Clinician hesitation prior to clozapine initiation: is it justifiable?†

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Summary
Clozapine has been endorsed by national clinical guidelines for 10 years and yet underutilisation and delay to initiation remain rife. Although there will be good clinical reasons for clozapine not being initiated for some patients, it is hypothesised here that for others, clinicians’ attitudes and preferences are the most likely predictive factors.

Declaration of interest
M.X.P. holds a Clinician Scientist Award supported by the National Institute for Health Research (NIHR) and has also received consultancy fees, lecturing honoraria, and/or research funding from Janssen-Cilag, Eli Lilly, Endo, Otsuka and Wyeth, and has previously worked on two clinical drug trials for Janssen-Cilag.

The views expressed in this publication are those of the author and not necessarily those of the National Health Service, the NIHR or the Department of Health.

Clinician hesitation

Ever since John Kane and colleagues reported that clozapine was superior to chlorpromazine in terms of efficacy for patients with treatment-resistant schizophrenia,† clinicians have debated the relative merits of clozapine as the only licensed drug for use in such patients. Avoidance of – or hesitation before – clozapine initiation is rife, despite current clinical guidelines advocating otherwise. This is most recently evidenced by a naturalistic study for patients commenced on clozapine reported by Howes et al. in this issue, which examined the time taken to initiate clozapine following two adequate treatment trials with two different antipsychotics. Treatment episodes for each antipsychotic were categorised as to whether or not each treatment episode was ‘adequate’ in terms of dose and duration of treatment trial, in keeping with guidelines,† but evaluation of adherence was not possible. As with any retrospective study design, missing and incomplete data are inevitable and this study excluded a third of eligible patients owing to missing clinical notes, and further disregarded 91/825 treatment episodes for the remaining patients owing to incomplete prescribing data. For patients who received two adequate treatment trials (12/149, 87%), the subsequent mean time to delay for clozapine initiation was 47.7 months (range 0–219), which constitutes a reduction of approximately 1 year in comparison with a similar earlier study.† Howes et al concluded that the delay to clozapine initiation highlights a lack of clinician adherence to national clinical guidelines.† However, the recorded clinical reasons for that theoretical delay are notably missing and these might highlight the challenge in achieving two adequate trials on treatment with an antipsychotic in terms of dose, duration and adherence; but one wonders how they might fully account for the upper range of delay of up to 18 years.

See pp. 481–485, this issue.

Are interim prescribing strategies justifiable?

Although clozapine initiation is avoided, for sound clinical reasons or otherwise, switching multiple times between antipsychotics is commonplace. Howes and colleagues† noted that, on average, patients received more than five different antipsychotic treatment episodes before clozapine initiation and that the mean number of different adequate treatment episodes was 2.8, reduced from 4 in the earlier study.‡ Other interim strategies include use of two or more antipsychotics at the same time as well as above licensed dose prescribing, either for a single antipsychotic or for a combination of two or more regularly prescribed antipsychotics. If ‘as required’ antipsychotics are also considered, then rates of antipsychotic polypharmacy are likely to be even higher. This finding is in keeping with a Danish study, which reported that two-thirds of psychiatrists interviewed would rather combine two antipsychotics than use clozapine.† As Howes and colleagues† rightly point out, there is little empirical evidence to support either regular polypharmacy or high dosing. At best, one could argue that individualised prescribing using antipsychotic polypharmacy or above licensed doses be viewed as an N of 1 study, taking place after options endorsed in guidelines have been exhausted (including clozapine), and then only with a clearly documented clinical and psychopharmacological rationale, systematic monitoring of symptoms and side-effects and with a view to discontinuation if no clinical benefit is seen after a pre-determined period of time.

Fool’s gold . . .

So why are clinicians delaying clozapine initiation? Farooq & Taylor§ highlight a possible perception among clinicians that clozapine is a dangerous therapeutic agent. In the UK, it was noted that clozapine was associated with an increased risk of death and that pneumonia was the most common single cause, followed by lung cancer.‡ Alternatively, in a larger-scale study in Finland, risk for all-cause mortality for antipsychotics was found to be lowest for clozapine, and this was attributed in particular to a lower risk of death from suicide.‡ Clinicians have been found to rate weight gain, hypersalivation and blood monitoring as the most problematic issues for clozapine but that a quarter of psychiatrists overestimated the risk of agranulocytosis.† Assuming that there is
a good, supportive service provision for phlebotomy, there may be further uncertainty regarding the appropriateness of forced blood tests on the ward in the context of a compulsory treatment order. In this situation it is critical that the multidisciplinary team is given the opportunity to understand the role that clozapine can play within the care plan and is in agreement with the strategy. For Black and ethnic minority patients with lower than average white cell counts at baseline, clozapine may not be initiated owing to the lack of consideration of benign ethnic neutropenia. Non-adherence to taking clozapine is also a key concern, not least because clozapine is no exception to this rule. That said, studies continue to show that patients tolerate its side-effects or have a good clinical response to it and are less likely to hospitalise with a diagnosis of schizophrenia. None the less, antipsychotics for patients after discharge from their first inpatient admission are being evaluated. In a more recent large observational study, clozapine was found to have a significantly lower risk of rehospiatilisation than risperidone and other second-generation antipsychotics for patients after discharge from their first hospitalisation with a diagnosis of schizophrenia. None the less, there will always be a subgroup of patients for whom clozapine does not have a therapeutic effect even with a dose that achieves therapeutic plasma concentration levels, and the need for augmentation strategies is warranted. It remains to be determined whether these predominantly include patients with primary treatment resistance or with treatment resistance that emerges over time, possibly as a consequence of inconsistent antipsychotic treatment.

**Targets for changing prescribing behaviour**

Even with a gold standard drug, not all patients will be able to tolerate its side-effects or have a good clinical response to it and clozapine is no exception to this rule. That said, studies continue to show that clozapine underutilisation and that this varies by region. Although there will be good clinical reasons for clozapine not being initiated for some patients, it is hypothesised here that clinicians’ knowledge, attitudes and preferences are more likely to be predictive factors for explaining the variation in clozapine prescribing rates and that these will need to be addressed before adherence to clinical guidelines for clozapine is likely to improve. Drawing on the literature on potential underutilisation of antipsychotic long-acting injections and therapeutic drug monitoring for antipsychotic plasma concentration levels, it is anticipated that for clozapine there will be some specific aspects. These are likely to include: clinicians’ perceptions of side-effects and knowledge of the management of side-effects; potentially paternalistic concern regarding patient attitudes to and adherence with clozapine and the associated regular blood tests; service-level logistical restraints, including access to a laboratory for drug plasma concentration levels; clinician ambivalence regarding superior efficacy of clozapine in treatment-resistant illness; and lack of sufficient knowledge and ongoing experiential knowledge of prescribing clozapine. Endorsement by members of the multidisciplinary team also would appear to be critical and this could be compromised by lack of training in psychopharmacology.

The National Audit for Schizophrenia (NAS) for England and Wales is due to report its findings later this month (December 2012) and will shed light on clinician preference, by evaluating whether or not patients are even offered clozapine after two different adequate antipsychotic treatment trials. However, the results will be on a trust-by-trust basis and then aggregated for England and Wales, but it is also within each trust that clinicians’ attitudes to clozapine should be considered as to whether or not clinicians’ attitudes and preferences are the primary cause for hesitation before clozapine initiation. Consequently, methods to increase rates will need to consider aspects of knowledge, attitudes and preferences before a change in prescribing behaviour is likely to occur. This will require local champions with good knowledge in clinical psychopharmacology, and without hindrance by service-level factors, to address the key concerns within each trust.

**References**


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First received 29 May 2012, final revision 28 Jul 2012, accepted 5 Sep 2012