

Is haematological monitoring actually needed with clozapine treatment?

Olav Nielssen 

Australian & New Zealand Journal of Psychiatry
2020, Vol. 54(2) 132–133
DOI: 10.1177/0004867419856693

© The Royal Australian and
New Zealand College of Psychiatrists 2019
Article reuse guidelines:
sagepub.com/journals-permissions
journals.sagepub.com/home/anp



Two recently published meta-analyses from a team led by an Adelaide-based haematologist cast doubt on the value of haematological monitoring of patients receiving clozapine, certainly past the first year (Myles et al., 2018, 2019). In the first, the authors analysed 108 studies with more than 450,000 patients who had blood counts while being treated with clozapine, and found rates of mild neutropenia (neutrophil count [NC] < 1500) of 3.8%, severe neutropenia (NC < 500) of 0.7% and mortality from complications of agranulocytosis of 0.013%, or 1 in 7700 treated patients (Myles et al., 2018). Those rates of neutropenia were close to the point prevalence in otherwise healthy members of the community of between 0.4% and 4.5% for NC < 1500, and between 0.08% and 0.57% for NC < 1000 (Hsieh et al., 2007). The rates of neutropenia after the first year of monitoring was even lower, as 89% of events occurred in the first 12 months of treatment. In the second study recently published in the *ANZJP*, the authors compared the rates of neutropenia observed in patients treated with clozapine compared to other antipsychotic medications from 20 controlled trials with 1260 patients, who were monitored for an average of 2.4 years (Myles et al., 2019). The rates of neutropenia for those treated with clozapine were not significantly different to those observed in people treated with antipsychotics other than clozapine.

The cause of clozapine-induced agranulocytosis (CIAG) is assumed to be an auto-immune reaction to, or direct toxicity of the ionised metabolite

nitrenium, a process that takes place in leukocytes and may itself be related to a genetic vulnerability (Wicinski and Weclawicz, 2018). However, the two epidemiological studies do not confirm a causal connection between clozapine treatment and neutropenia, even though neutropenia is relatively common among people being treated with clozapine. The risk ratio of neutropenia in patients treated with clozapine and other antipsychotics, including chlorpromazine, olanzapine, risperidone and haloperidol, which are medications that have been widely prescribed without any concern being raised about the haematological implications, were on average 1.45, although with overlapping confidence intervals (Myles et al., 2019). Moreover, a high proportion of patients who take clozapine are also taking another antipsychotic medication, as well as other types of medication with similar metabolism pathways and the potential for drug–drug interactions.

The findings raise a number of important questions. The first is, should we be performing routine haematological monitoring of all patients on antipsychotic medication or, for that matter, all patients on any psychotropic medication? Based on the risk ratios and confidence intervals reported in the studies comparing other antipsychotics with clozapine, and the absence of clinical evidence of an association between these widely prescribed medications and neutropenia, the answer is probably no, although the current RANZCP guidelines recommend a full blood count at baseline and again at 24 weeks and annually for all antipsychotic medications. The question is

then, are we wasting health resources and subjecting mentally ill patients to excessive regimentation and discomfort by insisting on indefinite haematological monitoring? Based on the risk ratios identified by meta-analysis, and the actual mortality from complications of agranulocytosis in patients treated with clozapine, the answer would be yes, at least after the first year. We should then ask ourselves, have we deprived many patients of at least a trial of the best available treatment for schizophrenia because of our estimate of their likely compliance with blood monitoring? There is no doubt that clozapine is a superior treatment for many patients with schizophrenia. There is evidence from both large controlled studies and meta-analysis that treatment with clozapine is associated with reduced symptoms, better cognitive function and better social function; reduced all-cause mortality; and reduced incidence of both violence and suicide. The lower overall mortality of patients on long-term clozapine treatment puts the anxiety about rare haematological and even cardiac complications into perspective, as the annual rate of suicide alone of people with schizophrenia is an order of magnitude greater than

Faculty of Medicine and Health Sciences,
Macquarie University, North Ryde, NSW,
Australia

Corresponding author:

Olav Nielssen, Faculty of Medicine and Health Sciences, Macquarie University, PO Box 4001, North Ryde, NSW 2113, Australia.
Email: olav.nielssen@mq.edu.au

the mortality from the complications of clozapine. Guidelines suggest that between 20% and 30% of patients with chronic forms of schizophrenia should be receiving clozapine. Among New South Wales Forensic Patients, who receive optimal rehabilitation, 43% are being treated with clozapine, whereas only 3.9% of a large sample of homeless people with psychotic illness have ever received that treatment, despite often having severe and chronic illness. A study from Queensland estimated the proportion of patients with schizophrenia receiving clozapine at about 8.3%, in keeping with what we know about the suboptimal care of people with schizophrenia in this country.

Myocarditis and cardiomyopathy during clozapine treatment are a separate concern, although a population-based study found the rates of adverse cardiac events to be very low and were also comparable to those observed in people taking other antipsychotic drugs (Rohde et al., 2018). It may even be the case that the regular review by doctors

and nurses at clozapine clinics is actually part of the therapeutic effect of clozapine, and it would be a shame if an unintended consequence of a change in monitoring regimes was less frequent review of patients with severe forms of schizophrenia. However, the final question is addressed to us as a profession. Isn't it our job to synthesise scientific evidence and provide the best advice to our patients regarding treatment, within our area of expertise? Based on the findings of these important papers, we should review the protocols for haematological monitoring of patients being treated with clozapine in order to reduce the barriers to treatment with the most effective antipsychotic medication currently available.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Olav Nielssen  <https://orcid.org/0000-0001-5172-2781>

References

- Hsieh MM, Everhart JE, Byrd-Holt DD, et al. (2007) Prevalence of neutropenia in the U.S. population: Age, sex, smoking status, and ethnic differences. *Annals of Internal Medicine* 146: 486–492.
- Myles N, Myles H, Xia S, et al. (2018) Meta-analysis examining the epidemiology of clozapine-associated neutropenia. *Acta Psychiatrica Scandinavica* 138: 101–109.
- Myles N, Myles H, Xia S, et al. (2019) A meta-analysis of controlled studies comparing the association between clozapine and other antipsychotic medications and the development of neutropenia. *Australian and New Zealand Journal of Psychiatry* 53: 403–412.
- Rohde C, Polcwiartek C, Kragholm K, et al. (2018) Adverse cardiac events in out-patients initiating clozapine treatment: A nationwide register-based study. *Acta Psychiatrica Scandinavica* 137: 47–53.
- Wicinski M and Weclawicz MM (2018) Clozapine-induced agranulocytosis/granulocytopenia: Mechanisms and monitoring. *Current Opinion in Hematology* 25: 22–28.