

# Clozapine Monitoring in Clinical Practice: Beyond the Mandatory Requirement

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Clozapine is effective in treatment resistant schizophrenia; however, it is underutilised probably because of its side effects. The side effects are also the potential reasons for clozapine discontinuation. A mandatory requirement for its use is regular monitoring of white blood cell count and absolute neutrophil count. However there are many side effects that need monitoring in clinical practice considering their seriousness. This article tries to summarise the clinical concerns surrounding the serious side effects of clozapine some of which are associated with fatalities and presents a comprehensive way to monitor patients on clozapine in clinical practice. It emphasizes the need to broaden the monitoring beyond the mandatory investigations. This may help in improving the safety in clinical practice and increasing clinician confidence for greater and appropriate use of this effective intervention.

**KEY WORDS:** Clozapine; Adverse effects; Drug monitoring; Practice guideline; Safety.

## INTRODUCTION

Patients with schizophrenia are known to have increased vulnerability for physical comorbidity and mortality. In addition, various neuroendocrine, cardiovascular and metabolic side effects of the antipsychotic medications increase the clinical concern further. There are however particular issues with clozapine.

Clozapine, referred to as the gold standard for the treatment of schizophrenia,<sup>1</sup> is the most underutilized medication; i.e., it is prescribed in only a proportion of eligible patients. The reported proportions, however, vary considerably in different regions, e.g., it is around 10-20% in United States,<sup>2</sup> 14.5-15.9% in hospitalised schizophrenia patients in 9 Asian countries;<sup>3</sup> whereas higher figures have been reported by studies in China (31.9%),<sup>4</sup> Australia (33.3%) and the United Kingdom (54%).<sup>5,6</sup> Its initiation is also usually delayed.<sup>7</sup> One of the major reasons of its inadequate use is the concern over serious side effects such as agranulocytosis, myocarditis, gastrointestinal hypo-

motility and metabolic side effects.<sup>2,8</sup> It has been reported in one study that the standardised mortality ratio was significantly raised for patients receiving clozapine.<sup>9</sup>

The side effects have been found as potential reasons for clozapine discontinuation, which include: neutropenia or agranulocytosis, thrombocytopenia, electrocardiogram (ECG) changes, QTc prolongation, tachycardia, atrial flutter, myocarditis, cardiomyopathy, fever, syncope, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma, neuroleptic malignant syndrome, ileus, liver enzyme elevation and seizure.<sup>10</sup> It may be highlighted that these side effects can be detected, prevented, minimized and treated,<sup>2</sup> which may decrease serious consequences including fatalities.

We intended to review the literature on the serious side effects and fatalities related to clozapine and available suggestions of monitoring to provide a comprehensive clozapine monitoring strategy in routine clinical practice.

## SERIOUS ADVERSE EFFECTS AND FATALITIES

### Haematological Adverse Effects

The reported incidence of clozapine-induced agranulocytosis varies between 1% to 2%.<sup>11,12</sup> The observed mortality rate ranges between 0.1 and 0.3 per thousand, and the case-fatality rate is between 2.2 and 4.2 per thousand.<sup>8</sup>

**Received:** November 24, 2015 / **Revised:** February 20, 2016

**Accepted:** February 21, 2016

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The incidence of leukopenia or agranulocytosis decreases over time following initiation of clozapine therapy, e.g., in the second 6 months of treatment it is reported to be 0.70 per 1,000 patient-years and after the first year, 0.39 per 1,000 patient-years.<sup>13)</sup> The estimated case fatality rate of clozapine-induced agranulocytosis was 4.2% to 16%, depending on whether a granulocyte colony-stimulating factor is used.<sup>13)</sup>

It has been reported that discontinuation of white blood cell (WBC) monitoring after 6 months of starting clozapine has similar mortality associated with other medications or even with life in general involving accidents.<sup>13)</sup> Based on this, some authors suggest that in well informed patients wishing to stop monitoring, it may be justifiable.<sup>13)</sup> However, late onset clozapine-induced agranulocytosis has been reported,<sup>14-16)</sup> which suggests the probable need for continued monitoring for reducing mortality.

### Cardiovascular Adverse Effects

Myocarditis and cardiomyopathy are rare but serious side effects of psychotropic medications and have been specifically reported with clozapine.<sup>17)</sup> However these are potentially reversible complications. A review of literature suggested that the risk of potentially fatal myocarditis or cardiomyopathy related to clozapine is low (0.015% to 0.188%).<sup>18)</sup> However, in one study, fatal outcome was associated with 46% people with clozapine induced myocarditis.<sup>19)</sup> Most of the fatalities due to clozapine induced myocarditis have been reported during the first 6 weeks of treatment.<sup>19,20)</sup> A study found obesity, longer duration of clozapine treatment and creatine kinase levels more than 1,000 U/L significantly associated with fatal compared with non-fatal cases. There were no significant differences in gender, age, smoking status, dose at onset or concomitant sodium valproate use.<sup>20)</sup>

Clozapine is associated with postural hypotension,<sup>21)</sup> and in fact, among the atypical antipsychotics this risk is considered to be highest with clozapine.<sup>22)</sup> Although rare, orthostatic hypotension may lead to neurocardiogenic syncope.<sup>17)</sup>

Clozapine is known to have low effect on QTc.<sup>22)</sup> Clozapine may not independently contribute to pathologic prolongation of the QTc interval, but it may occur in patients with other concurrent risk factors.<sup>18)</sup> It is a clinical concern as QTc prolongation is associated with arrhythmic risk and may lead to dizziness, syncope, ventricular fibrillation and sudden death in specific conditions like Torsade de pointes.<sup>17)</sup>

### Metabolic Side Effects

Diabetes, hypercholesterolemia, hypertriglyceridemia and obesity have been reported to be significantly associated with clozapine.<sup>23,24)</sup> Including these specific abnormalities, metabolic syndrome with a reported range of 43.2% to 70.4% is also associated with clozapine,<sup>25-28)</sup> which is a known cause of increased cardiovascular events and mortality.<sup>29-31)</sup>

Besides diabetes, the glycaemic dysregulation associated with clozapine range from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma.<sup>8,32)</sup> Diabetic ketoacidosis has been reported to be associated with fatalities.<sup>33,34)</sup> The calculated incidence rate for diabetic ketoacidosis in clozapine treated patients was at 1.2 to 3.1 per thousand and the case-fatality rate was 20% to 31%. Obesity, especially body mass index (BMI) more than 30 kg/m<sup>2</sup> have been found to increase the risk of mortality in patients receiving clozapine.<sup>20)</sup>

Considerable proportion of patients on clozapine are observed to have dyslipidaemia including hypertriglyceridemia and hypercholesterolaemia.<sup>27,35)</sup> It is well established that dyslipidaemia increases the risk of cardiovascular and cerebrovascular morbidity and mortality.

### Neurological Adverse Effects

It is known that clozapine lowers seizure threshold. Reported proportions of patients on clozapine having seizures range from 1.1% to 20%,<sup>36-39)</sup> and associated fatalities have been reported.<sup>9,40)</sup> Convulsions are dose related,<sup>33)</sup> and higher plasma clozapine concentrations have been linked to an increased risk of seizures.<sup>41)</sup> However, it is reported that the relationship between dose and occurrence of seizures has not been statistically significant.<sup>42)</sup> In addition to seizures, clozapine-induced electroencephalogram (EEG) abnormalities like slowing and spikes have also been reported to be related to clozapine dose and plasma level.<sup>37)</sup> Besides this, autonomic adverse effects of clozapine are common, but are usually easily managed.<sup>21)</sup>

### Other Serious Side Effects

Constipation, which is a common side effect of clozapine, can have serious consequences sometimes.<sup>21,43)</sup> The incidence for gastrointestinal hypo-motility has been reported to be 4 to 8 per thousand, which has a case-fatality rate of 15% to 27.5%.<sup>8)</sup>

## CLOZAPINE MONITORING

Monitoring for the haematological side effects of cloza-

pine is carried out mandatorily in a few countries; whereas the information from many countries is not available. It has been reported that without a monitoring service mortality rate from agranulocytosis increases.<sup>33)</sup> While white cell monitoring is mandatory there are possible variations in different countries for example blood sugar is included in Japan.<sup>44)</sup>

In the United Kingdom, as a mandatory requirement for prescribing clozapine, white cell count with a differential count monitoring is required weekly for the initial 18 weeks, then fortnightly for up to one year, and then monthly.<sup>33,45)</sup> Monitoring is continued throughout treatment and for at least 4 weeks after discontinuation.

British National Formulary mentions monitoring guidelines for antipsychotics in general,<sup>45)</sup> which are understandably relevant for clozapine too. At the start of therapy with antipsychotic drugs, full blood count, urea and electrolytes and liver function test (LFT) are required and then annually thereafter.<sup>45)</sup> Clozapine has been associated with hepatic failure and it is suggested that LFT is carried out at baseline and at 4-6 month interval.<sup>22)</sup>

It is suggested that patients with schizophrenia should have physical health monitoring (including cardiovascular disease risk assessment) at least once per year.<sup>45)</sup> Specifically there should be BMI and waist circumference measurements at baseline and 1 month, 3 monthly and then yearly.<sup>22)</sup> Weight should be measured for all patients on antipsychotics at baseline, subsequently at frequent intervals during the first 3 months, at 3 months and then yearly. Patients taking clozapine require more frequent monitoring of these parameters: every 3 months for the first year, then yearly.<sup>45)</sup>

Blood pressure monitoring is advised before starting therapy and frequently during dose titration of antipsychotic drugs including clozapine.<sup>45)</sup>

An ECG may be indicated, before starting antipsychotic drugs, particularly if there are cardiovascular risk factors and personal history of cardiovascular disease. It is also suggested to have an ECG if the patient is being admitted as an inpatient.<sup>45)</sup>

Routine monitoring for myocarditis is suggested for the first 4 weeks of clozapine, and in the presence of evidence consistent with myocarditis discontinuation of clozapine is advised. Investigation by cardiac imaging will give a measure of severity and need for intervention.<sup>20)</sup>

Fasting blood glucose should be checked at baseline, after one month's treatment, then every 4-6 months in patients taking clozapine.<sup>45,22)</sup> Lipid profile should be measured at baseline, at 3 months and then yearly for patients

taking antipsychotics; however for patients on clozapine it is advised that it is done 3 monthly in the first year.<sup>45)</sup>

It is known that prolactin is not elevated with clozapine,<sup>46)</sup> rather a report suggested decrease in prolactin,<sup>47)</sup> which suggests prolactin monitoring is not required for clozapine. However patients on different antipsychotics before clozapine may have their prolactin raised and it may be worthwhile to monitor prolactin in patients with symptomatic hyperprolactinaemia to evaluate any change following their switch to clozapine.

The usefulness of monitoring of plasma clozapine level in the prevention of adverse effects secondary to raised concentrations have been emphasized.<sup>42)</sup> It may also help with optimising dosage, monitoring of adherence, drug interactions and the effect of changes in smoking habit. However, it is not a mandatory requirement. It involves measurement of plasma levels of clozapine and norclozapine (N-desmethyl-clozapine, a major metabolite of clozapine) six hours or more after the last dose of the drug (a 'trough' sample). Monitoring of clozapine level has been suggested if the dose is 600 mg per day or more,<sup>48)</sup> which can be done 3 monthly.<sup>49)</sup> Other indications where it may be appropriate to check clozapine level are change in smoking habit, adherence concerns, troublesome adverse effects and yearly if the treatment is successful.<sup>49)</sup> There are variations in the reported plasma concentrations where therapeutic response was obtained, however a range of 350-400 µg/L is considered to be an adequate trial.<sup>1,50)</sup> It has been proposed to maintain a safe therapeutic maximum clozapine level of 600 µg/L beyond which there is an increased risk of adverse effects.<sup>49,51)</sup>

Smoking has a considerable effect on clozapine dose requirement. Plasma clozapine may rise markedly within 3 to 5 days of smoking cessation and may fall rapidly if a patient on a constant dose of clozapine starts smoking. Therefore careful monitoring is essential if there is a change in smoking habit. Smoking cannabis has the same effect as smoking tobacco, whereas nicotine replacement therapy, chewing tobacco or taking 'snuff' do not affect plasma clozapine concentrations when the drug is taken at a constant dose.<sup>49)</sup>

Besides cessation of smoking, there are other factors which can influence plasma clozapine level. Plasma levels are generally lower in males and younger patients, and higher in Asians.<sup>22)</sup> The use of cytochrome P450 inhibitors, such as antifungals, oral contraceptives, fluvoxamine, cimetidine, erythromycin, ciprofloxacin and caffeine can increase clozapine level;<sup>49,52,53)</sup> similarly, carbamazepine, phenytoin and possibly other enzyme inducers

like phenobarbitone and rifampicin may decrease plasma clozapine. Fluvoxamine can increase clozapine level considerably and there are reported fatalities.<sup>49)</sup> There are differences in reports about other selective serotonin re-uptake inhibitors; both increase,<sup>54,55)</sup> and no effect<sup>49)</sup> have been reported.

It has been suggested that many side effects of clozapine e.g. increases in weight and serum glucose and triglyceride levels are related to its active metabolite, norclozapine.<sup>56)</sup> Interestingly, fluvoxamine decreases norclozapine by inhibiting the CYP450 1A2 isoenzyme. Based on this some studies suggest that careful co-administration of fluvoxamine and a low dose of clozapine,<sup>57)</sup> may decrease norclozapine levels, while maintaining therapeutic clozapine levels; which may reduce side effects such as sedation, weight gain, metabolic disturbances and neutropenia, and may increase efficacy.<sup>58)</sup> However, considerable concern remains with fluvoxamine-clozapine combination, as the increase in clozapine level in an individual patient may not be predictable.<sup>59)</sup> In these circumstances, especially when drug interactions are a possibility, monitoring clozapine level becomes imperative.

An EEG is not routinely required for clozapine treatment but patients may benefit in certain conditions e.g. it may be particularly indicated for patients who have known pre-existing compromised brain function or seizures. Although EEG abnormalities are frequently reported with clozapine;<sup>38,60)</sup> and observed to be dependent on plasma levels;<sup>61)</sup> they do not necessarily predict the occurrence of seizures.<sup>60)</sup> In combination with serum clozapine levels EEG may identify patients who could benefit from a reduction in clozapine dose/serum levels;<sup>37)</sup> and this may help determine the need for valproate.<sup>22,62)</sup> It has been claimed that change in the theta frequency in quantitative EEG may indicate clozapine treatment adequacy better than the serum level.<sup>63)</sup> Interestingly, it has also been reported that pre-treatment EEG data may predict the clinical response to clozapine in treatment resistant schizophrenia; although this needs to be replicated in a larger sample.<sup>64)</sup>

## SUGGESTION FOR CLOZAPINE MONITORING IN CLINICAL PRACTICE

Based on the available clinical evidence of various po-

**Table 1.** Clozapine monitoring in clinical practice

Investigations	Baseline	Further testing frequency*	Yearly*
WBC count, DC, ANC	×	Weekly for 18 weeks <sup>†</sup> , fortnightly up to one year, and then monthly	
FBC	×		×
Urea and electrolytes	×		×
LFT	×		×
Lipids	×	3 monthly for first year	×
FBG <sup>‡</sup>	×	1 month, every 4-6 months	
ECG	×	After dose changes	×
Physical examination	×	Weekly during titration <sup>†</sup>	×
BP, postural drop	×	Acute monitoring. Frequently during dose titration <sup>†</sup>	×
Pulse	×	Acute monitoring. Frequently during dose titration <sup>†</sup> , definitely in the first 1-2 months	×
Temperature	×	Acute monitoring. Frequently during dose titration <sup>†</sup>	
Weight	×	Frequently during first 3 months, every 3 months for first year	×
BMI	×	1, 3, 4-6 monthly	×
Waist circumference	×	1, 3, 4-6 monthly	×
Cardiovascular monitoring	×		×
Smoking status	×	Regularly at follow-up	
Review of co-prescribed medications	×	Regularly for drug interactions, as additional medications are prescribed	
Serum clozapine		As necessary. 3 monthly, if dose is 600 mg or more	×
Prolactin		Not specifically needed for clozapine, consider when relevant	
EEG		When relevant	

\*All the investigations/evaluations should be done more frequently if clinically indicated.

<sup>†</sup>Acute monitoring: Monitor BP, pulse, temperature, after first dose, hourly for at least 3 (preferably 6) hours afterwards; This may not be required if the first dose is given at bedtime. Thereafter patient should be seen at least once a day (twice a day if faster titration is used), and BP, pulse, temperature should be monitored before and after the morning dose. Daily monitoring should be continued for at least two weeks or until there are no unacceptable adverse effects. Twice weekly monitoring may then be undertaken until a stable dose is reached. Thereafter monitor during blood testing.<sup>22,33)</sup>

<sup>‡</sup>Glycated haemoglobin (HbA1c) can also be checked.

WBC, white blood cell; DC, differential count; ANC, absolute neutrophil count; FBC, full blood count; LFT, liver function test; FBG, fasting blood glucose; ECG, electrocardiogram; BP, blood pressure; EEG, electroencephalogram; BMI, body mass index.

tentially life threatening side effects and the risk of cardiovascular and metabolic disorders, further monitoring of clozapine is required beyond the mandatory haematological investigations. It is worth considering the need to update clinical guidelines for clozapine monitoring. We propose here a plan for clozapine monitoring in clinical practice based on the available evidences (Table 1).

## INTERVENTIONS FOLLOWING MONITORING

Specific actions are undertaken based on the monitoring findings. Clozapine must be discontinued immediately if either the WBC count is less than  $3,000/\text{mm}^3$  or the absolute neutrophil count (ANC) is less than  $1,500/\text{mm}^3$  at any time during treatment; and these patients must not be re-exposed to clozapine.<sup>33)</sup> If the WBC count is between  $3,500$  and  $3,000/\text{mm}^3$  or ANC count is between  $2,000$  and  $1,500/\text{mm}^3$ , clozapine is continued with twice weekly blood monitoring until stabilisation or improvement. Discontinuation of clozapine is recommended if the eosinophil count rises above  $3,000/\text{mm}^3$  or if the platelet count falls below  $50,000/\text{mm}^3$ .<sup>33)</sup>

Clozapine must be stopped if myocarditis or cardiomyopathy is suspected. Patient should be evaluated by cardiologist; and if myocarditis or cardiomyopathy is confirmed, patient should not be re-exposed to clozapine.<sup>22)</sup>

In addition to the investigations and specific assessments for clozapine, there is a need for usual monitoring relevant for any other medications concurrently prescribed for the patient. Monitoring for adverse effects should be considered regularly during each follow up. In addition to patient reported side-effects and clinical enquiry, use of a check-list or a side effect scale may be helpful. Clinical status such as symptomatic improvement or deterioration should be monitored preferably by a standardised scale supporting clinical assessment. This is especially important as a proportion of patients do not respond to clozapine and may require addition of other psychotropic medications.<sup>65,66)</sup> In these scenarios clinical benefit should be balanced against the increased risk of side effects.

A structured approach to clozapine monitoring may improve the confidence of the clinicians leading to increase in the use of this effective but highly underutilised medication. In this regard, a specifically dedicated clozapine clinic may be helpful.

### ■ Acknowledgments

Authors wish to thank Quality of Life Research and

Development Foundation and Black Country Partnership NHS Foundation Trust, United Kingdom for technical and literature support. There was no funding for this article.

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