Mask Off? Lithium Augmentation for Clozapine Rechallenge After Neutropenia or Agranulocytosis: Discontinuation Might Be Risky

To the Editor: Neutropenia (defined as an absolute neutrophil count [ANC] < 1,500 cells/mm^3) occurs in 3%–5%[1,2] of individuals taking clozapine, and agranulocytosis (defined as an ANC < 500 cells/mm^3) occurs in 0.38%–0.81%.[3,4] To mitigate the risk of recurrent dyscrasia, lithium and granulocyte colony-stimulating factor may be added when clozapine is restarted.[5–8] In a systematic review, Manu et al[6] reported that 94% (33/35) of successful clozapine rechallenges included lithium augmentation. Although lithium may, on average, increase ANC by 88% of baseline values,[9] little is known about the long-term need for lithium after clozapine rechallenge, especially given known side effects. Do individuals develop neutropenia or agranulocytosis after lithium is discontinued?

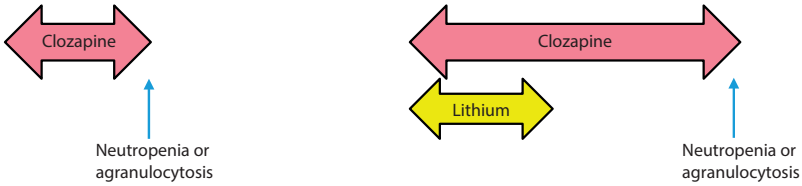
Methods. We conducted a PubMed search through December 10, 2017, using the MESH terms "clozapine" AND "lithium" AND "neutropenia" OR "agranulocytosis."

Results. The search returned 94 articles. Twenty-seven[5–7,10–33] articles described reports of lithium augmentation in clozapine rechallenge after neutropenia or agranulocytosis (Supplementary Table 1), totaling 94 individual patients. Lithium augmentation was successful in 82 of 94 cases (87.2%). We examined the outcome of individuals whose lithium was discontinued after successful clozapine rechallenge. Of 2 individuals (mean time to dyscrasia was 28 days; range, 14–42), both developed neutropenia after lithium was discontinued (Figure 1). We also examined the outcome of individuals who were coprescribed lithium and clozapine (without prior blood dyscrasias), after which lithium was discontinued. Of 6 individuals, 4 developed neutropenia and 2 developed agranulocytosis (mean time to dyscrasia was 38 days; range, 6–120; Figure 2).[34,36] Of the 2 agranulocytosis cases, 1 responded immediately to granulocyte-macrophage colony-stimulating factor and the other died due to infectious complications (Figure 2).[34,36] Of the 4 cases that developed neutropenia, 2 were restarted on lithium and continued clozapine treatment.[21,31]

Discussion. Similar to Manu et al,[6] we found that lithium augmentation to clozapine can be a successful strategy after neutropenia or agranulocytosis. Our findings raise concern about lithium discontinuation after successful clozapine rechallenge, although our search was limited by a very small sample size and potential publication bias. The use of lithium in patients taking clozapine has raised a number of concerns, including lithium potentially masking impending neutropenia or agranulocytosis.[5,15,37] Our finding of a short time to dyscrasia after lithium discontinuation (approximately 1 month) suggests the possibility of a masking effect, although it is possible that lithium may be protective against blood dyscrasias due to its previously established protective effects of progenitor cells, stimulation of granulocyte colony-stimulating factor production and release, and independent stimulation of progenitor proliferation.[9] Another concern regarding ongoing use of lithium is the potential development of adverse neurologic events,[38] and 1 of our reviewed cases of lithium augmentation reported new-onset seizures.[17]

Conclusion. In efforts to minimize polypharmacy, clinicians unfamiliar with lithium's role of increasing the ANC may attempt

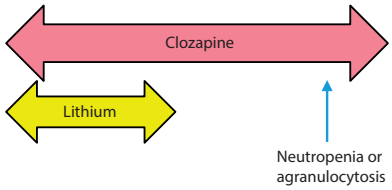
Figure 1. Reported Cases of Lithium Discontinuation After Successful Clozapine Rechallenge



Article	Time On Clozapine Prior to Initial Dyscrasia (days)	Lowest Reported Initial Neutrophil Count (cells/mm^3)[a]	Time Off Clozapine Prior to Clozapine Rechallenge (days)	Time From Clozapine Restart to Lithium Discontinuation (days)	Time From Lithium Discontinuation to Dyscrasia (days)	Recurrence of Dyscrasia After Lithium Was Stopped	Lowest Reported Absolute Neutrophil Count After Rechallenge (cells/mm^3)[a]	Comments
Dumas et al[33]	600	1,370	365	420	14	Yes	800	Lithium was stopped due to intractable tremor; absolute neutrophil count fell to 800 cells/mm^3 and recovered 2 weeks after clozapine was stopped
Mattai et al,[32] case 3	Unclear	1,260	252	182	42	Yes	Neutropenia with an unspecified absolute neutrophil count	One patient had developed neutropenia with clozapine and was restarted on clozapine and lithium successfully. After lithium was discontinued, the patient developed neutropenia, requiring lithium rechallenge; the combination was well tolerated

[a]Articles varied in neutrophil measure (cells/mm^3, cells/uL, cells/L, and percentage of total white blood cell count); where possible, these were converted to cells/mm^3.

Figure 2. Reported Cases of Lithium and Clozapine Cotherapy and Development of Neutropenia or Agranulocytosis After Lithium Discontinuation



Article	Time on Lithium Prior to Dyscrasia (days)	Time on Clozapine Prior to Dyscrasia (days)	Time From Lithium Discontinuation to Dyscrasia (days)	Lowest Reported Absolute Neutrophil Count (cells/mm^3)[a]	Comments
Gerson et al[34]	Unclear	42–63	6	0	Case of a failed clozapine challenge with prophylactic lithium. The patient, who had been successfully challenged, was discontinued off lithium; consequently, the patient developed agranulocytosis and soon thereafter died from complications. The patient was also on coadministered carbamazepine, which was not discontinued
Pinninti et al[31]	330	330	14	900	Notably, the patient initially developed neutropenia (1,000 cells/mm^3) after 1 week of clozapine treatment. The patient was not discontinued and was started on lithium; 11 months into treatment with combination clozapine and lithium, lithium was discontinued, and 2 weeks later the patient developed neutropenia again
Sporn et al[21]	180	180	42	3,000 white blood cell count (dropped from 6,000–8,000)	The patient developed blood dyscrasia 6 weeks after lithium discontinuation during the first clozapine/lithium challenge. The patient was started on the combination of clozapine and lithium (1 year after prior treatment) and successfully stabilized for 5.5 months
Madeb et al[35]	60	60	30	50	The patient developed diabetes insipidous and required lithium discontinuation; the patient was started on valproic acid. Within 1 month of lithium discontinuation and valproic acid start, the patient developed agranulocytosis
Imbarlina et al,[36] case 2	56	14	14	Approximately 1,500	Lithium was discontinued after 8 weeks of treatment, then clozapine was started; 2 weeks later, the patient developed neutropenia. Notably, the patient was restarted on clozapine alone 2 weeks after discontinuation and again developed neutropenia
Imbarlina et al,[36] case 3	1,095	1,215	120	<1,500 (indicates neutropenia)	Lithium was discontinued due to renal failure, and valproic acid was started; 4 months later, the patient developed neutropenia, which required clozapine discontinuation

[a]Articles varied in neutrophil measure (cells/mm^3, cells/uL, cells/L, and percentage of total white blood cell count); where possible, these were converted to cells/mm^3.

to discontinue it, especially since it most likely does not play a significant role in augmenting the efficacy of clozapine.[39] Given no reports of safe lithium discontinuation in the literature, lack of efficacy does not appear to be a reasonable consideration in deciding whether to discontinue the medication. Therefore, we would encourage caution in discontinuation of lithium after a successful clozapine initiation, especially in the setting of rechallenge. Given the limited reports on this topic, we support more active reporting on rechallenge augmented with lithium and more work to elucidate the mechanism of clozapine-induced blood dyscrasias to disentangle the putative lithium masking issue.

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Supplementary Material

Article Title: Mask Off? Lithium Augmentation for Clozapine Rechallenge After Neutropenia or Agranulocytosis: Discontinuation Might be Risky

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List of Supplementary Material for the article

1. Supplementary Table 1. Reports of Lithium Augmentation in Clozapine Rechallenge With Enumerated Succeeded and Failed Cases

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Supplementary Table 1. Reports of Lithium Augmentation in Clozapine Rechallenge With Enumerated Succeeded and Failed Cases

Report	Summary	Number of Succeeded Cases	Number of Failed Cases
(1)	Literature review of 30 rechallenged cases after neutropenia/agranulocytosis who were additionally treated with g-csf either prophylactically, or as needed. Five cases were also co-administered lithium (prophylactically for blood dyscrasia). Of these two failed rechallenge.	3	2
(2)	Retrospective analysis of 51 rechallenged patients, 19 of whom had previously developed neutropenia. Of the 19 with previous neutropenia 16 were co-administered lithium during challenge. Four of the 16 failed rechallenge. Of those who failed rechallenge clinical characteristics are shared.	12	4
(3)	Case series of three successful rechallenge cases after neutropenia. All were stable after rechallenge for at least a 24 month period.	3	0
(4)	Case of clozapine rechallenge after lithium addition in setting of previous drop in ANC with clozapine use.	1	0
(5)	Case of clozapine challenge with prophylactic lithium after previous quetiapine induced neutropenia.	1	0
(6)	Case series of 10 patients successfully rechallenged on clozapine with prophylactic lithium after prior episode of neutropenia. One of these was of a patient who failed	10	0

	rechallenge twice and when finally augmented with lithium was successful. Two of these were patients who had ANC's >1.5 on previous failure. One was a patient with prior neutropenia not associated with clozapine.		
(7)	Case of patient of Ashkenazi Jewish origin failing clozapine rechallenge with prophylactic lithium with consequent protracted (27 day) blood dyscrasia.	0	1
(8)	Case of patient successfully rechallenged on clozapine and prophylactic lithium after having previously developed neutropenia (in setting of combined clozapine and valproic acid).	1	0
(9)	Case of patient who failed clozapine challenge, but eventually succeeded with combination clozapine and lithium.	1	0
(10)	Successful rechallenge in benign ethnic neutropenia patient with three previous failures due to neutropenia, successful finally on combination clozapine and lithium.	1	0
(11)	Patient rechallenged after previous neutrophil decline in setting of clozapine treatment. Patient challenged on combination clozapine, lithium, and single dose of g-csf.	1	0
(12)	Retrospective analysis of 25 clozapine rechallenged patients (with prophylactic lithium) who had previously developed CIN. One of these was unsuccessful, going on to develop an atypical infection raising suspicion for lithium having masked blood dyscrasia. In the one patient dyscrasia was more rapid, though not more severe.	24	1
(13)	Two cases who had previously developed neutropenia, with ANC <1.5, and went on to successfully tolerate clozapine rechallenge in setting lithium augmentation.	2	0
(14)	Case series of two cases, both previously developing neutropenia in setting of clozapine treatment, one of the	2	0

	two cases had developed neutropenia after lithium was discontinued. Both patients were subsequently successfully rechallenged on clozapine with prophylactic lithium.		
(15)	Case of a patient who successfully was rechallenged on clozapine and lithium after a previous clozapine failure due to neutropenia.	1	0
(16)	Case series of two patients. First patient developed neutropenia in setting of clozapine treatment, was subsequently successfully rechallenged on clozapine with aid of lithium. Second patient failed first challenge of clozapine, having developed agranulocytosis. Second patient was started on lithium after first clozapine discontinuation for purpose of increasing blood counts, with successful response to lithium.	1	0
(17)	Case of patient who failed clozapine challenge due to neutropenia, was subsequently successfully rechallenged with prophylactic lithium.	1	0
(18)	Case of patient who developed neutropenia with clozapine treatment, was discontinued, later restarted on clozapine and lithium with successful rechallenge.	1	0
(19)	Case of patient who developed agranulocytosis shortly after first clozapine challenge, was later successfully rechallenged with clozapine and lithium co-administration.	1	0
(20)	Case of patient who developed neutropenia with initial clozapine challenge, when rechallenged with combination vitamin c, lithium, and clozapine was unsuccessful, developing agranulocytosis shortly after rechallenge.	0	1

(21)	Case of patient who developed agranulocytosis on previous clozapine challenge. Patient was successful in clozapine rechallenge with combination lithium.	1	0
(22)	Retrospective analysis of 172 children challenged with clozapine. Of these 24 patients developed neutropenia requiring clozapine discontinuation, 20 of the 24 were subsequent rechallenged once more. Seven of the rechallenged patients were rechallenged with co-administered lithium. One of the patients rechallenged with co-administered lithium failed rechallenge.	6	1
(23)	Case of patient who failed previous clozapine challenge due to neutropenia was successfully rechallenged on combination lithium and clozapine.	1	0
(24)	Case of a patient who was successfully rechallenged on clozapine with prophylactic lithium after previous CIN. At first rechallenge with lithium augmentation patient had done well, however, when lithium was discontinued patient developed neutropenia requiring clozapine discontinuation with subsequent improvement in neutrophil count. Patient was eventually again rechallenged with prophylactic lithium and has been stable on the combination.	1	0
(25)	Case series of 7 patients with previous neutropenia who were successfully rechallenged with prophylactic lithium. Only two of the seven cases had developed previous neutropenia in the setting of clozapine use. All, but 1 were continued on lithium and clozapine. Subject 3, who was discontinued off lithium re-developed neutropenia, but successfully tolerated clozapine with lithium rechallenge.	6	1

(26)	Case of a patient successfully rechallenged on clozapine with prophylactic lithium after previous neutropenia. Patient was on clozapine for 14 months, but eventually required lithium discontinuation due to an intolerable tremor. The patient subsequently developed repeat neutropenia within two weeks requiring clozapine discontinuation.	0	1
(27)	Review of patients rechallenged on clozapine subsequent to previous adverse events. Discussed cases reporting on 35 patients rechallenged with co-administered lithium after prior neutropenia or agranulocytosis. Their reviewed articles have been reviewed above and we did not include Manu et al's numbers to avoid redundancy.	As above	As above
Total		N=82	N=13

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