Clozapine Use In Personality Disorder and Intellectual Disability

Introduction

While it is generally recognised that the treatment of both Borderline and Dissocial Personality Disorder (BPD and DPD) is predominantly psychological, targeted drug treatment of individual symptoms may be helpful for some patients (Cloninger, 1998). Over recent years, there have been several randomised controlled trials evaluating the use of psychotropic medication in personality disorder, but none to date with clozapine (Goldberg et al. 1986, Bogenschutz and George 2004). These trials of drug treatment are in comparison at least as good as those of other interventions, although the treatments have seldom persisted beyond a few weeks (Tyrer and Bateman 2004).

In people with Intellectual Disability (ID) the diagnosis of BPD or DPD is carefully made due to the possibility of diagnostic overshadowing between personality characteristics, intellectual ability, autism, mental illness and/or challenging behaviour (Royal College of Psychiatrists, 2001). The diagnosis of personality disorders in people with ID can sometimes be contentious and in routine clinical practice is limited to those with mild and borderline ID . In the UK, the rate of personality disorders is around 7% for patients in contact with community ID teams and 50-60% within forensic ID services. Personality disorders diagnosed in both these settings tend to be those in the borderline and dissocial categories (Alexander et al., 2007; Alexander and Cooray 2003; Naik et al., 2002).

The evidence for drug treatment of BPD and DPD in ID is limited to case reports or small case series. Day (1988) reported a case series of twenty people with ID and personality disorder with history of offending behaviour and showed that 70% were prescribed

psychotropic medication.(Day, 1988) Naik *et al.* (2002) noted that in their sample of adults with ID and personality disorder, a third had co-morbid mental illnesses but 90% were receiving psychotropic medication (Naik et al., 2002). Mavromatis (2000) described a significant clinical improvement with the use of Olanzapine in two patients and a Fluoxetine and Semisodium Valproate combination in a patient with ID and BPD (Mavromatis, 2000). Alexander et al. (2007) explored the target symptoms for pharmacological treatment and discussed the framework of five main symptom domains within personality disorders in ID. Behaviour dyscontrol was present in 93%, affective dysregulation in 77%, self-injurious behaviour in 52%, cognitive perceptual symptoms in 47% and anxiety in 33%. 82% of subjects had features in ≥2 domains (Alexander et al., 2007).

With regard to clozapine, there is a growing evidence base in support of its use in the context of BPD and DPD. Thalayasingam *et al.* (2004) described a case series of 24 patients with an ID and mental health difficulties who were treated with clozapine, of which three had a personality disorder and a favourable response to treatment. Of the three, one did have a co-morbid schizophrenia and another a bipolar disorder (Thalayasingam et al., 2004). Biswas *et al.* (2006) described a significant and sustained improvement in both mood and impulsivity over a period of four years in a person with ID & BPD receiving treatment with clozapine (Biswas et al., 2006).

In this case series we have attempted to identify long-term outcome of treatment, of 5 patients with ID and personality disorders at the end of a 36 months of treatment with clozapine by:

1. Comparing the severity of symptom clusters (Tables 1 & 2). The symptoms have been rated on a 4 point Likert scale of severity.

2. Comparing the number of admissions to the inpatient psychiatric unit before and after starting clozapine.

Case studies

Case A

A is a 36-year-old female with mild ID (55<IQ<70), BPD, epilepsy and depressive disorder. Her mother had a history of mental health problems. There was no history of ID in the family. She is the youngest of five siblings. She was born after prolonged labour, suffering from seizures a few days after birth. She had delayed development of speech, language and social skills. She also suffered from abuse, neglect and parental separation during her childhood. She lived at home with her mother until the age of seventeen, but due to severe behavioural problems was seen by a child psychiatrist and later placed in residential care, where she presented with physical and verbal aggression towards others, noisy behaviour, damage to property, threats of self-harm, constant reassurance seeking and self-injurious behaviour including severe head banging, frequent overdoses and cutting herself.

Over a four year period, she was admitted to the inpatient psychiatric unit on 5 occasions, some of them under the Mental Health Act (MHA) 1983. During this time she was also placed in different residential homes, but these placements broke down due to her severe challenging behaviour. She was admitted once more several years later due to challenging behaviour in the form of repetitive demands and impulsively aggressive and self- injurious behaviour, where she remained an inpatient for one year. During this time clozapine was initiated after unsuccessful treatment with different antipsychotic medications over years. She then gradually started to show a reduction in her behaviours. Additionally, she started

engaging in behavioural treatment programmes, went for visits in the community without incidents and consented to take her psychotropic medication. During admission, psychosocial support from the various members of the Multi-Disciplinary Team (MDT) continued as before. She was eventually discharged into a supported living scheme under a Care Programme Approach (CPA), where she has remained to date with no further admissions or serious incidents.

Case B

B is a 37-year-old female with mild ID, BPD, dissocial traits and depressive disorder with psychotic symptoms. Her brother has ID and schizophrenia, her mother suffers from depressive disorder and her biological father has a history of schizophrenia. At birth, she suffered from breathing difficulties and was neglected by her mother due to post-natal depression. She had delayed milestones and only started to walk at the age of two years and uttered her first words at the age of three. She attended a special school till the age of sixteen, as she needed help with reading and writing. During her childhood and adolescence her mother had severe mental health problems and was in hospital for a prolonged period; it was during this time that her father repeatedly emotionally and sexually abused her. She was later taken into foster care.

By the time that she came into contact with mental health services, she presented with features of depression and psychotic symptoms (including nihilistic delusions). She was admitted to an in-patient ward and detained under the MHA 1983. During her initial stay in hospital she was initiated on olanzapine, with which she was non-compliant. She continuously threatened to blow up the drug trolley and made statements of wanting to take her life. She tried to strangle herself using a stereo cable and undergarments, cut her wrists

using pieces of broken CDs, head-butted windows and once put her foot under the wheel of a car, causing soft tissue injury. She had also disclosed that she could feel a metal object being inserted into her vagina by an old lady. She was then initiated on both zuclopenthixol decanoate (depot antipsychotic) due to her non-compliance and paroxetine (antidepressant). Towards the end of her stay in hospital, she became compliant with medications and was reinstated on olanzapine. After she was discharged to live with her mother and stepfather, she developed a relationship with a man and moved to her own flat, but this relationship lasted for only 3 weeks and it subsequently became clear that she was not able to cope on her own. She started drinking heavily and made threats to self-harm.

She was admitted 8 times over the next few years, some of the admissions under the MHA (1983) and was tried on various psychotropic medications including olanzapine, zuclopenthixol decanoate, chlorpromazine, amisulpiride and paroxetine with no long term benefits. She also received intensive support from the psychology team and nursing staff on the ward.

In her last hospital stay she was initiated on clozapine, upon which she responded well. She was eventually discharged with supervised community treatment aftercare provisions. She is currently settled in her mental state and is functioning well with support in the community.

Case C

C is a 32-year-old female with mild ID, BPD and DPD. She has no family history of mental illness or ID. She was born at full term without any reported perinatal complications. She had delayed developmental milestones and attended a special school. She also suffered from

several traumatic childhood experiences including childhood sexual abuse, domestic violence and parental divorce. During her childhood she displayed several behavioural problems, as a result of which at the age of 11, she was admitted to a residential school for children with learning difficulties and behavioural problems. She was seen by a psychiatrist and was prescribed antidepressants and also had some counselling sessions.

She came into contact with ID psychiatric services during early adulthood, mainly in times of crisis when she would present frequently with risk-taking/ dangerous behaviour including absconding from home, threatening to jump off buildings, property damage, self-cutting, making emergency telephone calls and assaulting police officers. She also reported feelings of abandonment, and hopelessness. There were no sustained periods of low mood or psychotic symptoms.

It was difficult for the psychiatric team to engage her in any meaningful therapeutic work due to her impulsivity and presenting in crises. She was tried on a number of psychotropic medications including mood stabilisers (carbamazepine and lithium), antidepressants (fluoxetine, trazodone, sertraline, paroxetine and fluvoxamine), anxiolytics (diazepam, lorazepam and propranolol) and antipsychotics (zuclopenthixol dihydrochloride, flupentixol decanoate, thioridazine, risperidone, olanzapine, sulpiride, amisulpiride, droperidol and haloperidol) over years with no long-term benefits.

Despite a high level of support from the MDT in the community, she required frequent admissions to the inpatient unit. These admissions were precipitated by self-harm or aggressive behaviour, and persisted during the admission on the ward in the form of aggression, breaking objects, absconding and self-harm.

During her last admission, a trial of clozapine was considered in view of her high levels of impulsivity and arousal and lack of response to numerous previous medications and non-pharmacological approaches. By the end of the sixth week of treatment she was well enough to go to several periods of home leave following which she was subsequently discharged to live in the community. There was a significant reduction in her impulsivity and emotional lability following initiation of clozapine. She was able to recognise early warning signs, which could lead to a crisis and could start engaging with the psychiatric team. Her mood has remained euthymic and she has been stable in the community for the past four and a half years without any need for further admission.

Case D

D is a 28 year old female with a history of mild ID, BPD and schizophrenia. She was born with her umbilical cord around her neck; however there were no other antenatal or perinatal complications. She showed delayed developmental milestones and was placed on a statement of special educational needs at the age of 5. There was no history of ID in her family. D's parents separated when she was a teenager.

She first became known to the adult ID team at the age of 19, when she was referred with suspected depression by her GP. Following a series of life events she was diagnosed with adjustment disorder with features of depression. However, in the community she was noted to display challenging behaviours; she attempted to run away from home, expressed paranoid ideas and complained of hearing voices, for which she was started on olanzapine. Over the following 9 years, D was admitted to hospital 4 times, some of which under the Mental Health Act (1983). During these admissions, she was assessed by several consultant

psychiatrists as well as clinical psychologists, all of whom agreed that in addition to her treatment resistant psychosis, D showed features of BPD, including impulsiveness, hostility, uncontained emotions and difficulties with self-identity. It was the multi-disciplinary team's view that these repeated admissions were often prompted by emotional strain at home, which D was unable to cope with. She made multiple allegations of abuse about members of staff involved in her care and her family, coupled with becoming verbally abusive, at times violent to property and threatened suicide. D also reported auditory and visual hallucinations.

During her latest admission under the MHA, D was treated with psychological input, as well as a variety of antidepressants (including paroxetine, citalopram and mirtazapine) in combination with mood stabilisers and/or antipsychotics (e.g. risperidone, olanzapine, sodium valproate, amisulpiride and aripiprazole), all with limited clinical impact. D also displayed clear psychotic symptomatology (e.g. formal thought disorder, delusions of control, neologisms and hallucinations in various modalities) independent of the features of BPD, resulting in a diagnosis of Schizophrenia.

At the time of writing this article, D has been on clozapine for over 4 years. With the introduction of clozapine, abusive and aggressive outbursts disappeared and she has shown much less evidence of emotional volatility since. Although from time to time in reaction to stressful family and social situations D makes threats of self-harm or report hearing voices, these are amenable to distraction techniques and engaging her in meaningful activities. She lives in supported living accommodation with one-to-one support during the daytime, and is participating in college and structured daily activities. Over the past 4 years, D has only needed one informal admission during a community crisis which lasted about 10 days and was successfully discharged back to her supported living placement again.

Case E

E is a 48 year old married lady with a mild ID and BPD. She suffered sexual and emotional abuse during childhood and early adulthood. As a result, she presented with maladaptive behaviours such as aggression, auditory pseudo-hallucinations, self-harm and suicide attempts in order to deal with stressful situations. She had frequent admissions to the ID inpatient unit under the MHA over several years. Since she could not be managed in the community she was transferred to a low secure out of county mental health unit to address her severe aggressive and self-harming behaviour. After a few years she was transferred to a rehabilitation unit under Section 3 of the MHA while being on several psychotropic medications including an antidepressant, a typical antipsychotic and Lorazepam (on a PRN basis), but continued to be aggressive and self-injurious. Additionally, she would not go out of the unit to visit the community or participate in activities. A few weeks after her transfer, she was started on clozapine with her consent and was taken off her typical antipsychotic medication. She responded well and was successfully discharged to live in a supported living accommodation in the community within 18 months of starting clozapine.

At the time of writing this report, she has been on clozapine for over 4 years while remaining stable in the community without presenting with any serious aggression, self-harm or suicidal attempts. She has however had two short term periods of admission in crisis (each less than two weeks) in the context of bereavement and ideas of self-harm after her young son died. She lives in supported living with her husband with minimal staff support and remains in frequent contact with her family as well as regularly engaging in leisure activities.

Discussion

In people with ID and personality disorder five symptom domains that have been suggested for targeting should psychotropic medication be considered are:

1. Cognitive-perceptual (psychosis-like) symptoms
2. Symptoms of affective dysregulation
3. Symptoms of behavioural dyscontrol, impulsivity or aggression
4. Anxiety symptoms and
5. Self-injurious behaviour (Bhaumik and Branford, 2005; Alexander et al., 2007).

Table 1 illustrates the presentation of any or all of the five symptom clusters and their severity before starting clozapine in our patients. Table 2 shows the same clusters three years after continuous treatment of the patients with clozapine. All five cases reported are females, and indeed BPD tends to be diagnosed more frequently in females than males, though DPD is more common in males.

In the general population, most drug treatment studies in adults have been on Cluster B personality disorders (particularly Borderline and Dissocial) and have shown that low doses of antipsychotics, Selective Serotonin Reuptake Inhibitors (SSRIs) and mood stabilisers are useful for irritability, hostility and aggression. It has been suggested that cognitive-perceptual symptoms should be treated with low dose antipsychotics; affective dysregulation symptoms with SSRIs, MAO inhibitors and mood stabilisers; and impulse-behavioural dyscontrol symptoms with SSRIs, MAO inhibitors, lithium, valproate, carbamazepine and clozapine (Gunderson and Hoffman, 2007).

In people with ID, Mavromatis (2000) described three case reports illustrating the complexity of diagnostic assessment in individuals with BPD and ID providing direction in adapting and tailoring treatment, both behavioural and psychopharmacological, with subjective improvements reported (Mavromatis, 2000). However, the long term outcome of treatment was unavailable. In this case series, outcome over a three year follow-up period, demonstrated sustained improvement. It is likely that while symptom clusters may remain unchanged and stable over time, nonetheless the severity and intensity reduces markedly with treatment with clozapine as noted by direct measurements on the Likert scale and by using proxy variables - hospital re-admissions.

Natural spontaneous remission is unlikely to occur so dramatically and improvements sustained over a three year period in all of the above cases. No changes in their multidisciplinary treatment programme, social circumstances or life-changes could explain the recovery in each of the cases as all of them were receiving these treatment modalities before initiating clozapine. A placebo effect is unlikely due to the clear temporal correlation between initiation of clozapine and treatment response; this same reason making it similarly unlikely to have occurred to previous psychological, pharmacological or social treatments. With the notable exception of Case D, there is no evidence to suggest schizophrenia in any of the cases, although majority of them presented with short lived quasi psychotic symptoms/pseudo-hallucinatory experiences. The dose of clozapine used in each of the five cases was much below the 400-800mg/day recommended range for schizophrenia. The clinical response was noted within 3-6 weeks of initiating the clozapine in all cases. The only side effects reported by the patients have been a mild day time over-sedation, increased appetite and weight gain and drooling which has been mainly during sleep.

In all cases, the decision to initiate clozapine was not taken lightly. Clozapine was only started if patients were admitted several times under section. Additionally an informed consent was taken along with a request from a second opinion doctor to authorise the out of licence use of clozapine. Patients were informed about regular monitoring, registered with clozapine clinic and remained compliant to regular Full Blood Count and other side effects monitoring by their community nurses/ ID psychiatrists. In all 5 cases, clozapine replaced another antipsychotic medication which had been used unsuccessfully to manage severe aggressive and self-injurious behaviours. In some of the patients, several antipsychotic medications had been unsuccessfully used over years for the management of life threatening symptoms. Use of clozapine in all 5 cases resulted in significant improvement in their quality of life as all of them were successfully taken off Mental Health Act section and discharged from hospital to live in a supported living accommodation. Additionally, they all started participating in various social and leisure activities of their choice and college education while living near to their families. These were not possible prior to treatment with clozapine in spite of involvement of the multidisciplinary team and using other pharmacological as well as non-pharmacological approaches.

Clozapine mainly blocks D_1 and D_4 receptors and its effects on D_2 receptors are relatively less than traditional antipsychotics. It also blocks $5HT_2$ receptors, which may be the reason for its superior efficacy, as it has been postulated that excessive impulsivity reflects central serotonergic system dysfunction and that clozapine may improve this due to its potent $5HT_2$ antagonistic activity.

Clozapine prescription has numerous potential risks. Regular haematological monitoring is indicated owing to the possibility of developing neutropenia and potentially fatal

agranulocytosis (in 0.01-0.1%) (Fleischhacker, 1992). Other side-effects include hypersalivation, metabolic syndrome, reduced seizure threshold, constipation, tachycardia, myocarditis, cardiomyopathy, pulmonary embolism and extrapyramidal symptoms among others (Farooq and Taylor, 2011; Mistry and Osborn, 2011). Additionally, clozapine's sedative and anticholinergic effects may cause worsening of cognition in patients with ID (Sajatovic et al. 1994). However, unlike many other antipsychotics, clozapine is not associated with inducing hyperprolactinaemia as a side effect (Mortimer, 2011). Less commonly occurring side-effects include acute pancreatitis (Martin, 1992), neuroleptic malignant syndrome (DasGupta and Young, 1991), hepatitis, interstitial nephritis, paralytic ileus and priapism (Ziegler and Behar, 1992). Recently published NICE guidelines (NICE, 2009) acknowledge the paucity of studies in relation to treatment and management of personality disorder (Lindsay et al., 2007). The guidelines recommend specialist input from ID services for assessment, diagnosis and management when dual diagnosis of BPD and ID is suspected.

Conclusion

It is likely that clozapine prescription brought about a reduction in impulsivity, a core hallmark of BPD, increasing 'thinking time' in each of the 5 cases, enabling the use of alternative coping strategies rather than maladaptive responses when faced with real or imagined stressors. Each of the 5 people described developed a more positive outlook to life, had an increased self-esteem and self-confidence. They also showed significant improvements in their ability to meaningfully interact and engage with support workers and professionals in the ID team over a sustained period and increased use of adaptive and socially acceptable coping strategies over time. As with any other treatment, the potential

adverse effects with clozapine needs to be regularly monitored and weighed up carefully against the benefits derived.

Recent literature recommends earlier introduction of clozapine in treatment resistant schizophrenia (Farooq and Taylor, 2011; Mistry and Osborn, 2011). Similarly, our clinical experience of working with patients who have a diagnosis of personality disorder and complex life threatening symptoms also shows that clozapine would clinically be a highly valuable alternative to other pharmacological approaches, especially when psycho-social strategiesalone could not manage the risks adequately. Use of clozapine under robust monitoring (though unlicensed in the management of personality disorders), as an adjunct to non-pharmacological approaches, will in our opinion facilitate engagement and compliance and ensure the safety and quality of life of the patients with severe personality disorders in the community.

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