

Editorial

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.

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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 colleagues² 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.⁴ 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.⁵ As Howes and colleagues² 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.

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,¹ 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*² 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,³ 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 (129/149, 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.⁴ Howes *et al* concluded that the delay to clozapine initiation highlights a lack of clinician adherence to national clinical guidelines.³ 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.

Fool's gold . . .

So why are clinicians delaying clozapine initiation? Farooq & Taylor⁶ 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.⁷ 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.⁸ 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.⁵ Assuming that there is

[†]See pp. 481–485, this issue.

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.⁹ Non-adherence to taking clozapine is also a key concern,¹⁰ not least of all because clozapine reinitiation can take longer than the period of non-adherence.

Managing the risk of diabetes and cardiovascular side-effects of clozapine requires routine physical health monitoring, including metabolic parameters and an electrocardiogram, but this is now true of all antipsychotics. Pharmacological strategies to assist with some other side-effects include: anti-epileptic prophylaxis for risk of seizures for clozapine concentrations > 500 µg/l; hyoscine hydrobromide for hypersalivation; and regularly prescribed laxatives for constipation.^{3,11} Aripiprazole 5–10 mg/daily is also sometimes used to counter the effect of the risk of weight gain or oversedation; however, this is not endorsed by current clinical guidelines.

... Or a gold standard?

There is further potential cause for concern that clozapine is not always found to be effective in terms of symptom reduction for patients with treatment-resistant schizophrenia, although plausible explanations include that some studies limited the upper dose of clozapine to 400 mg/day.^{6,12} In a recently reported study, clozapine was not found to be superior to chlorpromazine, but 30% of individuals randomised to chlorpromazine were also exposed to clozapine during the 9-year follow-up phase.¹³ On the other hand, in the CULASS study, the first of two key randomised controlled trials in the era of second-generation antipsychotics, clozapine was superior with regard to symptom reduction.¹⁴ In phase II the CATIE study, time to antipsychotic discontinuation due to poor response was significantly longer for those on clozapine *v.* commonly prescribed second-generation antipsychotics.¹⁵ In randomised controlled trials for clozapine, few trials titrate the dose according to plasma concentration levels (target range 350–500 µg/l)¹¹ which is required due to inter-individual metabolic variability caused in part by factors such as smoking.^{16,17} Thus, it is quite possible that suboptimal doses are being evaluated. In a more recent large observational study, clozapine was found to have a significantly lower risk of rehospitalisation than risperidone and other second-generation antipsychotics for patients after discharge from their first hospitalisation with a diagnosis of schizophrenia.¹⁸ 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.⁴

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 clozapine underutilisation and that this varies by region.^{5,19} 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 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 injections²⁰ and therapeutic drug monitoring for antipsychotic plasma concentration levels,²¹ 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)²² 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 improve 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,²³ and without hindrance by service-level factors, to address the key concerns within each trust.

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psychiatry in the movies

Fraud at the polls: Charles Foster Kane defeated

Peter Byrne

Jerry Seinfeld has no time for Olympic Silver winners: 'of all the losers, he was the best loser'. After 5 decades at the top of *Sight and Sound's* 10 yearly critics' poll, Orson Welles' first film has been beaten into second place. Ignore the hyperbolic (i.e. lying) headline above: *Vertigo* (1958) is a convincing winner, though not in the directors' poll where *Citizen Kane* achieves a respectable second place to Ozu's *Tokyo Story*. But leave talk of second best to Shakespeare's beds. A masterpiece has not been devalued and Welles' authority is undiminished. *Citizen Kane* grandstands the life of Charles Foster Kane – from boy to legend to lonely old man, though not in that order. The story unfolds through conventional dramatic scenes, stylish flashbacks, contemporary newsreel (many complained of its scratches and hisses – Welles deliberately dragged original prints of this section across the floor), 'talking heads' to reporter Thompson, and montages of headlines, stills and film. Many of the performances are at once film debuts and career bests. Alongside intense human interest, mysteries abound: Rosebud? Why the angry young man? Benevolent democrat (Democrat even) or demagogic narcissist? Does wealth corrupt him or the purposelessness of his power? Set aside its technical mastery, and the film still deserves repeated viewing to establish where the Truth lies. Its insights into the uses and abuses of media invoke the Leveson Inquiry.

Welles made his name with theatre productions of Shakespeare's better known tragedies, but his protagonist – as written and acted by him – owes much to *Coriolanus*. He is the patriarch who will speak for the people. Outside of Shakespeare, few dramas have successfully interwoven the political with the personal. The idea to pastiche the life of newspaper magnate William Randolph Hearst was co-writer Mank's (Herman J. Mankiewicz). Mank and Welles won the film's only Oscar. On Hearst's instructions, all nine of the film's nominations were booed at the Awards ceremony. Welles shared the final title credit as director with his cinematographer Greg Toland, where most stills from this film could hang proudly on a gallery wall. The fourth creative talent (of many) is editor Robert Wise, best known for directing the *Sound of Music* (1965). Conflicting claims about original ideas' ownership followed: Rosebud was Mank's first bicycle.

The question remains as to how a story this sad can be projected so beautifully. A voiceover tells us Kane loses his estranged wife and only son in a car accident. Feel-good cinema trades on nostalgia, but Kane explores attachment and loss, and the lies we tell ourselves before acting them out. Kane channelled his frustrations into Kane the Art Collector. The abandoned Art pieces of his Xanadu Palace are among the closing visual images, recalling Yeats:

'Players and painted stage took all my Love
And not those things that they were Emblems of.'

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