Clozapine is considered the antipsychotic agent of choice in the treatment of treatment-resistant schizophrenia, offering reduction in core positive symptoms for 50% of patients. These include hallucinations, delusions and thought disorder, as well as suicidality. Clozapine is considered the antipsychotic agent of choice in the context of increased cardiac muscle mass associated with HCM. In the absence of any clinical compromise, it was not felt to be of concern. Clozapine was continued with good effect on mental state. Troponin levels gradually reduced and the patient remained well.

Conclusions
While multiple cases of clozapine-induced cardiotoxicity have been reported in the literature, its implications for pre-existing structural disease are unclear. This case report suggests that clozapine can be safely introduced in pre-existing HCM, explores strategies for monitoring and highlights the importance of liaising with experienced cardiologists.

Case presentation
A 36-year-old man with treatment-resistant schizophrenia and known hypertrophic cardiomyopathy (HCM) was admitted to a specialist unit for a trial of clozapine. His psychiatric illness was characterised by multimodal hallucinations and delusions combined with low mood and poor motivation. The diagnosis of HCM was made 3 years previously following a routine electrocardiogram (EKG), and he had remained asymptomatic throughout this time; there were concerns about the risk of initiating clozapine given his pre-existing cardiac condition. Baseline investigations were performed as per local guidelines prior to commencing clozapine; these were within normal limits other than a mildly raised troponin level of 54 ng/L (normal <16 ng/L), which was attributed to the HCM. In addition, baseline transthoracic echocardiography (TTE) was performed which showed no change in the structural heart disease in comparison with previous TTEs.

Clozapine was started at 12.5 mg daily and up-titrated to 150 mg twice daily over 14 days as per our institute’s guidelines. The patient was monitored with regular testing of troponins, inflammatory markers and ECG. On day 18, the troponin level increased to 1371 ng/L. Creatine kinase and inflammatory markers remained stable. No changes in ECG or TTE were noted and the patient remained clinically asymptomatic.

Cardiology opinion was sought and reported that the finding of an isolated elevated troponin was likely to reflect a ‘troponin leak’ in the context of increased cardiac muscle mass associated with HCM. In the absence of any clinical compromise, it was not felt to be of concern. Clozapine was continued with good effect on mental state. Troponin levels gradually reduced and the patient remained well.

Declaration of interest
None.

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Case presentation
The patient was a 36-year-old British male of Iranian decent with a diagnosis of treatment-resistant schizophrenia. He was single, unemployed and living with his family. He was referred for a trial of clozapine in the context of an established diagnosis of HCM (Fig. 1). At the time of admission, he presented with multimodal hallucinations, thought disorder, delusional beliefs and psychosomatic symptoms; he had no cardiovascular symptoms. On admission, he scored 40 on the Psychotic Symptom Rating Scales (PSYRATS) and 80 on the Depression Anxiety Stress Scale (DASS). He had previously trialled a number of antipsychotic...
agents with limited improvement, including aripiprazole, paliperidone, amisulpride and risperidone. Flupentixol and olanzapine had been moderately successful in treating his positive symptoms, but had to be stopped because of adverse motor effects. At the time of admission, he was on amisulpride 800 mg and sertraline 100 mg for low mood.

Relevant past medical history includes the diagnosis of HCM, made 3 years prior following the finding of an abnormal ECG. Further diagnostic investigations had included TTE, 24-h Holter monitoring and cardiovascular magnetic resonance imaging (CMR). During the 3-year follow-up period, the patient had been asymptomatic and was not felt to be at significant risk of sudden cardiac death (Table 1). He was taking bisoprolol 7.5 mg daily – this being the agent of choice in those with HCM to help ameliorate the potential risk of arrhythmic demise and outflow obstruction associated with HCM. Other cardiovascular risk factors include a 17 pack/year smoking history and hypercholesterolaemia controlled with atorvastatin 40 mg daily.

The patient leads a moderately active lifestyle without limitation.

On arrival to our unit, the patient had a heart rate of 76 beats per minute (bpm) in sinus rhythm. A baseline ECG (Fig. 2) was carried out to monitor for any changes once clozapine was started. He was stable and asymptomatic at the time. Body mass index was high at 32 kg/m². He was hypertensive at 145/90 mmHg. Baseline cardiac biomarkers showed a troponin of 54 ng/L (normal <16 ng/L) and creatine kinase of 224 IU/L (normal <150 IU/L).

Cardiology advice was sought given the history of HCM and abnormal findings. The cardiology opinion concluded that the abnormalities in the cardiac biomarkers represented the patient’s own normal baseline levels – this being the agent of choice in those with HCM to help ameliorate the potential risk of arrhythmic demise and outflow obstruction associated with HCM. Other cardiovascular risk factors include a 17 pack/year smoking history and hypercholesterolaemia controlled with atorvastatin 40 mg daily.

The patient leads a moderately active lifestyle without limitation.

Table 1 Major clinical risk factors for sudden cardiac death in HCM a

| Major clinical risk factors for sudden cardiac death | HCM a |
|-----------------------------------------------------|-------|
| Age (younger patients may be more at risk)          |       |
| Non-sustained VT                                    |       |
| LV hypertrophy >30 mm                               |       |
| Syncope                                             |       |
| Family history of sudden death                      |       |
| Left atrial diameter                                |       |
| LV outflow tract obstruction                        |       |
| Blunted exercise BP response                        |       |

a. From Elliot et al11

VT, ventricular tachycardia; LV, left ventricle; BP, blood pressure
He returned to a stable social functioning, with minor residual symptoms and increased levels of engagement and motivation. There has been no evidence of worsening of his cardiomyopathy, either clinically or with subsequent investigation. The patient has led a moderately active lifestyle, engaged well with other aspects of therapy and showed increased interest in his care.

Initiating clozapine therapy in patients with pre-existing HCM requires liaison with Cardiology for expert opinion, as well as close monitoring for any evidence of cardiac decompensation. There are currently no evidence-based guidelines for initiating clozapine in such patients; nonetheless, we show that clozapine can be initiated safely in patients with HCM with careful monitoring and titration.

In our case, despite evidence of structural cardiac disease, the patient was deemed to be at low risk for sudden cardiac death, without obstructive disease and with normal cardiac function. Clozapine was commenced at 12.5 mg and titrated up to 150 mg b.d. as per our own institution’s guidelines; this included regular monitoring with ECG and blood testing. Baseline abnormalities required close liaison with our Cardiology colleague; however, the patient’s course was uneventful and the treatment successful.
Despite its efficacy, cardiac side-effects of clozapine can generate concerns about its use in patients with pre-existing cardiovascular disease. Common side-effects include orthostatic hypotension, reported in up to 75% of treated patients,13 in addition to a well-documented, benign tachycardia seen in up to 25% of patients.14

Clozapine is also associated with more severe forms of cardiac toxicity, most notably myocarditis,15-17 dilated cardiomyopathy18 and pericarditis.7 Development of any of these conditions requires cessation of the causative agent but is often reversible with appropriate treatment. Acute myocarditis can be life-threatening however, and in some, it may not be reversible, leading to significantly increased long-term morbidity and mortality. Currently, there are no established risk factors by which to identify those who may be at increased risk of developing these significant side-effects, and as such, patients starting clozapine are subjected to regular investigations to monitor for any change. It remains unknown whether those with pre-existing cardiac disease are at increased risk.

In our patient, a mildly increased baseline troponin was felt to relate to the increased muscle mass of the left ventricle seen in HCM. Troponin is a more specific myocardial marker than creatine kinase, and the brief elevation during the course of clozapine up-titration probably represents a very mild, self-limiting myocarditis. The underlying mechanism of cardiotoxicity by clozapine remains unclear. Several different mechanisms have been proposed, and it is likely that a combination of these is causative in susceptible individuals. It remains to be determined whether the pathophysiological processes at play in HCM, itself a condition with a wide genetic and phenotypic presentation, pose a greater short- and long-term risk for those concurrently treated with clozapine.

It is interesting to briefly mention the well-documented cardiotoxic effects of chemotherapeutic agents. Anthracyclines and HER2 antagonists are associated with the development of both acute and late onset cardiomyopathy.15 Several different modes of action are thought to underlie these, some of which have also been described in animal models of clozapine cardiotoxicity.16 It may well be that a similar mechanism of action is attributable to all these agents, and as such, it is very interesting to also note that early treatment with angiotensin-converting enzyme (ACE) inhibitors (standard prognostic anti-heart failure medication) results in a protective effect against the development of cardiotoxicity in both animal models receiving clozapine17 and humans receiving chemotherapy.18 A new subspecialty has emerged, cardiac-oncology, which facilitates best research, investigation and management in order to optimise the treatment and outcomes of those patients with cardiotoxic effects of chemotherapy. One pragmatic suggestion is the need for an analogous “cardio-psychiatric” team involving, but not limited to, specialists in psychiatry and cardiology. Such a collaboration would provide the most comprehensive care, given the complexity of managing both pre-existing and iatrogenic cardiac disease because of antipsychotic medication. To that end, Table 2 sets out our suggested regime for the monitoring of cardiotoxicity in patients undergoing clozapine initiation and up-titration with known structural heart disease.

| Table 2 | Proposed monitoring regime in those with structural heart disease. Troponin elevation ≥2 times baseline |
|-------------------|-------------------------------------------------|
| **Timeline**      | **Investigations**                             |
| At baseline       | Temperature, CRP, troponin, ECG, TTE           |
| Daily             | Temperature, heart rate                        |
| 24-h post dose increase | CRP, troponin, ECG                           |
| In the event of ongoing fever or abnormal CRP/troponin | Temperature (CRP, troponin) ECG, TTE        |
| 6 weeks post final dose increase | Temperature, CRP, troponin, ECG, TTE          |
|                   | CRP, C reactive protein, ECG, electrolycardiogram, TTE, transhoracic echocardiography |

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