

# Olanzapine-induced acute necrotising pancreatitis leading to recurrent multiple organ dysfunction syndrome

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## SUMMARY

A married mother in her 50s acutely developed vomiting, diarrhoea and severe epigastric pain 2 weeks following discharge from an acute psychiatric inpatient unit. She presented to the emergency department complaining of a 2-day history of the above symptoms. Blood tests revealed neutrophilia, grossly raised inflammatory markers and amylase levels triple the normal range. Based on radiological investigations, she was treated for necrotising pancreatitis that quickly escalated to multi-system organ failure and a lengthy intensive care unit admission. Common causes of pancreatitis, including cholelithiasis, alcohol and other drugs, were ruled out. Despite this, she suffered recurrent episodes of pancreatitis with significant morbidity. Olanzapine, started during her psychiatric admission, was determined to be the offending agent. Two years following the discontinuation of olanzapine, the patient has had no further episodes of acute pancreatitis.

## BACKGROUND

Olanzapine has been observed and documented to be associated with acute pancreatitis.<sup>1–10</sup> The likelihood of adverse events due to olanzapine is possible on average according to the Naranjo Scale (a validated adverse drug event rating scale).<sup>11</sup> The likely mechanism of action is acute hypertriglyceridaemia.<sup>2–4 6–8</sup> The authors would like to present a case of olanzapine-induced acute pancreatitis with an aim to inform our practice: patients commencing olanzapine treatment should have triglycerides measured before treatment and monitored throughout its course. This case aims to emphasise that clinicians should be suspicious of olanzapine-induced pancreatitis when other causes are ruled out.

## CASE HISTORY

A married mother of two adult children in her 50s was referred by her general practitioner for an acute psychiatric assessment following a 2-day history of agitation, paranoia and delusions of persecution. She presented with a 2-week history of

reduced appetite and insomnia, as well as an acute disturbance in her concentration and mood. The patient had no previous psychiatric history. She was diagnosed with an acute schizophrenia-like psychotic disorder (International Classification of Disease, 10th revision (ICD-10) code of F23.2) and voluntarily admitted to the acute mental health unit where she was prescribed olanzapine 10 mg/night. She remained an inpatient for a total of 20 days. During this time, baseline blood investigations including a complete blood count, renal profile, liver profile and fasting lipid profile were reported as within normal limits. She was discharged on olanzapine 10 mg/night and sertraline 100 mg/day. Community follow-up was arranged.

Two weeks following discharge from the acute mental health unit, the patient presented to the emergency department with a 2-day history of vomiting, diarrhoea and severe epigastric pain. Her medical/surgical history was unremarkable, and her only prescribed medications were those prescribed on discharge 2 weeks earlier. Collateral history from family confirmed compliance with prescribed medication with no evidence of overdose. The patient's mental state was unchanged from psychiatric discharge, and there was no evidence of acute mental illness. On examination, the patient was tachycardic with a heart rate of 135 beats per minute, hypotensive with a blood pressure of 92/68 mmHg and febrile with a temperature of 38.6°C. Abdominal examination revealed tenderness in the epigastrium with rebound tenderness. Cardiorespiratory examination did not reveal any abnormalities. Examination of the central and peripheral nervous system was grossly intact. Initial blood tests revealed amylase of 763 U/L (reference range 40–140 U/L), C reactive protein >320 mg/L (reference range 0–5 mg/L), white blood cells  $34 \times 10^9$ /L (reference range  $4 \times 10^9$ – $10 \times 10^9$ /L), neutrophils  $31.2 \times 10^9$ /L (reference range  $2 \times 10^9$ – $7.5 \times 10^9$ /L)



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and triglycerides of 414mg/dL (reference range <150mg/dL). The patient was treated for severe sepsis, and computed tomography (CT) of the abdomen and pelvis revealed acute necrotising pancreatitis of the head and neck. The patient quickly deteriorated into multi-system organ failure, including acute renal failure requiring haemodialysis, acute respiratory syndrome requiring intubation and ventilation, and portal vein thrombosis. She remained in intensive care for 30 days receiving supportive treatment. She made a full recovery and was discharged home with regular medications unchanged from admission.

Less than a month after discharge, the patient was readmitted to intensive care unresponsive secondary to recurrent pancreatitis and *Clostridium difficile* infection, encephalopathy and disseminated intravascular coagulation leading to haemorrhagic shock. Again, there was no evidence of acute relapse of psychosis. Collateral history reported compliance with medications including olanzapine 10mg/night. She spent two more months in intensive care but again made a full recovery.

One month post-discharge from the second intensive care unit admission, the patient again presented to the emergency department with a radiographic confirmed acute pancreatitis complicated by bowel ischaemia requiring resection and ileostomy. The following 8-month hospitalisation—spent between intensive care and the general surgical ward—was complicated by a hospital-acquired infection, but the patient again ultimately made a full recovery. In addition, she required extensive multidisciplinary rehabilitation to improve her mobility and function in activities of daily living, which continued after discharge to her home. The patient was seen by liaison psychiatry during her surgical admission. They recommended a change in her antipsychotic therapy due to the risk of olanzapine-induced pancreatitis. The patient was given a trial of aripiprazole 10mg/day and then continued on that medication. She has had no further episodes of pancreatitis. Her mental health has remained stable without relapse, and she is engaging well with her community mental health team.

## INVESTIGATIONS

Results discussed in the above case history are included below.

### Imaging on the first medical presentation to emergency department

CT abdomen and pelvis on first medical presentation: acute pancreatitis with parenchymal necrosis of head and neck. No acute peripancreatic collections. Cholelithiasis.

Magnetic resonance cholangiopancreatography (MRCP): haemorrhagic exudative peripancreatic phlegmon with acute necrotic pancreatitis. No acute

peripancreatic collection. Cholelithiasis but no MRCP evidence of choledocholithiasis.

### Imaging on the second medical presentation to emergency department

CT abdomen and pelvis: the body and the tail of the pancreas appear viable. The head, neck and uncinate processes of the pancreas are necrosed. Calcified stones are present in the gallbladder. No biliary or pancreatic ductal dilation.

### Imaging on the third medical presentation to emergency department

CT abdomen and pelvis: necrosis of head, body and neck of the pancreas. Gallstones, no CT features of cholecystitis or biliary obstruction.

MRCP: uncomplicated gallstones. No bile duct calculi.

## DIFFERENTIAL DIAGNOSIS

The primary diagnosis for the above case is olanzapine-induced acute necrotising pancreatitis.

Common causes of pancreatitis were investigated and excluded in each presentation, including alcohol, drugs and biliary obstruction. In this case, the patient had no further episodes of pancreatitis once she transitioned to alternative antipsychotics, providing additional evidence that olanzapine was the offending agent.

## OUTCOME AND FOLLOW-UP

The patient fully recovered following her third hospital admission with acute pancreatitis. The surgical team worked with her community mental health team to initiate treatment with an alternative antipsychotic, aripiprazole 10mg/day. The patient has not had any further episodes of pancreatitis since the medication switch. Her mental state has remained stable without relapse.

## DISCUSSION

Acute pancreatitis has been documented to be a possible adverse drug reaction of olanzapine. A literature review was conducted to collate published articles addressing this question.

The authors searched PubMed with Boolean terms: 'acute OR necrotising' AND 'pancreatitis' AND 'olanzapine'. Results of the search produced 26 full-text articles. One paper was duplicated, 2 did not have English translations and 13 were irrelevant to the literature review question. In total, 10 articles published between 1999 and 2018 were identified: 8 case reports and 2 case series. Demographics varied widely among described patients: aged 22–72 years and 75% male.

Please see [table 1](#) for a summary of documented cases of olanzapine-induced pancreatitis. There were multiple indications for olanzapine treatment, including bipolar disorder, schizophrenia, schizoaffective disorder, cognitive impairment and

**Table 1** Summary of olanzapine-induced pancreatitis cases included in the literature review

Study	Sex	Age	Diagnosis	Olanzapine dose	Duration of olanzapine treatment	Alcohol	Triglyceride level (mg/dL, reference range <150)	Outcome (once olanzapine discontinued)
Baysal <i>et al</i> <sup>1</sup>	M	44	Schizophrenia	10 mg/day	3 weeks	None	–	Full recovery
Waage <i>et al</i> <sup>2</sup>	M	42	Paranoid psychosis	10 mg/day	19 months	None	415	Full recovery
Bracamonte <i>et al</i> <sup>3</sup>	F	69	Bipolar disorder	10 mg/day	22 months	–	92	Full recovery
Buszek <i>et al</i> <sup>4</sup>	M	36	Bipolar disorder	20 mg/day	6 weeks	None	5185	Full recovery
Kerr <i>et al</i> <sup>5</sup>	F	41	Depression	5 mg/day	3 months	None	–	Full recovery
Kerr <i>et al</i> <sup>5</sup>	M	18	Bipolar disorder	10 mg/day	2 years	Occasional	–	Full recovery
Kerr <i>et al</i> <sup>5</sup>	M	52	Schizoaffective disorder	20 mg/day	1 year	Occasional	–	Full recovery
Samanta <i>et al</i> <sup>6</sup>	M	32	Bipolar disorder	10 mg/day	2 months	None	560	Full recovery
Vaidyanathan <i>et al</i> <sup>7</sup>	M	25	Paranoid schizophrenia	15 mg/day	14 days	None	163	Full recovery
Rossor <i>et al</i> <sup>8</sup>	M	36	Schizoaffective disorder	10 mg/day	6 weeks	–	1899	Full recovery
Doucette <i>et al</i> <sup>9</sup>	F	72	Cognitive decline	5 mg/day	6 days	–	–	Fatal

neuropsychiatric symptoms of multiple sclerosis. Duration of treatment with olanzapine varied from 6 weeks to 2 years, with doses ranging from 5 to 20 mg/day in both tablet and oral dispersible administration form. Clinicians in all cases were confident in ruling out any confounders of acute pancreatitis, in particular alcohol, gallstones and other drugs. The majority of the cases made use of radiological investigation to rule out cholelithiasis<sup>1–8</sup> (one exception was a patient with a previous history of cholecystectomy within the decade prior to presentation<sup>9</sup>). In addition, a concurrent accidental verapamil overdose may have confounded one case, but the authors proposed that olanzapine was the causative agent.<sup>9</sup>

Hypertriglyceridaemia was the most common proposed cause of olanzapine-induced acute pancreatitis. Seven cases measured and documented acute hypertriglyceridaemia in the context of olanzapine use.<sup>4–8</sup> Plasmapheresis was required and integral to recovery in one patient with a profoundly raised triglyceride level.<sup>4</sup> Authors from gastroenterology recommended that patients be screened and treated for hypertriglyceridaemia prior to starting treatment with olanzapine.<sup>5</sup>

Naranjo score, a validated tool for determining the probability of adverse drug reaction,<sup>11</sup> was discussed in multiple cases. Three case reports suggest a Naranjo

score between 4 and 6 correlating to either a possible or a probable association between olanzapine and adverse reaction.<sup>3,9</sup> A larger case series of 41 cases of atypical antipsychotic-induced pancreatitis suggest a Naranjo score of 4 for olanzapine (possible adverse drug reaction) and that only 10% of cases between 1999 and 2015 have produced a score suggesting probable adverse drug reaction.<sup>10</sup>

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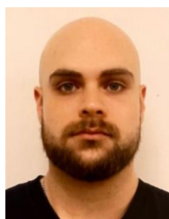
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## Learning points

- Clinicians should consider measuring serum triglycerides before commencing olanzapine treatment and then managing accordingly with appropriate agents.
- Patients on olanzapine treatment should be monitored for hypertriglyceridaemia.
- Clinicians should be suspicious of olanzapine-induced pancreatitis when common causes are ruled out.

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