HHS Public Access

Author manuscript

Clin Schizophr Relat Psychoses. Author manuscript; available in PMC 2019 December 26.

Re-titration rates after clozapine-induced neutropenia or agranulocytosis: A case report and literature review

Mina Boazak, M.D.[1], **Benjamin Kahn, BSc**[1], **Lindsay Cox, D.O.**[2], **James Ragazino, M.D.**[1], **David R. Goldsmith, M.D.**[1], and **Robert O. Cotes, M.D.**[1]

[1]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine

[2]Department of Psychiatry & Behavioral Sciences, University of Miami Leonard Miller School of Medicine

Abstract

Clozapine-induced neutropenia occurs in 3–5% of individuals treated with clozapine. Current US guidelines require interruption of clozapine when the absolute neutrophil count (ANC) drops below 1000 cells/mm^3. There is minimal available guidance for what dosing schedule to use when restarting clozapine after an episode of neutropenia. Here, we present a case of a 50-year-old Caucasian female with a history of schizoaffective disorder who was successfully rechallenged on clozapine one month after developing clozapine-induced neutropenia (ANC 600 cells/mm^3). To understand published re-titration rates of clozapine after neutropenia, we conducted a literature review using a using the PubMed database and found only seven case reports that unambiguously reported a clozapine dosing schedule during re-challenge. All were successful except one, a case of clozapine rechallenge after agranulocytosis. Including this case presentation, six out of eight cases restarted clozapine more cautiously than recommended by the US guidelines for a new clozapine initiation. We cannot comment what role a slower or more rapid titration plays in a successful rechallenge after neutropenia with the available evidence. We encourage researchers to publish their dosing schedule in detail after an episode of neutropenia or agranulocytosis.

Keywords

clozapine; neutropenia; agranulocytosis; rechallenge; re-titration rate; schizophrenia

Introduction

The median incidence of schizophrenia is 15.2/100,000 persons (1) and treatment resistance is estimated in 20–30% of cases (2). Clozapine is the only antipsychotic medication with unique efficacy in treatment resistant schizophrenia (3, 4). However, clozapine has several notable hematologic side effects with neutropenia, defined as an absolute neutrophil count (ANC) <1500 u/L(5), occurring in 3–5% of patients (6, 7). Agranulocytosis, defined as an ANC <500 u/L (5), occurs in 0.38 – 0.91% of individuals in the first year of treatment (8–10). It has been hypothesized that clozapine-induced neutropenia and clozapine-induced

Corresponding Author: Mina Boazak, 12 Executive Park Dr NE, Suite 331Atlanta, GA 30329, Telephone: (404) 727-8370; Fax: (404) 727-4746, Mina.boazak@emory.edu.

agranulocytosis have different mechanisms (11, 12). When clozapine was commercially released in the United States in 1990, the Food and Drug Administration (FDA) developed a registry and mandated routine monitoring of white blood cell counts (WBC) and ANC for individuals prescribed clozapine. This registry reduced mortality from agranulocytosis by approximately 92% (13). Yet, prescriber concerns remain about hematologic side effects (14) and utilization of clozapine remains low in the US (15).

Clozapine-induced neutropenia and its management has important implications for a patient's medical and psychiatric stability. In 2015, the FDA released new guidelines (Table 1) requiring only ANC monitoring, changing the lowest ANC needed to start clozapine, and developing an algorithm for individuals with benign ethnic neutropenia (5). Under the current guidelines, treatment with clozapine must be interrupted when the ANC drops below 1000 cells/mm^3 (for individuals without benign ethnic neutropenia). However, abrupt discontinuation can lead to an exacerbation of psychosis, a clozapine withdrawal syndrome, and potentially catatonia (16–18). Prescribers find themselves grappling with starting another antipsychotic or considering a re-challenge of clozapine after neutrophil counts have improved in circumstances of discontinuation. Whiskey and Taylor (19) recommended that restarting clozapine after neutropenia be contemplated on a case by case basis, with consideration to 1) possible drug interactions known to depress bone marrow function, 2) concurrent medical conditions that may cause neutropenia, and 3) the presence of benign ethnic neutropenia. Yet, there is little practical guidance for how long to wait before re-starting clozapine or at what rate to titrate clozapine after an episode of neutropenia or agranulocytosis. Here, we present a case of a successful re-challenge on clozapine after an episode of clozapine-induced neutropenia, and we review the literature on the re-titration rate after clozapine-induced neutropenia and agranulocytosis.

Case Report

L.F., a 50-year-old Caucasian female, with a long standing history of schizoaffective disorder, depressed type and hypothyroidism who presented to our inpatient facility for persistent auditory hallucinations, delusions, suicidality, and intermittent catatonia. In the three months prior to presentation, she had four psychiatric hospitalizations for decompensated psychosis and one life-threatening suicide attempt. On initial presentation to our facility, the patient's mental status examination was remarkable for severe disorganization, paranoia, response to internal stimuli, and endorsement of auditory hallucinations. Per the patients personal care home owner, the patient had decompensated to such an extent as to be unable to care for herself. Due to failures on numerous prior antipsychotics (including quetiapine, risperidone, ziprasidone) the patient was started on clozapine. Olanzapine 5mg nightly was used to bridge the clozapine titration and the patients remaining home medications, fluoxetine 40mg daily, mirtazapine 30mg nightly, and levothyroxine 50mcg daily were continued. The initial clozapine titration was conducted on an inpatient service and was well-tolerated. During this time the patient was titrated from 25mg to 300mg through the course of 2.5 weeks. Once discharged the patients titration continued, and she was stabilized on a regimen of clozapine 600 mg nightly, fluoxetine 40 mg daily, mirtazapine 30 mg nightly, and levothyroxine 50 mcg for hypothyroidism. Three months into her treatment, the patient had a decline in ANC from 2700 cells/mm^3 to 1700

cells/mm^3, and due to guidelines at the time her labs were monitored twice-weekly until rebounding to over 2000 cells/mm^3, which occurred after fourteen days. Six months after starting clozapine, mirtazapine was discontinued due to improvement in affective symptoms. She remained out of the hospital vastly improved. Nine months after starting clozapine, the patient remained on weekly monitoring with weekly blood draws due to the decline in her ANC at three months. At this time the patient had another, more abrupt, decline with her ANC dropping to 1300 cells/mm^3 as compared to 4400 cells/mm^3 the week prior. Per the guidelines at the time, clozapine was stopped, however the patients remaining medication, including fluoxetine 40mg daily and levothyroxine 50mcg daily, were continued. Infection was ruled out by clinical interview and normal vitals. Due to the patients recurrent psychotic symptoms olanzapine 10mg daily was started on the second day after clozapine discontinuation. At the time the patients ANC was 1200 cells/mm^3, though had dropped to a nadir of 600 cells/mm^3 the day after olanzapine initiation. Despite this drop olanzapine was continued. ANC levels started to climb with the patient achieving a low normal value (1800 cells/mm^3) ten days after the nadir. Three weeks into the discontinuation of clozapine, our patient continued to have poorly controlled psychotic delusions and hallucinations, and olanzapine was increased from 10mg to 40mg over the following month. Three months into the discontinuation of clozapine, she remained severely psychotic with continued auditory hallucinations, delusions, disorganization, and worsening negative symptoms.

Given the severity of her symptoms, suicide attempt within the past year, previous failures on other antipsychotic medication, and current failure of olanzapine, re-challenge of clozapine was pursued. After extensive discussion with Ms. L.F., who was in agreement, she was readmitted to the hospital in order to re-titrate clozapine under direct monitoring. The day of clozapine initiation the patient's ANC was 3000 cells/mm^3. Clozapine was advanced at a rate of roughly 12.5mg/day, occasionally holding the dose steady for 2–3 days to assess for response, prior to increasing the next dose. Three days into the start of clozapine titration the patients ANC had declined to 1800 cells/mm^3 and as a result lithium carbonate was started and continued at 900mg daily for its leukocytotic effects. Throughout the hospital titration, the ANC ranged from 1800 to 5100 cells/mm^3. After 2 weeks of inpatient clozapine titration reaching a total of 75 mg at bedtime, the patient's symptoms had showed improvement with decreased disorganization and hallucinations, as well as reduced voluntary expression of delusional content. She was then discharged to outpatient services with continued titration at a rate of roughly 25mg/week. Please see Figure 1 for the relationship between clozapine dose and ANC levels. To date, L.F. has been on clozapine for 2 years, has reached a dose of 450 mg at bedtime, and has had ANC levels consistently above 3500 cells/mm^3. Her delusions and hallucinations are under good control, although still present. Olanzapine was slowly tapered off and she remains on lithium 900 mg daily, fluoxetine 40mg daily, and levothyroxine 50mcg daily. The clinical evaluations, including vitals, physical exams, and laboratory evaluations, including complete blood counts, basic metabolic panels, lithium levels, and thyroid function testing have been unremarkable throughout the course of her care.

Discussion

The case presented is an example of a successful rechallenge of clozapine after neutropenia. Previously reported risk factors for neutropenia include duration of time on clozapine (20), previous instances of neutropenia (21), and genetic factors such as higher frequencies of ABCB1 3435TT, and homozygosity for $GSTT1^{null}$ (22). Concurrent sodium valproate use with clozapine has mixed evidence as a risk factor for neutropenia (23, 24). Other antipsychotics also carry a risk of neutropenia; a recent Icelandic study demonstrated an equivalent risk of neutropenia from clozapine in comparison to other antipsychotics (25). Amongst antipsychotics that can cause neutropenia, our patient had a trial of olanzapine subsequent to her initial development of neutropenia. With the start of olanzapine the patient's ANC declined further, however, her ANC recovered within a total of 10 days, which is slightly less than 10.5 days; the median time to neutrophil recovery following clozapine-induced neutropenia/agranulocytosis (26). Nonetheless, in selecting antipsychotics for treatment of patients recovering from clozapine-induced neutropenia or agranulocytosis, clinicians should be cautious and restrict their use of agents with a documented history of neutropenia, such as olanzapine (27). In addition to olanzapine potentially exacerbating or protracting the patients neutropenia, we considered two other concurrent medications, fluoxetine and mirtazapine, that could have theoretically contributed to neutropenia (28, 29). However, neutropenia due to fluoxetine has been rarely reported and mirtazapine was discontinued three months prior to L.F. developing neutropenia. The US clozapine prescribing information provides guidance for how to initiate or restart clozapine for patients without neutropenia. For a new clozapine start, it is recommended to start clozapine at 12.5 mg daily or twice daily, and increase the dose by 25 to 50 mg per day, if tolerated, targeting 300 to 450 mg per day by the end of two weeks (30). If treatment is discontinued (2 or more days since the last dose), clozapine can be re-initiated at 12.5 mg once or twice daily, and if well-tolerated, the dose can be increased to the previous therapeutic dose more quickly than recommended for initial treatment (30). However, there is no specific information for how to re-titrate clozapine after neutropenia or agranulocytosis.

To address this gap, we conducted a search of PubMed from inception to December 5, 2017 using MESH terms "clozapine" AND "rechallenge", "clozapine" AND "after" AND "neutropenia", "clozapine" AND "after" AND "agranulocytosis", "clozapine" AND "rechallenge" AND "agranulocytosis", and "clozapine" AND "rechallenge" AND "neutropenia". The search resulted 467 articles, with 31 relevant to rechallenge after neutropenia or agranulocytosis. Three were systematic reviews (31–33), four were retrospective analysis (34–37), and 24 were case reports (38–61). In all, these reports represented 146 unique patients, of whom 37 (25%) failed rechallenge, comparable to previous rates (31). Only seven studies, all case reports, unambiguously reported clozapine re-titration dosing schedules during rechallenge (39, 49, 50, 53, 56, 57, 59). Refer to Figure 2 for a comparison of published titration speeds. Five were cases of rechallenge after neutropenia (ANC <1500 cells/mm^3) and two were cases of rechallenge after agranulocytosis (ANC<500 cells/mm^3). Only one of the seven cases, an individual who had previously developed agranulocytosis, failed rechallenge (56). Time between prior blood

dyscrasia and rechallenge was provided for five cases and ranged from 4 days to 4 years. The one failed case was rechallenged after 4 years.

Detailed re-titration rates were rarely published after episodes of neutropenia or agranulocytosis from clozapine. Of those published, each case re-titrated clozapine either at the rate recommended by the FDA for a new clozapine initiation (n = 2) or more cautiously (n =5). No cases exceeded the rate indicated by the FDA for a new clozapine initiation. Since there was only one failed rechallenge in the context of agranulocytosis (and none for neutropenia), we cannot comment if a slower titration speed is safer than a more rapid titration. The one individual that developed agranulocytosis after rechallenge was initially titrated slowly, but was later increased 200mg to 300mg over one day, and developed agranulocytosis shortly thereafter.

It is difficult to speculate from the available evidence what role the titration speed played in the eventual success or failure after re-titration. More research is needed both on this subject and on the appropriate time delay to restarting clozapine after an episode of neutropenia or agranulocytosis. Additionally, six cases out of seven cases in our analysis reported use of either lithium or G-CSF to increase the ANC (39, 46, 49, 56, 57, 59), clouding the role of the titration speed. Lithium and G-CSF can have protective role against neutropenia or agranulocytosis, but the evidence supporting this strategy is not incontrovertible, as demonstrated by the one failed case reported here (56) and other reports (32, 34, 36). If clinicians are to initiate lithium or G-CSF, they need to conduct appropriate monitoring. Laboratory testing for lithium includes baseline and interval renal function testing, thyroid function testing, a pregnancy test where appropriate, and trough lithium levels. Hematologic consultation should be arranged prior to the initiation of G-CSF. Our conclusions are limited by a small sample size and our review was limited to one database. Other rechallenges have likely been completed (either successfully or unsuccessfully) without being published. It is also unclear if other factors during clozapine re-titration caused clinicians to restart clozapine more cautiously, such as tolerability. In conclusion, we have summarized the available published titration speeds after an episode of neutropenia or agranulocytosis for clinicians considering a clozapine rechallenge for their patients. We encourage researchers to report details around the re-titration rate after neutropenia in future descriptions of this phenomenon.

References:

1. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008;30:67–76. [PubMed: 18480098]
2. Conley RR, Buchanan RW. Evaluation of Treatment-Resistant Schizophrenia. Schizophrenia Bulletin 1997;23:663–674. [PubMed: 9366002]
3. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796. [PubMed: 3046553]
4. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, Swartz MS, Perkins DO, Keefe RS, Davis CE, Severe J, Hsiao JK, Investigators C. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 2006;163:600–610. [PubMed: 16585434]
5. Clozapine REMS: Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers 09/15.

6. Senechal A, Landry P, Deschamps R, Lessard M. [Neutropenia in a patient treated with clozapine in combination with other psychotropic drugs]. Encephale 2002;28:567–569. [PubMed: 12506270]
7. Lee J, Takeuchi H, Fervaha G, Powell V, Bhaloo A, Bies R, Remington G. The Effect of Clozapine on Hematological Indices: A 1-Year Follow-Up Study. J Clin Psychopharmacol 2015;35:510–516. [PubMed: 26267420]
8. Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. J Clin Psychiatry 1998;59 Suppl 3:3–7.
9. Safferman A, Lieberman J, Alvir JJ, Howard A. Rechallenge in clozapine-induced agranulocytosis. The Lancet 1992;339:1296–1297.
10. Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. N Engl J Med 1993;329:162–167. [PubMed: 8515788]
11. Wicinski M, Weclewicz MM. Clozapine-induced agranulocytosis/granulocytopenia: mechanisms and monitoring. Curr Opin Hematol 2017.
12. Roge R, Moller BK, Andersen CR, Correll CU, Nielsen J. Immunomodulatory effects of clozapine and their clinical implications: what have we learned so far? Schizophr Res 2012;140:204–213. [PubMed: 22831769]
13. Honigfeld G Effects of the clozapine national registry system on incidence of deaths related to agranulocytosis. Psychiatr Serv 1996;47:52–56. [PubMed: 8925346]
14. Gee S, Vergunst F, Howes O, Taylor D. Practitioner attitudes to clozapine initiation. Acta Psychiatr Scand 2014;130:16–24. [PubMed: 24004162]
15. Olfson M, Gerhard T, Crystal S, Stroup TS. Clozapine for Schizophrenia: State Variation in Evidence-Based Practice. Psychiatr Serv 2016;67:152. [PubMed: 26522679]
16. Shiovitz TM, Welke TL, Tigel PD, Anand R, Hartman RD, Sramek JJ, Kurtz NM, Cutler NR. Cholinergic rebound and rapid onset psychosis following abrupt clozapine withdrawal. Schizophr Bull 1996;22:591–595. [PubMed: 8938913]
17. Goudie AJ. What is the clinical significance of the discontinuation syndrome seen with clozapine? J Psychopharmacol 2000;14:188–192. [PubMed: 10890315]
18. Wadekar M, Syed S. Clozapine-withdrawal catatonia. Psychosomatics 2010;51:355–355 e352. [PubMed: 20587767]
19. Whiskey E, Taylor D. Restarting Clozapine after Neutropenia. CNS Drugs 2007;21:25–35.
20. Munro J, O'Sullivan D, Andrews C, Arana A, Mortimer A, Kerwin R. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. Br J Psychiatry 1999;175:576–580. [PubMed: 10789357]
21. Dunk LR. Rechallenge with clozapine following leucopenia or neutropenia during previous therapy. The British Journal of Psychiatry 2006;188:255–263. [PubMed: 16507968]
22. van der Weide K, Loovers H, Pondman K, Bogers J, van der Straaten T, Langemeijer E, Cohen D, Commandeur J, van der Weide J. Genetic risk factors for clozapine-induced neutropenia and agranulocytosis in a Dutch psychiatric population. Pharmacogenomics J 2017;17:471–478. [PubMed: 27168101]
23. Malik S, Lally J, Ajnakina O, Pritchard M, Krivoy A, Gaughran F, Shetty H, Flanagan RJ, MacCabe JH. Sodium valproate and clozapine induced neutropenia: A case control study using register data. Schizophr Res 2017.
24. Kando JC, Tohen M, Castillo J, Centorrino F. Concurrent use of clozapine and valproate in affective and psychotic disorders. J Clin Psychiatry 1994;55:255–257. [PubMed: 8071281]
25. Ingimarsson O, MacCabe JH, Haraldsson M, Jonsdottir H, Sigurdsson E. Clozapine treatment and discontinuation in Iceland: A national longitudinal study using electronic patient records. Nord J Psychiatry 2016;70:450–455. [PubMed: 27049594]
26. Atkin K, Kendall F, Gould D, Freeman H, Liberman J, O'Sullivan D. Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. Br J Psychiatry 1996;169:483–488. [PubMed: 8894200]
27. Malhotra K, Vu P, Wang DH, Lai H, Faziola LR. Olanzapine-Induced Neutropenia. Ment Illn 2015;7:5871. [PubMed: 26266027]

28. Bavle A Fluoxetine-induced neutropenia. Indian J Psychiatry 2012;54:388–389. [PubMed: 23372249]
29. Civalier KA, Krahn LE, Agrwal N. Repeated episodes of neutropenia triggered by mirtazapine. Psychosomatics 2009;50:299–300. [PubMed: 19567774]
30. Novartis Pharmaceuticals: Clozaril(R) [package insert] 2017.
31. Manu P, Sarpal D, Muir O, Kane JM, Correll CU. When can patients with potentially life-threatening adverse effects be rechallenged with clozapine? A systematic review of the published literature. Schizophr Res 2012;134:180–186. [PubMed: 22113154]
32. Lally J, Malik S, Krivoy A, Whiskey E, Taylor DM, Gaughran FP, Flanagan RJ, Mijovic A, MacCabe JH. The Use of Granulocyte Colony-Stimulating Factor in Clozapine Rechallenge: A Systematic Review. J Clin Psychopharmacol 2017;37:600–604. [PubMed: 28817489]
33. Simon L, Cazard F. [Clozapine rechallenge after neutropenia in resistant schizophrenia: A review]. Encephale 2016;42:346–353. [PubMed: 27109327]
34. Kanaan RA, Kerwin RW. Lithium and clozapine rechallenge: a retrospective case analysis. J Clin Psychiatry 2006;67:756–760. [PubMed: 16841625]
35. Dunk LR, Annan LJ, Andrews CD. Rechallenge with clozapine following leucopenia or neutropenia during previous therapy. Br J Psychiatry 2006;188:255–263. [PubMed: 16507968]
36. Meyer N, Gee S, Whiskey E, Taylor D, Mijovic A, Gaughran F, Shergill S, MacCabe JH. Optimizing outcomes in clozapine rechallenge following neutropenia: a cohort analysis. J Clin Psychiatry 2015;76:e1410–1416. [PubMed: 26646037]
37. Prokopez CR, Armesto AR, Gil Aguer MF, Balda MV, Papale RM, Bignone IM, Daray FM. Clozapine Rechallenge After Neutropenia or Leucopenia. J Clin Psychopharmacol 2016;36:377–380. [PubMed: 27232877]
38. Friedman J, Yeboah E, Hermenau M. Addition of Filgrastim (Neupogen) for Clozapine Rechallenge in the Case of Parkinson Disease Patient. Clin Neuropharmacol 2017;40:233–234. [PubMed: 28922288]
39. Eseonu C, Carlson J. Clozapine rechallenge in refractory schizophrenia. Am J Psychiatry 2010;167:602–603. [PubMed: 20439404]
40. Lertxundi U, Sanchez P, Hernandez R, Elizagarate E. A case of agranulocytosis secondary to rechallenge with clozapine following severe neutropenia during previous therapy. J Clin Psychiatry 2011;72:1659. [PubMed: 22244024]
41. Gopalakrishnan R, Subhalakshmi TP, Kuruvilla A, Jacob KS. Clozapine re-challenge under the cover of Filgrastim. J Postgrad Med 2013;59:54–55. [PubMed: 23525060]
42. Papetti F, Darcourt G, Giordana JY, Spreux A, Thauby S, Feral F, Pringuey D. [Treatment of clozapine-induced granulocytopenia with lithium (two observations)]. Encephale 2004;30:578–582. [PubMed: 15738861]
43. Silvestrini C, Arcangeli T, Biondi M, Pancheri P. A second trial of clozapine in a case of granulocytopenia. Hum Psychopharmacol 2000;15:275–279. [PubMed: 12404322]
44. Sperner-Unterweger B, Czeipek I, Gaggl S, Geissler D, Spiel G, Fleischhacker WW. Treatment of severe clozapine-induced neutropenia with granulocyte colony-stimulating factor (G-CSF). Remission despite continuous treatment with clozapine. Br J Psychiatry 1998;172:82–84. [PubMed: 9534838]
45. McKnight C, Guirgis H, Votolato N. Clozapine rechallenge after excluding the high-risk clozapine-induced agranulocytosis genotype of HLA-DQB1 6672G>C. Am J Psychiatry 2011;168:1120.
46. Suraweera C, Hanwella R, de Silva V. Use of lithium in clozapine-induced neutropenia: a case report. BMC Research Notes 2014;7:635. [PubMed: 25214394]
47. Khan AA, Harvey J, Sengupta S. Continuing clozapine with granulocyte colony-stimulating factor in patients with neutropenia. Ther Adv Psychopharmacol 2013;3:266–271. [PubMed: 24167701]
48. Nunes EA, Rezende TM, Morais SL, Crippa JA, Dursun SM, Baker GB, Hallak JE. Clozapine treatment of patients with refractory schizophrenia, concurrent dengue infection and hematological abnormalities: three case reports. Ther Adv Psychopharmacol 2013;3:83–88. [PubMed: 24167679]
49. Huguet G, Lillo-Le Louet A, Darnige L, Loo H, Krebs MO. Réintroduction de la clozapine chez les patients souffrant de schizophrénie résistante « super répondeurs », après neutropénie sous clozapine : à propos d'un cas. L'Encéphale 2013;39:S42–S48.

50. Wu S-Y, Liu C-C, Hsieh MH. Successful re-exposure to clozapine following uneventful rechallenge with olanzapine in a patient with neutropenia related to both agents. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2008;32:1089–1090. [PubMed: 18407390]
51. Toni-Uebari TK, Rees J. Successful rechallenge with clozapine following 'red alert'. BMJ Case Rep 2013;2013.
52. Kutscher EC, Robbins GP, Kennedy WK, Zebb K, Stanley M, Carnahan RM. Clozapine-induced leukopenia successfully treated with lithium. Am J Health Syst Pharm 2007;64:2027–2031. [PubMed: 17893412]
53. Jauss M, Pantel J, Werle E, Schroder J. G-CSF plasma levels in clozapine-induced neutropenia. Biol Psychiatry 2000;48:1113–1115. [PubMed: 11094146]
54. Bavle A, Vidhyavathi M. Case report of clozapine-induced neutropenia and rechallenge. J Neuropsychiatry Clin Neurosci 2015;27:e61. [PubMed: 25716496]
55. Frankenberg FR, Stormberg D & Gerson SL. Unsuccessful re-exposure to clozapine. . Journal of Clinical Psychopharmacology 1994;14:428–429. [PubMed: 7884027]
56. Hazewinkel AW, Bogers JP, Giltay EJ. Add-on filgrastim during clozapine rechallenge unsuccessful in preventing agranulocytosis. Gen Hosp Psychiatry 2013;35:576 e511–572.
57. Small JG, Weber MC, Klapper MH, Kellams JJ. Rechallenge of Late-Onset Neutropenia With Clozapine. Journal of Clinical Psychopharmacology 2005;25:185–186. [PubMed: 15738753]
58. Munshi T, Mazhar M, Hassan T. Clozapine reinitiation following a "red result" secondary to chemotherapy. Neuropsychiatr Dis Treat 2013;9:1267–1271. [PubMed: 24039428]
59. Ghaznavi S, Nakic M, Rao P, Hu J, Brewer JA, Hannestad J, Bhagwagar Z. Rechallenging with clozapine following neutropenia: treatment options for refractory schizophrenia. Am J Psychiatry 2008;165:813–818. [PubMed: 18593787]
60. Yamaki N, Hishimoto A, Otsuka I, Sasada T, Boku S, Saito T, Yasuda Y, Yamamori H, Ikeda M, Ikeda M, Sora I, Iwata N, Hashimoto R. Optimizing outcomes in clozapine rechallenge following neutropenia using human leukocyte antigen typing: A case report. Psychiatry Clin Neurosci 2017;71:289–290. [PubMed: 28097743]
61. Joffe G, Eskelinen S, Sailas E. Add-on filgrastim during clozapine rechallenge in patients with a history of clozapine-related granulocytopenia/agranulocytosis. Am J Psychiatry 2009;166:236. [PubMed: 19188296]

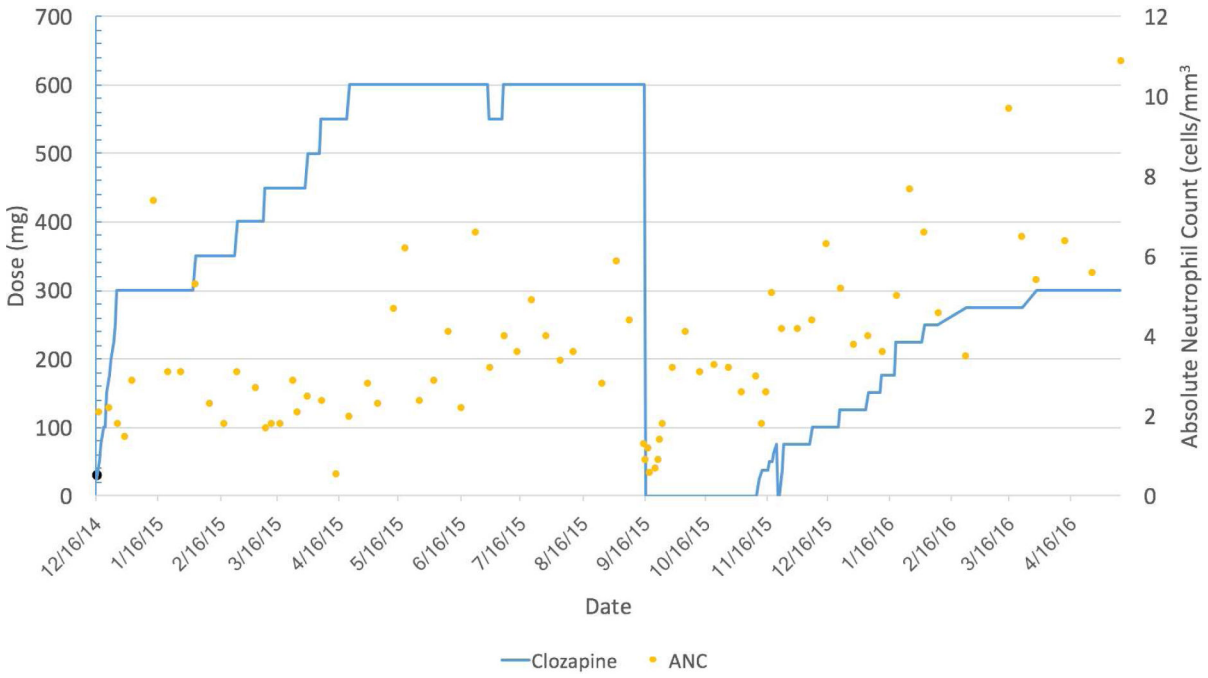

Figure 1:
Clozapine dose against scatter plot of absolute neutrophil counts over time.

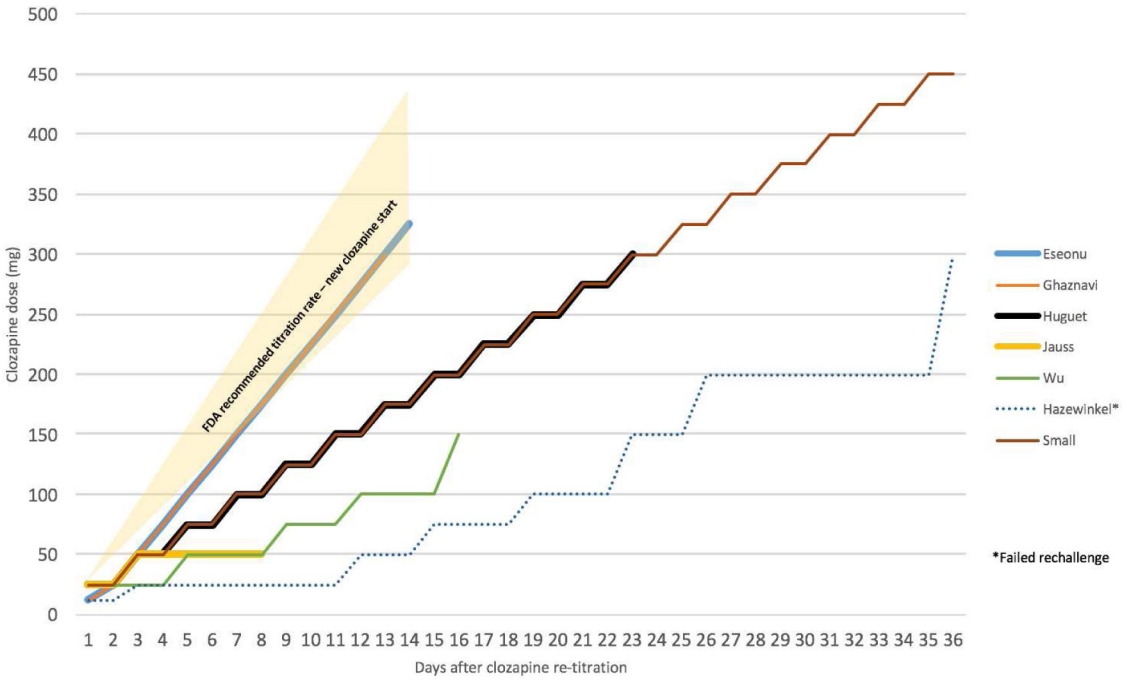

Figure 2:
Reports of clozapine re-challenge with published re-titration rates

Table 1:

Comparison of U.S. Absolute Neutrophil Count (ANC) monitoring guidelines for clozapine before and after 2015

ANC (μL)	Before 2015	After 2015
≥ 2000	Initiate treatment. Monitor weekly from initiation to 6 months, then every 2 weeks from 6–12 months, then monthly after 12 months	Initiate treatment. Monitor weekly from initiation to 6 months, then every 2 weeks from 6–12 months, then monthly after 12 months
1500 to 2000	Continue treatment (mild neutropenia). Monitor two times weekly until ANC ≥ 2000/μL, return to patient's last ANC monitoring interval	Normal Range. Monitor as above.
1000 to 1499	Interrupt treatment (moderate neutropenia). Daily until ANC ≥ 1500/μL, then two times weekly until ANC ≥ 2000/μL. May rechallenge after ANC ANC ≥ 2000/μL though need weekly monitoring for one year.	Continue treatment (mild neutropenia). Monitor three times weekly until ≥ 1500/μL. Once ANC ≥ 1500/μL, return to patient's last ANC monitoring interval
500 to 999	Interrupt treatment (severe neutropenia). Do not rechallenge. Monitor daily ANC ≥ 1500/μL, then weekly ANC ≥ 2000/μL. Monitor at least four weeks after discontinuation.	Interrupt treatment (moderate neutropenia). Monitor daily until ANC ≥ 1000/μL, then three times weekly until ANC ≥ 1500/μL. Once ANC > 1500, check ANC weekly for 4 weeks, then return to last "Normal Range" ANC monitoring interval.
< 500	Interrupt treatment (agranulocytosis). Do not rechallenge. Monitor daily ANC ≥ 1500/μL, then weekly ANC ≥ 2000/μL.	Interrupt treatment (severe neutropenia). Do not rechallenge unless prescriber determines benefits outweigh risks. Monitor daily until ANC ≥ 1000/μL, then three times weekly until ANC ≥ 1500/μL

Adapted from Clozapine REMS (15) and Novartis Prescribing Information (28)

Table 2:

Previous reports of clozapine re-challenge with published re-titration rates and reported outcome

Report	Lowest reported ANC (in cells/mm^3) on first clozapine challenge	Time between clozapine interruption and rechallenge	Rate at re-challenge	Lowest reported ANC (in cells/mm^3) after rechallenge	Additional notes
Rechallenge After Neutropenia					
Eseonu et al. 2010	Only reported to have previous episode of neutropenia	>2 years	Day 1: 12.5mg, Day 2: 25mg Day3 on wards; titrated at 25mg daily increments until reaching 325mg	No reported trough value. Starting ANC was 4100 cells/mm^3. No recurrence of neutropenia reported.	Patient was on olanzapine 30mg/day and started on lithium 300mg/day 1 week prior to clozapine initiation. Once clozapine dose of 325mg/day was reached olanzapine was tapered to discontinuation.
Ghaznavi et al. 2008	900	2 years	Day 1:12.5 mg, Day 2: 12.5mg BID, Day 3 onwards: titrated at 25mg increments daily to 300mg eventually discharged with a dose of 325mg	5400	After initial clozapine failure the patient was rechallenged within 1 week and re-experienced neutropenia with a nadir ANC of 850 cells/mm^3. On final, and successful, rechallenge patient was concurrently treated with lithium 300mg daily.
Huguet et al. 2013	Unclear	unclear	Started at 25mg and increased by 25mg every three days to a dose of 300mg	1800	Patient with neutropenia and three previous failures. Last, and successful, attempt was with concurrent filgrastim 0.3 mg twice weekly.
Jauss et al. 2000	<1000	4 days	Day 1 and 2: 25mg, Day 3 onwards: 50mg	~3500	Patient stable on a combination of clozapine, levodopa, and metixen.
Wu et al. 2008	880	21 days	Day 1: 25mg Day 5: 50mg, Day 9: 75mg, Day 12: 100mg, Day 16: 150mg	WBC ~6000 (No ANC)	Did not report ANC values on re-challenge. Preceding clozapine re-challenge patient was started on olanzapine 10mg, which was suspected of prolonging neutropenia.
Rechallenge After Agranulocytosis					
Hazewinkel et al. 2013	Only reported to have had a previous episode of agranulocytosis	4 years	Day1: 12.5, Day 3: 25mg, Day12: 50mg, Day 15: 75 mg, Day 19: 100mg, Day 23: 150mg, Day 26: 200mg, Day 36: 300mg	<100	During titration patient was treated with G-CSF at a roughly weekly basis, escalating to daily treatments in the context of worsening neutropenia.
Small et al. 2005	WBC 1800+ granulocyte 11% (~200)	Not indicated	25mg every 3–4 days until 800mg	WBC of 4500 + granulocyte 48% (~2200)	At some point during titration patient was started on lithium (unknown dose).