Title: Late onset neutropenia in long term clozapine use: a challenge for treatment and prognosis.

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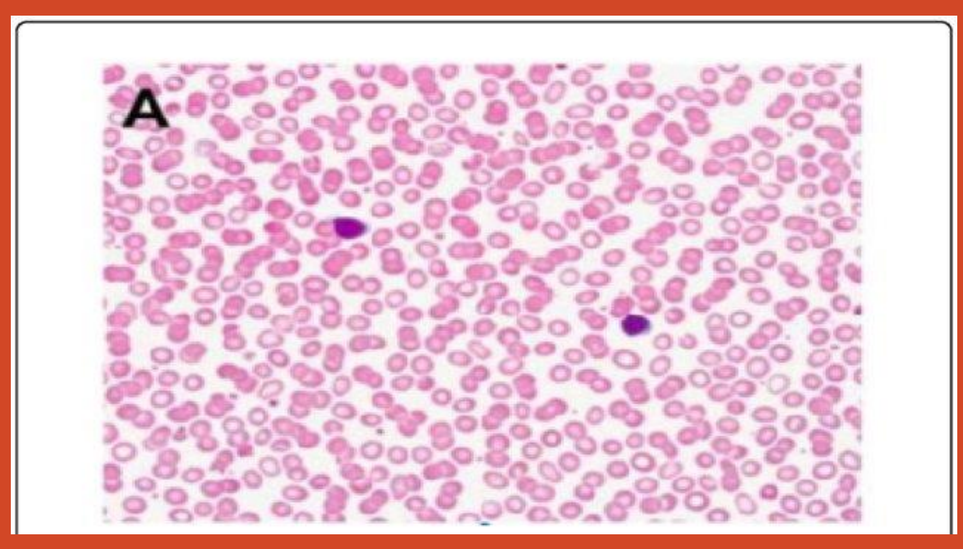
Background:

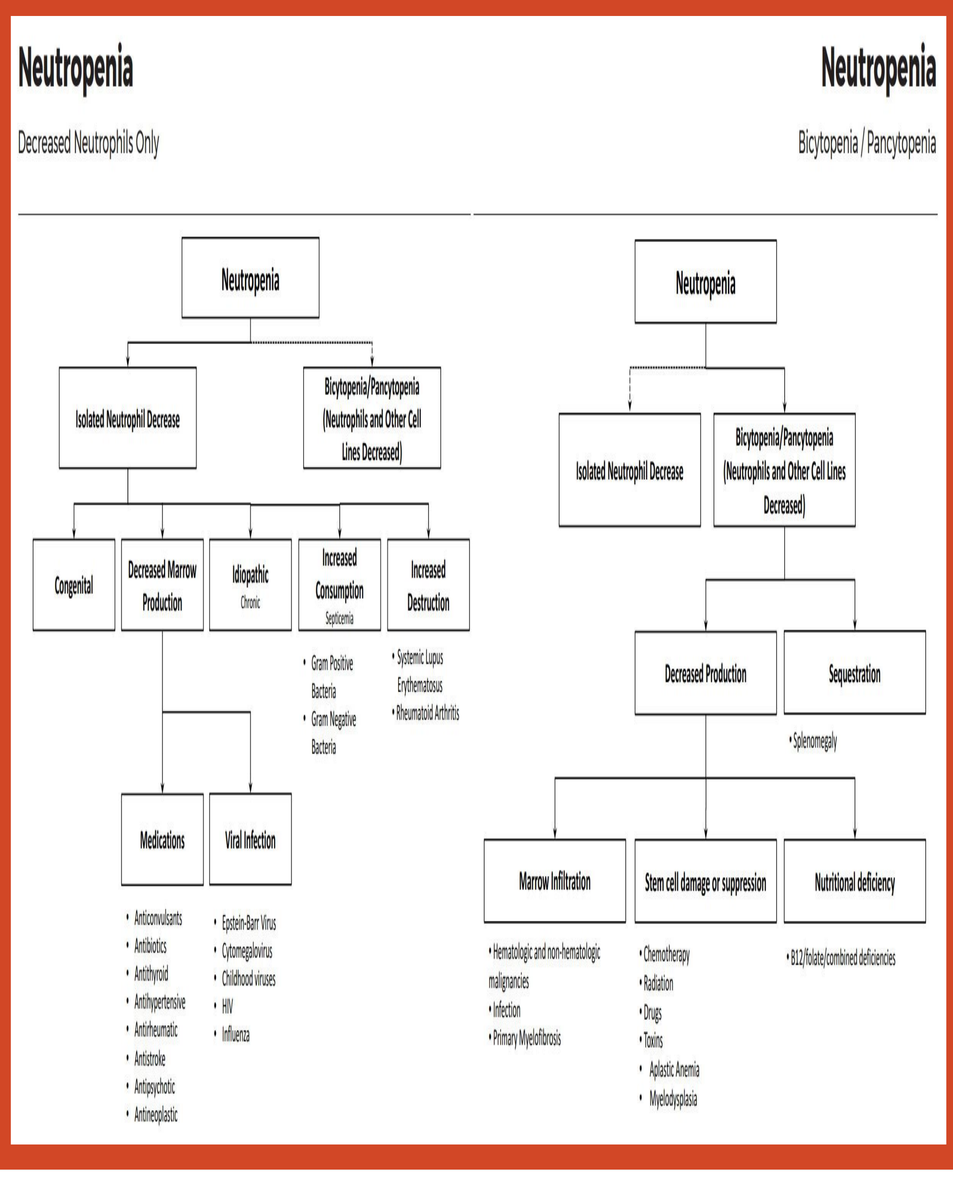
Treatment resistant schizophrenia (TRS) affects 20-23% of schizophrenic patients. A recommended medication for treating TRS is clozapine which works on many molecular targets. Such varied action can result in increased tendency toward side effects, the most well known being neutropenia (3%) and agranulocytosis (1%). There are many genetic, immunological and iatrogenic reasons for neutropenia in clozapine use. Despite its side effects and complicated action, evidence based medicine has identified clozapine as being the most effective treatment for TRS. The following case outlines recurrent neutropenia after fourteen years of successful clozapine use. It was necessary for the patient to follow a complicated treatment path involving close monitoring of blood levels, the initiation of lithium and the regular use of filgrastim, a granulocyte colony stimulating factor (G-CSF). Clozapine treatment was continued due to a failure of other anti-psychotic medications to treat her symptoms adequately. This aim of this report is to outline the treatment of clozapine induced neutropenia.

Methods:

Female with TRS was admitted to an acute mental health unit in Cork due to deterioration in her mental state secondary to discontinuation of clozapine treatment (as a result of neutropenia). The patient had been taking clozapine for fourteen years. Following trials of other anti-psychotics which were ineffective, lithium and GM-CSF, filgrastim, was prescribed in 2019 with hopes to improve her WBC level. The possibility of ongoing lithium use in combination with clozapine led to the decision to re-challenge with clozapine. The patient responded well to clozapine re-challenge utilizing the advice of on-site haematology, however, suffered recurrent neutropenic results.

Figure 1: Blood film showing neutropenia





Results:

Strategies to avoid neutropenia included use of lithium, use of neupogen as a rescue treatment and prophylactic use of neupogen. Haematology have recommended a low threshold to administer neupogen in the case of neutropenic reoccurance. Haematology are currently working out a schedule for the patient to take neupogen prophylactically, this could avoid neutropenic results and further guarantee her mental state as she would continue her use of clozapine.

Graph 1: Neutrophil level 2018

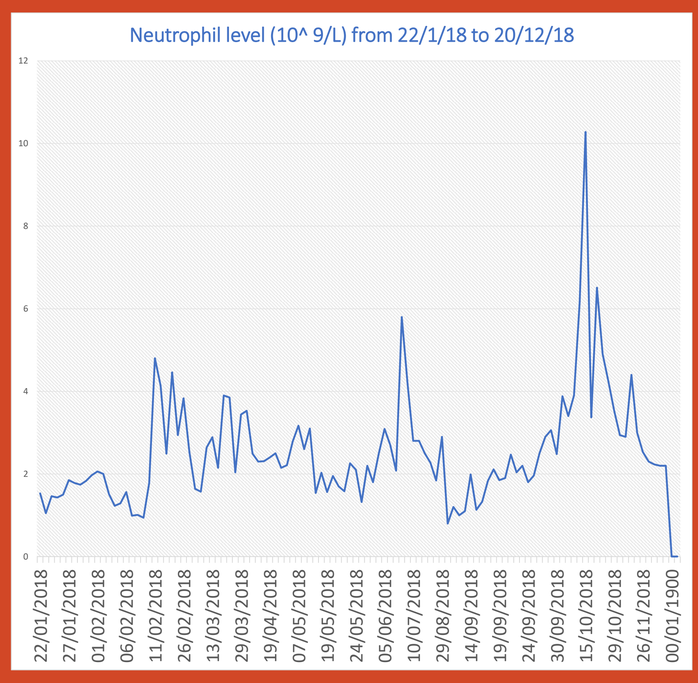


Figure 1 displays the neutrophil level from 22/1/18 to 20/12/18. The x axis displays dates of neutrophil results and the y axis shows neutrophil levels on serum testing. Late January 2018 to 11th of February 2018 showed a period of neutropenia (between 1.0 $x10^9$/L and 2.0 $x10^9$/L). What follows is a period of green/amber results with later falls in neutrophil levels to below 2.0 $x10^9$/L. The spikes in neutrophil levels seen in the graph represent results above 1.5 $x10^9$/L. This co-incides with prescription of lithium which was started on 10/3/18.

Graph 2: Patient neutrophil levels 2019

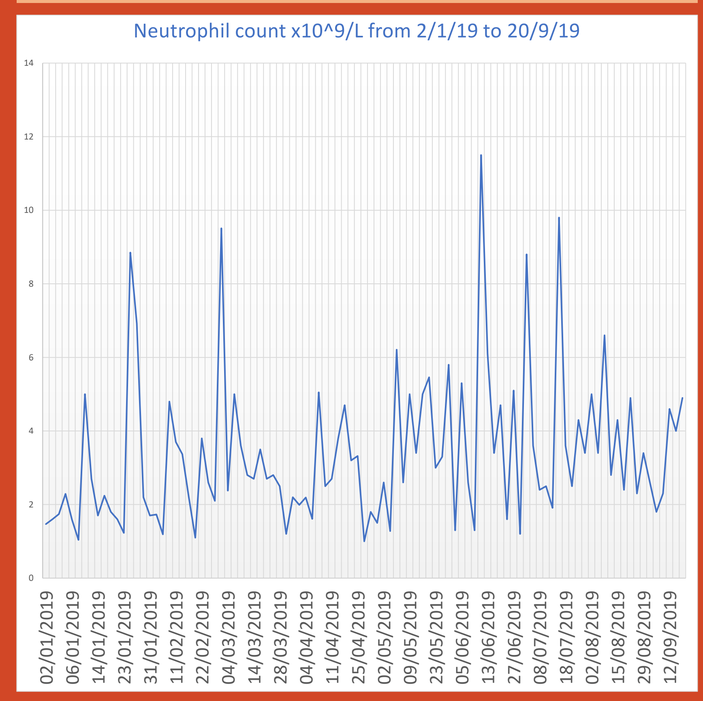


Figure 2 displays the neutrophil level from 2/1/19 to 20/9/19. The x axis displays the dates of neutrophil results and the y axis shows the neutrophil levels on serum testing. Commencement of rescue Filgastrim given on an as needed basis in March 2019 shows a period of stability in baseline ANC, more spikes representing neutrophil levels greater than 2.0 $x10^9$/L and less episodes of neutropenia.

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Figure 3: Neutrophil count post-neupogen

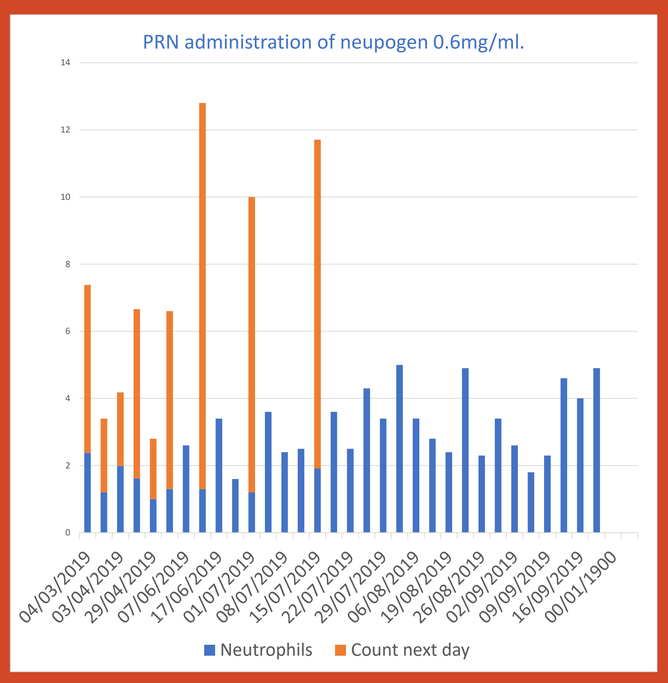

Figure 3 displays the dates of administration of neupogen 30mu, given as needed when neutropenia occurs from March 2019. The x axis shows the dates of neupogen administration and the y axis displays the neutrophil count one day post-neupogen administration. The blue columns represent the ANC prior to giving neupogen and the orange columns represents neutrophil levels one day following neupogen administration. Green light results indicating adequate levels of neutrophils are seen from July 2019.

Discussion:

Cytokines such as G-CSF and GM-CSF are effective in stimulating granulocyte production, which shortens the duration of agranulocytosis.[1] Bone marrow precursor cell levels need to be sufficient prior to cytokine use.[2] There is scope for co-administration of cytokines and lithium in severe neutropenia or refractory cases and conveniently, reliable patients can be coached to self-administer injections of G-CSF.[2] There is no known contra-indication to the continuation of lithium treatment and regular filgastrim injections in conjunction with clozapine as part of long term treatment.[2]

Best practice will continue to change in an attempt to avoid and treat clozapine-induced neutropenia. Recent research debates the need to consider intervention in cases of mild-moderate neutropenia and the latest FDA guidelines, 2015 recommend that neutropenia be monitored using absolute neutrophil count only without surveillance of the total white cell count.[3] Past criteria have proven too rigid, resulting in patients avoiding retrial of clozapine in treatment resistant schizophrenia.[3] Mild-moderate cases of neutropenia have been shown to be a common and benign finding.[3]

Conclusions:

Research into cases re-commenced on clozapine and co-prescribed GM-CSF have demonstrated a 78% success rate compared with co-prescription of lithium which correlates with a 60% success rate. There is no known contra-indication to the continuation of lithium treatment and regular neupogen injections in conjunction with clozapine as part of long term treatment. The patient in this case is currently achieving consistent green light results over the previous six months, despite this vigilance is required which will require careful monitoring and haematology involvement.

Bibliography:

1. **Whiskey E, Taylor D.** Restarting clozapine after neutropenia evaluating the possibilities and practicalities. CNS Drugs. 2007; 21, 25–31.
2. **Myles N, Myles H, Clark SR, Bird R, Siskind D**. Use of granulocyte-colony stimulating factor to prevent recurrent clozapine-induced neutropenia on drug rechallenge: A systematic review of the literature and clinical recommendations. Aust. New Zeal. J. Psychiatry. 2017; 51, 980–989.
3. **Sultan RS, Olfson M, Correll CU, Duncan EJ**. Evaluating the effect of the changes in FDA guidelines for clozapine monitoring. J. Clin. Psychiatry. 2017; 78, 933–939.