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BJPsych Editorial

Clozapine monitoring requirements: is it time for an update?

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Oloyede and colleagues advocate for updating haematological monitoring requirements for clozapine, arguing that current protocols overestimate the risk of clozapine-induced agranulocytosis. Their research suggests that stringent monitoring may unnecessarily limit access to clozapine, a crucial treatment for resistant schizophrenia. The editorial supports calls for international consensus to carefully weigh the pros and cons of relaxing monitoring guidelines while ensuring comprehensive care for patients.

Keywords
Treatment-resistant schizophrenia; clozapine; agranulocytosis; haematological monitoring; pharmacovigilance.

In this issue, Oloyede and colleagues[1] advocate for updating the haematological requirements for clozapine to increase access to this important drug. Their research indicates that the current system overestimates the incidence of clozapine-induced agranulocytosis (CIA), adding to the growing body of evidence suggesting a lack of significant CIA risk in the medium and long term. As we commemorate the 30th anniversary of the first request to reconsider the blood monitoring requirements,[2] this editorial supports the call for a new international consensus.

The history of blood monitoring requirements for clozapine

Clozapine is the only licensed medication for treatment-resistant schizophrenia (TRS); TRS affects a subgroup of patients where there is a lack of response to two other antipsychotics. First synthesised in 1958, clozapine was launched in Europe in the 1970s. In Finland, clozapine was marketed in February 1975. However, its commercialisation was halted on 28 July of the same year after reports of nine fatal haematological dyscrasias[3] and soon after in the rest of Europe.

In 1988, a landmark study by Kane and Meltzer in the USA, where clozapine continued to be used off-license, provided evidence of its superiority in treating TRS. Clozapine was reintroduced in the UK in 1990 under strict blood monitoring protocols, initially overseen by the manufacturer. In 1994, this responsibility was taken over by the Committee of Safety of Medicine, which later became part of the Medicines and Healthcare Products Regulatory Agency.

The first haematological monitoring protocol, established in 1990, required a white blood count (WBC) and absolute neutrophil count (ANC) above 3000/mm^3 and 1500/mm^3, respectively, before initiating clozapine and for its continuation. The protocol mandated weekly WBC checks for the first 18 weeks after initiation, followed by biweekly checks until the end of the first year.

After the first year, monitoring was reduced to every 4 weeks and continued indefinitely. Increased monitoring was required when WBC was between 3000 and 3500/mm^3 or ANC between 1500 and 2000/mm^3, a situation termed an 'amber alert'. During an amber alert, blood counts were performed twice a week until the resolution or discontinuation of the drug. A 'red alert' was defined by a WBC <3000/mm^3 or ANC <1500/mm^3, necessitating immediate discontinuation of clozapine, and a recommendation that clozapine not be re-initiated in future.

These requirements have remained unchanged in the UK since 1990, except for recognising benign ethnic neutropenia (BEN). BEN is a condition characterised by lower-than-average neutrophil counts found in certain ethnic groups, particularly individuals of African, Middle Eastern and West Indian descent, without an increased risk of infection or adverse health outcomes. In these patients, clozapine can be initiated despite lower WBC and ANC counts, provided a haematologist agrees.

In 2015, the Food and Drug Administration (FDA) in the USA also recognised BEN. Additionally, the FDA dropped the WBC requirements in favour of ANC-only monitoring and lowered the threshold of the ANC for treatment interruption from 1500/mm^3 to 1000/mm^3; changes that have not yet been adopted in the UK, despite evidence of their benefit.

Dropping clozapine barriers

Despite its efficacy in treating individuals with TRS and evidence of reduced re-admission to hospital rates, all-cause mortality and suicide prevention,[4] clozapine remains underused globally. A commonly cited barrier to clozapine initiation and continuation is the need for indefinite blood monitoring. Considering the low prescription rate per capita in the UK, which is less than half of what is needed, it is assumed that reducing barriers to prescription will lead to increased access.

Indeed, several research and professional groups have advocated for reducing blood monitoring requirements beyond a certain period. For instance, the Netherlands Clozapine Collaboration Group was one of the first to suggest, in 2013, that 'if a mentally competent and adequately informed patient explicitly wants to stop having routine blood tests, this can be permitted after the first six months of clozapine treatment'.[5] However, there is still no consensus on changing the current guidance in the UK.

Methods of monitoring

The effects of clozapine on neutrophils appears binary, in that although clozapine may cause agranulocytosis (i.e. severe neutropenia), it does not increase the risk of milder forms of neutropenia. The current monitoring thresholds, however, capture patients with cases of milder and more transient forms of neutropenia.

In this issue, Oloyede and colleagues,[1] investigate what the effects of a more specific approach to defining agranulocytosis might be. The authors aim to disambiguate between true agranulocytosis and transient neutropenia by classifying neutropenia using both a 'threshold-based' (a single ANC < 0.5/mm^3), and 'pattern- based' approach

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(requiring two consecutive ANCs <0.5 mm^3). The authors analysed blood results from over 3000 patients on the UK Clozaril non-rechallenge database over a 20-year period. This includes all patients who had an ANC < 1.5/mm^3 or a WBC < 3 mm^3.

The authors find that of the patients on the database 20% fulfilled the threshold-based criteria and 11% fulfilled the pattern-based criteria. These findings suggest that current approaches may be markedly overestimating the prevalence of CIA, and leading to unnecessary discontinuation of treatment. There are important limitations to their findings, however, not least that clozapine will have been discontinued at the initial blood result, potentially thereby arresting the decline in neutrophils. The argument that current monitoring requirements are overstringent is, however, in keeping with a growing body of evidence.

Is indefinite blood monitoring needed or not?

The short answer is no. CIA is a very rare event. Meta-analytic evidence,[6] using data from over 260 000 patients across 36 studies, showed a pooled prevalence of 0.4% (95% CI 0.3–0.6%). The incidence of CIA also diminishes drastically over time. This was evident from the first descriptions in the Finland pharmacovigilance study, where dyscrasias appeared between 16 and 107 days after initiation. Most guidelines worldwide reflect this acute, time-limited effect, with relatively intense initial blood monitoring (ranging from 18 to 56 weeks), after which the requirement is relaxed to monthly.

The latest studies question the need for long-term monitoring to detect CIA. In a large study involving 15 973 people starting clozapine in Australia and New Zealand, the cumulative incidence of serious neutropenia leading to cessation was 0.9% at 18 weeks and 1.4% at 2 years.[7] The weekly incidence of serious neutropenia was 0.001% by the second year of treatment. The authors suggested that unless clinically indicated, haematological monitoring could be ceased after 2 years altogether. During the COVID-19 pandemic, requirements for monthly blood monitoring were globally relaxed for practical reasons. A recent study showed no deleterious impact of this practice, although the follow-up was limited and the sample size relatively small.[8]

Other studies suggest more caution. A recent study using patient data in Finland,[9] covering the period from 1972 to 2014, assessed the incidence of agranulocytosis among clozapine users (n = 14 037) and users of other antipsychotics (n = 50 283), identifying 398 patients with agranulocytosis. The incidence was higher among clozapine users (17.33 *v.* 2.10 events per 10 000 person-years) compared with the control group, with a cumulative incidence over 22 years of 1.37% *v.* 0.13%, respectively. Importantly, the risk of CIA decreased over time, starting at an adjusted odds ratio of 36.01 and decreasing to 4.37 after 54 months (4.5 years) compared with the general population. Interestingly, the study found that the risk of agranulocytosis appears to be associated with antipsychotics as a group within the first 6 months. However, the risk of clozapine after 3 years was like that of other antipsychotics.

Whether the proposed duration of monthly monitoring is 2 or 3 years, the justification for mandatory blood tests beyond that point for preventing CIA is weak. The prospect of time-limited monitoring might encourage patients and clinicians to prescribe clozapine. Importantly, a reduced haematological requirement has significant cost implications, which could be especially relevant to countries with limited resources and developing health systems.

Wider considerations

Whereas the use of blood monitoring for CIA safety may not be necessary, other aspects remain unclear. For instance, the evidence linking decreased blood monitoring requirements with increased access to clozapine has yet to be established. A study by Oloyede and colleagues could not find conclusive evidence of a relationship between the stringency index (a proxy for how strict the monitoring criteria are) and clozapine prescription per capita.[10] Moreover, to our knowledge, there is no evidence suggesting that loosening clozapine monitoring in the Netherlands has effectively increased prescriptions either.

The reduction in blood monitoring is based on the premise that symptoms or signs of agranulocytosis (fever, mouth ulcers and sore throat) will be identified by the clozapine user and communicated to the health service. It is frequently mentioned that the long-term risk of agranulocytosis associated with clozapine is similar to that of carbamazepine (among others). Interestingly, there have been no fatal cases of carbamazepine-associated agranulocytosis in the UK in the past 15 years, despite it being prescribed to more people and not having mandatory blood monitoring. However, no studies have shown users' knowledge level of these symptoms and how to react. TRS can be considered the severe end of the illness spectrum, with greater cognitive impairment. It is a relapsing illness that, by definition, might reduce insight and judgement during acute episodes.

The history of mandatory blood monitoring for clozapine is a tale of success. No medication is free of side-effects, even fatal ones. The pharmacovigilance service in Finland halted clozapine after 6 months on the market when 0.4% of the approximately 1800 people prescribed the drug experienced a fatal reaction. The subsequent mandatory monitoring requirement has reduced this risk to 0.013% (1 in 10 000). We must exercise maximum caution to prevent clozapine from regaining its reputation as a 'death drug.'

Another word of caution is that studies have specifically focused on CIA, generally excluding cases of patients where another agent might have caused agranulocytosis. The evidence suggesting that clozapine has an additive agranulocytosis risk when combined with other drugs is unclear. Polypharmacy is common in people diagnosed with TRS, which enhances the risk of inadvertently combining pro-agranulocytosis drugs.

Finally, there is a broader consideration beyond the monitoring itself. The perceived risk of fatal side-effects is why clozapine is the only medicine requiring ongoing specialist intervention and specialist monitoring in psychiatry. As a result, patients are rarely discharged to primary care and typically remain under the care of community services, with some exceptions. By removing the blood monitoring requirement, we risk that a significant proportion of patients with TRS who are treated with clozapine might join the over 70% of people with schizophrenia in the UK who are exclusively managed by primary care, with the known risk of disengagement. At a time when campaigns are advocating to increase awareness of other serious side-effects of clozapine (e.g. myocarditis, pneumonia or ileum, to name a few), it seems counterintuitive to decrease the support given to this population even further.

What to do next?

There is increasing evidence that the risk of CIA reduces significantly after 2–3 years, and that current monitoring thresholds are overly stringent both in terms of ANC cut-offs and duration of monitoring. The call to update and simplify mandatory requirements is becoming louder and should be listened to. However, this change might have an impact on the delicate and often precarious support network for those with the most severe form of schizophrenia. Ensuring patients continue to receive comprehensive care must remain our primary aim.

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