There is limited evidence relating to the treatment of psychotic symptoms in Huntington’s disease (HD); therefore, treatment decisions are based on clinical consensus and expert opinion. In this article, Dr Majothi et al. describe the use of clozapine in an unlicensed manner in HP, which proved to be safe and effective.

Huntington’s disease (HD) is an autosomal dominant degenerative disease of the brain. HD presents as a triad of motor, cognitive and neuropsychiatric symptoms. The most characteristic motor symptom is chorea but bradykinesia, dystonia, rigidity can also occur. Cognitive symptoms include poor decision making, planning, memory and emotional processing. Depression, apathy irritability and paranoid psychosis are the common neuropsychiatric symptoms. The prevalence of HD is 10.6–13.7 individuals per 100 000 in the western population.

The disease is caused by the expansion of CAG (cytosine, adenine, guanine), a polymorphic trinucleotide repeat. CAG encodes for glutamine in the exon 1 of the N-terminus in the Huntington (HTT) gene found in chromosome 4p16.3. The HTT protein causes neuron dysfunction and death. For full penetrance of HD the number of CAG repeats would be greater than 40 and for partial penetrance between 36 and 39 repeats. A diagnosis is made either clinically, testing for the trinucleotide repeat expansion, or predictively, based on family history and following appropriate genetic counselling, testing for the trinucleotide repeat expansion.

There is limited literature available on treating psychosis in Huntington’s disease. This case study adds to the very limited number of case reports published in this area and demonstrates the safe and effective management of psychosis in Huntington’s disease using clozapine.

### Treatment of psychosis in Huntington’s disease with clozapine

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There is limited evidence relating to the treatment of psychotic symptoms in Huntington’s disease (HD); therefore, treatment decisions are based on clinical consensus and expert opinion. In this article, Dr Majothi et al. describe the use of clozapine in an unlicensed manner in HP, which proved to be safe and effective.

<table>
<thead>
<tr>
<th>Study citation</th>
<th>Brief summary</th>
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<tr>
<td>Altintas M, Akdur OA, Kesebir S. Huntington Disease, psychosis and clozapine treatment: A case report. Klinik Psikofarmakoloji Bulteni 2014;24</td>
<td>Demonstrated use of clozapine at dosage of 300mg daily to treat psychosis in HD</td>
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<tr>
<td>Goel D, Butt R. Clozapine as mono-therapy in the management of Huntington’s Chorea. Int J Neuropsychopharmacol 2012;15:170</td>
<td>Doses of up to 100mg clozapine daily used to treat psychosis, resulting in amelioration of psychotic symptoms</td>
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<td>Adam D. A case of Huntington’s disease presenting with psychotic features. Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2014;27:250–3</td>
<td>Demonstrated use of doses of up to 200mg of clozapine daily, resulted in benefits to psychotic symptoms and improved social functioning</td>
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presented more paranoid and avoided going out of the house. He refused food and believed his family were trying to poison him and take over his house. He was hostile towards his family requiring admission under the Mental Health Act.

On the ward he reported thought interference, paranoid and persecutory delusions and delusions of reference. There were mild choreiform movements affecting the trunk and upper limbs. He believed that he was 29 years old when his actual age was 49 years. He described the ward as a film set and all staff, patients and family members were actors and his part in the film was to be abused by people around him. He stated that he worked for the Queen and was in contact with her via the TV and radio. He stated that he had met a celebrity singer and they planned to marry in the near future. Routine blood investigations on admission reported a raised HbA1c of 75mmol/L, patient had type 1 diabetes mellitus treated with insulin and raised prolactin level of 1571miu/L. However, the patient was asymptomatic. An MRI in July 2018 reported mild bilateral caudate nucleus atrophy.

The patient was prescribed oral aripiprazole for psychotic symptoms, which he initially declined, but subsequently adhered to; doses were titrated to 30mg daily. The patient was observed by staff to be a bit warmer and less irritable on aripiprazole; however, his psychotic symptoms persisted and continued to be disturbing for the patient. He continued to lack insight into his condition and did not believe he required any treatment. Due to lack of response to aripiprazole treatment after six weeks, aripiprazole was cross titrated with risperidone up to 3mg twice daily. The patient was willing to engage in conversations with ward staff, with a noticeable improvement in mood, and engaged in ward activities while on risperidone. However, severe psychotic symptoms persisted while on risperidone, which were disturbing for the patient. A short trial of amisulpride followed at doses of 400mg daily, which did not achieve any psychotic symptom control.

Clozapine was deemed a suitable next step due to treatment failure with three antipsychotics over a period of a five-month inpatient admission. Due to lack of evidence in the use of clozapine literature review was conducted to establish case reports for use of clozapine in the treatment of psychosis in Huntington’s disease (documented in Table 1). From the literature searches, cases studies identified documented use of clozapine doses up to 300mg daily in the treatment of psychosis in HD. Clozapine is not licensed for the treatment of psychosis in HD, the prescribing was therefore off-label. When prescribing off-label it is important to discuss the risk-benefits of such treatments with patients and obtain informed consent where appropriate.

Clozapine was prescribed as a slow titration: day one 12.5mg in the morning; day two 12.5mg twice daily; day three 12.5mg in morning and 25mg at night; day four 25mg twice daily. Thereafter the dose was slowly titrated upwards at weekly intervals. Routine monitoring, which included pre-dose lying and standing blood pressure, temperature, pulse and monitoring, was completed 1, 2, 3 and 4 hours post-dose. From day 2 to day 16 pre-dose monitoring was conducted, then two-hour post dose and pre-evening dose monitoring. The dose of clozapine was titrated to 100mg in the morning and 350mg at night. While on clozapine the patient engaged with staff, accepted medication and routine weekly clozapine bloods. At a dosage of 425mg daily given in divided doses the clozapine plasma levels were 0.25mg/L and norclozapine 0.14mg/L. The clozapine dosage was further increased to 500mg daily in divided doses. Hypersalivation occurred with clozapine use and was managed with hyoscine hydrobromide. With clozapine treatment, clinical presentation improved significantly, in that the patient was less distressed by the intensity of his psychotic symptoms and achieved behavioural control to function better in activities of daily living with improvement in his mood. While on clozapine the patient’s symptoms improved to the extent that he was discharged from inpatient care to a supported placement.

Discussion
Psychosis is a rare symptom complex that occurs in Huntington’s disease and has a negative impact on the quality of life for patients. Psychiatric manifestations vary and may precede motor and cognitive changes. Personality changes and depression occur most commonly. Estimates of the prevalence of paranoid schizophrenia-like symptoms vary between 1% to 25% of cases. The risk of developing psychosis seems to be greater in patients who develop early-onset HD.

The neurotransmitters GABA and acetylcholine are implicated in HD. Psychotic symptoms in HD are rare, it is proposed to be initiated from the loss of inhibitory GABAergic function and the increase in dopamine turnover due to selective survival of type II spiny interneurons. The increase in dopamine turnover may lead to the psychotic feature in HD. It has also been postulated that the HD gene could
lower the threshold for the emergence of a schizophrenic phenotype, in the presence of a low load of small effect schizophrenia genes the HD gene may behave as a large effect schizophrenia gene.9

For full penetrance of HD, the number of CAG repeats would be greater than 40 and for partial penetrance between 36 and 39 repeats.1,6 Interestingly our patient did not have a family history of HD. The presence of a high number of mutated repeats in the normal range has an increased propensity to further expand upon transmission, moving into the pathogenic range. This means that de novo mutations can occur in previously unaffected families.10 Patients showing features consistent with a certain repeat expansion disease, but who lack a family history of similar disease, may have repeat mutations. In the absence of a documented family history clinicians should therefore not rule out a genetic test to confirm or exclude the suspected diagnosis.10

There is limited evidence with regard to the treatment of psychotic symptoms in Huntington’s disease, therefore, treatment decisions are based on clinical consensus and expert opinion. Antipsychotic drugs can be useful in treating psychosis in HD, but there are no randomised controlled trials to support the treatment choice, the treatment is therefore empirical. Clozapine in this case was used in an unlicensed manner, as clozapine is licensed for treatment-resistant schizophrenia. Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for an adequate period of time. We applied the same principles to initiate clozapine for psychosis in HD as for treatment-resistant schizophrenia.

Clozapine was prescribed initially at very low doses and with a slow titration due to the risk of worsening type 1 diabetes and potential for developing serious adverse side-effects. Clozapine was titrated to 500mg daily – higher than previously published case reports. Clozapine is considered a high-risk drug due to the risk of developing agranulocytosis, paralytic ileus, cardiomyopathy and endocarditis. In patients with organic brain disease, clinicians need to use psychotropic drugs cautiously due to the potential of increased sensitivity to drug effects. In this case clozapine was titrated at weekly intervals and carefully monitored for any adverse effects before increasing the dosage further.

Clozapine plasma levels were 0.25mg/L at daily dosages of 450mg clozapine, there is therefore scope to increase the dosage further to achieve optimal clinical response. However, this must be balanced to minimise any adverse effects and ensure doses do not cause toxicity. The minimum clozapine level to achieve therapeutic response has been postulated to be 0.2mg/L and evidence suggests increasing it beyond 0.6–0.83mg/L does not improve clinical response.8

Conclusion
We described a patient who developed psychosis in Huntington’s disease, its clinical assessment and the multidisciplinary management of symptoms, given the absence of effective disease-modifying therapies.

This case report demonstrates use of antipsychotics in Huntington’s disease to manage psychotic symptoms. After a lack of treatment response with aripiprazole, risperidone and amisulpride, clozapine has been effectively prescribed to dosages of 500mg daily for managing psychosis in Huntington’s disease, notably at higher dosages than previous case studies.

**Declaration of interest**
No conflicts of interest were declared.

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**References**