Case reports of patients with treatment-resistant schizophrenia and related psychotic disorders intolerant to clozapine responding to high doses of quetiapine

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Introduction

Treatment-resistant schizophrenia and related psychotic disorders remain a major therapeutic challenge. Clozapine has undoubtedly been the gold standard treatment for this patient group. However, a significant proportion of patients develop intolerance to clozapine. There is limited available evidence to support the use of alternative treatment strategies.

In this case report we present two diagnostically different cases, where stabilization on clozapine was followed by discontinuation due to the development of neutropenia. These cases were subsequently managed with high doses of quetiapine, which produced a satisfactory clinical response.

Case reports

Our first case is a 45-year-old man diagnosed with schizoaffective disorder. He was referred to mental health services at the age of 18 and received extensive input from forensic psychiatry services due to severe disruptive behaviours, characterized by severe aggression, violence and crime whilst under the influence of manic symptoms, auditory hallucinations (which were command in nature) and delusions of persecution and grandiosity.

He remained predominantly an inpatient between 1994 and 2007, mainly in medium- and high-security units. He was initiated on trifluoperazine (1994) and then lithium, fluphenazine decanoate (1995) at 200 mg/fortnightly which was above the British National Formulary (BNF) limit, all of which produced poor responses. Clozapine was initiated in 1995 and produced a reasonable response by alleviating his delusions and controlling his behaviour. Unfortunately he developed neutropenia and clozapine was discontinued in 1996. This immediately led to major deterioration with severe aggressive behaviour warranting emergency electroconvulsive therapy (ECT). He subsequently was initiated on olanzapine, risperidone, sulpiride, quetiapine and lithium individually (up to BNF maximum limits) with poor responses.

In early 2006, lithium 1000 mg/day and sulpiride 2400 mg/day combined also had minimal effects. Quetiapine was added to augment this combination at up to 800 mg/day. In 2007, he himself requested a further dose increase as he personally experienced significant improvement in his symptoms. His dose was further increased up to 1200 mg/day under close monitoring, to which he further responded significantly. Quetiapine was well tolerated with no major concerns being reported.

He was successfully discharged from the forensic setting in 2007 to a normal community placement, which marked as a significant progress for a patient who had spent nearly 12 years of his life as an inpatient in a forensic setting. To date he remains well in the community.

Our second case is a 50-year-old woman diagnosed with paranoid schizophrenia. She had presented to services in 1999 and was treated with the following drug combinations: fluoxetine and trifluoperazine 20 mg; risperidone 4 mg and venlafaxine 225 mg; fluphenazine decanoate depot and risperidone 6 mg orally. All of these combinations produced a poor response.

In 2001, clozapine was initiated and appeared the only medication to produce some reasonable

improvement enabling her to be treated in the community. However, in 2008 she developed neutropenia from clozapine leading to its discontinuation. This resulted in a major relapse warranting hospital admission. She then had trials of medications which included amisulpride 1200 mg/day, olanzapine up to 30 mg/day (above BNF maximum) and aripriprazole 30 mg/day, all of which failed to control her symptoms. The team had to finally rechallenge her with clozapine with limited further options.

She immediately developed red results due to neutropenia and clozapine was completely stopped. She was then initiated with risperidone at 8 mg/day, which produced minimal response and severe extrapyramidal side effects, necessitating discontinuation.

She quickly relapsed and was eventually readmitted as an inpatient, exhibiting severe incongruous laughter, agitation, hostility, verbal aggression, delusions of persecution and control, somatic passivity and auditory hallucinations. As quetiapine had not been considered previously, it was initiated with the dose increased up to 750 mg daily. At the 750 mg dose, it was noted that only her behavioural symptoms had responded. She became less agitated and more amenable. However, her delusions and hallucinations persisted. At this stage a trial of a high dose of over 750 mg/day (above BNF limit) was considered as she had failed to respond adequately to various combinations as listed above.

When the dose of quetiapine reached 1000 mg daily, noticeable improvement was produced in her delusions and hallucinations. She reported feeling 'much improved'. The dose was eventually increased up to 1400 mg daily with close monitoring. This dose was well tolerated. The only side-effect reported was that of sedation, which improved by switching her from the once-daily modified release formulation of 1400 mg/day to the standard formulation of quetiapine administered in divided doses of 400 mg (morning) and 1000 mg (night). She eventually reported herself to be 'very much improved' and 'back to her normal self'. She was successfully discharged from inpatient care back into the community.

Discussion

Clozapine and quetiapine have some pharmacological similarities, which include the quick dissociation from D2 receptors. This shared property may explain the efficacy of high-dose quetiapine in the above two cases which have previously only responded to clozapine. Kapur and Seeman have discussed this property in their neuroimaging study on antipsychotic drugs' fast dissociation from D2 receptors [Kapur and Seeman, 2001].

Interestingly, in both of our patients, doses of quetiapine up to 800 mg/day only had an effect on reducing their behavioural symptoms, but their delusions persisted. It was only when the doses went up to 1000 mg/day that significant benefits were gained for the psychotic symptoms. In the small open-label study of 35 patients [Nagy, 2005] there were similar findings of quetiapine only being able to control behavioural symptoms at doses up to 800 mg and doses above this level were necessary to adequately treat psychotic symptoms.

The above findings raise the question of what is an adequate dosage of antipsychotic drug for resistant patients. It is possible that quetiapine acquires unique properties at higher dosages which improves antipsychotic efficacy or it may be that some patients are rapid metabolizers who require higher doses of quetiapine to gain therapeutic benefits. Despite this uncertainty, it would be worth considering high-dose antipsychotic therapy in patients who have partially responded to conventional doses (i.e. below BNF limits), who are not experiencing significant side-effects, in order to achieve further improvement.

Our first case was diagnosed with schizoaffective disorder with mood and psychotic symptoms. Although he was already on sulpiride and lithium, the addition of quetiapine produced a significant response at a dose of more than 800 mg daily. Quetiapine has been granted licences for maintenance therapy in bipolar disorder and for treating acute mania and bipolar depression. It is therefore not surprising that the mood-stabilizing properties of quetiapine can be of benefit in patients suffering from schizoaffective disorder. Interestingly, in the case series of seven patients who responded to high-dose quetiapine published by Pierre, one case also had a previous history of clozapine intolerance and a diagnosis of schizoaffective disorder [Pierre, 2005]. In our second case, noticeable improvement in behavioural symptoms was gained from quetiapine, which could also be due to its mood-stabilizing properties.

A 12-week open-label trial [Boggs, 2008] had patients treated on a high dose of quetiapine which also included one case similarly being intolerant to clozapine responding to high-dose quetiapine.

So, do the pharmacological similarity between quetiapine and clozapine in terms of D2 receptor occupancy and quetiapine's mood-stabilizing properties support the use of high-dose quetiapine as a suitable alternative to clozapine in treatment-resistant psychosis? Our two cases add to the small body of published evidence in support of this approach. Most of the existing evidence base consists only of case reports and small open studies.

In a recently published randomized, double-blind, placebo-controlled study [Honer, 2012] high doses of quetiapine did not show any major difference in the efficacy of quetiapine at above BNF doses. However, this study excluded patients previously treated with clozapine and the primary goal was to analyse the safety and tolerability of quetiapine in high doses.

Our case reports have specifically focused on patients intolerant to clozapine and the doses used (1200–1400 g/day) were higher than the mean dose used in the Honer study (1144 mg/day). Our case reports further highlight the possibility that high-dose quetiapine could yet be a useful strategy in cases of clozapine intolerance. Larger-scale, double-blind controlled studies will be helpful to investigate this promising approach further in this challenging patient group.

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Conflicts of interest

The authors declare no conflicts of interest in preparing this article.

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