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A multidisciplinary approach to establishing clozapine in a patient with schizophrenia and comorbid ASD: a case report

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Abstract

Background There is substantial symptom overlap in psychosis and autism spectrum disorder (ASD) and co-morbidity is common. In addition, antipsychotic response may be moderated by the co-occurrence. Individuals with ASD may be at greater risk of some clozapine adverse effects and occasionally, its use may be contra-indicated.

Case presentation We present the case of a patient with ASD with psychosis unresponsive to multiple antipsychotics, but extra precaution was required with clozapine.

Conclusion A multidisciplinary approach is required to establish clozapine in a patient with schizophrenia and ASD

Key points

- Response to antipsychotic treatment may be moderated by the presence of ASD symptoms.
- There may be challenges to the use of clozapine in people with ASD.
- There are few absolute contraindications to clozapine use but important clinical consequences to delay in its initiation. Treatment should not be withheld once treatment resistance is confirmed.
- A multidisciplinary approach is required to establish clozapine in a patient with schizophrenia and ASD.

Keywords Schizophrenia, Psychosis, Autism spectrum disorder, Clozapine, Case report

Introduction

There is significant overlap in the symptoms of ASD and psychosis [1]. ASD is characterised by difficulty in social interactions, restricted interests, repetitive behaviours and cognitive impact [2]. People experience these symptoms at varying severity hence ASD is known as a spectrum disorder. Schizophrenia symptoms also exist along a spectrum and can present with a similar feature alongside delusions/hallucinations and negative symptoms [3].

Studies have suggested that people with neurodevelopmental disorders have an increased vulnerability to psychosis, due to common information processing impairments which can increase the risk of psychosis [1, 4]. The presence of symptoms in both ASD and psychosis exist on a continuum, adding to the complexity and

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ambiguity of diagnosis in this population [1]. A plethora of studies have explored the links between ASD and psychosis and reported significant common findings in genetic studies, neuroimaging data and cognitive features, further complicating the ability to separate the disorders when co-occurring [5–7]. In the face of diagnostic uncertainty, the management of illness can appear very challenging.

Studies suggest that antipsychotic treatment response can be moderated by the presence of ASD, which increases the likelihood that there will be some elements of treatment resistance – that can be an indication for the use of clozapine [8]. The nature of ASD can present additional challenges to the use of clozapine which are discussed in this report.

Case report

The patient is a 21-year-old Caucasian male from the United Kingdom, he was first referred to the Complex Psychosis Service (CPS) after a period within the Early Intervention in Psychosis (EIP) Team and Child and Adolescent Mental Health Services (CAMHs). The CPS is a service within Kent and Medway NHS and Social Care Partnership Trust (KMPT) in the United Kingdom, that specialises in the treatment of complex and treatment resistant psychotic disorders [9].

The patient was first referred to mental health services aged 15 years. While he had a diagnosis of ASD from age 3 years, he had been coping well both in his personal life and at school. The patient and his family identified several social stressors that precipitated the presentation of his psychotic features. He experienced a period of bullying at school and was also undertaking his General Certificate of Secondary Education (GCSE) exams which he found highly stressful.

The patient had persecutory and paranoid beliefs that he would cause "Armageddon" if he failed any of his exams. He experienced auditory hallucinations with the voices being negative and taunting in nature and he thought that people were able to read his thoughts and believed his father would try to shoot him in the night. This paranoia led him refusing to eat his food as he also believed his mother was trying to poison him. It was clear that his symptoms had a significant impact on his day-to-day functioning. Due to this, he moved from mainstream education to a special school which supported people with ASD and learning disabilities.

There is a family history of mental health disorders in the maternal grandmother's brother who had a diagnosis of schizophrenia and grandmother's sister who was under psychiatric care with an uncertain diagnosis.

Initially, he had no formal diagnosis when he was first seen within the early intervention service, but it was agreed that his symptoms were psychotic in nature. However, there was some question as to whether this linked to his ASD diagnosis rather than a psychotic disorder. A referral was made to the CPS for clarity regarding treatment options which is explored in the treatment section of this report.

Formulation

Due to the childhood diagnosis of ASD, there was a level of uncertainty among professionals surrounding diagnosis. Any potential underlying organic causes such as autoimmune or metabolic disorders were ruled out over time with multiple investigations taking place. A neurology review was requested including a Magnetic resonance imaging (MRI) scan and there were no abnormalities reported.

It was important to note the main characteristics of the ASD prior to the patient's presentation to mental health services in order to differentiate between the two disorders. He had prior difficulty in social situations, maintaining eye contact and understanding other people's intentions. However, there was a clear change in his perceptual experiences and functioning when his auditory and visual hallucinations started aged 15 years. He continued to experience psychotic symptoms despite different pharmacological and psychological treatments.

The patients' parents were his main carers and provided critical background information and were able to undertake a high level of monitoring within the community. Alongside a Multidisciplinary team (MDT) approach, this enabled the team to make an informed decision that psychosis was the primary cause of distress and poorer functioning as there had been a step change from the childhood ASD presentation.

Treatments

The patient was offered both pharmacological and psychological treatment for psychosis. This was initially joint working with CAMHs and EIP due to the patients age and presenting need. When he turned 21 he was stepped up to his local community mental health team as he had completed 3 years with EIP.

Psychological

The patient had active involvement from the psychology team and completed Eye Movement Desensitisation and Reprocessing (EMDR) as well as Cognitive Behavioural Therapy. The patient engaged well with these interventions and developed useful coping mechanisms which he utilised to manage his symptoms. He developed cue cards which he continues to use to help him to challenge his negative beliefs. The patient also engaged with a patient reporting method called dialogue plus which supported the team to monitor his own symptoms. The dialogue plus is a self-rated scale where patients rate their

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satisfaction with various aspects of their life and healthcare [10].

Pharmacological

Prior to the consideration of clozapine, the patient was treated with; risperidone 6 mg daily started in June 2018, aripiprazole 10 mg was added in Dec 2020 due to hyperprolactinaemia, risperidone was cross titrated to quetiapine 700 mg in August 2021 finally, a cross titration from quetiapine to olanzapine 20 mg took place in January 2022 all with limited symptom reduction. During the cross titration from quetiapine to olanzapine the patient experienced two tonic-clonic seizures. He had febrile convulsions during his childhood, but mum reported this had not been a problem since approximately 6 years of age. Consequently, he was referred to neurology team where an EEG was completed as well as an MRI noting no structural abnormalities or epileptic focus. The patient, on the recommendation of neurology was then prescribed sodium valproate 500 mg daily to manage seizure activity and the cross titration to olanzapine 20 mg continued with no further complications.

After an extended period on olanzapine the symptoms of psychosis remained inadequately treated. The patient continued to present as highly anxious and was prescribed pregabalin to help alleviate his anxiety with some positive effect. However, soon after starting the pregabalin he began to experience some word finding difficulties. Despite this, pregabalin was continued to support management of his anxiety. The patient and his carers considered that he remained unwell.

It was agreed with the family that a trial of clozapine would be in the patient's best interest. However, there were significant concerns about the further risk of seizures, noted as a contraindication to clozapine [11, 12]. Considering the patient's history of seizure activity, it was agreed that a community titration would not be appropriate. An acute inpatient admission was also ruled out at the time considering the extent of the patient's ASD needs. Many different options were considered including a community titration with a specialist epileptic nurse present and staying in the family home. This option was ruled out as the carers believed this would also cause distress due to the patients ASD; private inpatient care provision was considered and excluded because of the ASD needs and monitoring requirements for seizures. Given the main concern was around the seizure risk, a specialist epilepsy centre was approached, and a referral was made to Chalfont Epilepsy Centre [13].

The team at Chalfont had a breadth of experience in working with ASD however, no experience of a clozapine titration at the centre. The clinical team were concerned regarding the limited psychiatric cover available at this site. Multiple interdisciplinary planning and monitoring meetings took place between the Epilepsy Centre, the CPS team and the carers to ensure all members of the MDT were aware of the patient's complex needs, as well as the policy for clozapine titration and the staff requirements.

It was agreed that the patient would complete a clozapine titration at Chalfont with his carer staying over and ongoing access to advice on clozapine titration from the CPS as necessary. The carers had several concerns about the process; foremost among these were the risks of cross titration from olanzapine to clozapine and impact on seizure risk versus psychosis symptom control. It was agreed that a slow cross titration was the optimal forward but with careful monitoring of symptoms and seizure activity. In conjunction with the CPS team a cross titration over 32 days was developed. It was agreed the first sixteen days would be in Chalfont as this was the most high-risk period; and if all went well, the patient would finish the titration at home with support from the Home Treatment Team. Clozapine was initiated at 12.5 mg once daily. This was added to his baseline olanzapine dose of 17.5 mg daily (in two divided doses). At the end of week 1, the olanzapine dose was reduced to 15 mg daily (in divided doses) and clozapine increased to 25 mg twice daily. At the end of week 2, olanzapine was further reduced to 10 mg daily while clozapine increased to 50 mg twice daily. By end of week 3, olanzapine dose was reduced to 5 mg daily and clozapine upped to 100 mg twice daily. At the end of week 4, olanzapine was discontinued and clozapine increased to a final dose of 150 mg twice daily. Monitoring included daily blood pressure, temperature and pulse. Weekly blood monitoring of full blood count, troponin and C-reactive protein (CRP).

The titration was successful although, periods of tachycardia were noted and a referral to a cardiologist was made to monitor this. No seizure activity was noted, and the patients mental state remained stable during the titration. At the dose of 300 mg daily, his clozapine level was 0.37 mg/L and norclozapine level, 0.15 mg/L. There was a modestly beneficial effect on symptoms, but this will continue to be monitored over the next six months to determine the impact of clozapine. The patient continues to engage with the service and is reviewed on a weekly basis. He continues to attend college and has a high level of support from his family and services to manage his ongoing presentation.

Discussion

Differentiating between symptoms of psychosis and ASD is a difficult task, which can result in people waiting for prolonged periods to receive appropriate treatment. In parallel, people may also receive inappropriate treatment due to misdiagnosis [14]. This case narrative illustrates the difficulties for patients, carers and clinicians in the

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presence of co-occurring disorders presenting with complex presentations and their assessment and treatment.

Psychosis is often misdiagnosed in people with ASD particularly when occurring at times of high stress and developmental changes due to symptom overlap [15]. This report presents a longitudinal approach to the diagnosis of psychosis in a person with ASD focusing on continuous symptom monitoring to ensure an appropriate diagnosis and in turn appropriate treatment pathway. These challenges in the assessment, diagnosis and treatment of such cases are well reported and similar cases like ours have been reported [16, 17]. The patient discussed in this report was identified as treatment resistant during his time in EIP services however, clozapine was not initiated until he was moved on to a community mental health team. This supports evidence of the reluctance to clozapine use in EIP services illustrating the delay in initiation of clozapine in patients who are already diagnosed with a treatment resistant disorder [18].

In this case, although clozapine has not yet led to complete symptom control however, the team and family report some improvement. The patient reported that he feels clozapine has helped him in managing his bad thoughts and the mother notes he is able to concentrate for longer periods without becoming distracted and a reduction in his need to use coping strategies. This is something that the team will continue to monitor within the community always considering the benefit vs. risk for this patient. It is important to build a thorough understanding of individual characteristics within those who are neurodivergent, listening and working collaboratively with carers and families is a critical aspect of this process, and allows for appropriate treatment changes when required [19].

This report highlights the need to comprehensively assess neurodivergent patients to ensure the correct diagnosis. Clinicians working within mental health should be aware that psychotic features are more likely to present in those with neurodiversity [1, 4] and training needs to ensure they feel confident and comfortable to work towards distinguishing the symptomatology of ASD and psychosis.

One final point is that despite the formal contraindications to the use of clozapine, with appropriate support from specialist multidisciplinary teams, it is still entirely possible to safely initiate clozapine even in high-risk patients. It is imperative that clinicians adopt a solution focussed approach to managing risk – especially in the context of clozapine prescribing, where it is often the only pharmacological intervention suitable for a person with treatment resistant psychosis [20]. Although we have discussed excellent multidisciplinary joint working in this review, it is important to note that the patient continues to face difficulties in joint working following his cardiology referral because of clozapine-induced tachycardia. All too often a battle faced for those prescribed clozapine.

Studies continue to highlight that clozapine is grossly under prescribed hence many patients endure symptoms inadequately managed [21]. This report encourages clinicians to prescribe clozapine with the support of specialists even in the face of contraindications. It is a salutary note that it took over two years from considering clozapine to completing the clozapine titration discussed in this study.

Limitations

This case report is limited by the absence of standardised rating scales, which restricts objective assessment of symptom severity and treatment response. The medical workup was incomplete, reducing diagnostic certainty. Additionally, distinguishing between ASD and primary psychosis, as well as anxiety and paranoia, was challenging—particularly in the context of trauma—highlighting the complexity of overlapping psychiatric presentations.

Conclusion

There is a complex relationship between autism spectrum disorder and psychosis. Through this report we propose the routine use of a thorough multidisciplinary assessment to establish the specific issues that are causing distress and impairing function [18]; this can then support the planning and monitoring of the necessary therapy - in this case use of clozapine in a patient with comorbid schizophrenia and autism spectrum disorder complicated further by a history of seizure disorder. This complex case highlights the benefits of working with specialist teams such as the complex psychosis service within Kent and Medway NHS Partnership Trust, and the Chalfont epilepsy centre in supporting clinicians and carers/families to decide on appropriate treatment pathways.

Abbreviations

ASD	Autism Spectrum Disorder
CAMHS	Child and Adolescent Mental Health Service
CPS	Complex Psychosis Service
CRP	C-Reactive Protein
EEG	Electroencephalogram
EIP	Early Intervention in Psychosis
EMDR	Eye Movement Desensitisation and Reprocessing
GCSE	General Certificate of Secondary Education
MDT	Multidisciplinary team
MRI	Magnetic Resonance Imaging
KMPT	Kent and Medway NHS and Social Care Partnership Trust

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Authors' contributions

Initial draft was written by MB. AS reviewed the initial draft and supplied additional materials. Critical revision and intellectual content were added by

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EW and SS and the final draft produced by EW. All authors read and approved the final manuscript.

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Competing interests
The authors declare no competing interests.

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