



Invited Review

Clozapine in the treatment of refractory schizophrenia: a practical guide for healthcare professionals

R. J. Flanagan^{1,2,*}, J. Lally^{2,3,4}, S. Gee⁵, R. Lyon^{6,†}, and S. Every-Palmer⁷

¹Precision Medicine, Networked Services, Bessemer Wing, King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK, ²Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London SE5 8AF, UK, ³Department of Psychiatry, Mater Misericordiae University Hospital, 63 Eccles Street, Dublin 7, Ireland, ⁴Department of Psychiatry, Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin 2, Ireland, ⁵Pharmacy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, UK, ⁶Department of Pharmacy, Sussex Partnership NHS Foundation Trust, Chichester Centre, Graylingwell Drive, Chichester, West Sussex PO19 6GS UK, and ⁷Department of Psychological Medicine, University of Otago, Wellington, PO Box 7343, Newtown, Wellington 6242, NZ

*Correspondence address. Precision Medicine, Networked Services, Bessemer Wing, King's College Hospital NHS Foundation Trust, London SE5 9RS, UK. E-mail: robert.flanagan@nhs.net

†In memory of Ray Lyon (1954–2020)

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Abstract

Background: Clozapine remains the only medication licensed for treating refractory schizophrenia. However, it remains underutilized in part due to concerns regarding adverse events.

Sources of data: Published literature.

Areas of agreement: Common adverse events during clozapine treatment include sedation, hypersalivation, postural hypotension, dysphagia, gastrointestinal hypomotility, weight gain, diabetes mellitus and dyslipidaemia. Rare but serious events include agranulocytosis, cardiomyopathy, myocarditis, pneumonia, paralytic ileus and seizure.

Areas of controversy: It remains unclear how best to minimize clozapine-induced morbidity/mortality (i) during dose titration, (ii) from hypersalivation and (iii) from gastrointestinal hypomotility. It is also unclear how

clozapine pharmacokinetics are affected by (i) gastrointestinal hypomotility, (ii) systemic infection and (iii) passive exposure to cigarette smoke. Whether monthly haematological monitoring needs to continue after 12 months of uninterrupted therapy is also a subject of debate.

Growing points: There is a need for better management of serious clozapine-related adverse events in addition to agranulocytosis. There is also a need for better education of patients and carers, general practitioners, A&E and ITU staff and others of the problems posed in using clozapine safely.

Areas timely for developing research: There is a need for more research on assessing clozapine dosage (i) as patients get older, (ii) with respect to exposure to cigarette smoke and (iii) optimizing response if adverse events or other factors limit dosage.

Key words: clozapine, schizophrenia, treatment-refractory, adverse events, safe use, morbidity, mortality

Introduction

Clozapine is the only drug with proven efficacy in schizophrenia that does not respond to other antipsychotics (treatment refractory schizophrenia, treatment resistant schizophrenia, TRS).^{1,2} Clozapine is also indicated in patients with schizophrenia who show severe, untreatable adverse neurological reactions to other antipsychotics, including second-generation antipsychotics.³

Treatment with clozapine decreases overall mortality in schizophrenia, in part by reducing suicidality.⁴ Clozapine may also limit substance misuse.^{5,6} International guidelines for the treatment of schizophrenia recommend that clozapine be offered after someone fails to respond adequately to trials of at least two other antipsychotics, excluding discontinuations due to side effects.¹ This is because clozapine is no more efficacious than other antipsychotics as a 'first-line' treatment for schizophrenia *per se* and secondly because there is a recognized risk of blood dyscrasias especially in the first 3 months of clozapine treatment.^{1,7} Dispensing of clozapine in most countries is dependent on the results of mandatory haematological monitoring, although whether monitoring needs to continue beyond 12 months of successful therapy is the subject of debate.⁸

Although clozapine tends not to produce extrapyramidal effects, other adverse events (AEs) not

only limit its widespread use but also pose especial problems in the safe use of the drug.^{2,9,10} In the US, clozapine's 'black box' warning highlights the risk of severe neutropenia (agranulocytosis), myocarditis, cardiomyopathy, seizures and profound hypotension. However, there are also serious risks from clozapine-induced gastrointestinal hypomotility (CIGH) and pneumonia.^{11,12} Training in the recognition of these and other adverse effects of clozapine among those involved in the care of patients taking clozapine varies greatly.¹³ The increase in antipsychotic-related fatal poisoning in England and Wales that has occurred since 2001 is largely attributable to an increase in unintentional deaths related to (i) clozapine and (ii) co-exposure to opioids, principally diamorphine and methadone.¹⁴

In the UK and in many other parts of the world, clozapine is licenced to treat not only TRS in patients aged 18 years and older but also Parkinson disease psychosis. The dose for this latter condition is 5- to 10-fold lower than in TRS.¹⁵ Off-label uses of clozapine include treatment of schizophrenia in patients younger than 18 years, bipolar disorder, depressive disorders, borderline personality disorder, substance misuse disorders, suicidality, aggression, tardive dyskinesia and tardive dystonia.¹⁶ The regulations surrounding the use of clozapine in TRS also apply to these latter groups of patients. In addition, clozapine-treated patients inevitably come

into contact with services other than mental health services.¹⁷

The aim of this paper is to outline the special considerations associated with the safe use of clozapine. We have performed a narrative literature review in order to summarize the prescribing and monitoring of the drug for those who may not be familiar with its everyday use in TRS. No new data were either generated or analysed in support of this review.

Use of clozapine in treating refractory schizophrenia

Clozapine prescription and dispensing

In the UK, clozapine is prescribed for TRS on a named-patient basis by a consultant psychiatrist. Three brands of clozapine are available: Clozaril (Mylan; 25 and 100 mg tablets), Denzapine (Britannia; 25, 50, 100, and 200 mg tablets and 50 mg/mL oral suspension) and Zaponex (Leyden Delta; 25 and 100 mg tablets and 12.5, 25, 50, 100 and 200 mg orodispersible tablets). It is assumed that the brands and formulations are clinically equivalent. Each brand comes with its own monitoring service, but the suppliers jointly operate a 'non-rechallenge' database that aims to ensure that no patient who has suffered agranulocytosis due to clozapine is given the drug again. Similar arrangements apply in many other countries.

Pharmacists, pharmacy technicians and pharmacies supplying clozapine must be registered with the supplier. Consultants prescribing clozapine are also registered with the supplier. Haematology monitoring may be either arranged by the supplier or performed locally, and the result is communicated to the supplier. Registrations must be changed if the supplier changes.

Initiating clozapine

The supply of clozapine in the UK is dependent on satisfactory haematology results (Haematological abnormalities section). A full blood count (FBC) must be performed before clozapine is given and

then weekly for the first 18 weeks of treatment, fortnightly for the next 34 weeks, and monthly thereafter. Clozapine is usually initiated in hospital but can be initiated safely in the community.¹⁸ Continued dispensing of clozapine is conditional upon satisfactory haematology results. Avoiding sudden withdrawal from clozapine is important for the patient because of the risk of rebound psychosis. Moreover, if doses are missed for more than 48 hours, then the clozapine initiation process must begin again.

Once the decision to initiate clozapine is taken, baseline FBC, body weight, fasting glucose/lipids and liver function tests (LFTs) (Table 1), lying/standing blood pressure (BP) and ECG should be recorded. Clozapine has a dramatic hypotensive effect in a clozapine-naïve subject (Blood pressure changes section); hence, the dose is cautiously titrated upward over the first 2–4 weeks, and the patient's temperature, pulse and BP are monitored, and any AEs are recorded. LFTs should be repeated after 2 weeks. Typically, the dose regime is day 1: 12.5 mg, days 2–3: 25 mg, days 3–4: 50 mg and so on until a clinically effective, well tolerated dose is reached. A slow rate of titration may help reduce the incidence of AEs such as neutropenia (Haematological abnormalities section) and myocarditis (Myocarditis and cardiomyopathy section) but has to be balanced against the need to mitigate the patient's symptoms as quickly as feasible.

For people prescribed clozapine for TRS, the usual maintenance dose lies between 300 and 600 mg per day (regulatory maximum 900 mg per day) but there is wide variation. Usually, a greater proportion if not all of a daily dose is given at night due to its sedating effects. However, owing to high inter-individual variability in clozapine metabolism, people may experience potentially serious toxicity such as constipation (Gastrointestinal hypomotility section) with daily doses as low as 100 mg, albeit rarely. It is advisable to measure plasma clozapine at 1 week to ensure that the patient is not a very poor metabolizer of clozapine (Plasma clozapine and norclozapine monitoring section). There is a debate as to whether patients of Asian ethnicity may require lower daily doses of clozapine on

Table 1 Clinical chemistry measurements suggested for patients prescribed clozapine¹⁹

Pre-clozapine (baseline evaluation)	After 4 weeks	Four to six monthly	12 months and then annually
Urea and electrolytes, LFTs,* fasting blood glucose or HbA1c,† fasting lipids and cholesterol, creatine phosphokinase activity (CPK)	LFTs,* fasting blood glucose,† fasting lipids and cholesterol	Urea and electrolytes, LFTs,* fasting blood glucose or HbA1c,† fasting lipids and cholesterol	Fasting blood glucose or HbA1c,† fasting lipids and cholesterol

*Including prothrombin time (international normalized ratio, INR)

†HbA1c may be a more useful screening test for diabetes during maintenance clozapine therapy (i.e. at 3 months or later) than fasting blood glucose in patients who may not report symptoms of hyperglycaemia. It would not usually be requested more frequently than every 6–8 weeks.

average than Caucasians, but this does not negate the need for dosage to be individualized. On the other hand, young, male smokers have sometimes been given doses above the maximum licenced dose in order to maintain effective plasma clozapine concentrations.²⁰

Plasma clozapine and norclozapine monitoring

Clozapine therapeutic drug monitoring (TDM), i.e. the measurement of plasma clozapine and *N*-desmethylclozapine (norclozapine, the principal plasma metabolite of clozapine) can help check adherence, guide dosage, and minimize the incidence of dose-related AEs. Most, but not all people with TRS show a moderate/good response to clozapine at a pre-dose ('trough') plasma concentration between 0.35–0.60 mg L⁻¹, but there is considerable variation in both response and AEs.²¹ Once a good response has been achieved, the optimal pre-dose plasma clozapine concentration may be 0.25 mg L⁻¹ or less, concentrations at which a lower incidence of AEs might be expected.²²

The part played by norclozapine in the antipsychotic action of clozapine is unclear.²³ There is no information that relates plasma norclozapine concentration to clinical effect other than the observation that plasma norclozapine is on average ~70% of the plasma clozapine concentration (plasma clozapine:norclozapine ratio 1.55) when plasma clozapine is 0.35–0.60 mg L⁻¹. However, this ratio increases at higher plasma clozapine concentrations suggesting

either dose-dependent impairment of clozapine *N*-demethylation, or that the sample was taken before absorption and tissue distribution of clozapine from the last dose had been completed.²⁴ Secondly, norclozapine has on average a longer plasma half-life than clozapine, and thus is less likely to change with sample time in relation to the time of the last dose than the plasma clozapine itself, and this may help in interpreting individual patient results over time if adherence is questioned, for example.

Multiple regression analysis of the effect of dose, age, sex, body weight, smoking habit and the plasma clozapine:norclozapine ratio (an index of a patient's ability to metabolize clozapine), explained some 50% of the observed variation in plasma clozapine in one study of predominantly Caucasian patients.²⁵ Variations in (i) adherence, (ii) sample timing after the last dose, (iii) bioavailability due to clozapine's effect on the gastrointestinal tract (Gastrointestinal hypomotility section) and (iv) the effect of covert or passive smoking may contribute to the rest of the observed variation.

In this context, if pre-dose plasma clozapine is found to be very high (>2 mg L⁻¹, 0.4% of samples in the audit cited above) it may continue to rise for some time after significantly reducing/stopping the drug, possibly reflecting continued absorption as gut motility returns.²⁴

Smoking habit

On average the clozapine dose requirement of smokers is decreased by 50% if that same person

stops smoking, and *vice versa*.²⁵ Note that marijuana (cannabis) smokers (i) often smoke tobacco as well as cannabis, and (ii) marijuana smoke contains higher concentrations of polycyclic aromatic hydrocarbons, the agents responsible for this effect, than tobacco.²⁶

Smoking is a problem with clozapine because of its narrow 'therapeutic window', i.e. the difference between an ineffective dose and a toxic dose of clozapine is small when used in TRS. In practice, this means that if a non-smoker showing a good response to clozapine starts smoking regularly, they will begin to lose the benefit of the drug in 48 hours or so.²⁷ On the other hand, if someone, especially a young male smoker, suddenly stops smoking and the dose is not cut promptly they will become at risk of serious, possibly life-threatening toxicity within a few days or weeks.

Stopping smoking may be a consequence of admission to hospital, or even the presence of a respiratory infection (Infection section). The problem is compounded if inpatients in smoke-free units go on leave as they may smoke again while outside the unit and of course dose adjustments will need to be made after discharge if the patient starts smoking again. There could be an increasing effect on clozapine dose requirement up to about five or so cigarettes a day, but anything above that will likely have no further effect.²⁸

Nicotine replacement therapy (NRT) or 'vaping' is not thought to have an effect on clozapine dose requirement. The same applies to the use of snuff or chewing tobacco. As to passive smoking, there are anecdotal reports of clozapine toxicity in non-smokers when a partner has stopped smoking, so this possibility should not be neglected. The converse may apply where non-smokers taking clozapine start spending time in spaces where people smoke. We know from the epidemiology of lung cancer that there is enhanced risk from passive smoking due to exposure to polycyclic hydrocarbons and/or other constituents of tobacco smoke, hence there may also be an effect on clozapine clearance.

One observation that is not understood is that clozapine gradually accumulates in some patients

over time, other factors such as stopping smoking seemingly notwithstanding, possibly because the capacity to metabolize (eliminate) the drug becomes saturated (Plasma clozapine and norclozapine monitoring section). Sometimes this may go unrecognized until the patient suffers a convulsion, paralytic ileus, or other serious AE, but sometimes it is detected by routine measurement of plasma clozapine and norclozapine.²⁴

Drug-drug interactions

The only really dangerous drug-drug interaction with clozapine is that with fluvoxamine, which inhibits most if not all of the enzymes involved in clozapine elimination. Clearly, fluvoxamine co-prescription with clozapine must be avoided in normal circumstances. However, if a patient refuses to take an adequate dose of clozapine, or if the maximum licensed dose proves inadequate, then cautious co-prescription might be considered, but this is employed only rarely.²⁹

Some antibiotics, such as ciprofloxacin, may also inhibit clozapine metabolism.³⁰ Caffeine and some other SSRIs (sertraline, paroxetine, fluoxetine) do not affect clozapine dose requirement at the doses seen in clinical practice.²⁴ Oral contraceptives, however, may inhibit clozapine metabolism.³¹ On the other hand, carbamazepine, phenytoin and rifampicin enhance clozapine dose requirement and should not normally be co-prescribed. Moreover, carbamazepine is itself a risk factor for neutropenia.

Age, sex, body weight, and clozapine dose requirement

Body weight usually has only a small effect on clozapine dose requirement. However, on average women need some 20% less than men to achieve the same plasma clozapine concentration other factors such as smoking notwithstanding.²⁵ Secondly, clozapine dose requirement decreases with increasing age. For one thing the body becomes less efficient at metabolizing (eliminating) the drug. In addition, older

people tend to smoke less. There is thus a need to review the dose as people get older to minimize the risk of dose-related clozapine toxicity.^{32,33} These observations are in line with the fact that late-onset schizophrenia usually responds to relatively lower clozapine dosage.

In the UK, some 50–60% of patients with TRS will respond to clozapine, with a 30% response rate achieved at 6 weeks of clozapine treatment with up to 60–70% responding at 1 year.¹ On the other hand, there are of course patients with TRS who show minimal or no response. If adherence and dosage are both thought adequate as evidenced by repeated measurement of plasma clozapine and norclozapine, then augmentation with a further antipsychotic, for example, amisulpride or aripiprazole, may be considered. Augmentation with electroconvulsive therapy for persistent positive symptoms³⁴ and combination with certain antidepressants (fluoxetine, duloxetine and citalopram) for persistent negative symptoms may also be contemplated.³⁵ Note that there is no evidence that SSRIs other than fluvoxamine inhibit clozapine metabolism in clinical practice (Drug-drug interactions section).

Be all this as it may, the evidence base in clozapine augmentation trials in TRS is conflicting. However, there is some evidence for benefit from aripiprazole augmentation in reducing negative symptoms.³⁶ In any event it is advisable to maintain the pre-dose plasma clozapine concentration below 1 mg L⁻¹, and preferably below 0.6 mg L⁻¹, otherwise if augmentation is successful then it will be unlikely that clozapine dosage will be altered. Attempts at augmentation should be discontinued if they are not beneficial.

Infection

Rarely, increases in plasma clozapine are reported in conjunction with lung or other infections in non-smokers. Such increases have been attributed to the inhibitory effects of (unspecified) cytokines released as a result of the infection on clozapine metabolism.^{12,37} However, other possibilities for increased plasma clozapine at constant dose in patients admitted to hospital include (i) either

covert smoking, or removal from a cigarette smoke-containing environment prior to admission, (ii) improved adherence and (iii) alterations in gastrointestinal motility that could affect clozapine pharmacokinetics (Gastrointestinal hypomotility section). Moreover, sometimes large increases in plasma clozapine at constant dose have been observed in the absence of either infection, or other possible explanations such as smoking cessation.²⁴

Adverse events on clozapine

Approximately 40% of patients discontinue clozapine treatment within 2 years.^{38,39} Cessation is usually related to either non-adherence, or AEs.⁴⁰ The normal clinical approach is to identify and manage AEs if possible and to discontinue clozapine only as a last resort (Table 2). In some cases, clozapine may even be re-trialled after certain life-threatening AEs that necessitated stopping the drug.⁴¹

Blood pressure changes

Hypotension usually occurs during clozapine dose titration, i.e. in the first 2 weeks of treatment, with tolerance usually developing over 4–6 weeks. Not all patients become tolerant, however, and dose reduction may be necessary although this has to be balanced against the risk of losing response. Even ultra-cautious dose titration can prove fatal on very rare occasions. There is potential for confusion when clozapine is prescribed and dispensed on the basis of a planned titration rate, but then the titration rate is altered on clinical grounds using the drug already dispensed.

Tolerance to the hypotensive effect of clozapine is quickly lost hence if a patient misses clozapine doses for more than 48 hours then dose titration must recommence. However, with adequate monitoring, including measurement of plasma clozapine and norclozapine, it may be possible to increase the dose more quickly than when the drug was initiated provided the initial initiation went smoothly. Missed doses may occur if there has been a problem in supply, a problem in getting FBC measurements, a condition such as neutropenia or other con-

Table 2 Some common problems associated with clozapine use and recommended actions

Observation	Possible cause	Possible consequences of inaction	Action required
Clozapine not taken for >48 hours	Non-adherence Failure in FBC testing Failure of supply Medical emergency	Possibility of fatal hypotension if recommenced on same dose or if too rapid re-titration	Repeat clozapine initiation protocol
Raised temperature, flu-like symptoms	Neutropenia/ agranulocytosis Pneumonia Myocarditis Cardiomyopathy	Life-threatening infection Life-threatening infection Heart failure	Urgent FBC, CRP, troponin and echocardiogram. Consider hospital admission. Consider prophylactic antibiotics
Low WCC/neutrophil count	Impending agranulocytosis	Life-threatening infection	Urgent FBC, troponin and echocardiogram. Consider hospital admission. Consider prophylactic antibiotics
Low blood pressure	Sample taken in the morning Recent non-adherence	Inappropriate break in treatment Possibility of fatal hypotension	Re-do FBC noting time of sample collection Review and re-initiate clozapine if necessary
Gastrointestinal hypomotility/ constipation	Clozapine dose too high Laxatives not prescribed or not taken	Possibility of fatal hypotension Life-threatening ileus, peritonitis, toxic megacolon	Cautious dose reduction Review dose and laxative regime – if severe stop clozapine and urgent hospital referral
Dysphagia	Stopped smoking Clozapine dose too high	Choking	Measure plasma clozapine and adjust dose as necessary
Akathisia	Clozapine dose too high	Increased risk of convulsions, constipation, etc.	Measure plasma clozapine and adjust dose as necessary
Severe sialorrhoea	Dose too high	Bronchopneumonia Relapse due to non-adherence	Review dose and consider adjunct drug treatment
Relapse	Non-adherence Started smoking/passive exposure to cigarette smoke Substance misuse	Self-harm Fatal hypotension if normal clozapine dose given Self-harm Self-harm. Fatal poisoning from illicit substances	Measure plasma clozapine and adjust dose as necessary Caution patient as to the effect of smoking on the response to clozapine. Measure plasma clozapine and adjust dose as necessary Substance misuse assessment
Lowered plasma clozapine	Poor adherence Started smoking	Loss of response Loss of response	Counsel patient as to the dangers of not taking clozapine as prescribed Review dose. Counsel patient as to the dangers of smoking while taking clozapine
Poor/no response	Clozapine ineffective or poorly effective even if taken as prescribed (6–12 months)	Inappropriate risk of clozapine AEs	Review dose and exposure to cigarette smoke. Ensure adherence by plasma clozapine measurement. Consider augmentation strategies

dition such as faecal impaction that necessitated withholding clozapine, or the patient may have either forgotten, or decided not to take the drug.

The marked hypotensive effect has further consequences. If another patient either deliberately takes, or is unintentionally given a dose of clozapine, the outcome may be fatal. Similarly, if a patient prescribed clozapine who has become non-adherent in the community is suddenly given their normal dose, the outcome likewise may be fatal. It is therefore essential that if patients are admitted to hospital, particularly if the admission is due to a relapse in mental health, prior adherence to clozapine is established. If this is not possible a cautious approach to clozapine dosage must be adopted.

The 12.5 or 25 mg clozapine tablets enable dose initiation at 12.5 mg or even 6.25 mg per day, but if a patient is prescribed oral suspension, reinitiation necessitates carefully measuring out 0.25 or 0.125 mL of the 50 mg mL⁻¹ suspension via a syringe. This procedure can cause gross errors that may prove fatal.

Hypertension is not as common as hypotension on clozapine and is usually associated with long-term treatment. Raised blood pressure may be managed in line with standard guidelines.

Haematological abnormalities

The best-recognized AE of clozapine is severe neutropenia (agranulocytosis), which occurs in 3.8–8 per 1000 of those prescribed the drug. The mortality rate was 0.01–0.03%, and the case-fatality rate 0.22–0.42% when assessed in 2011/12.⁴² Leucocyte production almost invariably recovers once clozapine is withdrawn. Nowadays, judicious use of cytokines, granulocyte colony stimulating factor (G-CSF, filgrastim) or granulocyte-macrophage colony stimulating factor (GM-CSF, sargramostim), is usually effective in promoting prompt return of the white cell count (WCC) to 'safe' values and together with antibiotic cover means that such episodes once recognized are rarely fatal.⁴³ Occasionally, however, there are unexpected reactions to cytokine therapy

such as thrombocytosis.⁴⁴ GM-CSF may be effective if G-CSF has failed.⁴⁵

Most patients given clozapine show an initial rise in the neutrophil count, which is followed by a return either to, or below baseline values. A warning sign of impending agranulocytosis may be either a continued fall, or a further rise in the neutrophil count followed by a drop below a guide value (Table 3). In some patients, neutropenia, defined by normative data in Caucasian populations, occurs in individuals from other ethnic groups who are otherwise healthy and who do not have repeated or severe infections. This condition is known as benign ethnic neutropenia (BEN) and occurs in 25–50% of Africans and some other ethnic groups in the Middle East including Yemenite Jews and Jordanians. This group of patients show no increase in the incidence of infections and have a response to infection similar to those with a 'normal' WCC. Clozapine is often dispensed to such individuals in consultation with a haematologist.

A complicating factor is that the WCC exhibits diurnal variation, with counts in the afternoon usually being higher than in the morning.⁴⁶ Reliance on early morning phlebotomy may thus result in clozapine being stopped unnecessarily. There are other issues, notably that factors other than clozapine may cause neutropenia, which may, or may not progress to agranulocytosis. This in turn raises the dilemma that if clozapine was not the cause of the neutropenia/suspected agranulocytosis, then clozapine may be being withheld from someone who needs it. Thus cautious reintroduction of clozapine may be deemed appropriate in conjunction with haematological advice.⁴⁷ However, if clozapine was the cause of the (impending) agranulocytosis, progression to agranulocytosis is likely to be more rapid and more severe than in the initial episode.⁴⁸

G-CSF has been used to support clozapine rechallenge after neutropenia and indeed cytokines have been used to maintain the WCC with the aim of preventing clozapine discontinuation.^{43,49} These compounds are given by injection, and hence are not suitable for long-term use. Oral lithium has also been used to stimulate leucocyte production, but requires

Table 3 Clozapine and blood dyscrasias: guidelines for the UK/Ireland

Dyscrasia	Explanation	No of cells (nL ⁻¹)		
		Normal range (BEN)*	Caution in dispensing (BEN)*	Advise stop clozapine then confirm result
Leucopenia	Deficiency in total white cells (leucocytes)	3.5–11 (3–11)	3–3.5 (2.5–3)	<3.0
Neutropenia	Deficiency in neutrophil granulocytes	2–8 (1.5–8)	1.5–2 (1.0–1.5)	<1.5
Agranulocytosis	Severe deficiency in granulocytes	-	-	<0.5
Thrombocytopenia	Deficiency in platelets	130–400	-	<50

*BEN = benign ethnic neutropenia—prescription allowed after haematology review

careful monitoring and there are concerns such as possible masking of an impending clozapine-induced agranulocytosis and whether it is safe to discontinue lithium once the WCC has recovered.⁵⁰ This is important because lithium will not protect against clozapine-induced agranulocytosis, and hence, it should not be used in rechallenging patients who have suffered a fall in the WCC that necessitated clozapine withdrawal.

There is also an increased risk of eosinophilia with clozapine (eosinophil count >0.7 nL⁻¹). Eosinophilia may be more common in women, although no sex difference was identified in data from the Italian Clozapine Monitoring System.⁵¹ Eosinophilia occurs typically after 3–5 weeks of therapy and resolves spontaneously,⁵² but may suggest tissue damage such as myocarditis (Myocarditis and cardiomyopathy section). Note that anaemia, bicytopenia, lymphopenia, leucocytosis and thrombocytopenia may also occur.⁴⁶

Other adverse effects of clozapine

In addition to the effects of clozapine on the bone marrow and on blood pressure, clozapine has a range of other effects, many of which are dose related, and some of which are life threatening. These include sedation, hypersalivation, CIGH, nocturnal enuresis, sexual side effects, difficulty in waking, and disturbed temperature regulation.

Sedation

Sedation affects some 50% of people taking clozapine, although tolerance usually develops over time. Weighting the dose to the evening helps minimize day-time sedation, although this may exacerbate the risk of bronchopneumonia (Bronchopneumonia section).

Sinus tachycardia

Sinus tachycardia occurs in some 25% of clozapine-treated patients. The average increase in heart rate is 10–15 beats min⁻¹. It is often dose related. Tachycardia is often time limited with resolution in 4–6 weeks for most patients. It usually responds to cautious dose reduction and is not normally a reason to stop clozapine, but this may be challenging because there is a risk of reduced efficacy. On the other hand, patients sometimes need less clozapine once they have shown an initial good response to the drug.²²

If tachycardia persists, a cardioselective β -blocker such as bisoprolol may be used if not contraindicated by other factors— β -blockers should not be used in the first 6–8 weeks of treatment, for example, to avoid masking a developing myocarditis.⁵³ Bisoprolol is preferred to atenolol, which is associated with increased risk of glucose dysregulation and CIGH. Ivabradine might be considered if the use of a β -blocker fails due to either lack of response, or intolerability.⁵⁴

Myocarditis and cardiomyopathy

Myocarditis and cardiomyopathy are potentially fatal. These problems appear to be significantly more common with clozapine than with other atypical antipsychotics but are still relatively rare. Myocarditis can only be diagnosed definitively by endomyocardial biopsy and histological examination of heart muscle, a procedure rarely performed in life.

Myocarditis is more likely in the first 3 months of clozapine treatment, but cardiomyopathy may occur at any stage. If WCC $<3.5 \text{ nL}^{-1}$, monitor for possible myocarditis as well as agranulocytosis. Eosinophilia and flu-like symptoms such as unexplained fever, fatigue, and lethargy alongside vague chest discomfort, angina pectoris, palpitations, tachypnoea, dyspnoea, orthopnoea, hypotension, 'narrowed pulse pressure' ($<25\%$ difference between systolic and diastolic pressures), persistent resting tachycardia and respiratory crackles may be warning signs. Because myocarditis may progress quickly to cardiac failure, it is crucial to monitor for it in the early weeks of clozapine use, and if strongly suspected, to discontinue clozapine.

Some of the features that may be interpreted as impending myocarditis such as raised CRP may simply be one of the many adaptive responses to responses clozapine such as the increases in the neutrophil count (Haematological abnormalities section) and in plasma hepatic enzyme activity (Hepatitis, interstitial nephritis, and pancreatitis section). A slower rate of titration may help limit the extent of these responses and thus allow treatment to continue (Initiating clozapine section).

Some authors recommend baseline laboratory monitoring, with or without follow-up testing, for C-reactive protein (CRP), creatine kinase MB, and troponin, but there is no clear consensus of the procedure to be followed for the first three months in all patients prescribed clozapine. This being said, monitoring should include baseline electrocardiography, echocardiography as part of a cardiac consultation if patients have cardiac disease or other risk factors e.g. WCC $<3.5 \text{ nL}^{-1}$, and monitoring of CRP and troponin as indicated.⁵⁵

The clinical presentation of cardiomyopathy can be highly variable. It may present as progressive heart failure but can remain asymptomatic before more overt manifestations such as cardiac failure/death. ECG changes, sinus tachycardia, atrial or ventricular arrhythmias, and left ventricular hypertrophy may occur. Chest X-ray may suggest cardiac enlargement. Pulmonary venous congestion, pulmonary oedema, and hypereosinophilia may occur.⁵⁶

Gastrointestinal hypomotility

CIGH is an under-recognized, but highly prevalent and potentially fatal clozapine AE. Constipation is the most commonly reported problem,⁵⁷ but CIGH can also result in dysphagia (difficulty swallowing), gastroparesis, ileus, bowel obstruction, faecal aspiration, colon perforation, toxic megacolon, 'acute abdomen', and death. Dysphagia on clozapine can lead to choking and in some cases vomiting and/or inhalation of food particles, which in turn may precipitate pneumonia.⁵⁸

Bowel motility studies suggest CIGH occurs in at least 75% of patients given clozapine. Problems can develop at any time in treatment and are often difficult to diagnose, with many patients not complaining of symptoms until serious pathology has developed.⁵⁹ The incidence of serious gastrointestinal hypomotility has been estimated as 4–8 per 1000 clozapine treated patients in a 1-year period and the case-fatality rate at 15–27.5%.⁴²

CIGH is an anticholinergic and antiserotonergic effect hence other products with these effects should be used with caution in patients taking clozapine.⁶⁰ There is a risk that anticholinergics used to treat clozapine-induced hypersalivation may exacerbate CIGH. Prophylactic laxatives(s) such as senna (with or without docusate) and/or polyethylene glycol, for example, movicol, should be prescribed.^{60–62}

Hypersalivation

Hypersalivation occurs towards the beginning of treatment in some 30–80% of patients given clozapine. It may be dose-related and/or due to disruption of the swallowing reflex. It is especially troublesome

at night. Tolerance often develops, but if not reduce the dose if possible, then if necessary, increase the dose more slowly than before. At night raise the height of the pillow and cover it with a towel. Ensure adequate hydration. Chewing gum may help during the day. Cautious use of peripheral anticholinergics may help (benzhexol, chewing hyoscine hydrobromide, pirenzepine). Use of anticholinergics, such as atropine or ipratropium bromide sublingually may help, and may reduce the systemic anticholinergic burden. α_2 -Adrenergics such as clonidine (measure blood pressure) and lofexidine, have also been tried.

Bronchopneumonia

Pneumonia is being recognized increasingly as a risk in clozapine-treated patients.^{63–67} There is a high case fatality rate.⁶⁸ It has been suggested that drainage of saliva into the lungs at night is a factor in the aetiology of this problem.⁶⁹ Another possible factor is dysphagia (Gastrointestinal hypomotility section). A further factor may be that clozapine has a sedative effect in many patients, especially at night when the majority of the dose is usually administered to minimize day-time sedation. Clozapine may also cause immunoglobulin deficiency that may enhance the risk of infection.⁷⁰ Smoking itself is also a risk factor for pneumonia.

Lung infections in clozapine-treated patients who smoke pose especial problems because (i) they may be admitted to a non-smoking hospital, (ii) they may not either want, or be able to smoke as normal hence the effective dose of ‘smoke’ may be reduced, and (iii) they may be treated with an antibiotic that may inhibit clozapine metabolism. The simple fact of the acute illness may also exacerbate CIGH, which may in turn affect clozapine pharmacokinetics.

Venous thromboembolism

Clozapine can lead to pulmonary embolism by various mechanisms including immobility, weight gain, metabolic syndrome, and increased platelet aggregation. The condition is rare, but mortality is some 30%.^{71,72}

Seizures

There is thought to be an increased risk of abnormal EEG findings, myoclonus, grand mal seizures, confusion, and delirium if the (pre-dose) plasma clozapine is $>1 \text{ mg L}^{-1}$. Although seizures feature on the clozapine ‘black box warning’, this to an extent reflects the situation before the TDM of clozapine was widely available and the profound effect of stopping smoking on clozapine dose requirement was appreciated.⁷³ In one audit of a clozapine TDM service (104 127 samples, 26 796 patients), plasma clozapine was 1 mg L^{-1} or more in 8.4% of samples.²⁴ No deaths were reported in this survey.

It has been suggested that prophylactic sodium valproate should be considered if there is concern about the possibility of seizures. However, (i) valproate is contra-indicated in females of child-bearing potential, and (ii) is a risk factor for neutropenia hence it is used with caution,⁷⁴ and may be best avoided particularly during the titration phase and early months of treatment. Topiramate, lamotrigine, and gabapentin have all been advocated for use in seizure prophylaxis, but all have potential drawbacks in clinical use. Indeed, it has been suggested that anticonvulsants should not be used as a primary prophylaxis for clozapine-induced seizures.⁷³

Temperature regulation

Some 5% of patients given clozapine experience fever during the initial stages of treatment. Although this usually resolves after a few days, neutropenia, myocarditis, NMS, hepatitis, pancreatitis, nephritis, and colitis must be excluded nevertheless. Other AEs associated with fever (heat stroke, pneumonia, pulmonary embolism, necrotizing colitis) are independent of the duration of clozapine exposure.⁷⁵

Heat stroke is rare, but should it occur the mortality is of the order of 50%. The problem may be due to disruption of hypothalamic thermoregulatory pathways and may be exacerbated in hot weather by inappropriate perception of body temperature. As with CIGH, it is important to warn carers of this potential problem. Key features are a raised core temperature ($>40^\circ\text{C}$) and CNS dysfunction.⁷⁶

Weight gain/dyslipidaemia/diabetes

The risks of weight gain and dyslipidaemia, in some cases progressing to type 2 diabetes, emphasize the need for regular monitoring of blood glucose and plasma lipids. The incidence of clozapine-induced diabetic ketoacidosis has been estimated at 1.2–3.1 per 1000 clozapine users, with a case-fatality rate of 20–31%.⁴²

Use of the minimum effective clozapine dose together with dietary and lifestyle advice are obvious interventions although the evidence that higher clozapine doses are associated with more weight gain is weak.⁷⁷ Similarly, there is no strong evidence to recommend routine prescription of add-on medication for weight reduction.⁷⁸ Use of the antidiabetic drug metformin in clozapine-treated patients has been advocated,^{79–81} although there is a report of pancreatitis associated with metformin and clozapine.⁸²

Neuroleptic malignant syndrome

NMS has been described after clozapine, albeit rarely. The outcome of clozapine rechallenge after NMS was favourable (no recurrence of NMS) in 92% ($n=11$) of cases after clozapine-associated NMS and in 79% ($n=30$) of those given clozapine following NMS associated with a different antipsychotic. Most (82%; $n=14$) people with clozapine-associated NMS had no recurrence on receiving a different antipsychotic. No deaths were reported with any of these rechallenges.⁸³ The mechanism by which clozapine gives rise to NMS remains unknown.

Hepatitis, interstitial nephritis, and pancreatitis

An asymptomatic 2- to 3-fold elevation of plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity occurs in 30–50% of patients given clozapine. This usually resolves after 6–12 weeks.⁸⁴ Icteric hepatitis is uncommon (0.06%), and fatal fulminant hepatic necrosis is very rare (0.001%). The mechanism underlying these effects is unknown. There seems to be no relation to the risk of neutropenia/agranulocytosis. Nevertheless, jaundice should be looked for and

LFTs performed at the end of the first week of treatment. If the LFTs remain high, either the rate of titration should be reduced, or treatment suspended. It is important to exclude paracetamol overdose as a cause of deranged liver function. There are two reports of successful clozapine rechallenge after hepatitis.⁸⁵

Interstitial nephritis and pancreatitis are likewise rare, but serious AEs to clozapine.^{85,86} Clozapine rechallenge seems unlikely to be successful should either occur.

Continuing patient care

Patients and carers

Patients, relatives, and other carers must be informed of the factors inherent in the safe use of clozapine. These include (i) the importance of continued adherence and the need to contact their doctor if two or more day's doses have been missed, (ii) the risks inherent in altering smoking habit (and of passive smoking) without discussing the required alteration in clozapine dosage with their psychiatrist, (iii) the need to report flu like and other symptoms that may be indicative of impending neutropenia/myocarditis/cardiomyopathy, (iv) the dangers of CIGH including dysphagia and constipation and (vi) the increased risk of pneumonia in patients taking clozapine over and above the enhanced risk of smoking. Moreover, there must be guidance as to what action to take once an issue possibly related to clozapine has been identified.

Health care professionals

Nurses and other mental health staff need to be made aware of the issues listed above (Patients and carers section) that may complicate clozapine treatment including especially the need to ensure adherence and to monitor exposure to cigarette smoke. The Glasgow Antipsychotic Side-effects Scale for Clozapine (GASS-C) is a clinical tool that aims to enable systematic assessment of the subjectively unpleasant side-effects of clozapine.⁸⁷ In addition, such staff

need to be able to recognize possible warning signs of clozapine-related AEs such as fever, cough, dysphagia and constipation.

Active monitoring for the possible presence of CIGH should be instituted, and again, there must be guidance as to what action to take once an issue possibly related to clozapine has been identified. The most commonly-reported presentations of serious CIGH are abdominal pain and abdominal distension (sometimes referred to as ‘clozapine belly’), occurring in 73 and 55% of cases, respectively,⁸⁸ but the significance of these signs is often missed.

The patient’s general practitioner must be informed that their patient has been prescribed clozapine and must be aware of the special issues surrounding the safe use of the drug.¹⁰ The fact of prescription of clozapine should be recorded on the patient’s electronic prescribing record, so that it appears in the patient’s summary care records if they are admitted to hospital. Issues do arise because clozapine is prescribed in secondary care, but treatment of some of the AEs such as CIGH is delegated to primary care. General practitioners must not only recognize clozapine AEs, but also report them to the prescriber.

Emergency care

First responders, A&E, admission wards and ITU staff need to have ready access to information on the likely serious AEs that may result from clozapine. These include not only neutropenia/agranulocytosis and seizures, but also the various manifestations of CIGH such as constipation and choking, as well as the possible presence of chest infection and cardiac complications (myocarditis and cardiomyopathy). They also need to be aware of the special issues surrounding the prescription and dispensing of clozapine and the need to liaise with specialists (psychiatrists, mental health pharmacists) in order to maintain clozapine treatment unless contraindicated by other factors. For example, if someone taking clozapine is admitted to a medical or other non-smoking unit, their smoking status must be assessed promptly and their clozapine dose reduced if

necessary. Because clozapine may not appear on a patient’s GP summary care record, any patient admitted with a significant mental health diagnosis such as schizophrenia, but not on medication to treat it should be followed up in case they are either on clozapine, or possibly a long acting antipsychotic given by injection.

Conclusions

Although clozapine is uniquely effective in TRS, it is associated with a range of AEs, some of which are life-threatening. However, it can be used safely with careful monitoring. This is important because there are no alternatives at present to clozapine with comparable efficacy in TRS. It is thus incumbent upon clinicians to carefully assess and manage clozapine-related AEs not only to ensure patient safety but also to help reduce inappropriate and unnecessary clozapine discontinuation.

Biographical details

Prof Robert J Flanagan BSc PhD Chem FRSC ERT MCSFS FRCPath FRCP Ed HFCMHP Hon FFFLM is Consultant Clinical Scientist, Precision Medicine, King’s College Hospital and Visiting Professor, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King’s College London. He has published over 250 scientific papers and five books. Particular interests have been treating mental illness especially as regards use of antipsychotics, notably clozapine, and the diagnosis of substance misuse, especially of volatiles such as butane. He has acted as a consultant to the United Nations Office for Drugs and Crime and to the World Health Organization. He is a past president of the British Academy of Forensic Sciences.

Dr John Lally MB MSc MRCPsych PhD is a consultant psychiatrist at the Department of Psychiatry, Mater Misericordiae University Hospital, Dublin, Ireland and Visiting Researcher at the Institute of Psychiatry, Psychology & Neuroscience, King’s College London. His clinical and academic interest is in

treatment resistant psychosis, complex psychopharmacology, physical health comorbidities in mental disorders and medical education.

Dr Siobhan Gee MPharm PhD PGDip MFRPSII is the principal pharmacist for liaison psychiatry at King's Health Partners, covering Guy's and St. Thomas', King's College Hospital and the South London and the Maudsley NHS Foundation Trusts. Her clinical interest is in the use of psychotropics in people with comorbid physical illness, and her specialist field of research is prescribing practices in treatment resistant schizophrenia.

Mr Ray Lyon BPharm FCMHP was the Chief Pharmacist—Strategy for Sussex Partnership NHS Foundation Trust. His specialist areas of interest included (i) improving adherence to medication, (ii) developing the role of the pharmacy for people with a mental health problem and (iii) reducing the use of antipsychotics in people living with dementia.

Dr Susanna Every-Palmer PhD FRANZCP Adv Cert Forensic Psychiatry MSc MB ChB is a consultant forensic psychiatrist and Head of the Department of Psychological Medicine at the University of Otago, Wellington and the Director of Area Mental Health Services at the Central Regional Forensic Service, covering New Zealand's lower north island. Her clinical and much of her academic practice relates to the treatment of severe mental illness. Her PhD focussed on the mitigation of clozapine adverse effects and she has published extensively in this area.

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