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Case Report

CLOZAPINE RECHALLENGE WITH LITHIUM AFTER DOUBLE INDUCED NEUTROPENIA: A CASE REPORT

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Abstract

Clozapine is a second generation antipsychotic drug, which has been acknowledged as the gold standard for treating both positive and negative symptoms of treatment-resistant schizophrenic patients, despite its severe side effects, such as neutropenia. Evidence suggest rechallenging after clozapine-induced neutropenia. Nevertheless, no official guidelines exist in case that rechallenge fails. We present the case of a fifty-six year old man suffering from treatment resistant schizophrenia. The patient was diagnosed with chronic psychosis and was treated with clozapine, presenting good response. The patient developed clozapine induced neutropenia, only to be rechallenged after the neutrophil count returned at a normal range. However, another neutropenia incidence followed, and clozapine had to be ceased once more. Determining that the benefits outweighed risks, we attempted a second rechallenge with the adjustment of clozapine's dosage and the addition of Lithium carbonate. Since then, the patient did not develop any blood dyscrasia. What is more, the improvement in both psychopathology and functionality is ongoing. The mechanism of clozapine's action upon neutrophils remains unclear. The same goes for Lithium. Since literature suggests that both drugs have an effect on the bone marrow, resulting in opposite actions it only seems logical that Lithium could be used in preventing clozapine-induced neutropenia. Considering that the lack of guidelines leads to a restrain towards clozapine rechallenge after neutropenia incidence, more so after double induced neutropenia, more research is needed on the matter in the interest of a better quality of life for treatment resistant schizophrenia patients.

Key-words: Clozapine, Lithium, schizophrenia, resistant schizophrenia, neutropenia, clozapine-induced neutropenia,

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INTRODUCTION

Since the introduction of chlorpromazine in Psychiatry as an antipsychotic agent in 1952, many breakthroughs have been made in this field. Nevertheless, even after the second-generation antipsychotics' launch in the pharmaceutical industry, psychiatrists faced the problem of treatment resistant schizophrenia (TRS). It was not until the 90's that a long-discredited agent would shed some light in this domain. Reference is made to the molecule Clozapine.

Clozapine is an atypical neuroleptic agent identified in 1959 by the pharmaceutical company Walder Laboratories and introduced in the market at the early 70's **(1),** only to be withdrawn a few years later in 1975, due to alarming reports of fatal agranulocytosis in Finland **(2).** Around 1990, clozapine was approved by the FDA, after a pivotal study by Kane et al that proved its superior efficacy compared to chlorpromazine in TRS **(3)**. Since then it has been acknowledged as the gold standard for treating both positive and negative symptoms of treatment-resilient patients, which seems to be the case for up to one third of patients suffering from schizophrenia **(4).**

Clozapine molecule has a complex structure which accounts for its multiple binding affinities and therefore its pharmacologic profile. Same as every atypical antipsychotic, this agent presents a combined antagonism to dopamine and serotonin receptors. Clozapine's effect on dopamine receptors situated in several neurological pathways throughout the brain reduces both positive and negative symptoms of schizophrenia and improves cognition as well as mood. Its antagonistic action upon D2 Dopaminergic receptors seems to be more fable and short-lived than the one upon D1-dopamine receptors, without being clear if the latest represents an antagonism or an agonism **(5,6).** This second-generation antipsychotic is also known to have a high affinity for D4 dopamine receptors and a weaker one for D3 receptors **(6).**

Apart from its preference to dopaminergic receptors, clozapine has a high affinity for serotonin receptors as well, and especially for the 5HT2B and the 5HT2A subtypes, with a robust antagonistic action on the latest. As a result, dopamine release is enhanced in certain brain regions and thus cognitive and affective symptoms of schizophrenia are improved. What is more, the risk of extrapyramidal symptoms (EPS) is decreased **(7).** Clozapine seems to bind strongly upon the 5HT2C, 5HT6, 5HT7 and other serotonin receptors, as well as the 5HT1A receptor which is activated thus causing dopamine release in the prefrontal cortex (PFC) **(8).**

Another pharmaceutical property of clozapine is sedation, an action that is stimulated by blocking either M1-muscarinic cholinergic or H1-histminic or a1-adrenergic receptors or all of them at once. What is more, mood is improved. Antihistaminic and anticholinergic properties are also responsible for the anxiolytic effect of the drug **(9).** In addition to this, Clozapine's partial and full agonistic activity on other subtypes of muscarinic receptors (M2, M3, M4) results in an improvement of cognitive functions. This is partially due to a metabolite, N-Desmethylclozapine (NDMC), and its nootropic attributes to the hippocampus and the PFC **(10).** Finally, clozapine appears to have an antagonistic action for the NMDA receptor's glycine site, concluding in stabilizing DA neurons in both the PFC and the midbrain **(11).**

Clozapine's affinity to the multiple forenamed receptors is not devoid of adverse effects. Although second generation antipsychotics are known to cause EPS at a lower scale due to a looser attachment to D2 dopamine receptors, as mentioned before, adverse reactions derived from its antidopaminergic, antimuscarinic, antihistaminic and adrenergic receptor blocking properties can be quite common and challenging. Weight gain, excessive sedation (20-40%), somnolence, dizziness, constipation (15-60%), metabolic syndrome, tachycardia (12-17%), orthostatic hypotension (8-13%) and excessive salivation (12-40%) are all products of clozapine's actions **(12,13).** Not so frequent but potentially lethal side effects include myocarditis, seizures and pulmonary embolism, ileus and bowel ischemia, liver disfunction, neuroleptic malignant syndrome and angioedema **(14).**

The most disturbing side effect however, seems to be clozapine-induced blood dyscrasias and specifically neutropenia and agranulocytosis. Seen respectively in about 2-3% and 1% of the

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treated with clozapine patients these life-threatening adverse reactions limit the drugs' more widespread use **(15,16).** Nearly 25 % of the patients cease clozapine on account of its side effects, with neutropenia being the main cause of discontinuation **(17).** The process through which Clozapine causes those blood abnormalities is unclear, but it is speculated to be a heritable trait **(18) .**

Despite its side effects, as mentioned before, clozapine remains the gold standard for TRS, being the first line treatment after the failure of two antipsychotic trials according to treatment guidelines **(19).** Even if a patient is not responding to other neuroleptics, the response-ratio to clozapine is as high as 30 to 60 % **(4, 20, 21, 22, 23).** Apart from TRS, clozapine has shown efficacy as an anti-aggressive and anti-suicidal drug in patients with schizophrenia **(24)** and bipolar disorder as well **(25) .**

Due to the abovementioned adverse effects of clozapine, careful monitoring is applied in many countries before and after the initiation of the drug. More frequently it includes complete blood count with emphasis given on white blood cell (WBC) count and absolute neutrophil count (ANC), ECG, troponin levels, weight measurement, vital signs, lipidic profile and liver functioning tests, with different protocols implemented by each country **(25).** The one guideline that seems to apply for the majority of them is mandatory WBC and ANC count.

For the initiation of clozapine, a WBC and ANC minimum count of 3000/mm^3 and 1500/mm^3 respectively must be obtained, according to the FDA **(26).** Exception is made for Benign Ethnic Neutropenia (BEN), in which the limitation of clozapine's use is ANC count of at least 1000/mm^3 **(27).** If the patient's blood sample does not comply with the criteria above at any time during treatment clozapine should be discontinued **(28),** especially if ANC falls below 1000/mm^3 and if the benefits do not surpass the hazards **(26).**

Rechallenging after a neutropenia incidence is a difficult decision. However, guidelines and evidence suggest it is a logical clinical option **(29).** FDA is in favor of rechallenging if patients' WBC does not fall below 2000/mm^3. Clozapine REMS program suggests it might be the only solution in some cases, even after moderate and severe clozapine-related neutropenia **(26).** A study carried out by Manu et al in 2012 concludes that 70 % of the patients who developed neutropenia because of clozapine, were rechallenged successfully without neutropenia re-appearing **(30).** Nevertheless, no official guidelines exist for this 30% that rechallenge has failed.

CASE REPORT

G.K is a 56-year-old Caucasian man with a 25-year history of paranoid schizophrenia, appearing both positive and negative symptoms, as well as suicide attempts. For the last few years his mental health had deteriorated and his functionality had dropped off. As a result, he had been through many hospitalizations and received a wide range of neuroleptics, making him suitable to be characterized as a treatment resistant schizophrenia patient. As such he was referred to our psychiatric clinic. Upon his admission in the hospital he was under risperidone in the form of long-acting injection (50mg/15days), pipamperone (40 mg twice a day) levomepromazine (25mg daily) amisulpride (400mg three times a day) and biperiden (2mg twice a day) and he displayed the profile of a chronic psychotic patient with a GAF scale assessment of around 38.

In our unit, we performed cross tapering with clozapine on an outpatient basis. Before the patient was administered with clozapine a complete blood count was carried out, as well as an electrocardiogram, BMI measurement, reference biochemical blood analysis including lipidemic profile, blood sugar levels, liver and kidney functioning tests, electrolytes and troponin. Subsequently, blood count was monitored weekly in order to be in vigilance for changes of the WBC count. The initiation of clozapine and its gradual up-titration on a dosage of 350mg daily was followed by an amelioration of both negative and positive symptoms and an improvement on the GAF scale, with the patient's functionality ascending on the GAF scale from 38 up to 70.

One month after the completion of clozapine's titration, the first signs of WBC decline appeared, with an absolute count of

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WBC slightly over 4000/μL . However, it was not until during the fourth month after clozapine›s initiation that neutropenia developed. The patient's white blood cells and neutrophils (NEU) reached the point of 3380/μL and 810/μL respectively, which corresponds to a moderate blood dyscrasia. Hence, clozapine administration was ceased and a complete physical examination was performed. The absence of pathological findings, the failure of the patient to respond to other drugs suitable for schizophrenia, as well as the severity of the patient's mental condition, taking into account previous suicide attempts, led us to a first rechallenge.

After the restoration of WBC and NEU, about a week later, we re-administered clozapine. Nevertheless, the following month, neutropenia reappeared, with a WBC and NEU count of 3040/μL and 630/μL respectively which corresponds to a much more serious neutropenia with high risk for infection. That was the case for our patient, who presented a positive CRP and signs of GI tract infection. Thus, clozapine was withdrawn, the patient's infection was treated with antibiotics and daily blood tests were performed.

A rapid recovery of the WBC and NEU, was followed by a second rechallenge by our part, taking into account the impressive improvement of the patient's condition concerning both schizophrenia symptoms and functionality. This time, the addition of lithium carbonate in the treatment at a dosage of 300 mg per day (Li 0,33 mEq/L) and the adjustment of clozapine's dosage (200mg/day) in order to avoid neutropenia was crowned with success. No further leukopenia was observed, due to a Lithium induced true leukocytosis. What is more, for the last ten months the patient has not developed neutropenia and has managed to stabilize, even mitigate, his mental condition, while the improvement of his functionality is ongoing.

DISCUSSION

Lithium has been approved by the FDA since 1979 for the prophylaxis of manic episodes **(31)** and has been used both in the acute phase of mania and in preventing its re-occurrence. What is more, it is used as a stabilizer and as an amplifying agent in affective disorders **(32).** Another important property is that it is linked with a reduction in suicidality in patients with mood disorders **(33).** It also has an off-label use in neutropenia (32). This last indication has been the thematic area for many mental health researchers. It has been observed that Lithium causes an increase in circulating neutrophils and accelerates their production from the bone marrow through an expansion of progenitor cells **(34).**

After many research on the topic, it seems that a plasma concentration of Lithium greater than 0.3mEq/L is efficient to produce and sustain leukocytosis especially neutrophils and eosinophils. To be more specific, it has been observed that an increase of neutrophils occurs for a week and followed by stabilization of their number (35). This action is thought to take place through stimulation of GM-CSF (granulocyte-macrophage colony stimulating factor) and CFU-GM (granulocyte-macrophage progenitors), as well as through an increase in life expectancy and number of CFU-S (multipotential stem cells) **(35).** So as long there is a sufficient in quantity group of precursor cells for it to act upon and a proper concentration of the drug in plasma, Lithium can cause leukocytosis. Except for the direct stem-cell stimulation, other theories have been proposed such as stimulation of cytokines, redistribution of demarginated leukocytes, and increased cortisol production **(36).**

The abovementioned action of Lithium has already been exploited in cases of faulty or inadequate neutrophil count caused by cytotoxic drugs **(35)** or even after carbamazepine-induced neutropenia, Felty syndrome and other types of WBC depression **(37,38).**

As mentioned before, clozapine can cause leukopenia. The risk of neutropenia or agranulocytosis induced by clozapine is not as high as other side effects caused by the medication. These adverse effects occur most commonly during the first six to eighteen weeks of therapy (16), then having the same relative risk of appearing as in any other atypical antipsychotic. However, this does not make them less life-threatening.

The mechanism through which clozapine induces neutropenia and agranulocytosis remains unclear even though many

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hypotheses have been expressed. It has been advocated that clozapine leads to a dose-dependent suppression of GM-CSF, followed by an inadequate increase of GM-CSF on the subsequent hematopoietic stress, also caused by the drug **(39).** Another study, concludes that a nitrenium ion derived from clozapine could be the reason for neutropenia through direct action upon the bone marrow rather than a toxicity upon the peripheral neutrophils **(40).** In 2018, Wiciński et al focus again on the nitrenium ion action, supporting the theory that neutropenia is more likely to be immune mediated rather than toxic **(41).** Whatever the mechanism might be, clozapine-associated blood dyscrasias remain one of the main reasons for the medication's withdrawal.

Lithium has been suggested and used of in cases of clozapine-induced leukopenia and in preventing its recurrence or its development in the first place. Kanaan et al published a retrospective case analysis of patients rechallenged with clozapine co-administered with Lithium, after clozapine induced blood dyscrasias concerning a five year long period, resulting in supporting the theory that Lithium prevents recurrence of neutropenia. It also points out that the recurrence's possibility of happening was 4% while the patient is under co-administration of clozapine and Lithium **(42).** The same year, another study was publicized, that included 53 patients rechallenged with clozapine in conjunction with lithium. The results were in agreement with the abovementioned, presenting a majority of patients not featuring neutropenia anew after co-prescription of lithium and clozapine **(43).**

A few years later, Ghaznavi et al present a case of a late-onset neutropenia caused by clozapine, one that had been rechallenged successfully with lithium. In their work, is pointed out once again the fact that lithium causes true leukocytosis and great importance is attached to the fact that the co-administration of clozapine and lithium could, in some cases, result in synergy concerning the drugs' side effects, such as seizures, tremors and agranulocytosis, with that however being temporary (during initiation period) or rare **(44).** In 2016, another report was published that presented the case of a clozapine rechallenge after neutropenia incidence with lithium's addition to the treatment. The co-treatment was crowned with success (neutrophils remained at a normal range and the patient's psychopathology improved), until neurological side effects led to the discontinuation of lithium. As a result, blood dyscrasia occurred anew **(45).**

The reference of international literature in long-term use of lithium to treat clozapine-induced neutropenia is sporadic. This lack of sufficient evidence concerning the co administration of lithium and clozapine after a neutropenia episode has made mental health practitioners skeptical towards using the combination. On the other hand, the failure of other antipsychotics on cases of TRS and the fact that precipitous cessation of clozapine, as in neutropenia for instance, is connected to relapse, sometimes unresponsive to typical antipsychotics **(46),** poses a dilemma whether to rechallenge in a way that ensures the patient's well-being and neutrophil count or not to rechallenge at all. This dilemma remains and is aggravated where the gray zone of the guidelines concerning clozapine rechallenge lies. Namely, when two episodes of neutropenia have occurred because of clozapine.

Summarizing all the above, should we accept the beneficial effect of Lithium in preventing the recurrence of blood dyscrasias, it only seems logical that it should be used during clozapine rechallenge after neutropenia incidence. However, the fact that evidence concerning both Lithium's and clozapine's mechanism of action upon neutrophils and bone marrow are scarce, makes lithium's capability of preventing clozapine-induced neutropenia seem only a logical presumption. Adding to that, the lack of explicit guidelines leads to a restrain, for the mental health practitioners' part, towards clozapine rechallenge after neutropenia incidence, more so after double induced neutropenia. All the above, make the need for more research on the matter crucial, in order for patients with TRS to have a second or even a third chance of a dignified and more qualitative way of life.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

REFERENCES

1. Hippius H. "A historical perspective of clozapine". J Clin Psychiatry. 1999;60 Suppl 12:22-3.

2. Amsler HA, Teerenhovi L, Barth E, Harjula K, Vuopio P. "Agranulocytosis in patients treated with clozapine. A study of the Finnish epidemic". Acta Psychiatr Scand. 1977 Oct;56(4):241- 8.

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 Sep;45(9):789-96.

4. Dan Siskind, Victor Siskind, Steve Kisely. "Clozapine Response Rates among People with Treatment-Resistant Schizophrenia: Data from a Systematic Review and Meta-Analysis». Can J Psychiatry. 2017 Nov;62(11):772-777.

5. Tauscher J, Hussain T, Agid O, Verhoeff NP, Wilson AA, Houle S, Remington G, Zipursky RB, Kapur S. "Equivalent Occupancy of Dopamine D1 and D2 Receptors With Clozapine: Differentiation From Other Atypical Antipsychotics". Am J Psychiatry. 2004 Sep;161(9):1620-5.

6. Nucifora FC Jr, Mihaljevic M, Lee BJ, Sawa A. "Clozapine as a Model for Antipsychotic Development". Neurotherapeutics. 2017 Jul;14(3):750-761.

7. Stephen M. Stahl. (2017) "Essential psychopharmacology: prescriber's guide, 6th edition", Cambridge University Press, pp. 177-187.

8. Rollema H, Lu Y, Schmidt AW, Zorn SH. "Clozapine increases dopamine release in prefrontal cortex by 5-HT1A receptor activation". Eur J Pharmacol. 1997 Nov 5;338(2): R3-5.

9. Stephen M. Stahl. (2013) "Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications, 4th edition". Cambridge University Press, pp.171-172

10. Weiner DM, Meltzer HY, Veinbergs I, Donohue EM, Spalding TA, Smith TT, Mohell N, Harvey SC, Lameh J, Nash N, Vanover KE, Olsson R, Jayathilake K, Lee M, Levey AI, Hacksell U, Burstein ES, Davis RE, Brann MR. "The role of M1 muscarinic receptor agonism of N-desmethylclozapine in the unique clinical effects of clozapine". Psychopharmacology (Berl). 2004 Dec;177(1-2):207-16.

11. Schwieler L, Engberg G, Erhardt S. "Clozapine modulates midbrain interaction with the NMDA receptor complex". Synapse. 2004 May;52(2):114-22.

12. Mohammad Masud Iqbal, Shivale Swati, Alka Aneja, Mohammad Touhid Iqbal, Esha Aneja, Sumala Haque. "Most Common Side Effects of Clozapine and Their Management". International Journal of Emergency Mental Health and Human Resilience, Vol. 18, No.4, pp. 1, ISSN 1522-4821

13. Nielsen J1, Correll CU, Manu P, Kane JM. "Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided?". J Clin Psychiatry. 2013 Jun;74(6):603-13; quiz 613.

14. Pasquale De Fazio, Raffaele Gaetano, Mariarita Caroleo, Gregorio Cerminara, Francesca Maida, Antonio Bruno, Maria Rosaria Muscatello, Maria Jose Jaén Moreno, Emilio Russo, Cristina SeguraGarcía. "Rare and very rare adverse effects of clozapine". Neuropsychiatr Dis Treat. 2015; 11: 1995– 2003.

15. 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 Jul 15;329(3):162-7.

16. 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 Oct;169(4):483-8.

17. Mustafa FA, Burke JG, Abukmeil SS, Scanlon JJ, Cox M. "«Schizophrenia past clozapine»: reasons for clozapine discontinuation, mortality, and alternative antipsychotic prescribing".

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Pharmacopsychiatry. 2015 Jan;48(1):11-4.

18. De With SAJ, Pulit SL, Staal WG, Kahn RS, Ophoff RA. "More than 25 years of genetic studies of clozapine-induced agranulocytosis". Pharmacogenomics J. 2017 Jul;17(4):304-311.

19. NICE. National Health and Care Excellence "Surveillance report 2017 – Psychosis and schizophrenia in adults: prevention and management (2014) NICE guideline CG178" Surveillance report Published 9 November 2017 https://www.nice.org.uk/guidance/cg178/resources/surveillancereport-2017-psychosis-and-schizophrenia-in-adults-prevention-and-management-2014-nice-guidelinecg178-pdf-6041007637189 (accesssed 25/8/2018)

20. Lally J, Gaughran F, Timms P, Curran SR, "Treatment-resistant schizophrenia: current insights on the pharmacogenomics of antipsychotics". Pharmgenomics Pers Med. 2016 Nov 7;9: 117-129.

21. Dan Siskind, Steve Kisely, Rachel Land, Lara McCartney. "41.1 WHAT DO META-ANALYSES TELL US ABOUT CLOZAPINE'S EFFICACY AND EFFECTIVENESS FOR TREATMENT REFRACTORY SCHIZOPHRENIA?". Schizophr Bull. 2018 Apr; 44(Suppl 1): S66.

22. Barnes T and the Schizophrenia Consensus Group of the British Association for Psychopharmacology. "Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology". Journal of Psychopharmacology 2011;25: 567–620.

23. PeggyStephens. "A review of clozapine: An antipsychotic for treatment-resistant schizophrenia". Comprehensive Psychiatry Volume 31, Issue 4, July–August 1990, Pages 315-326.

24. Helio Elkis, Peter F. Buckley. "Treatment-Resistant Schizophrenia". Psychiatric Clinics of North America, 39(2), 239–265.

25. Nielsen J, Young C, Ifteni P, Kishimoto T, Xiang YT, Schulte PF, Correll CU, Taylor D. "Worldwide Differences in Regulations of Clozapine Use". CNS Drugs. 2016 Feb;30(2):149-61.

26. FDA. Clozapine REMS Program. "Clozapine and the Risk of Neutropenia:A Guide for Healthcare Providers", September 2015, updated january 2 of 2018, https://www.clozapine-ems.com/CpmgClozapineUI/rems/pdf/resources/Clozapine_REMS_HCP_Guide.pdf (accessed 3/10/18).

27. Manu P, Sarvaiya N, Rogozea LM, Kane JM, Correll CU. "Benign Ethnic Neutropenia and Clozapine Use: A Systematic Review of the Evidence and Treatment Recommendations". J Clin Psychiatry. 2016 Jul;77(7): e909-16.

28. Nilamadhab Kar, Socorro Barreto, and Rahul Chandavarkar. "Clozapine Monitoring in Clinical Practice: Beyond the Mandatory Requirement". Clin Psychopharmacol Neurosci. 2016 Nov; 14(4): 323–329.

29. Manu P , Lapitskaya Y, Shaikh A, Nielsen J. "Clozapine Rechallenge After Major Adverse Effects: Clinical Guidelines Based on 259 Cases". Am J Ther. 2018 Mar/Apr;25(2): e218-e223.

30. 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 Feb;134(2-3):180-6.

31. Shorter E. "The history of lithium therapy." Bipolar Disord. 2009 Jun;11 Suppl 2:4-9.

32. Stephen M. Stahl. (2017) "Essential psychopharmacology: prescriber's guide, 6th edition", Cambridge University Press, pp. 385-391.

33. Stephen M. Stahl. (2013) "Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications, 4th edition". Cambridge University Press, pp. 371-373.

34. Rothstein G, Clarkson DR, Larsen W, Grosser BI, Athens JW. "Effect of lithium on neutrophil mass and production." N Engl J Med. 1978 Jan 26;298(4):178-80.

35. Ricardo O. Bach, Vincent S. Gallicchio. (1990) "Lithium and cell physiology", Springer-Verlag, chapter 6 pp. 82-93.

36. Whiskey E, Taylor D. "Restarting clozapine after neutropenia: evaluating the possibilities and practicalities." CNS Drugs. 2007;21(1):25-35.

DOI: 10.26386/obrela.v1i4.103 ISSN 2585-2795

37. Fawcett J. Kravitz HM. "The long-term management of bipolar disorders with lithium. carbarnazepine, and antidepressants." J Clin Psychiatry 1985; 46:58-60.

38. Brewerton TD. "Lithium counteracts carbamazepine-induced leukopenia while increasing its therapeutic effect." Biol Psychiatry. 1986 Jun;21(7):677-85.

39. Sperner-Unterweger B, Gaggl S, Fleischhacker WW, Barnas C, Herold M, Geissler D. "Effects of clozapine on hematopoiesis and the cytokine system." Biol Psychiatry. 1993 Oct 15;34(8):536-43.

40. Pirmohamed M, Park K. "Mechanism of clozapine-induced agranulocytosis: current status of research and implications for drug development." CNS Drugs. 1997 Feb;7(2):139-58.

41. Wiciński M, Węclewicz MM. "Clozapine-induced agranulocytosis/granulocytopenia: mechanisms and monitoring." Curr Opin Hematol. 2018 Jan;25(1):22-28.

42. Kanaan RA, Kerwin RW. "Lithium and clozapine rechallenge: a retrospective case analysis." J Clin Psychiatry. 2006 May;67(5):756-60.

43. Dunk LR, Annan LJ, Andrews CD. "Rechallenge with clozapine following leucopenia or neutropenia during previous therapy." Br J Psychiatry. 2006 Mar;188: 255-63.

44. 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 Jul;165(7):813-8.

45. Rémy Dumas, Pierre Bardin, Christian Vedie, "Long-Term Treatment of Clozapine-Induced Leukopenia With Lithium: Fast-Onset Agranulocytosis Following Lithium Discontinuation." Prim Care Companion CNS Disord. 2016; 18(1): 10.4088/PCC.15l01841.

46. Esposito D, Rouillon F, Limosin F. "Continuing clozapine treatment despite neutropenia." Eur J Clin Pharmacol. 2005 Jan;60(11):759-64. Epub 2004 Nov 30.