RC PSYCH
ROYAL COLLEGE OF PSYCHIATRISTS

POSITION STATEMENT PS01/26

Clozapine for treatment-resistant schizophrenia

The case for timely and appropriate use

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Contents

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Executive summary

Context and rationale

There is convincing evidence that clozapine improves outcomes in patients with treatment (medication) resistant schizophrenia (TRS), where other medications have been tried but have not been effective. Clozapine is the only antipsychotic medication recommended by evidence-based national guidelines for this indication, and study findings strongly suggest that the likelihood of response is maximised if clozapine is started soon after a diagnosis of TRS has been made.

However, it has been estimated that only a small proportion of patients whose illnesses fulfil the eligibility criteria for treatment with clozapine are currently prescribed this medication, often with a significant delay in its initiation; these are both factors that could compromise outcomes for patients with TRS.

There are a number of potential barriers to the timely use of clozapine, which can be related to the attitudes and actions of clinicians and patients as well as issues in the relevant clinical services.

Purpose and scope

This position statement sets out practical, clinical and system-level strategies to support the appropriate and timely use of clozapine in patients with TRS, with the aim of improving clinical outcomes and reducing avoidable delays in care.

Key recommendations

1. National consensus guidance on the screening, monitoring, and management of clozapine side effects should be developed centrally to support psychiatrists in using this medication safely.
2. NHS mental healthcare providers should provide a community-based clozapine initiation service to reduce the reliance on hospital admission to start this treatment.
3. The clinical services responsible for monitoring ongoing clozapine treatment should be adequately and appropriately staffed and resourced to ensure timely access to clinicians with the relevant clinical expertise and to provide safe monitoring for side effects throughout treatment.
4. Greater adoption of technological advances, such as point-of-care testing for obtaining full blood counts and plasma clozapine levels, should be encouraged to make monitoring more convenient and more acceptable to patients, for example, by minimising the number of healthcare appointments required.

Background

Evidence for the use of clozapine in treatment-resistant schizophrenia

Treatment-resistant schizophrenia (TRS) is defined by the presence of at least moderate to severe psychotic symptoms, which are associated with functional impairment and are persistent despite serial trials of at least two antipsychotic medications that were adequate in terms of dosage, duration, and level of adherence.[1] It should be noted that whilst it is generally referred to as 'treatment-resistant' schizophrenia, it is more appropriately termed 'medication-resistant' schizophrenia. In people with first-episode psychosis, almost a quarter will warrant a diagnosis of TRS,[2-5] while the overall prevalence in those with established illness has been consistently found to be around 30%.[6]

National evidence-based guidelines[7,8] recommend that clozapine is offered first-line to those with TRS. As well as improving the persistent psychotic symptoms, there is strong evidence that clozapine treatment is associated with an improved quality of life as well as lower risks of hospitalisation, involvement in crime, and premature mortality.[9-14] The established reduction in hospital admissions[15] and subsequent length of stay[16] means that clozapine also has significant cost-effectiveness benefits compared with other antipsychotic medications.[17,18] These benefits may be greater if clozapine is initiated in the community.[19]

Evidence for the timely use of clozapine

Clozapine has been consistently found to be superior to other antipsychotic medications for the treatment of TRS.[20,21] The earlier that clozapine is started for TRS, the better the outcomes.[22-26] Therefore, a delay in initiating clozapine may contribute to poorer clinical outcomes, including a greater risk of rehospitalisation.[22,24,27,28] For example, the findings of one study suggested that, for female patients, each year of delay in starting clozapine was associated with a 15% decrease in the likelihood of functional improvement.[29]

The current use of clozapine

In spite of this evidence base, it has been estimated that less than a third of potentially eligible patients currently receive clozapine in the UK,[30] lower than the majority of other European countries.[31] Significant geographical variations exist within the UK with less than 5% of potentially eligible patients prescribed clozapine in some areas.[30] Similarly, prescribing practice varies widely within EIP teams, from 0% of eligible patients being

offered clozapine in some areas to 100% of eligible patients being initiated on clozapine in others.[32]

Further, there are several demographic variables that appear to influence the use of clozapine. For example, women with TRS may be less likely to be prescribed this treatment,[33] and this may also be the case for patients from ethnic minorities[34] for a variety of reasons, including an under-recognition of/concerns relating to benign ethnic neutropenia.[35]

Current practice and gaps

Clozapine initiation is often substantially delayed.[30] The mean duration of treatment with other antipsychotic medications prior to clozapine initiation in the UK is four years, [36] and ranges from two to 10 years internationally.[20,37,38] These delays appear to represent an important unmet need,[1] given it can usually be established within approximately 12 weeks whether the illness has failed to respond to two adequate, consecutive trials of antipsychotic medication – a key criterion for a diagnosis of TRS.[39]

However, it should be acknowledged that there are a variety of possible reasons for a delay in starting clozapine. For example, a patient may have had reservations about the treatment and needed time to consider the potential risks and benefits. If ongoing substance use, such as cannabis, is a factor, this may perpetuate symptoms. Or, particularly for complex cases, the responsible clinician may have judged other treatment interventions to have a more favourable risk–benefit profile, and tried them first.[40] For example, a trial of an LAI antipsychotic preparation may have been prescribed where a patient with apparent TRS was suspected of poor adherence to their oral medication.

One commonly cited reason for delay is that time was spent conducting individual trials of medication regimens with only limited evidence of efficacy for TRS, such as high-dose or combined antipsychotic medications.[36,41-43] A significant majority of psychiatrists report they would trial up to four antipsychotic medications or trial a combination of an antipsychotic medication with either a second antipsychotic or mood stabiliser, before contemplating clozapine initiation.[44]

Barriers to clozapine use and potential solutions

Service-level barriers

Many of the opportunities to offer clozapine earlier in the treatment pathway lie within early intervention in psychosis (EIP) services.[45,46] However, clozapine has been found to be underutilised in such services.[47-49] Findings of the most recent National Clinical Audit of Psychosis (NCAP) in the UK indicate that only around half of eligible patients under the care of EIP services were offered clozapine.[32]

Diagnostic practices

This limited and delayed use of clozapine may partly reflect that EIP services are anchored in a recovery model and frequently allocate the ICD-10 diagnostic code F29 (unspecified non-organic psychosis) rather than F20 (schizophrenia). As clozapine is licensed only for the latter, this diagnostic practice may influence prescribing decisions, partly because of concerns related to off-label use. In addition, staff shortages, service fragmentation and administrative processes create system barriers to clozapine utilisation.[38,50,51,52]

Delivering physical health monitoring

The initial titration of clozapine requires frequent monitoring of physical health parameters, but access to inpatient or day hospital places for this purpose can be limited. Delivering the required monitoring may be within many community mental health services can also be challenging.

For example, there may be insufficient staff to facilitate daily monitoring visits, and it can be difficult to provide a co-ordinated service in rural areas where patient numbers are low, and the travel distances are considerable.

These challenges are reflected in a 2015 UK survey of 243 consultant psychiatrists, in which approximately a quarter reported having insufficient resources to initiate clozapine, and a similar proportion did not consider community initiation it to be safe.[2] Respondents citied service fragmentation and/or lack of community support as barriers to clozapine initiation.

Further, clinicians may have concerns about the availability, capacity and competency of local services that would be responsible for continuing physical health monitoring.[48,53,54] Screening for and managing both the troublesome and potentially serious side effects of clozapine requires an adequately resourced infrastructure with patients having access to clinicians with clinical expertise in the use of this medication.

Shared care with primary care services

A further systems-level barrier to the safe use of clozapine relates to complications that can arise when care delivery is shared with primary care. National clinical audits conducted by the Prescribing Observatory for Mental Health found that 28% of community patients prescribed clozapine did not have this medication recorded on their Summary Care Records (SCRs),[43] potentially compromising the ability of non-psychiatric medical services to be alert to potential side effects and, therefore, provide safe and appropriate care.

Potential solutions

Studies suggest that a specialised clozapine initiation service, with delegation of clozapine monitoring to a specialised team member or service, can increase the likelihood of clozapine being started.[50,51,55] One such service, the TREAT service, reported the successful initiation of clozapine in 66% of those patients agreeing to start such treatment[19] with, subsequently, a significant reduction in both inpatient bed days and outpatient clinical contacts (case study 1).[95]

Clinician-level barriers

Concerns about adverse effects

Concern about adverse effects is the most frequently cited reason for clinicians' reluctance to initiate clozapine.[51,56-58] They may substantially overestimate the risk of agranulocytosis,[59-61] which necessitates mandatory regular monitoring of white blood cell count and absolute neutrophil count.

In addition, clinicians may be cautious about the wide range of other adverse side effects associated with clozapine. These include more common but often burdensome problems, such as hypersalivation, sedation and nocturnal enuresis,[62] as well as less common but serious adverse effects, such as myocarditis, gastrointestinal hypomotility, and substantial metabolic disturbances.

Clinicians' concerns and sense of caution may be reinforced by clinical experiences: In the survey of consultant psychiatrists mentioned in the previous section,[52] almost half of the 243 respondents reported having been involved in the management of potentially serious side effects of clozapine in patients under their care.

Patient-level factors affecting prescribing complexity

Furthermore, certain patient-level factors – including pregnancy, breastfeeding, older age, ID and complex physical health comorbidities – increase the complexity of clozapine prescribing. These factors affect the overall risk–benefit profile for individual patients and, in cases where clozapine use is appropriate and initiated, it will often necessitate enhanced management, such as increased monitoring.

Consequently, this may reinforce clinicians' caution and contribute to hesitation in considering, initiating or managing clozapine.

Limited training and confidence

More broadly, there may be a more general lack of confidence among some clinicians about the adequacy of their training and experience in managing clozapine therapy[48,54] including the monitoring of side effects. For example, over half of 192 EIP clinicians surveyed reported that they had not received any training on clozapine treatment.[63]

Lack of standardised monitoring guidelines

While a formalised system does exist for screening for agranulcocytosis, there has historically been a lack of standardised monitoring guidelines for other potentially serious adverse effects, such as myocarditis.

Although recommendations for such monitoring have been published,[64-67] they are not entirely consistent, and the extent to which any have been adopted and systematically implemented across clinical services in the UK is unclear. A recent systematic review[68] identified a paucity of comprehensive monitoring guidelines and concluded there was an urgent need for more comprehensive, evidence-based versions to be developed.

Monitoring concerns

Clinicians' concerns about their responsibility for the ongoing monitoring of patients taking clozapine are supported by the findings of several *Prevention of Future Deaths* reports issued by coroners[69]. These reports have highlights instances of sub-optimal monitoring of clozapine and prompted the MHRA to issue guidance on specific aspects of safety monitoring.[70] For example, the MHRA recommends monitoring tobacco smoking , as changes in smoking habits can significantly affect plasma clozapine levels, with substantial implications for treatment efficacy and patient safety.[43, 70-72]

Encouragingly, an audit of clozapine prescribing practice in a large number of UK mental health services in 2020[73] found that physical health screening and side-effect monitoring was being conducted in line with recommended practice for the majority of patients. However, the audit also found that monitoring for clozapine-induced myocarditis during the initial risk period (using markers of inflammation, such as C-reactive protein, and cardiac damage, such as troponin) was inconsistent.

This variability may partly reflect differences between existing guideline recommendations. In addition, the reported use of these investigations may not always represent routine monitoring, but in some cases may reflect testing undertaken in response to emerging cardiac symptoms.

To help increase guidance and clinician support, the Royal College of Psychiatrists is developing a new tool – Wim's Protocol – for the safe monitoring of clozapine (including screening for gastrointestinal and cardiac adverse effects, with actions for prescribers),. This is due for publication later this year.

It is recommended that prescribers refer to existing resources for guidance (e.g. *The Maudsley Prescribing Guidelines*, local mental healthcare provider monitoring protocols) and, once published, the RCPsych protocol to ensure safe ongoing care for people taking clozapine.

Potential solutions

Targeted educational programmes may increase clinicians' confidence in the prescription of clozapine.[74] One study of a multi-faceted education programme –incorporating a guideline for clozapine treatment, presentations, and easy-access to advice from experts – increased subsequent usage by 40%.[75] Guidance on how to offer clozapine effectively to patients, including clear and individualised communication of risks and benefits, have also been published.[76]

International evidence further supports the value of structured, system-wide approaches. In New Zealand, Wheeler et al[37] demonstrated how an intervention focussed on regular audit, tailored feedback around barriers to improvement, education programmes, and the development of local clozapine guidelines led to an increase in the proportion of outpatients with a diagnosis of schizophrenia who were prescribed clozapine from 21% to 33%.

Similarly, a Canadian study[66] found that the development and implementation of a comprehensive interdisciplinary clozapine 'toolkit' – including clinician education and training, an educational brochure for patients, and standardised monitoring recommendations – improved clinicians' adherence to best-practice standards for laboratory and clinical monitoring.

Patient-level barriers

Survey feedback from both patients and clinicians alike suggests that patients' reluctance to have blood tests can be a barrier to initiating clozapine.[51,77]it is underutilised. Once patients have started clozapine, side effects such as hypersalivation, weight gain and constipation are the most common reason for discontinuation,[60] although patients may welcome the absence of extrapyramidal side effects.[78-81]

However, a significant majority of patients prefer clozapine to their previous antipsychotic medication,[82] reporting higher satisfaction and evidencing increased adherence despite a greater side-effect burden.[20,83] A 2022 systematic review conducted by Parkes et al[84] found that most patients reported positive experiences of clozapine, particularly in relation to the improvement of symptoms.

Similarly, Qurashi et al[85] reported that patients expressed a preference to remain on clozapine compared with previous medications. If clinicians underestimate patients' satisfaction with clozapine, this may bias them against its proactive use.[86]

It is therefore critical to hold a balanced and transparent discussion of the benefits and potential serious adverse side effects of clozapine in order to support informed decision-making. Clear documentation of this discussion is essential, as is establishing whether the patient possesses the mental capacity to decide whether to undergo the treatment and understands that they have the right to refuse the it if they decide to do so.

Potential solutions

The use of point-of-care testing (POCT) for the monitoring of neutrophils presents an opportunity to mitigate a barrier to blood monitoring. This system is more convenient for patients as FBC results are immediately available and medication can therefore be collected at the same appointment. Further, venous access can be difficult in some patients and offering the choice of finger prick (capillary) POCT testing may be helpful.[87-89]

Accurate and reliable POCT is now also available for determining plasma clozapine levels (case study 3),[87] although such tests may be of limited use when there is no immediate access to a clinician experienced in interpreting and acting on the results**.** The use of local anaesthetic creams (such as Emla) can also help reduce the discomfort associated with blood sampling. Patient information videos, including films of patients' experience of taking clozapine can also be very powerful . One project provides short films, which can be accessed through QR codes included with every dispensed prescription of clozapine, that cover issues such as recognising and managing side effects and blood monitoring (case study 4).

The College position

- A trial of clozapine treatment should be promptly considered for people with schizophrenia whose illness has proved to be refractory to adequate trials of standard treatment – regardless of age, place of residence, or the presence of comorbidities. This should be undertaken once treatment for any relevant co-morbid conditions has been optimised, and realistic interventions have been put in place to address potentially modifiable social and environmental factors that may perpetuate illness.

- Shared decision-making should underpin the initiation and continuation of clozapine with clinicians and patients working collaboratively to ensure informed, person-centred treatment decisions.

Recommendations for action

Workforce training and clinical expertise

- Clinicians should receive appropriate training in the use of clozapine, including access to educational resources on the identification, severity, prevention and management of adverse side effects, with particular emphasis on myocarditis and constipation.

- Clinical services responsible for monitoring ongoing clozapine treatment should be adequately and appropriately resourced and ensure timely access to clinicians with the relevant clinical skills and expertise.

Service provision and patient care

- Clozapine should be considered as a possible treatment option for all patients in EIP services with a diagnosis of TRS.

- Where feasible, mental healthcare providers should establish or provide access to specialist clozapine initiation services which have the ability to initiate treatment in community.

- Point-of-care testing for the initiation and monitoring of clozapine should continue to be supported by mental healthcare providers as both patients and clinicians find it acceptable and convenient.

Patient information

- Psychoeducational materials on clozapine treatment should be made widely available to patients and carers.

Governance and monitoring

- A standardised, evidence-based, monitoring guideline covering the range of adverse effects, including myocarditis and constipation, should be centrally produced and adopted by clinical services. (This is currently being developed by RCPsych.)

Quality improvement and evaluation

- Relevant clinical services should be encouraged to participate in the QI programme on the use of clozapine run by the Prescribing Observatory for Mental Health (POMH).

Case studies

Case study 1: TREAT community clozapine service

The TREAT service comprises a nurse and psychiatrist with expertise in TRS and dedicated time to support the assessment of TRS and initiation of clozapine. They work closely with community teams, attending team meetings and auditing patient records, to proactively identify patients at risk of treatment resistance. Having dedicated time allows the team to establish a diagnosis, ensure that the patient is suitable for clozapine initiation, and to perform the monitoring in the community. Once successfully titrated and when side effects are well controlled, patients can be discharged back to regular community services.

Case study 2: ECO education package

The Early Clozapine Offer (ECO) initiative provides an online programme, developed in partnership with Maudsley Learning, focussed on improving recognition of treatment resistant schizophrenia, its subsequent treatment with clozapine and the monitoring requirements of the medication.

This has been successfully piloted within an EIP service with questionnaire data confirming its acceptability and usefulness. To complement the online training programme, a prescribing guideline for psychosis has been developed, which will be available online for clinicians to access. It provides guidance for clinicians on how to manage common side effects and provides a protocol for clozapine discontinuation in both emergency and elective scenarios, as well as providing guidance on managing discontinuation symptoms.[89]

Case study 3: POCT for clozapine levels and FBC

Point-of-care testing (POCT) presents an opportunity to mitigate the barrier of blood monitoring. Various studies have evidenced patient and clinician preference for POCT in this context with reduced waiting times for a result, acceptability compared with blood tests and flexibility identified as key benefits.[86,87]

In a 2018 survey, Kelly et al found that clinicians believed the introduction of POCT would improve care and increase the likelihood of clozapine prescription.[76] This evidence suggests implementing services utilising POCT for clozapine initiation and monitoring could reduce patient and clinician hesitancy to prescribe.

Kamhi-Nesher et al[90] explored the feasibility and reliability of the use of POCT blood monitoring for clozapine in an outpatient setting. Both patients and clinicians preferred POCT as opposed to traditional phlebotomy especially with regards to the immediacy of the result. POCT clozapine levels can also facilitate the assessment of adherence and whether increased plasma concentrations are causing side effects.

The evidence suggests that clozapine POCT may be useful in an acute psychiatric inpatient setting. A novel case series demonstrated the potential for POCT to reduce length of stay, improve patient adherence to monitoring and facilitate rapid and safe re-titration.[91] Furthermore, the option for more regular monitoring of plasma clozapine levels using POCT, with the provision of quicker results, allows for a more accurate assessment of appropriate dosing for individual patients and may reduce the impact of adverse effects that are dependent on plasma clozapine levels.[92,93]

Case study 4: QR codes for clozapine

The Central and North West London NHS Foundation Trust pharmacy department worked in partnership with their trust medicines co-production group to create a media solution to enhance the provision of medicines information. The innovative digital initiative used QR codes to develop emotionally engaging videos to deliver information and to educate patients, carers and healthcare professionals about clozapine. The scripts for all four videos were co-produced and co-designed with patients and carers.

All videos are accessible via a QR code which is routinely attached to the outer packaging of all clozapine prescriptions supplied to patients by their pharmacy dispensary, Additionally, the QR codes are available via their electronic prescribing and medicines administration system (EPMA) to support healthcare professionals with shared decisions and education regarding prescribing and administering clozapine.

At the end of each video, there is an opportunity for the viewer to provide feedback, and 81% report finding the videos helpful in improving understanding of the subject.

(For more information about this digital initiative, contact:
Yogita Dawda, consultant pharmacist at Mental Health at Central & North West London NHS Foundation Trust: yogita.dawda@nhs.net)

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