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Mask off? Lithium augmentation for clozapine rechallenge after neutropenia or agranulocytosis: discontinuation might be risky

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To the Editor:

Neutropenia (defined as an absolute neutrophil count <1500 cells/mm³) occurs in 3–5%^{1,2} of individuals on clozapine, and agranulocytosis (defined as an ANC <500 cells/mm³) occurs in 0.38–0.81%^{3,4}. To mitigate the risk of recurrent dyscrasias, lithium and/or granulocyte colony-stimulating factor have been added when clozapine is restarted^{5–8}. In a systematic review, Manu et al reported that 94% (33/35) of successful clozapine rechallenges included lithium augmentation. Though lithium may on average increase ANC by 88% of baseline values⁹, 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 up to December 10, 2017 using the MESH terms “clozapine” AND “lithium” AND “neutropenia” OR “agranulocytosis”.

RESULTS:

The search returned 94 articles. 27 articles described reports of lithium augmentation in clozapine rechallenge after neutropenia or agranulocytosis [supplement Table 1], totaling 94 individual patients. Lithium augmentation was successful in 82/94 (87.2%) of cases. We examined the outcome of individuals whose lithium was discontinued after successful clozapine rechallenge. Of two individuals (mean time to dyscrasia was 28 days; range 14–42), both developed neutropenia after lithium was discontinued (Figure 1a). We also

examined the outcome of individuals who were co-prescribed lithium and clozapine (without prior blood dyscrasias), after which lithium was discontinued. Of six individuals, four developed neutropenia and two developed agranulocytosis (mean time to dyscrasia was 37.67 days; range 6–120; Figure 1b). Of the two agranulocytosis cases, one responded immediately to granulocyte-macrophage colony stimulating factor (GM-CSF) and the other died due to infectious complications (Figure 1b). Of the four cases that developed neutropenia, two^{10, 11} were restarted on lithium and continued clozapine treatment.

DISCUSSION AND CONCLUSION:

Similar to Manu et al⁶, 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. though our search was limited by a very small sample size and potential publication bias. The use of lithium in patients on clozapine has raised a number of concerns, including lithium potentially masking impending neutropenia or agranulocytosis^{5, 12, 13}. Our finding of a short time to dyscrasia after lithium discontinuation (~1 month) suggests the possibility of a masking effect, though it is possible that lithium may be protective against blood dyscrasias due to its previously established protective effects of progenitor cells, stimulation of G-CSF production and release, and independent stimulation of progenitor proliferation⁹. Other concern regarding ongoing use of lithium is the potential development of adverse neurological events¹⁴, and one of our reviewed cases of lithium augmentation reported new onset seizures¹⁵.

In efforts to minimize polypharmacy, clinicians unfamiliar with lithium's role of increasing the ANC, may attempt to discontinue it, especially since it likely does not play a significant role in augmenting the efficacy of clozapine¹⁶. 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. 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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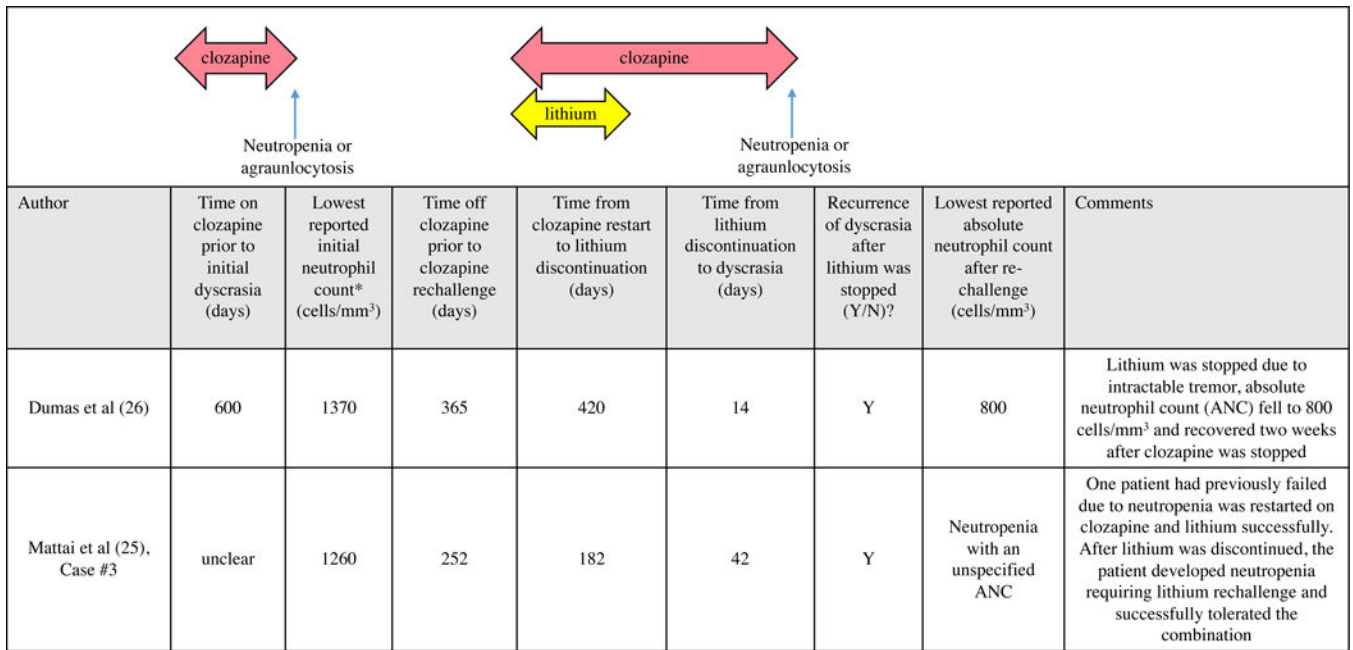


Figure 1a.
Reported cases of lithium discontinuation after successful clozapine rechallenge.

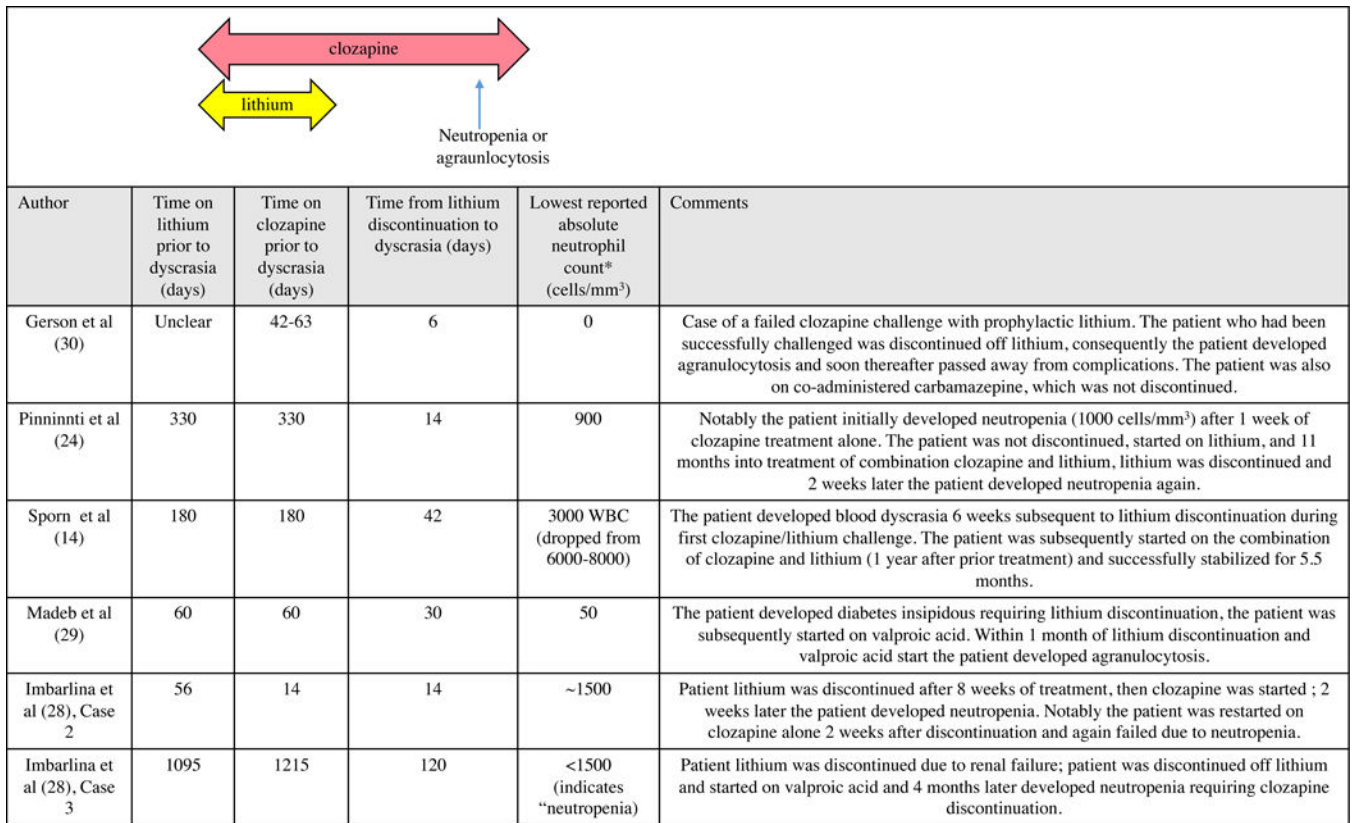


Figure 1b.
Reported cases of lithium and clozapine co-therapy and development of neutropenia/
agranulocytosis after lithium discontinuation.