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## The use of G-CSF in clozapine rechallenge: a systematic review

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Running title:

Granulocyte colony-stimulating factor in clozapine rechallenge

### Purpose/Background

Clozapine is associated with haematological abnormalities, with neutropenia and agranulocytosis of most concern. Granulocyte colony-stimulating factor (G-CSF) has been used to support clozapine rechallenge following neutropenia with the aim of maintaining the neutrophil count. This study aims to explore the practice, use, safety and efficacy of G-CSF in this context.

### Methods/Procedures

We conducted a systematic review to identify all studies investigating or describing G-CSF as a prophylaxis to enable continued clozapine treatment during a rechallenge.

### Findings/Results

We identified 32 reports of patients who received G-CSF either regularly ( $n = 23$ ), or as required ( $n = 9$ ) to support clozapine rechallenge following an episode of neutropenia necessitating discontinuation of clozapine. Seventy-five percent ( $n=24$ ) of published cases remained on clozapine with the use of continual prophylactic G-CSF or after single G-CSF administrations ( $N=8$ ). Seventy percent ( $n=16$ ) of cases in receipt of continual prophylactic G-CSF were successfully maintained on clozapine. However, one of the three episodes of rechallenge in those with a history of severe agranulocytosis ( $ANC < 0.1 \times 10^9/L$ ) had a recurrence of agranulocytosis at week 9.

## Implications/Conclusions

Our findings suggest that G-CSF can sometimes be safely used to support the maintenance of normal neutrophil counts and clozapine use post-neutropenia. Publication bias is an important limitation, however. Also, few reports clearly documented the presence or absence of an independent non-clozapine cause of the index neutropenia, which may have increased success rates. Furthermore, adverse events were not systematically recorded. Prospective studies are needed to determine safety, as if agranulocytosis occurs on clozapine while supported by G-CSF, there is no obvious alternate rescue therapy to promote granulopoiesis. From the available data, it is not possible to recommend this course of action for someone with a true clozapine agranulocytosis.

**Keywords:** granulocyte colony stimulating factors; G-CSF; GM-CSF; treatment-resistant; schizophrenia; clozapine; neutropenia; agranulocytosis

## Introduction

Clozapine remains the gold standard treatment for treatment resistant schizophrenia (TRS) (1) and is associated with clinical response in 50-60% of patients with TRS.(2, 3) However, its use is restricted due to the risk of potentially life-threatening adverse events. (4) In particular, clozapine use has a risk of agranulocytosis, and in many countries, the emergence of neutropenia, which can presage agranulocytosis, means that clozapine must be discontinued.(5)

Rechallenge after clozapine associated neutropenia carries significant risk, especially following an episode of clozapine-associated agranulocytosis (CIA) where recurrence of neutropenia on rechallenge occurs in 80% of patients in contrast to 30% following a neutropenia-related discontinuation.(6) In an earlier retrospective case review, 38% of cases overall developed a neutropenia on clozapine rechallenge, and for 85% of these the neutropenia occurred more quickly and was more severe than during the first clozapine trial.

Further, for 65% of the cases who developed a further neutropenia on rechallenge, the neutropenia was longer in duration than the original episode.(7)

More recently, granulocyte colony-stimulating factors (G-CSFs), and granulocyte-macrophage colony-stimulating factors (GM-CSFs) have been used in specialist centres with the aim of preventing the recurrence of neutropenia on clozapine rechallenge. However, this practice has not been systematically reviewed.

Therefore, in this study we aimed to synthesize the published data in order review the efficacy of G-CSF during clozapine rechallenge for the prevention of recurrence of clozapine associated neutropenia or agranulocytosis, to describe the dose and frequency of G-CSF used and to review adverse incidents.

## **Methods**

We performed a systematic literature search to identify all published interventional and observational studies, case series and case reports, up until September 2016, investigating or describing G-CSF use as either a regular or as required (PRN) administrations, to support resumption and maintenance of clozapine treatment. We defined as required administrations as those cases in which there was an a priori plan to administer G-CSF in single or consecutive G-CSF doses in the event of a neutropenic episode (as defined by the individual case reports), and where G-CSF was discontinued upon neutrophil recovery. Regular administration was defined as regular use of prophylactic G-CSF; even where the neutrophil count was normal or high. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standard.  
(8)

## ***Inclusion criteria***

Studies were included in this systematic review if they included: (1) participants (no age restriction) who had a clozapine rechallenge after an episode of clozapine associated

neutropenia; (2) participants who were treated prophylactically with regular G-CSF, or with as required administrations of G-CSF to enable continued clozapine use during rechallenge; and (3) were published in a peer reviewed journal.

### ***Exclusion criteria***

Studies were excluded if: (1) G-CSF was used to support the maintenance of clozapine treatment during chemotherapy; (2) if there were insufficient laboratory data to permit inclusion of the report and; (3) if G-CSF was not used to support continued clozapine use during a rechallenge.

### ***Information sources and searches***

Two independent reviewers (JL & SM) performed a search using Medline, EMBASE, Scopus and Google Scholar from inception until September 2016. The following search terms were used, both alone and in combinations: Granulocyte Colony-Stimulating Factor OR granulocyte-macrophage colony-stimulating OR GCSF OR G-CSF OR GMCSF OR GM-CSF AND clozapine OR clozaril OR denzapine OR zaponex OR leponex.

In addition, the reference lists of the retrieved articles and relevant review articles were examined for cross-references.

### ***Study selection and exclusion***

All abstracts meeting the criteria were obtained, and independently examined by the authors (JL and SM). The two appraisers applied the eligibility criteria to produce a list of full text articles. There was no search for unpublished works, although authors were contacted for clarification where necessary. Reference lists were searched for additional studies.

### ***Primary outcome***

The primary outcome was the continuation of clozapine with white cell and neutrophil count within the allowed ranges for continued clozapine prescription (i.e. WCC >  $3.0 \times 10^9/L$  and ANC >  $1.5 \times 10^9/L$ ) at the end of follow-up which was designated a “successful outcome”.

### ***Secondary outcomes***

Since filgrastim was the most common drug used, we examined for associations between the dose of filgrastim used and successful outcome. We recorded successful rechallenge rates for patients where the index episode was agranulocytosis (absolute neutrophil count <  $0.5 \times 10^9$ ) or severe agranulocytosis (ANC <  $0.1 \times 10^9/L$ ).

### ***Data extraction***

Articles included were critically reviewed by two authors (JL and SM) and the following information extracted where possible: age, gender, ethnicity, number of previous clozapine (re-)challenges, severity of initial neutropenia, G-CSF/GM-CSF dose, frequency and type of G-CSF used; duration of follow up; and successful outcome, defined as continuation of clozapine treatment or not, alternative causes of neutropenia, and adverse events. We did not undertake a risk of bias assessment of the included studies, as the majority were case series/reports.

## **Results**

### **Study selection, study and participant characteristics**

The study selection process, search results, and reasons for exclusion are given in figure 1.

The initial search yielded 766 references. After checking titles and abstracts, 57 full texts were screened. This selection process refined the number of relevant articles to 16 clinical reports, 6 of which were case series and 10 of which were case reports. No interventional or observational studies were identified.

We identified 32 episodes (in 31 patients) of clozapine re-challenge, where G-CSF was prescribed as maintenance prophylaxis (n=23)(9-19) or as single, as required administrations (n=9)(13, 14, 20-24) to enable continued clozapine treatment.

### **Cause of the initial neutropenic episode**

An appraisal of potential alternative explanations for the initial neutropenia (eg viral illness, other drug treatments) was documented in 6 of the 32 cases. Four cases provided sufficient information to indicate that a 'true' clozapine induced neutropenia or agranulocytosis had occurred,(9, 17, 20, 24) while in two cases, other contributing factors were identified. (15, 19)

### **G-CSF in clozapine rechallenge**

Twenty-three of the 32 cases identified received continual G-CSF as prophylaxis (mean duration of G-CSF use: 8.8 (4.2) months, median =11 months; range 1.25-13 months), while 9 received G-CSF as required (there were no cases reported where as required G-CSF was prescribed but not administered).

Seventy five percent (n=24) of cases remained on clozapine with the support of regular G-CSF (n=16) or after as-required G-CSF administrations (n=8) (mean duration of follow up: 11.8 (5.4) months, median =12 months; range 5-30 months), while in 25% (n=8) of cases clozapine was discontinued due to recurrence of neutropenia, or an attenuated response to G-CSF suggesting an enhanced risk of agranulocytosis leading to a clinician initiated discontinuation. Seventy percent (n=16) of cases in receipt of continual prophylactic G-CSF were successfully maintained on clozapine for an average follow up period of 10.9 (SD = 2.5) months (median 12 months; range 5-13 months). The mean time to clozapine discontinuation in those treated with continual G-CSF (n=6) was 3.0 (2.8) months (range =0.25-7 months). Seventy-eight percent were treated with filgrastim (n=25), 16% were treated with lenograstim (n=5) while the other two cases were treated with G-CSF (formulation not specified) and GM-CSF. Fifteen cases received G-CSF weekly and seven twice weekly, with two receiving filgrastim 480mcg daily. Seventy one percent of those

treated with continual filgrastim (n=15) and 50% of those treated with continual lenograstim remained on clozapine (n=1). The characteristics of G-CSF use and associations with continued clozapine use are shown in table 1.

Seventy-four per cent of cases where sex was specified were male (17 / 23), with 76% of white ethnicity (n=19) and 20% of black ethnicity (n=5). Eighty-four percent (n=16/19) of those of white ethnicity remained on clozapine compared to 60% (n=3/5) of those of black ethnicity.

### ***Previous neutropenic episode and outcomes during rechallenge***

Data were available for 17 of the cases regarding the degree of neutropenia at the index clozapine discontinuation, with seven cases having had agranulocytosis (ANC 0.1-0.5x10<sup>9</sup>/L), three with severe agranulocytosis (ANC <0.1x10<sup>9</sup>/L), while the other seven had neutropenia (ANC 0.5-1.5 x10<sup>9</sup>/L). All those with a documented ANC < 0.5x10<sup>9</sup>/L were prescribed continual G-CSF prophylaxis during rechallenge. Three from seven cases with a prior agranulocytosis failed rechallenge, as did one third (1/3) of those with a prior history of severe agranulocytosis. One case with an index episode of severe agranulocytosis had a recurrence of agranulocytosis (ANC =0.3x10<sup>9</sup>/L), on a first rechallenge, while treated with G-CSF 300mcg twice weekly, subsequently had a second rechallenge, supported on G-CSF 480 mcg twice weekly, and was successfully maintained on clozapine at the time of follow up(12.5 months), (mean ANC, =15.8 x10<sup>9</sup>/L; median ANC=10.5 x10<sup>9</sup>/L; range ANC= 3.7 x10<sup>9</sup>/L –51.3 x10<sup>9</sup>. (17)

### **Adverse events**

Only nine cases reported on adverse events relating to G-CSF use. Two had evidence of a rebound leucocytosis, (15, 20) while in another case, a mild subjective euphoria in the hours post G-CSF administration was reported.(9) The other six cases did not have any adverse events associated with G-CSF use. (13, 18, 22, 24)



## **Discussion**

In this first systematic review of the use of G-CSF to support clozapine re-challenge and maintenance, it appears that G-CSF is an effective strategy for some people. Seventy-five percent of cases were able to continue clozapine with the use of G-CSF, either as regular prophylaxis (70% success rate) or as required administrations (89% success rate).

Our review findings provide the largest synthesis of cases where G-CSF has been used to prevent recurrence of neutropenia and/or to allow for the continuation of clozapine. In the majority of published cases the use of G-CSF enabled clozapine to be continued for at least 10 months. This is in keeping with a recent systematic review, where clozapine rechallenge was successful in 78/112 patients (70 %) after neutropenia.<sup>(6)</sup> We identified that 60% of those with an index episode of agranulocytosis had a successful outcome with continual G-CSF use, a higher figure than the 3/15 patients (20 %) with a successful rechallenge after agranulocytosis in the review of Manu et al. That same review examined 11 cases of rechallenge after neutropenia in which seven patients successfully continued clozapine while receiving G-CSF.<sup>(6)</sup> Our review expands on this by identifying 32 episodes in which G-CSF was used to support clozapine rechallenge or clozapine continuation in cases where low neutrophil counts led to interruption of treatment.

Rechallenge after neutropenia or agranulocytosis is a risky enterprise and a complex clinical decision, especially as the long term consequences of maintenance G-CSF treatment in the absence of a primary haematological problem are unclear. Nevertheless, our findings suggest that, in some cases, G-CSF can be successfully used to facilitate the successful re-initiation and maintenance of clozapine, although there is insufficient data systematically examining adverse outcomes to be able to comment authoritatively on safety.

## ***Limitations***

Our findings must be viewed in relation to limitations in the primary study data. Only 6 of the reported cases provided an evaluation for non-clozapine related causes of the initial

neutropenia event. This raises the possibility that some of the index events may not have been a true clozapine induced neutropenia, but neutropenia secondary to alternative non clozapine factors, a commonly encountered scenario in specialist clinical practice. The risk of neutropenia recurrence during clozapine rechallenge depends on whether the index event was truly caused by clozapine or not. The paucity of data relating to this important factor in the cases identified in this review, means that some of the cases reported may not represent true clozapine-induced neutropenia. Any non-clozapine related neutropenic and agranulocytosis episodes, may have contributed to the successful rechallenge, raising the possibility of an overestimation of the rate of successful rechallenge.

There were no controlled studies available, and there is a need for caution in interpreting data relating to case reports and case series.<sup>(25)</sup> Case reports alone cannot provide an accurate or quantitative measure of the risk for complications or death associated with a drug or treatment intervention such as this. A publication bias in favour of cases in which rechallenge was successful is probable. Furthermore, unreported deaths or severe adverse reactions may have occurred during the use of G-CSF. A prospective placebo controlled trial to establish the efficacy of G-CSF in clozapine rechallenge would be the gold standard approach to establish this, though the rarity of clozapine rechallenge may make such a study impractical outside highly specialised centres. As such, multicentre observational and retrospective studies to establish the efficacy of G-CSF in clozapine associated agranulocytosis would be the first choice for future research.

## **Conclusions**

We provide further evidence that the use of G-CSF can support successful clozapine rechallenge after discontinuation because of an episode of neutropenia/agranulocytosis. However, given the paucity of systematically reported data on this topic and the reliance on case reports which may be subject to publication bias, these results should be interpreted

with caution. From the available data, it is not possible to recommend this course of action for someone with a true clozapine agranulocytosis.

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