitoring should be discussed openly with patients and their relatives. According to the authors, the outcome of these discussions should support a shared decision-making process to jointly decide the frequency and length of monitoring in each individual case of TRS.[253] However, further research on the consequences of these measures is likely required before their implementation can be considered.

Advice for daily practice:

- Concomitant administration of drugs with a high potency to cause agranulocytosis or neutropenia is contraindicated with clozapine use.
- The risk of agranulocytosis is increased in Asians, Ashkenazi Jews and older patients.
- Other factors affecting neutrophil counts include age, level of exercise, certain HLA gene polymorphisms, and diurnal effects; clozapine dosage is only weakly associated with neutrophil counts.
- The peak incidence of agranulocytosis and neutropenia is between weeks 6 and 18 after clozapine initiation.
- In case of agranulocytosis or neutropenia, exclude other causes such as infections, vitamin deficiency, concomitant medication, BEN or low baseline WBC counts.
- Strategies to artificially induce WBC and neutrophil counts (lithium, G-CSF) should be treated with caution, since they could mask agranulocytosis and may not protect from it.
- G-CSF should probably only be considered as a last resort intervention to treat agranulocytosis, not as prophylactic measure.
- In some cases, patients with low baseline WBC counts can be treated under BEN criteria in an off-license capacity.
- Aripiprazole, amisulpride and risperidone are among the safest alternative atypical antipsychotic drugs after clozapine discontinuation due to agranulocytosis or neutropenia. Among typical antipsychotics, haloperidol seems to be a relatively safe substitute.
- Be aware of the possibility of withdrawal or rebound effects following abrupt clozapine discontinuation.
- Re-challenge after a confirmed neutropenia/agranulocytosis is off-licence and should only be considered after an extensive risk-benefit analysis.

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