A case for adding fluvoxamine to clozapine

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Treatment-refractory schizophrenia affects at least 30% of all patients with schizophrenia. Clozapine remains the gold standard treatment as the chances of response with another non-clozapine medication are very low. However, initiating and then maintaining patients on clozapine can be a challenge due to a complex titration regimen, dose-related side-effects and the requirement for regular monitoring. In this article, Dr Sharma describes the successful addition of fluvoxamine to clozapine in a patient to achieve a therapeutic level of clozapine.

The utmost care should be taken to ensure optimisation of clozapine treatment because data are lacking on how to proceed if a patient should prove nonresponsive to clozapine. One of the strategies that has gained more recognition of late is that of achieving therapeutic clozapine plasma levels, especially in cases where clinical response is below expectation. It is generally accepted that serum clozapine levels below 0.35mg/L can be subtherapeutic and therefore should be optimised especially when clinical response is inadequate. Clozapine demonstrates marked variations in its metabolism and there is poor correlation between dose and plasma level.1 In clinical practice, these variations can play out in number of ways in an already highly complex patient population and clinicians are well advised to familiarise themselves with clozapine pharmacokinetics to realise the full potential of this complicated treatment regimen. Below we describe our experience of a young patient where we struggled to achieve plasma levels above the lower end of the therapeutic range and the steps we took to optimise treatment.

Presentation
A 26-year-old non-smoker male of mixed ethnicity (white and black Caribbean) was found to be having psychotic symptoms including delusions and hallucinations and admitted under the Mental Health Act. After poor response to adequate trials with two different antipsychotics (risperidone and olanzapine) over a period of five months, the illness was considered to be treatment-resistant schizophrenia. The patient was started on clozapine with a good initial response and he seemed to be more stable on a dosage of 300mg daily (125mg in the morning and 275mg in the evening) with low plasma levels (clozapine levels 0.17mg/L and norclozapine...

![Figure 1. CYP450/clozapine metabolism; smoking inducing/fluvoxamine inhibiting CYP1A2 (adapted from https://www.pharmgkb.org/pathway/PA166163661 (permission granted by PharmaGKB/Stanford University)](image_url)
0.10mg/L). Unfortunately once in the community he became noncompliant and started struggling with increased psychotic features including auditory hallucinations (commenting and commanding voices), passivity phenomena with lack of agency leading to a very distressing experience of ‘no longer being himself and being controlled by others’. This led to another admission and after few months his mental state became stable on clozapine 475mg daily and aripiprazole 15mg daily.

**Lack of benefit with maximum clozapine dose**

Following discharge the patient continued to voice distress about his anomalous experiences especially of ‘not being himself, feeling controlled by others and finding his actions, thoughts or feelings being totally alien with no sense of ownership’. Over a period of six months clozapine was increased in the community to a maximum of 900mg daily with a final plasma level of 0.33mg/L and norclozapine 0.25mg/L; clozapine:norclozapine ratio was 1.3, which indicates good compliance. Despite being on the maximum dosage there were no adverse side-effects such as weight gain, excessive sedation, hypersalivation or constipation as would be expected. Due to inadequate symptom control, the aripiprazole dosage was increased to 30mg daily but this did not result in any clinical benefit. Following this, lamotrigine was added, but again, there was no improvement in symptoms.

**Partial clozapine response: clinical issues**

Despite the patient showing significant improvement from an acute episode in hospital, which allowed him to live in the community, he continued to experience persistent symptoms causing significant distress and disability. As such, we considered this a partial response to clozapine treatment. Since the plasma levels were below the 0.35mg/L despite being on maximum licensed dosage of 900mg daily, and the patient did not demonstrate any adverse effects, the team considered ways to raise the plasma level to the therapeutic range.

**Input from pharmacy services about further treatment**

There was discussion with the pharmacy services and patient about further treatment options. Factors that could result in low levels were considered, such as compliance and smoking, but such factors were ruled out. It was therefore felt that the most likely explanation for low plasma levels, would be that the patient had an overactive enzyme system that was metabolising clozapine too rapidly. We considered using fluvoxamine to slow down clozapine metabolism, however, the local pharmacy services expressed concerns about unpredictability of the interaction and possible risks of toxicity and difficulties in monitoring the levels. They advocated using higher dosages of clozapine beyond the maximum of 900mg daily.

**Going above BNF maximum dosage of 900mg daily**

Increasing the dose of clozapine above BNF limits may be an option for some patients with insufficient response. Findings of a study of a national clozapine/norclozapine assay service in UK for the period 1997–2005 found three individual case studies of patients treated with clozapine in dosages greater than 900mg daily. The authors noted this to be due to rapid clozapine clearance secondary to genetic factors and heavy cigarette consumption, which necessitated the use of clozapine in dosages up to 1400mg daily, notably in a young male smoker. Dosages greater than 900mg daily are rarely justified in women, due to reduced liver clearance compared with men. Caution is needed where dosages above 600mg daily are used, if patients reduce the number of cigarettes smoked since this can significantly increase clozapine levels, resulting in toxic levels and an increase in side-effects. Our patient did not want to increase his clozapine dosage because of the increased number of tablets needed.

**Trial with low-dose fluvoxamine**

Our patient wished to trial with fluvoxamine and a plan was put in place with more frequent side-effects monitoring (including blood pressure and pulse rate) as well as measuring plasma levels two weeks later.

The patient was started on a low-dosage fluvoxamine 25mg daily and within a month of he began showing clinical improvement. Additionally, he reported sedation, weight gain and increased salivation. Clozapine blood levels in a months’ time were clozapine 0.78mg/L and norclozapine 0.49mg/L and at two months the levels were clozapine 0.95mg/L and norclozapine 0.61mg/L. There was a slight delay in obtaining the first assay sample due to confusion at the GP surgery as the blood sample was sent for routine monitoring rather than clozapine assay – this was spotted quickly and was rectified by giving the assay kit to
the patient who then made sure that the sample was posted to the assigned non-NHS laboratory.

**Therapeutic improvement upon adding fluvoxamine**

Due to an increase in side-effects, including occasional myoclonic jerks, the clozapine dosage was reduced over a period of time to 600mg daily (split dose) with level of clozapine 0.77mg/L and norclozapine 0.62mg/L. Recent mental state assessment revealed significantly less preoccupation with themes of passivity and improvement in hallucinatory experiences; the patient was also able to acknowledge that after a long time he was feeling ‘closer to his original or usual self’. He also started producing music, which has been his long-term ambition and agreed to referral for cognitive behaviour therapy.

**Discussion**

Around 30–50% of patients with treatment-resistant schizophrenia show inadequate response to clozapine resulting in ongoing symptoms and significant suffering and increased mortality. Interpatient variability in clozapine metabolism is considerable, and this, combined with the potential for other pharmacokinetic interactions, may make achieving therapeutic levels difficult despite adequate compliance and it is important for clinicians to familiarise themselves with such factors. In the absence of a better alternative to clozapine, clinicians must consider ways to optimise the treatment.

This may require clinicians needing to consider the idea of exploiting the pharmacokinetic profile of clozapine through supplementation with fluvoxamine once other factors have been excluded.

**Clozapine metabolism** Clozapine is metabolised in liver by the cytochrome P450 group of enzymes and factors such as genotype, age, sex, ethnicity and smoking status affect its metabolism by affecting activity of cytochrome P450. The CYP450 genes are very polymorphic and can result in reduced, absent, or increased enzyme activity. CYP1A2 is the main CYP isoform in clozapine metabolism and its activity is an important determinant of clozapine dosage accounting for 70% variation in metabolism.3

Case studies show that patients with more than one or more copies of CYP1A2*1F respond poorly to clozapine therapy and this is often associated with low plasma levels in schizophrenic patients who smoke.4 Among other CYP enzymes involved in clozapine metabolism one worth bearing in mind is CYP3A that can play a significant role.

Clozapine is largely metabolised through N-demethylation and N-oxidation. The main metabolite of CYP1A2 is N-desmethylclozapine, also known as norclozapine (NOR) but both enzymes (CYP1A2 and CYP3A4) may play a part in the formation of NOR depending on the clozapine concentration.

Excretion of the two clozapine metabolites also depends on the activity of a transmembrane transporter expressed in the liver and kidneys named ABCB1/p-glycoprotein, which, together with its polymorphisms, has been associated with regulation of clozapine availability.5 (See Figure 1 for clozapine metabolism.)

**Smoking** remains one of the commonest clinically relevant factors that influences clozapine metabolism. Polycyclic hydrocarbons in cigarette or cannabis smoke can induce the CYP450 system. Smoking as few as up to eight cigarettes per day can completely induce the CYP1A2 leading to lower plasma levels. Drinking caffeinated drinks is not uncommon in these patients and drinking the equivalent of three cups of coffee per day can appreciably inhibit CYP1A2. Considering that smoking and consuming caffeinated beverages often coexist, the competing actions can potentially result in unstable serum levels.

**Men** tend to have a higher level of hepatic isoenzymes than women, **Asians** generally have a higher plasma concentration than Caucasians given the same weight-adjusted dosage.6 The metabolism of clozapine can decrease as a result of progressive reduction in liver function in **ageing patients**.

**Drugs** that induce the CYP enzyme system lead to a decrease in plasma concentrations of clozapine and these include carbamazepine, phenytoin, rifampicin, barbiturates, St. John’s wort, amino-gluthemide and ritonavir, valproic acid in smokers and omeprazole in non-smokers. Both valproic acid and omeprazole are likely to be co-prescribed for patients on clozapine.

A patient’s phenotype of CYP1A2 and CYP3A4 can be determined by using probes like caffeine and midazolam respectively though these tests are not yet available in clinical practice. It remains important to remember that clozapine is primarily metabolised by CYP1A2 in most patients but some patients may have the CYP3A3/4 enzyme as the major metabolic pathway.
Adding fluvoxamine
Fluvoxamine potently inhibits CYP1A2 in a dose-dependent manner and its addition may increase the steady-state serum concentrations of clozapine by a factor of 5 to 10. It is thought that patients with fast CYP1A2 enzymes (one or more copies of CYP1A2*1F) will experience a more dramatic increase in clozapine levels from the addition of fluvoxamine, which may increase the probability of a response in patients where sufficient clozapine plasma levels cannot be achieved.7

Changes in clozapine level
The clozapine level rise is proportional to the administered dosage of fluvoxamine, with an estimated rise of 2–3 times with the addition of 25–50mg of fluvoxamine.8 However, there is great variation in the possible serum level rise,9 and close monitoring is crucial. In our case addition of 25mg led to a level increase of three times over a period of 6–8 weeks. The use of fluvoxamine may also reduce the number of tablets a patient is prescribed. Apart from potentially reducing the number of tablets that could be available for misuse by a third party, fewer tablets to take could also improve adherence.

Mechanism of fluvoxamine
Fluvoxamine inhibits mainly clozapine N-demethylation, which will increase the ratio of clozapine to its primary metabolite N-desmethylclozapine. This effect may improve the metabolic profile of patients on clozapine as the metabolic side-effects are thought to be more likely due to norclozapine.10 Our patient, though, gained a significant amount of weight despite the changes in ratio of clozapine to norclozapine.

On the other hand, the addition of fluvoxamine adds another medication to the regimen, increasing its complexity with the possibility of worsened adherence besides increasing the risk of side-effects as the plasma level increases. Since the effect of fluvoxamine on clozapine is difficult to predict, extremely high plasma levels can be produced rapidly thereby raising concerns about toxicity. A recent review11 of the clinical potential of adding adjunctive fluvoxamine to clozapine found that apart from raising clozapine levels in individual cases, the evidence was either poor or lacking for additional considerations, including improving metabolic side-effects, low mood and obsessional symptoms, some of which could have been worsened by clozapine itself, and to reduce the effect of smoking on clozapine levels.

Conclusion There is evidence to show12 that in a majority of patients clozapine treatment may not optimised for antipsychotic effects or side-effects though one hopes this will change with wider use of clozapine assays. Similarly, use of fluvoxamine for optimising clozapine treatment has not caught on, especially in the community setting, though we feel such a use should be considered for patients with partial or poor response and low plasma levels. Our case also highlights the value of clozapine assays in patients who are compliant; the test is not expensive and, bearing in mind the potential benefits, this test should certainly be considered by clinicians more often.

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References