A case report of olanzapine and related cardiac conduction changes

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The use of certain psychotropic medications can be associated with serious ventricular arrhythmia and sudden cardiac death. In this article, the authors use the QTc value in a patient treated with olanzapine for psychotic depression to highlight the challenges in balancing psychotropic medication against cardiac conduction changes.

The QT interval on the ECG is a measure of both depolarization and repolarization within the heart. It is measured as the distance between the beginning of the QRS complex and the end of the T wave. The QRS complex represents ventricular depolarization, while the distance from the end of the QRS to the end of the T wave represents repolarization within the heart. The length of the QT interval decreases as heart rate increases. QTc is the corrected QT value and is used to assess the conduction status within the heart.

QTc prolongation is defined as QTc values above 450 milliseconds in men, or 470 milliseconds in women. QTc values greater than 500 milliseconds are considered prolonged and appear to be associated with an increased risk of arrhythmias. QT interval is at best only modestly associated with torsade de pointes (TdP), but despite its difficulties it is the best predictor available. TdP can be self-limiting, causing only dizziness or syncope, but can progress to ventricular fibrillation and sudden death.

Olanzapine is a second-generation antipsychotic that acts as an antagonist at 5HT2A and D2 receptors. It is used in the treatment of schizophrenia, combination therapy for mania and preventing recurrence in bipolar disorder.

Certain psychotropic medications are linked to serious ventricular arrhythmia and sudden cardiac death. There is controversy over the association of QTc and arrhythmias, but strong evidence links QTc values over 500 milliseconds to increased risk of arrhythmias. According to the Maudsley Prescribing Guidelines olanzapine has a low effect on QTc.

Psychiatrists rely on the QTc interval in formulating a pharmacological plan and it is an important marker in the decision-making process.

We report the effects of olanzapine on the corrected QT interval (QTc) in the over 65-year-old population, alongside the follow up and management difficulties arising with this.

Case report
A 72-year-old woman was referred by her GP to the older adults community mental health team (CMHT). She was initially referred at the age of 69 years in 2013 with severe depression with psychotic symptoms. She was a retired midwife, lived alone in a retirement flat, and was independent of her activities of daily living.

The patient had a history of severe depressive disorder. The first depressive episode was around 35
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years ago in the context of marital problems. She was admitted informally and treated with electroconvulsive treatment. On discharge she was placed on amitriptyline, which was continued for approximately one year.

She remained well up until 2006 when she presented with paranoid ideas and command hallucinations. As she travelled frequently between her home country and England she had not kept her clinic appointments and had stopped taking her prescribed medications.

A return to England in 2012 revealed a gradual deterioration in her mental state with marked self-neglect, low mood, and insomnia. Her appetite was poor with associated weight loss of about 15Kg in a span of three years. She also experienced auditory hallucinations of a derogatory and commanding nature. She scored 14/15 on the Geriatric Depression Scale.

Mirtazapine 15mg daily was started with olanzapine 10mg at night. There was a gradual improvement with home treatment team (HTT) support. The patient had an episode of severe anxiety with palpitations and breathlessness with the attendance of the emergency medical team. An electrocardiogram (ECG) tracing showed a QTc of 454 milliseconds. Olanzapine was gradually stopped due to no improvement in symptoms in November 2013. Electroconvulsive therapy (ECT) was considered but she declined it. There was a gradual and marked improvement on olanzapine 10mg once daily, and venlafaxine 225mg XL once daily, so the patient was discharged to the CMHT, with HTT support, in January 2014.

Due to her weight gain and risk of diabetes, olanzapine was gradually reduced and she remained on olanzapine 2.5mg once daily. In December 2014; a routine ECG showed a QTc of 463 milliseconds with right bundle branch block (RBBB). Venlafaxine XL was reduced to 150mg once daily. She was referred to her GP for further investigations as she complained of palpitations.

When reviewed in June 2015 she continued to remain in a stable mental state whilst on olanzapine 2.5mg once daily and venlafaxine XL 150mg. Her weight also remained stable.

An ECG in September 2015 showed tachycardia of 107 beats, QTc 529 milliseconds with ST changes and RBBB. The medical team advised investigating reversible causes as the QTc was not dangerously prolonged. The ST changes and RBBB and were not considered significant unless the patient was symptomatic.

After a further decline she was informally admitted to a psychiatric hospital in September 2015. Physical examination and blood tests were both unremarkable. Repeat ECG showed a QTc of 509 milliseconds and a referral to cardiology made with weekly ECGs.

Venlafaxine and olanzapine were stopped with the slow introduction of sertraline 150mg once daily and aripiprazole 10mg once daily, which improved her mood and stopped auditory hallucinations. Her measured QTc was 487 milliseconds in October 2015. Cardiology advised that there was no immediate concern. As there was marked improvement she was again eventually discharged to the CMHT, with HTT support, in November 2015.

However, around May 2016 the patient reported deterioration in her mental state. Cardiology advised a trial of antipsychotics, with a close 12 lead ECG monitoring to ensure that her QTc would not exceed 480 milliseconds. An ECG from April 2016 showed a QTc of 500 milliseconds, so it was advised that there was no antipsychotic that could be added safely to the current medication regimen due to increased risk of inducing potentially life threatening polymorphic ventricular tachycardia (VT). Therefore she was continued on mirtazapine 45mg at night and aripiprazole 15mg once daily.

ECGs in August and September 2016 showed normal QTc, but as there was no improvement aripiprazole was changed to olanzapine. It was agreed to repeat ECGs twice weekly. ECG repeated showed QTc 477 milliseconds and 485 milliseconds. During the following week QTc was 461 milliseconds and 477 milliseconds and olanzapine was increased to 5mg at night. But the
next QTc was 489 milliseconds and 509 milliseconds with a following QTc reading of 463 milliseconds and 482 milliseconds.

There was a rapid deterioration in her presentation, which led to hospital admission in October 2016. Olanzapine was stopped and changed to risperidone. ECG showed RBBB with QTc of 471 milliseconds. A cardiology review suggested bifascicular block and advised an echocardiogram.

The echocardiogram in October 2016 reported a suboptimal study with visually non-dilated left ventricles with mild concentric hypertrophy; hyperdynamic contractility, visually mildly enlarged right ventricle with hyperdynamic function, and non-dilated atria with mildly increased aortic forward flow, likely due to hyperdynamic ventricular function.

There was a gradual improvement in the patient’s symptoms with good compliance with medication. She was also started on venlafaxine. ECG showed a QTc of 426 milliseconds. She was eventually discharged back to the CMHT, with HTT input, on risperidone 2.5mg once daily, mirtazapine 45mg at night and venlafaxine XL 75mg once daily. The QTc has remained within normal limit to date. Prolactin levels remain 1981mIU/L. A referral was made to the endocrinology team for raised prolactin levels. She remains under regular clinical review with the community psychiatric nurse and support worker.

Discussion
As this case highlights, there was an increase in the QTc interval with olanzapine in combination with other medications. The cardiology team advised close and regular lead ECG monitoring to ensure QTc does not exceed 480 milliseconds. It was also recommended that it was reasonable to achieve this level if there were no physical symptoms, such as syncope or palpitations, and if the patient was closely monitored due to a heightened risk of potentially life threatening polymorphic VT with raised QTc of 500 milliseconds.

The cardiologists advised it was necessary to balance the case of psychotic depression versus risk of sudden death due to polymorphic ventricular arrhythmia. They were unable to advise a specific combination of antipsychotic therapy but suggested that addition of any medication needed a repeat ECG within 48 hours to check the impact on QTc. The cardiologists strongly advised against continuation of any drug or drug combination that resulted in a QTc exceeding 500 milliseconds because of the increased risk of life threatening ventricular arrhythmia.

We were also advised to look at the drugs known to prolong QTc to be avoided in sudden arrhythmic death syndrome (SADS). Although olanzapine did not appear on this list it was suggested that it might mean that the impact may be less but not entirely ruled out, as there have been reports of this occurring previously.

Our patient responded well to olanzapine but this was associated with a prolonged QTc, which was noted on several readings. She became extremely unwell after the discontinuation of olanzapine. Although she was on other medication too, it was only after the switch to risperidone that her QTc reverted back to the normal range.

Olanzapine has been associated with cardiomyopathy in a patient with bipolar disorder taking olanzapine and lorazepam for 10 years when investigated for heart failure. Olanzapine possesses direct cardiac electrophysiological effects similar to those of class III anti-arrhythmics. These results offer a new potential explanation for QT prolonging effects observed during olanzapine treatment.

There is a reported case of first-degree heart block (prolonged PR interval) induced by olanzapine 10mg in a 12-year-old Caucasian with a diagnosis of bipolar disorder, attention deficit hyperactivity disorder, and obsessive-compulsive disorder. ECG returned to normal after olanzapine was discontinued and no other changes in medications were made, which suggests that the patient’s first-degree heart block (prolonged PR interval) was induced by the olanzapine.

There have been two reports of first-degree heart block in adults on olanzapine 50mg and 20mg, respectively, but the symptoms and ECG abnormalities resolved when doses were decreased to 40mg and 17.5mg. Although olanzapine remains a reasonable treatment choice for the more serious and treatment resistant cases of anorexia nervosa, careful consideration should be given for its use in children and adolescents due to first-degree heart block observed during treatment across this age group. Myocarditis and cardiomyopathy are associated with clozapine chlorpromazine, lithium, fluphenazine, risperidone, and haloperidol.

Conclusion
In summary, this case has demonstrated the difficulties that can be experienced in clinical practice when using psychotropic medication to treat and manage patients suffering from psychotic depression. Sudden cardiac death is a major cause of cardiovascular mortality. Ventricular arrhythmias and prolonged QTc interval are closely associated. Abnormal QTc prolongation on the electrocardiogram is
an independent risk factor for sudden cardiac death.\textsuperscript{10}

It has been noted that QTc interval and variability reach a peak shortly after awakening, which may reflect increased vulnerability to ventricular tachycardia and sudden cardiac death.\textsuperscript{11}

Although olanzapine kept our patient stable the ECG changes did not allow this treatment to continue further. The medical team were instrumental in guiding us through this. It is difficult to strike the right balance between physical and mental health but this case demonstrates that it is vital to achieve this while initiating treatment in the older adult population.

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**Declaration of interest**

No conflicts of interest were declared.

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