

# Hallucinations, prolonged QTc following fluoxetine overdose

Jemina Oremeyi Onimowo

## ABSTRACT

**Introduction:** Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) used in the treatment of depressive disorders. Cardiotoxicity and neurotoxicity have rarely been attributed to the use of fluoxetine. Several clinical studies showed that fluoxetine is less likely to cause significant cardiovascular toxicity even in overdose. Other studies showed that ingestions of 40–800 mg fluoxetine have generally produced minimal toxicity in adults. Of note, fluoxetine and ibuprofen increase toxicity of each other by pharmacodynamic synergism. **Case Report:** This is the case of widened QRS duration in a 21-year-old female with background depression. She had taken a mixed overdose of fluoxetine (600 mg), omeprazole (600 mg), ibuprofen (1200 mg), metronidazole (unclear amount). On admission she was hallucinating, profoundly agitated, tachycardic with a heart rate of 128 bpm, new broadening in QRS complex to 134 ms on electrocardiography, corrected QT (QTc) was 616 ms. Following discussion with TOXBASE, she was given 2 g magnesium sulfate, 1.4% sodium bicarbonate, admitted to high dependency unit for cardiac monitoring. She also needed sedation. **Conclusion:** This case is interesting from the point of view of broad

complex tachycardia that could result in cardiac arrest due to a prolonged QTc of 616 ms, as well as the visual and auditory hallucinations the patient had. It also raised the question of possibility of pharmacodynamic drug-drug interaction in which ibuprofen could have via synergism, potentiated the cardiotoxic effects of an otherwise generally safe SSRI; fluoxetine.

**Keywords:** Complex drug-drug interactions, ECG abnormalities, Fluoxetine overdose, Hallucinations, Prolonged QTc, SSRI overdose

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## INTRODUCTION

Fluoxetine has been approved by the Food and Drug Administration (FDA) for the treatment of depression, obsessive compulsive disorder, premenstrual dysphoric disorder and other mood disorders [1, 2]. The mechanism of action is by blocking serotonin reuptake and increasing serotonin stimulation of somatodendritic 5-HT<sub>1A</sub> and terminal autoreceptors [3, 4]. Fluoxetine is considered minimally toxic in overdose especially when compared to tricyclic antidepressants [4]. In spite of this, there have been rare descriptions of severe complications and even fatalities with doses in excess of 75 times prescription dose or as a mixed overdose [4, 5].

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A case of hallucinations and cardiac conduction abnormalities in a young lady resulting from fluoxetine over dose is described here. Researching into the side effect and pharmacodynamic profile of fluoxetine, ibuprofen, metronidazole, mebeverine and omeprazole which were co-ingested at the time, show that symptoms described in this case, have been documented as possible but very rare adverse effect in the high dose of fluoxetine [2]. There is the possibility that several complex drug-drug interactions could have contributed to the potentiation of its toxicity profile [5, 6]. Fluoxetine is a potent enzyme inhibitor, and significantly affects CYP2D6, CYP3A4 and CYP2C19 activity in vitro [6]. These enzymes are required for the metabolism of most drugs including ibuprofen, omeprazole and fluoxetine itself. An inhibitory effect will account for the persistence of these medications in the system. Ibuprofen is also capable of inhibiting CYP2C9/10 enzyme activity thereby further potentiating fluoxetine's activity as well [6, 7].

**CASE REPORT**

A 21-year-old female was presented to emergency department (resuscitation room) with background depression and asthma. Brought in by ambulance, she had presented with hallucinations and profound agitation following intentional mixed overdose of 600 mg fluoxetine, 600 mg omeprazole and unknown quantities of metronidazole, mebeverine and ibuprofen. There was no history of psychosis or congenital cardiac abnormalities. She had no known drug allergies.

On examination airway was self-maintained and patent, with spontaneous ventilation saturating 100% on room air, tachypnoeic with a respiratory rate of 20 cycles per minute. Peripheries were warm, well perfused and capillary refill time was less than two seconds with a heart rate of 135 bpm, blood pressure 132/48 mmHg and 12-lead ECG (find attached) showed tachycardia, prolonged QTc at 616 ms and wide QRS complex of 134 ms. She was confused and was having visual and auditory hallucinations with a GCS of 14/15. Temperature was 36.5° C and blood sugar 4.9 mmol/L. There was no evidence of muscle rigidity or hyperreflexia and nothing of significance was found on exposure.

Blood tests (laboratory and bedside venous blood samples (Table 1 and Table 2 ) where sent off and results did not show any significant abnormality. 12-lead electrocardiograms (Figures 1–3) were done and she was subsequently placed on cardiac monitoring.

TOXBASE was contacted via telephone and 2 g magnesium sulphate in view of the significant QTc of 616 ms and polymorphic ventricular tachycardia of 135 bpm, 500 ml of 1.4% sodium bicarbonate for the QRS prolongation at 134 ms were given as advised.

After she had been stabilized in the emergency department, she was transferred to the high dependency unit for cardiac monitoring and close observation. Thirty-

Table 1: Venous blood gas results and normal ranges

	Patient	Normal range
pH	7.421	7.350–7.450
PCO <sub>2</sub>	5.44 kPa	<6kPa
PO <sub>2</sub>	4.99 kPa	>8kPa
HCO <sub>3</sub> <sup>-</sup>	25.3 mmol/L	22–29
Base	1.0 mmol/L	-2.0–2.0
Na	145 mmol/L	133–146
K	3.4 mmol/L	3.5–5.3
Ca	1.15 mmol/L	1.13–1.32
Glucose	4.5 mmol/L	3.8–11
Lactate	2.1 mmol/L	0.6–2.5
Haemoglobin	157 g/L	115–170

Table 2: Laboratory biochemical results and normal ranges

	Patient	Normal range
Sodium	141 mmol/L	133–146
Potassium	3.8 mmol/L	3.5–5.3
Urea	2.8 mmol/L	2.5–6.2
Creatinine	58 umol/L	95–108
CCalcium	2.28 mmol/L	2.2–2.6
Phosphate	1.2 mmol/L	0.8–1.5
Magnesium	1.07 mmol/L	0.7–1.0
Paracetamol	<5 mg/L	<5
eGFR	> 90	>90

Liver function tests within normal range

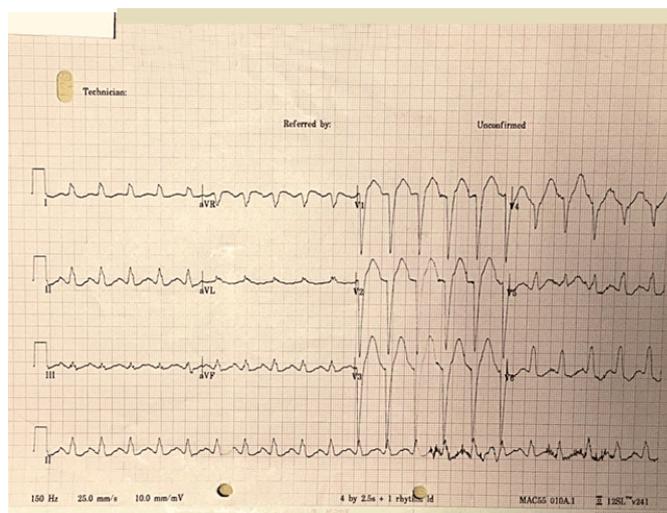


Figure 1: Electrocardiography post overdose showing prolongation of Qtc to 616 ms.

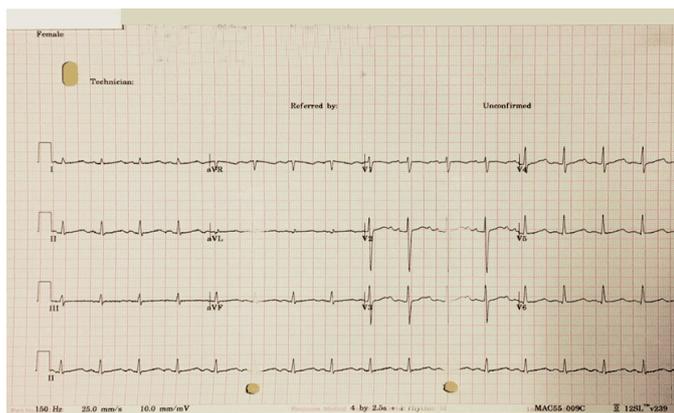


Figure 2: Electrocardiography post magnesium and sodium bicarbonate showing improvement of QTc and QRS complexes.

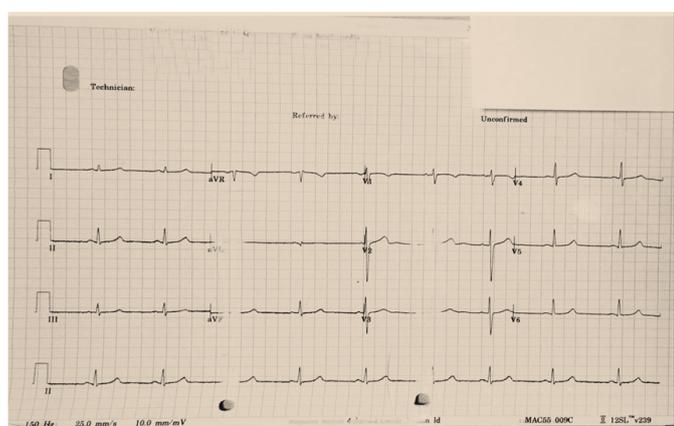


Figure 3: Electrocardiography 12 hours post intervention showing resolution of conduction abnormality.

six hours following this ordeal, both cardiac abnormalities and hallucinations had completely resolved. She was declared medically fit and subsequently reviewed and discharged by the mental health team, with outpatient follow-up.

## DISCUSSION

Searching through the databases, there is noticeably limited information available on the neurotoxic and cardiotoxic effects of fluoxetine. Those available do not associate it with any sinister effects even in overdose and in fact portray it as considerably benign [1, 10, 11]. None of the other medications co-ingested (ibuprofen, omeprazole, mebeverine, and metronidazole) could completely explain the conduction abnormalities, severe agitation as well as hallucinations in this case [1, 2, 8]. The side effects of ibuprofen rash, renal damage, headaches and hearing disturbances and increased risk of thrombotic events. Mebeverine was associated with rash, angioedema and allergic reactions. Metronidazole could cause peripheral neuropathy, pancreatitis and

seizures. Apart from ibuprofen common adverse effect profile did not include any form of cardiotoxicity [7, 8]. With omeprazole nausea, vomiting abdominal pain were features of its common side effects and in chronic use could result in dyselectrolytemia of which hypomagnesemia could potentially be of cardiac significance but is invariably quite rare [8].

On reviewing the report on 234 cases of fluoxetine overdose; tachycardia, drowsiness, tremor, vomiting and nausea were the most common side effects seen [9]. In a separate review of fluoxetine intentional overdose, by Pope and Zarea in 2016, none of the patients had any cardiac conduction abnormality on ECG [10]. A study of the toxicity profile of five SSRIs, noted that citalopram was responsible for over 68% of prolonged QTc and the conclusion was that the rest of the SSRIs, fluoxetine inclusive remained relatively safe in overdose [11].

In our index case, we noted that within six hours of ingestion of 600 mg of fluoxetine (on presentation) she had visual hallucinations and remained highly agitated with a GCS of 14/15. She was not known to have any previous episodes of delusions or hallucinations.

Conduction abnormalities related to fluoxetine, result from prolongation of repolarization the resulting long QT syndrome. This is brought about by blockade of hERG K<sup>+</sup> channel as well as disruption of protein channel trafficking [12].

Unlike in this case being discussed, reports of CNS and cardiac toxicity occurring together following fluoxetine overdose have rarely ever been described in literature. There is evidence in support of fluoxetine neurotoxicity with resultant generalized tonic clonic seizure and in another study the patient developed acute psychosis [13, 14].

The dramatic prolongation of her QTc and the clinical significance of this potentially leading to torsade de Pointes in this patient begs the question as to whether or not fluoxetine in itself is capable of this degree of cardiotoxicity, or whether there was some additive effect by some of the other medications she had ingested at the time. Of all the other drugs co-ingested, ibuprofen has a cardiac toxicity profile in its own right. It is a non-steroidal anti-inflammatory drug mediating its analgesic properties by inhibition of cyclooxygenase 2 [7, 8, 16] The results of an observational study by Pratt et al., showed that ingestion ibuprofen increased the chances of developing cardiac arrhythmias [15]. Multiple cases of ibuprofen overdose have reported narrow complex tachycardias [16, 17], and although in this report symptoms were of a polymorphic ventricular tachycardia, it is plausible that this nonsteroidal anti-inflammatory drugs (NSAIDs) characteristic of causing cardiac abnormalities could have potentiated the symptoms of adverse cardiotoxicity described here.

Investigating the drug-drug interactions show that fluoxetine and ibuprofen exhibit some pharmacosynergism of which both potentiate the activity of the other. Several studies denote that in the presence of

fluoxetine, NSAIDS are likely to increase the risk of upper gastrointestinal tract bleeding. But there is little documented research on ibuprofen in turn potentiating the toxic profile of Fluoxetine.

## CONCLUSION

This is a case of hallucinations, widened QRS and prolongation of QTc in a young female following a mixed drug overdose, primarily of fluoxetine. There is evidence of complex drug-drug interaction between the commonly prescribed antidepressant; fluoxetine and the easily available over the counter NSAID; ibuprofen which could be deleterious in situations of overdose and requires further research. Review of the ease of their accessibility and monitoring in combined use is of grave importance.

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## Author Contributions

Jemina Oremeyi Onimowo – Substantial contributions to conception and design, Drafting the article, Final approval of the version to be published

## Guarantor of Submission

The corresponding author is the guarantor of submission.

## Source of Support

None

## Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

## Conflict of Interest

Author declares no conflict of interest.

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