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The use of GCSF in clozapine rechallenge: a systematic review

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Abstract:	<p>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.</p> <p>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.</p> <p>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 <0.1x10⁹/L) had a recurrence of agranulocytosis at week 9.</p> <p>Implications/Conclusions Our findings suggest that GCSF can sometimes be safely used to support the</p>

	<p>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.</p>
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The use of G-CSF in clozapine rechallenge: a systematic review

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

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 show 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 0.1-0.5x10⁹/L), three with severe agranulocytosis (ANC <0.1x10⁹/L), while the other seven had neutropenia (ANC 0.5-1.5 x10⁹/L). All those with a documented ANC < 0.5x10⁹/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 =0.3x10⁹/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 x10⁹/L; median ANC=10.5 x10⁹/L; range ANC= 3.7 x10⁹/L –51.3 x10⁹. (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.(6) 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.(6) 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.⁽²⁵⁾ 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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Table 1. Characteristics of G-CSF use for those remaining on clozapine during rechallenge

	All patients	Remained on clozapine	Clozapine discontinued	X ² /T test; p value
Remained on clozapine:		24 (75%)	8 (25%)	
Continual G-CSF, n (%)	23 (72)	16 (70)	7 (30)	
G-CSF as required, n (%)	9 (28)	8 (89)	1 (11)	
G-CSF used:				
Filgrastim, n (%)	25	19 (76)	6 (24)	0.545; 0.405
Lenograstim, n(%)	5	3 (60)	2 (40)	
Filgrastim mean (SD) weekly dose mcg/week	680.4 (710.6)	504 (227.3)	450 (173.1)	0.434; 0.670
Filgrastim dose/week:				
>300mcg/week, n (%)	11	9 (82)	2 (18)	0.683; 0.365
≤ 300mcg/week, n(%)	12	8 (67)	4 (33)

Dear Dr David J. Greenblatt, 5th May 2017

Editor in Chief,

Journal of Clinical Psychopharmacology,

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

Authors: John Lally, Steffi Mailk, Amir Krivoy, Eromona Whiskey,

David M Taylor, Fiona P Gaughran, Robert J Flanagan, Aleksandar

Mijovic, James H MacCabe.

Thank you for your email on the 28th April 2017 requesting a revision of the article 'The use of G-CSF in clozapine rechallenge: a systematic review', subsequent to the first review process. We have enclosed a revised version of this manuscript. We believe all of the reviewer's concerns have been addressed in this version and we hope that it may now be accepted by the Journal of Clinical Psychopharmacology. We have retained our cautious approach regarding the use of G-CSF in clinical practice for clozapine rechallenge which is highlighted in our abstract and in the conclusion to our discussion.

This article is not currently under consideration for publication in another journal. The conflict of interest statement is complete within the electronic submission. All authors have contributed significantly; all authors are in agreement with the content of the manuscript. Below is our response to the reviewers' comments.

We thank you for kindly considering our paper and hope to hear from you soon.

Best wishes,

Dr John Lally on behalf of all authors.

Ref.: Ms. No. JCP-D-17-00025

The use of GCSF in clozapine rechallenge: a systematic review

The Journal of Clinical Psychopharmacology

Dear Dr. Lally:

The Editors would like you to Revise your paper according to their comments and those of the 2 reviewers (See BELOW).

Editors' Comments to Address (required):

We would like to reconsider a revised version of your manuscript. The reviewers had a number of observations that you will need to deal with as you work on the paper.

The Editors had the following additional points for revision.

We need to have the paper be much more circumspect about the strength of the data with respect to the drawing of definitive conclusions. As best we can tell, there are no controlled studies available. You are relying entirely on uncontrolled observations: case reports, case series, etc.

This amounts to pharmacovigilance data, which has huge limitations.

In this journal, we have presented a position on pharmacovigilance (2015; 35: 361-363), which you should cite and discuss.

The point is that you simply cannot draw any substantive conclusions about whether the use of G-CSF is or is not a reasonable approach to preventing or treating neutropenia associated with clozapine. Your revised manuscript will need to make this very clear.

Response: **JL et al** – We thank the editor for the opportunity to revise the manuscript in light of the reviewers comments.

We have modified the content to better reflect that we have not provided robust evidence for G-CSF use in clozapine rechallenge, in addition to the following which we provided in the original submission:

In our abstract we conclude with the following: "From the available data, it is not possible to recommend this course of action for someone with a true clozapine agranulocytosis."

We state the following in our discussion:

“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. “

And

“There were no controlled studies available, and there is a need for caution in interpreting data relating to case reports and case series.”⁽²⁷⁾ 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.”

We have referenced the Greenbalt et al editorial at the beginning of this paragraph.

And in the conclusion we state the following:

“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.”

Journal Style Items to Address/Check (required):

1. Brief Report Format: A Brief Report should be no more than 14 double-spaced pages in total length including abstract, text, reference list, tables, and figures. Place each figure and/or table on a separate page, and EACH is counted as ONE Page. The title page is not counted. Number pages.

2. ABSTRACT: Include the abstract in the manuscript file AND also in the separate abstract box online.

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3. Figures: Place each on a separate page at the end of the manuscript. Each figure must be labeled and include a legend either on the figure or on a separate page. Make sure figures pass the online art quality check for approved format before submitting a revision.

4. Reference List: Specific and General Items to Address/Check:

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We look forward to seeing your revised manuscript. Thank you for submitting your work to the Journal of Clinical Psychopharmacology.

Sincerely,

David J. Greenblatt, M.D.
Editor-in-Chief
and
Ms. Barbara Kern, Managing Editor
The Journal of Clinical Psychopharmacology
Tufts University School of Medicine
Boston, MA 02111

Email: barbara.kern@tufts.edu

Comments of the 2 Reviewers:

Reviewer #1:

The only problem that I have with it is the following statement:

"There are no clear criteria for clozapine rechallenge where clozapine treatment is suspended following neutropenia,(25)".

If I am interpreting the recently enacted Clozapine REMS Program correctly, it states clear criteria for clozapine re-challenges.

Response: **JL et al** –We thank the reviewer for their expert comment. We agree that this statement is ambiguous, and in light of the recent clozapine REMs program is inaccurate in relation to neutropenia. We have now removed the statement from our discussion.

Reviewer #2:

This is a worthwhile contribution to the question of successful rechallenge with clozapine after neutropenia or agranulocytosis. However, I consider that it could be substantially shortened (to 50%) and that this would improve the message.

The substantial proportion of the data on page 7 (results) could be presented more helpfully in a table.

Response: **JL et al:** We thank the reviewer for highlighting this. We have included a table, in place of some of the results, specifically in relation to associations with G-CSF formulation and doses used and favourable outcomes. We hope that this is acceptable. A cost-effectiveness analysis would add value.

Response: JL et al. We agree with the reviewer that this would be an interesting addition to the study, but we have not sought to conduct such an analysis based on the data available to use in this review.

Page 4, adverse incidences should be adverse events or adverse incidents.

Page 7, 'or an attenuated response to G-CSF, which, although not breaching licensing requirements, suggested an enhanced risk of agranulocytosis leading to a clinician initiated discontinuation.' is a bit turgid. Mention of the licensing requirements doesn't help and isn't relevant.

JL et al –We have updated the manuscript in relation to both of the above points.

Page 9, 'In the majority of published cases the use of G-CSF enabled clozapine to be continued for at least 18 months.' The results indicate successful continuation for up to 13 months. Is this an error, or does it come from somewhere else or what? Please clarify.

JL et al –We thank the reviewer for noting this. This is an error and should read 10 months.

Page 10, 'Most patients with clozapine rechallenge are not reported in the literature..' you can't make a statement like this without a reference. This is sufficient 'A publication bias in favour of cases in which [there is a favourable outcome] rechallenge was successful is probable.'

JL et al –We thank the reviewer for this suggestion and have updated as follows: "A publication bias in favour of cases in which rechallenge was successful is probable."

Page 10, the last sentence is incomplete. Is a prospective placebo controlled trial a realistic expectation? Perhaps a system of canvassing psychiatric services for cases of rechallenge is a more likely option.

JL et al –We thank the reviewer for highlighting this omission. This is now corrected and reads as follows:

“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.”

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JL et al –We thank the expert reviewer for their comments that have improved the quality of our work.