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Letter to the Editor: Protracted Neutropenia After Treatment With Non-Clozapine Antipsychotic Medications

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Letter to the Editor
Protracted Neutropenia After Treatment With Non-Clozapine Antipsychotic Medications

To the Editors:

Among antipsychotic medications, clozapine is known for inducing neutropenia, defined as an absolute neutrophil count (ANC) <1500/μL. Yet, studies suggest that a variety of non-clozapine antipsychotic medications are also implicated in the development of neutropenia.[1,2] Specifically, a meta-analysis concluded that there were no statistically significant differences in the incidences of neutropenia secondary to clozapine compared with incidences of neutropenia secondary to non-clozapine antipsychotic medications.[3] Although the United States Risk Evaluation and Mitigation Strategies stipulate specific ANC monitoring guidelines and parameters for clozapine because of risk of neutropenia and agranulocytosis, there are no established ANC monitoring guidelines for non-clozapine antipsychotic medications.

Although neutropenia may be asymptomatic, it can result in recurrent infections, fever, and sepsis. Moreover, although drug-associated neutropenia is typically transient, a patient may develop recurrent neutropenia in the future with another medication.[4–8] Hence, awareness of ANC is clinically relevant, even when using non-clozapine antipsychotic medications. To our knowledge, there are no reported cases of non-clozapine antipsychotic medication-associated neutropenia lasting for longer than 1 month. Herein, we present the case of a woman who developed a protracted course of neutropenia after treatment with 3 non-clozapine antipsychotic medications, which ultimately resolved with antipsychotic medication cessation and lithium treatment. Written consent to publish a report of the case was obtained. Information was deidentified to protect anonymity.

CASE REPORT

A 28-year-old White woman with non-Hashimoto hypothyroidism and no personal or family history of blood dyscrasias presented to our psychiatric clinic with dysphoric mood. She was taking levothyroxine 50 μg daily and reported not using other medications or substances. At the time, her presentation appeared consistent with bipolar II disorder. She was sequentially prescribed aripiprazole 15 mg daily and cariprazine 3 mg daily, which were discontinued after 1 and 2 months, respectively, because of lack of efficacy. Lurasidone was subsequently initiated and titrated to 40 mg daily; propranolol 10 mg twice daily was added for akathisia.

A baseline complete blood count with differential (CBC with diff), glycolated hemoglobin, and lipid profile were ordered before antipsychotic medication initiation. However, laboratory procedures were not completed until 6 months into lurasidone treatment. Absolute neutrophil count was found to be 1200/μL, decreased from 3800/μL as measured before any antipsychotic medication treatment. Her physical examination was unremarkable. With this decrement in ANC, as well as intolerable side effects, lurasidone and propranolol were tapered off; and her internist referred her to hematology/oncology and rheumatology for further evaluation.

A comprehensive workup revealed a positive antinuclear antibody (ANA) titer (1:1280). Rheumatoid factor, anti–scleroderma-70, anti-Ro, anti-La, anti-smith, ribonucleotide peptide, complements C3 and C4, double-stranded DNA, antihistone, cyclic citrullinated peptide, hepatitis B and C antibodies, and human immunodeficiency virus-1 p24-antigen resulted negative. Urinalysis, monoclonal protein evaluation, vitamin B12, folate, erythrocyte sedimentation rate, C-reactive protein, creatinine phosphokinase, and thyroid-stimulating hormone were all normal.

After lurasidone discontinuation, the patient's ANC remained low and fluctuated between 700 and 1400/μL over 12 weeks. Although no fevers were noted, she periodically endorsed fatigue. There were no changes made to her levothyroxine dose, and there were no other nonpsychotropic medications initiated during this time. Specialists suspected that her neutropenia was secondary to lurasidone treatment. She was started on 600-mg lithium-controlled release nightly. Serum lithium level and renal and thyroid function were monitored accordingly. After 6 months, her ANC normalized to 2400 to 2900/μL.

DISCUSSION

Neutropenia can be characterized as mild (ANC, 1000–1400/μL), moderate (ANC, 500–999/μL), or severe (ANC, less than 500/μL). Among other causes, the origin of neutropenia may be congenital, related to mutations affecting myeloid gene precursors. It may also occur secondary to medications, benign ethnic neutropenia, which typically affects individuals of African, Middle Eastern, and West Indian lineage, malignancies affecting bone marrow reserve, nutrient deficiencies, infections, autoimmune disorders, or hypothyroidism.[9–11] Of note, clozapine-induced neutropenia is associated with HLA-DBQ1 variants in individuals of European ancestry.[12] Although we did not pursue genetic or biochemical analysis for our patient, the Naranjo scores for aripiprazole (3), cariprazine (2), and lurasidone (3) suggest possible drug-associated neutropenia.[13]

While a literature search reveals no reports of cariprazine-associated neutropenia, neutropenia secondary to aripiprazole and lurasidone treatment has been reported.[6,8,14–16] Most cases of drug-associated neutropenia resolve within 1 month of medication cessation alone.[2,17] While our patient's ANC may have increased after cessation of the lurasidone alone, given that she still had neutropenia 12 weeks after its cessation, we decided to initiate lithium. Lithium, which is classically used off-label for clozapine-associated neutropenia, modulates neutrophil count by promoting granulocyte colony stimulating factor production and pluripotent stem cell proliferation.[18] Though not extensively reported, lithium may be useful for non-clozapine antipsychotic drug-associated neutropenia which persists after the suspected

offending agent has been discontinued, as may have been demonstrated in our case.

There are limitations that should be considered. As she was trialed on aripiprazole and cariprazine before lurasidone, ANC was not checked while she was on these medications, and there was not a washout period without antipsychotic medications, neutropenia may have been associated and potentiated by any of these medications. In addition, given that our patient had an elevated ANA titer, it is possible that an autoimmune disorder may have contributed to the development of neutropenia. Yet, ANA is not a specific measure of autoimmunity, and since the comprehensive autoimmune panel was otherwise unremarkable, this explanation is less likely. Drug-associated lupus, potentially secondary to propranolol, may also have resulted in both elevated ANA titer and neutropenia. However, the lack of antihistone antibodies points away from this possibility. Moreover, other infections may have contributed to her neutropenia; however, this is unlikely given the lack of C-reactive protein elevations or fever. Finally, White patients may have benign decrements in ANC for no apparent reason, although this is relatively less common.[19]

Overall, as seen in our patient, ANC can fluctuate in individuals prescribed non-clozapine antipsychotic medications, even in the absence of benign ethnic neutropenia, concomitant use of neutropenia-associated medications, or known blood dyscrasias. Although our patient had mild to moderate neutropenia and her antipsychotic medications were discontinued because of lack of efficacy or tolerability, had her ANC not been checked, continued antipsychotic medication use may have potentially resulted in persistent neutropenia or progressed to agranulocytosis. We therefore propose that baseline and routine CBC with diff monitoring in patients who are prescribed any antipsychotic medication is a worthy intervention. Because CBC is already ordered as part of the standard workup of first-episode psychosis and depressive disorders, and glycolated hemoglobin and lipid profiles are monitored at least once yearly in patients prescribed antipsychotic medications, baseline and routine monitoring of CBC with diff can practically be completed without concerns for any additional burden for compliance on the patient. As per Risk Evaluation and Mitigation Strategies, when prescribing clozapine, a decrease in ANC to the mild or moderate range is not necessarily a reason to discontinue it indefinitely. Similarly, we argue that decreases in ANC to the mild to moderate range of patients prescribed non-clozapine antipsychotic medications should not necessarily prohibit their use or be a reason to withhold treatment. Rather, routine monitoring may offer a chance for physicians to intervene and involve appropriate specialty services to elucidate reasons for neutropenia to help guide future treatment as deemed clinically necessary.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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Albuterol-Associated Hallucinations
A Case Report and Literature Review

To the Editors:

Albuterol (Teva Pharmaceuticals, Horsham, PA) is typically considered a relatively benign medication free from major drug interactions and serious side effects, which