The novel use of clozapine in an adolescent with borderline personality disorder

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Abstract

Background: Clozapine has been used to good effect in the treatment of adults with borderline personality disorder, but there is scant evidence of it being used in an adolescent population with these difficulties.

Methods: Clozapine was trialled in an adolescent with a clinical presentation consistent with an emerging borderline personality disorder.

Results: There was a large reduction in the number of incidents involving abuse to staff, or harm to self, in the 8 weeks after commencing clozapine therapy, compared with the 8 weeks prior, and also a large reduction in the number of episodes of the use of seclusion in the 13 weeks after commencing clozapine therapy, compared with the 13 weeks prior. The young person was also able to be reintegrated in to the ward environment once established on clozapine therapy, which had not been possible full-time, for a whole year prior.

Conclusions: Although limited by involving just one adolescent, this very preliminary data does nonetheless suggest that clozapine may have a role in treating adolescents with emerging borderline personality disorder when other treatment options have been exhausted.

Keywords: adolescent, aggression, borderline personality, clozapine, emotionally unstable

Introduction

Borderline personality disorder in the DSM-V [American Psychiatric Association, 2013], and emotionally unstable personality disorder in the ICD-10 [World Health Organization, 1992], are recognized as comparable entities. This type of personality disorder is characterized by affective instability, intense and unstable interpersonal relationships and marked impulsivity. Aggression to self or others, a chronic sense of emptiness, and/or a fear of abandonment also often dominate.

Borderline personality disorder has a 2% prevalence in the general population and a 20–40% prevalence amongst psychiatric service users [Binks *et al.* 2006; Linehan, 1993]. Personality disorder is, by definition, a burden to those with the disorder, but also to their friends and family, and to society as a whole [Coid *et al.* 2006]. Individuals with borderline personality disorder are less likely to work and less likely to own their own home [Coid *et al.* 2006]. The demand on

healthcare resources from people with this disorder is high [Horz *et al.* 2010; Pompili *et al.* 2005], but despite the input, up to 84% engage in suicidal behaviour [Soloff *et al.* 2002] with approximately 8% self-harming fatally [Pompili *et al.* 2005].

Personality disorders are a diagnostic category usually reserved for adults, although there are increasing numbers among the profession who feel that it can be diagnosed in adolescence [Miller *et al.* 2008] or even in childhood [Terr and Kernberg, 1990]. A recent review of child and adolescent consultant psychiatrists found that 37% felt that borderline personality disorder is a valid diagnosis in adolescents [Griffiths, 2011], which is all the more significant given that only 82% felt that it was a valid diagnosis in adults [Griffiths, 2011]. As Adshead and colleagues [Adshead *et al.* 2012] noted, the debate hinges on whether clinicians consider personality to only fully form in adulthood, or if they believe in the stability of some traits from childhood.

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The diagnostic manuals do allow for consideration of the diagnosis in adolescents, with the DSM-V [American Psychiatric Association, 2013] allowing

‘...borderline personality disorder to be diagnosed in adolescents when maladaptive traits have been present for at least one year, are persistent and all encompassing, and are not likely to be limited to a developmental stage or an episode of an Axis I disorder’.

The ICD-10 [World Health Organization, 1992] is more cautious, advising that ‘it is therefore likely that the diagnosis of personality disorder will not be appropriate before the age of 16 or 17 years’, but still clearly offering scope to formulate a young person’s difficulties along these lines in the later teenage years. What seems to be more acceptable, in practice, is to consider a provisional diagnosis of an ‘emerging’ personality disorder in those aged 17 or younger, provided that they exhibit the salient clinical features, in a suitably enduring fashion.

Controversy not only encompasses the diagnosis of borderline personality disorder, but also the treatment of it. In England and Wales, psychological therapy is considered appropriate by the National Institute for Health and Care Excellence (NICE), although the mode of therapy itself is not specified, except for the recommendation of a ‘comprehensive dialectical behavioural therapy programme’ for women who have a need to reduce their propensity to self-harm [National Institute for Health and Care Excellence, 2009].

With regards to pharmacological interventions, NICE states that ‘drug treatment should not be used specifically for borderline personality disorder or for the individual symptoms or behaviour associated with the disorder (for example repeated self harm, marked emotional instability, risk-taking behaviour and transient psychotic symptoms)’ [National Institute for Health and Care Excellence, 2009]. This does not preclude the drug treatment of comorbidities, and short-term drug treatment is acknowledged, in the body of the text, to be helpful in crises as a short-term measure, although this is not reflected in the summary. The guidelines do however very clearly state that antipsychotic medication should not be used in the medium to long-term management of the disorder.

The Maudsley prescribing guidelines, by contrast, do acknowledge that there is some evidence that the symptom clusters found in borderline personality disorder respond to antipsychotic medication [Taylor *et al.* 2012]. These are described as including ‘affect dysregulation, impulsivity and cognitive-perceptual symptoms.’ It even mentions clozapine’s possible efficacy in reducing aggression and self-harming behaviour, as indicated in open-label studies. The studies referred to are Chengappa and colleagues [Chengappa *et al.* 1999] and Bendetti and colleagues [Bendetti *et al.* 1998].

The study by Chengappa and colleagues [Chengappa *et al.* 1999] followed on from a case report [Chengappa *et al.* 1995] in which the use of clozapine was described in a 32-year-old woman with borderline personality disorder and psychotic symptoms, who had been in hospital for nearly 7 years, due primarily to risk to self, but who was safe to be discharged when clozapine was added to her previous medication regimen, 6 and a half years into her admission. Chengappa and colleagues [Chengappa *et al.* 1999] then selected a further 7 women aged 26–47 years, all with primary diagnoses of borderline personality disorder, but also with ‘persistent psychotic symptoms’, and found a reduction in a range of parameters, including the use of seclusion and restraint, and a reduced need for lorazepam to be administered on an ‘as required’ basis.

The second study, by Bendetti and colleagues [Bendetti *et al.* 1998], also selected recruits from patients with borderline personality disorder and ‘severe psychotic-like symptoms’. The sample size here was slightly larger at 12, and was mixed sex, with 2 male participants. Bendetti and colleagues titrated the clozapine against the ‘psychotic-like symptoms’ so patients received various doses between 25–100 mg/day. Results indicated a reduction in the psychotic-like symptoms on the Brief Psychiatric Rating Scale, as well as a decrease in impulsive behaviours, affective symptoms and a concurrent increase in functioning as measured by the Global Assessment of Functioning.

These are not the only studies to look at clozapine’s use in this way. Frankenburg and Zanarini trialled clozapine in 9 women and 6 men who had diagnoses of borderline personality disorder and atypical psychosis, although the efficacy demonstrated was primarily in the psychotic symptoms [Frankenburg and Zanarini, 1993]. Swinton

demonstrated a reduced need for additional nursing input, and decreased self injury in a sample of 5 women inpatients with borderline personality disorder aged 25–43 years [Swinton, 2001]. Ferrerri and colleagues described the use of clozapine in a young woman with borderline personality disorder, in whom the clozapine resulted in a complete resolution of self-harming behaviour, discharge from hospital and a return to her education [Ferrerri *et al.* 2004]. In 2010, Vohra published a case study, involving one 24-year-old woman, with borderline personality disorder but no additional psychotic or pseudopsychotic phenomena [Vohra, 2010]. This woman improved to such an extent that she expressed that she felt ‘totally in control of her life’. A recent study from St Andrew’s in Northampton, UK, trialled clozapine in 22 women with borderline personality disorder and demonstrated further positive results with regards to reduced symptom severity, reduced requirement for enhanced observation or additional medication, and a reduction in aggressive incidents [Frogley *et al.* 2013]. Fiona Mason, one of the authors, even challenged NICE to revise its guidelines in light of the results. She also indicated that the team intended to extend their findings to a large multicentre trial to produce more robust evidence for the role of clozapine in this disorder.

Since clozapine has been reported to have been successfully used to treat very enduring and resistant manifestations of borderline personality disorder, at least one group has extended its use, in a trial manner, to women with personality disorder and a learning disability [Fajumi *et al.* 2010]. Here they gleaned similar results, with a 35% reduction in self injury and a 48% reduction in the use of restraint 6 months after the initiation of clozapine, compared with 6 months before.

We have not found published reports of the use of clozapine in adolescents under the age of 18 years, who exhibit signs consistent with an ‘emerging personality disorder’. Clozapine has of course been safely used in children and adolescents with schizophrenia, and dosing guidance is available for its use in this way in the British National Formulary for Children [Joint Formulary Committee, 2013]. Notably when used in this age group, albeit for schizophrenia, an anti-aggressive effect has been demonstrated [Kranzler *et al.* 2005].

From the papers reviewed, it seems that clozapine was trialled in adults with borderline personality

disorder, due to a pharmacological argument for it being of potential benefit, particularly with regards to comorbid atypical psychosis or the pseudopsychotic experiences that often occur in borderline personality disorder [Frankenburg and Zanarini, 1993; Benedetti *et al.* 1998], and also with regards to the anti-aggressive effects seen in those treated with clozapine for schizophrenia [Frogley *et al.* 2012], and which have been replicated in children and adolescents [Kranzler *et al.* 2005]. This latter effect has particular potential benefit for those with high levels of self-harm, or aggression to others, in the context of personality disorder. Of course interest in both possible benefits also arose due to clinicians having exhausted other pharmacological and psychological therapeutic avenues, with little success and thus seeking to explore novel treatment options. It was this very scenario which resulted in the current authors’ experience of using clozapine in an adolescent with borderline personality disorder.

Case history

Written informed consent was given by the patient for this paper’s production and publication. This written consent was only accepted from the patient once both authors were satisfied that she had verbally demonstrated that she had capacity to give her consent.

The case is that of a 17-year-old young lady who was initially admitted to a psychiatric hospital in 2009, aged 13 years, and who progressed to an adolescent medium secure unit in 2010. She had features consistent with an emerging borderline, or emotionally unstable, personality disorder, and they had been evident and enduring since prior to her initial admission 4 years ago. For this patient, key features had been harm to self and others, including injuries to staff, which required accident and emergency (A&E) attention, and suicide attempts involving significant risk to self, such as trying to jump from the roof of a tall building. She also demonstrated a profound instability in affect and reported pseudopsychotic symptoms in the form of auditory hallucinations.

The patient had been treated with a full range of pharmacological options. She received various antipsychotics since first commencing regular oral risperidone aged 13 years. After risperidone she received zuclopenthixol, then olanzapine, both regularly, orally, as well as olanzapine, clopixol acuphase injection and a zuclopenthixol

depot intramuscularly. Sodium valproate was tried as a mood stabilizer (and continues) and promethazine was offered regularly at one point. An attention deficit hyperactivity disorder (ADHD) medication, methylphenidate MR, was trialled for a period, but the diagnosis of ADHD was not upheld and this was discontinued. The patient had also been on antidepressant medication, initially mirtazapine but later fluoxetine, throughout her current admission as the formulation encompassed a comorbid depressive illness.

As well as the pharmacological approaches, the patient also accessed a full range of psychological and social therapies, including a dialectical behavioural therapy informed group therapy, art therapy, occupational therapy, individual psychology, family therapy as well as a term time educational program and holiday period 'enrichment' program, which offered the young people activities during the day with a less academic focus.

Despite all of the above, the patient remained routinely emotionally dysregulated and presented ongoing significant risk to self and others. The extent of the physical aggression was such that it warranted several visits to A&E, both for the patient and for affected members of staff. Much of the patient's injury to self remained in the context of suicidal ideation.

Due to this seemingly intractable presentation, and the wish to preclude if at all possible this patient progressing to adult secure services and spending her life in such a setting, the multidisciplinary team discussed the option of clozapine. This was considered a valid treatment trajectory by the team, and the option was thus then taken to the local academic program for further peer discussion. Due to a positive consensus, a formal second opinion was sought locally.

Factors considered in the balance as to whether to initiate clozapine therapy or not, included the very restrictive management that was otherwise then necessary. The patient spent much of her time in a high care area with two members of nursing staff and therefore had very limited amounts of interaction with her peers. In addition, the patient expressed subjective distress and discontent at her situation and was willing to proceed down the avenue of trying an unlicensed treatment.

Concerns with regard to commencing the treatment included the high level of physical

monitoring required, including weekly blood tests. The risk of agranulocytosis was a key concern and the less acute, but arguably more damaging in the longer term, side effects of weight gain and constipation, as well as sedation, were also considered. There were also the issues of dysarthria and hypersalivation, which the patient already suffered with, and the concern that clozapine might exacerbate these.

On balance however it was felt, and most importantly, the patient agreed, that the risk-benefit equation fell in favour of trying clozapine therapy. The preliminary physical investigations were completed, but unfortunately the initial blood testing showed a slightly low white cell count. Although the white cell count was not so low as to preclude commencing the clozapine, the team decided to postpone doing so as a cautionary measure. The sodium valproate dose was reduced slightly, to 500 mg three times daily, and a course of multivitamin tablets was commenced to try and improve the white cell count; which did indeed respond favourably to this. Since commencing the clozapine, the Clozapine Patient Monitoring Service did advise on one occasion that a low white cell count had warranted a 'caution', however on no occasion did the white cell count reduce to the point where clozapine had to be withheld. There was an initial overlap period with the zuclopenthixol depot and the latter was then discontinued. Other medications which comprised of sodium valproate at the reduced dose, fluoxetine, multivitamin tablets, hyoscine hydrobromide and regular lactulose were all continued.

In order to try and objectively assess the impact of clozapine, we first used the overall rate of incidents and the types of incident reported in the 13 weeks prior to the initiation of clozapine and the 13 weeks post initiation of clozapine. This captured neatly the risk to self, risk to others, and the frequency of challenging behaviour. The overall incident rate had exactly halved, with 86 incidents having been recorded in the 13 weeks prior to clozapine being commenced and only 43 in the 13 weeks afterwards. In terms of the types of incident reported, we only had data for the 8 weeks before and 8 weeks after clozapine was commenced, but in that 8 week period we saw a drop in the incidents of abuse to staff from 23 incidents to just 8, and in the incidents of self-harm from 9 to just 2. Property damage, flooding, security related incidents, abuse to other young people, and accidents

such as 'slips, trips and falls' each occurred at least once in the 8 weeks before clozapine was commenced, and not at all in the 8 weeks afterwards. Interestingly incidents relating to challenging behaviour remained broadly constant before and after, being a modest proportion of incidents prior to clozapine and making up the largest single incident category in the 8 weeks afterwards (20 out of 32 incidents compared with 16 out of 55 before) as the frequency of other types of incident dropped markedly.

A second means of demonstrating the pronounced effect of the clozapine was to consider the number of incidents of seclusion before and after commencing the clozapine. In the 13 weeks prior to commencing clozapine the young person was secluded 13 times, but in the 13 weeks since commencement of clozapine she had been secluded just 3 times.

Additionally, since commencing the clozapine, it was possible to bring the patient back to the ward areas from high care, for increasing periods each day, to the current time where she is fully reintegrated on the ward offering her the company of other young people and a wider range of activities to partake in. This is the first time she has been managed on the ward full time for a year.

Despite the benefits as described above, the treatment has not been without its adverse effects. Key issues have been the side effects of constipation, slurring of speech, hypersalivation, weight gain, tachycardia, and sedation; the latter particularly in the initial 1–2 months. The sedation was tackled by reducing the dose of sodium valproate further still to 500 mg twice daily and this helped.

With regards to the dysarthria, by the second or third week of treatment it was noted that the patient's speech was markedly more slurred than before. The clozapine dose was reduced from 150 mg twice daily to 125 mg twice daily, with the patient's agreement. An improvement was thereafter seen, and the dysarthria is no worse currently than it was prior to commencing the clozapine. It was in response to the patient's tolerance of clozapine in this way that enabled us to establish what seems to be the most suitable dosing regime, and the patient thereafter continued on 125 mg twice daily.

With regards to the hypersalivation, the patient had previously been prescribed hyoscine hydrobromide

in both patch and tablet form at different times as she had experienced this side effect on other medications. She responded best to the tablets.

Constipation is again something that the patient complained of prior to commencing the clozapine, and due to the reports of fatalities in relation to bowel side effects of clozapine [Pegah *et al.* 2007], we are managing this actively with lactulose and, if required, macrogols.

We know that weight gain occurred for this young person, but the extent is not quantifiable as she does not consent to being weighed. From an informal visual assessment she is likely to be classed as 'overweight' but not as obese. Notably she remains physically active, and is of course encouraged to follow a healthy diet.

It has also been noted that the patient's heart rate has been affected by the clozapine, with an increase in rate from a baseline range of 67–92 bpm to a post clozapine initiation range of 90–113 bpm, with it usually being in the 90–99 bpm range. We are monitoring her signs and symptoms closely for any indication of myocarditis or cardiomyopathy, but reassuringly there have been none thus far.

Discussion

From our very limited venture into using clozapine for an adolescent girl with an emerging borderline personality disorder, there seems to be some promise in this treatment option. The previously intractable picture of the patient being involved in incidents, which usually involved harm to herself or to others, has shifted to such a marked reduction of these, with remaining incidents being primarily incidents involving challenging behaviour, that it is thus hard not to be encouraged. The overall reduction in half of the total number of incidents has exceeded even the treating team's hopes and expectations. Notably in the last 3 weeks of the 13-week post-clozapine time frame, the patient has been involved in only three incidents, suggesting that a further reduction in incidents and a further improvement in mental state and presentation may yet be achievable. The reduction in the need for seclusion has been particularly marked and may highlight the anti-aggressive impact of clozapine.

It is of course important to remember that what we have noted is a correlation rather than a definitive demonstration of cause and effect. It is not possible

for us to eliminate the possibility that a change in the environment, such as a particular length of time being nursed off the ward, caused, or at least contributed to, the perceived change in the patient's presentation. Similarly, we cannot know that interpersonal factors, such as the patient maybe having more staff interaction whilst in high care, were not also a driving force. However, that the reduced number of incidents continued after the patient had been reintegrated to the ward, and that she did not express any desire or need, either verbally or behaviourally, to have her previous social and environmental milieu reinstated, arguably suggests that perhaps these were not the salient forces.

Notably the treatment is off licence and not recommended in any guidelines nor in the British National Formulary. Indeed, as mentioned in the introduction, the NICE guidelines state clearly that antipsychotic drugs are not to be used in the medium- to longer-term management of borderline personality disorder [National Institute for Health and Care Excellence, 2009]. However, it is worth noting that the absence of recommendations for the use of antipsychotics, including clozapine, is not because they have been shown to demonstrate harm or be ineffectual, but rather that there is simply a paucity of evidence with regards to their effect at all. Duggan drew a parallel between the scepticism regarding the efficacy of medication in borderline personality disorder and that of chemotherapy in cancer treatment 30 years ago [Duggan, 2010].

The other concern is of course the side-effect profile of clozapine and the extent of physical health monitoring required, but for young people who are so severely debilitated by their presentation as our patient was, it does seem that the potential benefits can exceed the risks. This may be particularly the case for young people detained in secure hospitals who appear to be heading for years of hospitalization.

Clearly there are limited conclusions that we can draw from this trial in one young person, but in the context of the increasing evidence for clozapine's efficacy in adults with borderline personality disorder it seems reasonable to suggest that our findings indicate that its efficacy may extend to a younger, adolescent population.

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Conflict of interest statement

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

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