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# Acute Massive Pulmonary Thromboembolism Due to Acute Intoxication by Duloxetine: A Case Report

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**Abstract** Duloxetine (Cymbalta) is a potent serotonin norepinephrine reuptake inhibitor used for the management of major depression and pain associated with diabetic peripheral neuropathy. Cymbalta delayed-release capsules contain Duloxetine HCl equivalent to 20, 30, 60 mg of Duloxetine. The ingestion of high quantities of Duloxetine may have serious outcomes such as venous thrombosis, causing cardiac respiratory arrest. The Authors outline a case report of an elderly woman, suffering from depression, found dead in her apartment. The cause of death was attributed to acute massive pulmonary thromboembolism due to acute intoxication of Duloxetine bought the day before. The thesis supported by the authors and confirmed by the data from other studies is that a massive intake of Duloxetine drug increases considerably the medication's side effects such as somnolence, dry mouth, fatigue, insomnia, dizziness, constipation, considerable increases in recumbent systolic and diastolic blood pressure, and a small decrease in heart rate.

**Keywords** Duloxetine · Antidepressant · Toxicology · Pulmonary thromboembolism · Case report

## Introduction

Duloxetine hydrochloride, sold under the brand names Cymbalta, Ariclaim, Xeristar, Yentreve, is classified as an antidepressant drug; it is a serotonin norepinephrine reuptake inhibitor (SNRI). It was created by Lilly researchers[1] and issued by the U.S. Food and Drugs Administration (FDA) in August 2004 for treatment of major depressive disorder (MDD) and in February 2007 for management of generalized anxiety disorder.

In addition, Duloxetine and other antidepressants that act via serotonergic or noradrenergic mechanisms have analgesic properties. In September 2007, the FDA approved Duloxetine for managing pain symptoms caused by peripheral neuropathy, diabetes [1], and fibromyalgia [2].

Duloxetine hydrochloride is a slightly brownish white solid, which is somewhat soluble in water. Duloxetine is available by delayed-release capsules containing enteric-coated capsules of 22.4, 33.7, or 67.3 mg equivalent to 20, 30, or 60 mg of Duloxetine hydrochloride, respectively. These enteric-coated capsules are designed to prevent the drug from degradation in the acidic stomach environment.

The recommended dosage of Duloxetine is 40–60 mg/day for depression, 60 mg/day for neuropathic pain, and 80 mg/day for stress urinary incontinence [3].

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[1] David Robertson, David Wong, a co-discoverer of fluoxetine, and Joseph Krushinski are listed as inventors on the patent application filed in 1986 and granted in 1990. The first publication on the discovery of the racemic form of duloxetine known as LY227942, was made in 1988. The (+)-enantiomer of LY227942, assigned LY248686, was chosen for further studies, because it inhibited serotonin reuptake in rat synaptosomes two times more potently than (–)-enantiomer. This molecule was subsequently named duloxetine.

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Duloxetine has an elimination half-life of about 12 h (range 8–17 h), and its pharmacokinetics are dose-proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing. When administered orally, a daily dose of Duloxetine ranging between 30 and 129 mg shows the mean steady-state serum concentration at 0.040 mg/l [5].

The dose is proportional to the plasma concentration, which averages 0.95 ng/ml, ranging from 0.38 to 1.89 ng/ml [6, 7]. Orally administered Duloxetine hydrochloride is well absorbed. There is a median 2-h lag until absorption begins, with maximal plasma concentrations of Duloxetine occurring 6 h post-dose. Food does not affect the maximal plasma concentration of Duloxetine, but delays the time to reach peak concentration from 6 to 10 h, and it marginally decreases absorption by about 10%. There is a 3-h delay in absorption and a one-third increase in apparent clearance of Duloxetine after an evening dose as compared with a morning dose. The apparent volume of distribution averages about 1,640 l. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α1-acid glycoprotein [7].

Elimination of Duloxetine involves hepatic metabolism affecting two P450 isozymes, CYP1A2 and CYP2D6 [4]. The metabolites are primarily excreted into the urine in the form of glucuronide and sulphate conjugates [4]. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism with numerous metabolites. The major biotransformation pathways for Duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP1A2 and CYP2D6 catalyse the oxidation of the naphthyl ring in vitro. Metabolites found in plasma include 4-hydroxy Duloxetine glucuronide and 5-hydroxy, 6-methoxy Duloxetine sulphate. Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged Duloxetine are present in the urine. Most (about 70%) of the dose appears in the urine as metabolites of Duloxetine; about 20% is excreted in the faces. Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to pharmacologic activity of Duloxetine [7].

The literature reports the following common side effects associated with an Duloxetine overdose: nausea, headache, dry mouth, fatigue, insomnia, dizziness, somnolence, constipation, considerable increases in recumbent systolic and diastolic blood pressure, and a small decrease in heart rate [6, 7].

A review of the annual reports of the American Association of Poison Control Centers (AAPCC) shows that there has been an increase in fatal cases in which Duloxetine has been identified: 5 cases in 2005 [8], 11 cases in 2006 [9], 14 cases in 2007 [10], 18 cases in 2008 [11], 23 cases in 2009 [12]. Unfortunately, postmortem blood levels were documented in association with only four of those cases.

Most of the poisonings are caused by 'cocktail' drugs; in a few cases the intoxications are due to only Duloxetine abuse that caused pulmonary embolism [13].

There is a paucity of published data regarding the potential postmortem threshold blood levels for Duloxetine toxicity and lethality; the only published study found was recently conducted by the Los Angles County Coroner's Office and the Lehigh Valley Medical Center [13].

These researchers hope to conduct further studies about the postmortem Duloxetine levels in blood and particularly research into fatal cases where only Duloxetine is involved [13].

## Case Report

In June 2010, paramedics were called by the victim's acquaintance to the apartment of a 75-years-old white woman who was unresponsive.

The woman suffered major depression for approximately 1 year caused by the death of her son; she was undergoing treatment with a psychiatrist who prescribed psychotropic drugs. The woman was found lying supine on the bed next to a hand-written suicide note.

Antidepressant drugs found in the rubbish bin in the kitchen included:

- 1 Rivotril bottle, oral drops (clonazepam 25 mg/ml)
- 1 Cymbalta[2] blister containing 4 capsules (Duloxetine 60 mg), bought the day before (1 Cymbalta blister

[2] The efficacy of Cymbalta as a treatment for depression was established in 4 randomized, double-blind, placebo-controlled, fixed-dose studies in adult outpatients (18–83 years), meeting DSMIV criteria for major depression. In 2 studies, patients were randomized to Cymbalta 60 mg once daily ($N = 123$ and $N = 128$, respectively) or placebo ($N = 122$ and $N = 139$, respectively) for 9 weeks; in the third study, patients were randomized to Cymbalta 20 or 40 mg twice daily ($N = 89$) for 8 weeks; in the fourth study, patients were randomized to Cymbalta 40 or 60 mg twice daily ($N = 95$ and $N = 93$, respectively) or placebo ($N = 93$) for 8 weeks. There is not evidence that doses greater than 60 mg/day confer additional benefits. In all 4 studies, Cymbalta demonstrated superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAMD17) total score. In all of these clinical studies, analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics. In another study, 533 patients meeting DSMIV criteria for MDD received Cymbalta 60 mg once daily during an initial 12-week open-label treatment phase. Two hundred and seventy-eight patients who responded to open-label treatment (defined as meeting the following criteria at weeks 10 and 12: a HAMD17 total score ≤9, Clinical Global Impressions of

contains 28 capsules, meaning the woman ingested 24 capsules)
- 1 empty Triptich bottle (trazodone 25 mg/ml)
- 1 Mirtazepine blister containing 1 capsule (30 mg/capsule)

The doctor on the scene pronounced the cause of death as cardiac respiratory arrest possibly as a result of an overdose of her prescribed medication.

The postmortem examination was performed 1 day after death, and the cause of death was attributed to acute massive pulmonary thromboembolism due to acute intoxication by Duloxetine. Nothing in the patient's history was suggestive of a genetic predisposition to pulmonary embolism.

Furthermore, the patient was not alcoholic, and this is important because the alcoholism potentiates the Duloxetine toxicity.

Systematic chemical–toxicological analyses were performed on the blood, urine, bile, liver, and brain samples to investigate the presence of drug overdose found in the apartment that could justify the cardiac respiratory arrest death.

A peripheral blood sample was collected in a vial containing sodium fluoride. All other autopsy specimens were stored without preservative.

Solid tissues were homogenized within their own fluid or at 1:1 dilution (w/v) with distilled water. All biological specimens were refrigerated at 4°C.

Postmortem specimens were submitted for toxicology testing.

The presence of alcohol and toxic volatile or gaseous molecules in the peripheral blood samples were performed by headspace GCFID (flame ionization detection): there was no presence of alcohol in the blood; urine samples were screened by enzyme immunoassay (EMIT) to find traces of drug abuse from amphetamines and/or derivatives, methadone, cannabinoids, barbiturates, cocaine, opiates.

Quantification of basic drug levels in the organs and biological fluids was performed by GCMS (GC mass spectrophotometry) following liquid–liquid back extraction. Basic drugs were initially qualitatively detected on routine drug screening using GCNPD (gas chromatography with nitrogen–phosphorous detection) and GCMS. With positive screening, quantisation was undertaken using GCMS with a detection limit of 30 ng/ml.

Mirtazapine, Citalopram, and Duloxetine were identified in a basic drug screen. The presence of benzodiazepines molecules has not found in significant amounts.

The drug distribution into the tissues is summarized in Table 1.

**Table 1** Postmortem tissues distribution (ng/ml)

| | Mirtazapine | Citalopram | Duloxetine |
|---|---|---|---|
| Liver | 225 | 555 | 14,196 |
| Brain | 54 | 63 | 1,931 |
| Femoral blood | 31 | 59 | 1,209 |
| Urine | 960 | 559 | 1,496 |
| Bile | 2,246 | 345 | 16,385 |

## Discussion

Positive chemical–toxicological analyses conducted on biological samples of the deceased identified some of the drugs found in the apartment. The following antidepressant substances were detected in the organs and biological fluids: Mirtazapine, Citalopram, and Duloxetine.

Mirtazapine was detected in the blood at a concentration of 31 ng/ml; this concurs with the literature review as appropriate in subjects who have taken the drug in therapeutic doses [7, 14, 15].

The same considerations must be made regarding the hematic concentration of Citalopram found in the blood measuring (59 ng/ml). This concentration is also in accordance with the literature data, which indicates that an intake of a single drug tablet contains a concentration of Citalopram ranging from 42 to 52 ng/ml [7, 14, 15].

In continued consumption, Citalopram presents an average level in blood concentration of 79 ng/ml [16–18].

The data concerning to Duloxetina concentration in the patient's blood, showed a supra-therapeutic intake of this drug (1,209 ng/ml). The cause of death proclaimed by the coroner was due to acute intoxication by Duloxetine; he stated, 'It is more likely than not that she took too much of her antidepressant medication Duloxetine…'.

The literature shows the concentrations measured, which would mean the ingestion of the active principle ranging from 1,322 to 1,440 ng/ml (22–24 tablets of drug) [5, 19, 20].

In their studies, Anderson et al. [13] claim that the postmortem blood concentrations associated with the consumption of therapeutic doses of Duloxetine (60 mg/daily) are between 0.02 and 0.11 ng/ml. Only in case of

Footnote 2 continued
Severity ≤2, and not meeting the DSMIV criteria for MDD) were randomly assigned to continuation of Cymbalta at the same dose ($N = 136$) or to placebo ($N = 142$) for 6 months. Patients on Cymbalta experienced a statistically significant longer time to relapse of depression than did patients on placebo. Relapse was defined as an increase in yhe CGIS score of ≥2 points compared with that obtained at week 12, as well as meeting the DSMIV criteria for MDD at 2 consecutive visits at least 2 weeks apart, where the 2-week temporal criterion had to be satisfied at only the second visit.

descriptions of lethal intoxication by Duloxetine, postmortem blood concentrations measured between ND (not detected) and 0.59 ng/ml ($N = 12$); 9 out of 12 cases showed major postmortem blood concentrations than the normal therapeutic levels mentioned before.

In the case report, the supra-therapeutic doses confirmed by the massive blood concentrations observed could justify that somnolence, a reported side effect of Duloxetine, culminated a stupor that made the woman unconscious and unresponsive for an extended period. It should also be noted that the effect of drowsiness leading to immobilization is amplified in patients with more than 60 years who have already slowed motor movements. The patient was 75 years old and slowed motor movements due to age, so the immobilization due to Duloxetine was amplified considering the huge quantitative swallowed.

This situation produced, pronounced by the coroner, an acute massive pulmonary thromboembolism and may have been the cause of death. Forensic analysis of the woman's body indicated that the pulmonary thromboembolism occurred about 8 h after the onset of immobility. Premarketing Cymbalta clinical studies looking into MDD, using a sample population of subjects aged 65 years and above, showed that usage is associated with cases of clinically significant hyponatremia, leading to possible extreme consequences such as lethargy, decreased consciousness, and venous thrombosis [5, 7, 16].

The cause of venous thromboembolism is multifactorial, and several hypotheses have been proposed explaining the association between venous thromboembolism and psychotropic drugs. The use of these drugs might predispose to the possibility of venous thrombosis because of side effects such as sedation and immobilisation [21–23]. Specifically, three factors favour venous thrombogenesis: damage to the vessel wall; stasis or slowing blood flow; and abnormalities of coagulation, all of which are identified as possible side effects from Duloxetine [21–23].

Several studies of Duloxetine [24–26] suggest that at levels >700 ng/ml, this antidepressant drug may potentially contribute to the lethal pharmacodynamic substrate and precipitate a fatal outcome.

A significant study conducted by Rosendal [27] and Motykie [28] examines the cause of death on subjects at 18- and 65-years-old who use antidepressants like Duloxetine compared with subjects of the same age range who are nonusers of antidepressants. The study proved a strong correlation between users of Duloxetine and death from pulmonary embolism [27]. The researches conducted by Eli Lilly on elderly patients in order to market the Cymbalta show that comparing the users of antidepressants with nonusers, the risk of pulmonary embolism increases in proportion to age among those who use antidepressants, reaching a peak in the age range between 58- and 65-years-old [3].

The association between pulmonary embolism and antidepressant use is further supported by a higher proportion of venous thromboembolism among young users compared with young nonusers of antidepressants [27].

The statements made in the literature review and the toxicological results obtained affirm that the sedative effect of Duloxetine contributed to venous stasis, which caused a pulmonary thromboembolism in the patient [3, 6, 9].

However, the biological mechanism explaining the relationship between Duloxetine and venous thrombosis is unknown; further investigations are necessary to gain a better understanding of the drug and its potential role in causing deaths.

## Conclusions

Duloxetine is a relatively new antidepressant medication. This report provides case details where Duloxetine was found at a supra-therapeutic concentration, indicating the possibility that a greater dose than prescribed was taken. The toxicological results, the Coroner's statement, the data obtained, and the literature review all confirm that venous thrombosis would appear to be associated with the use of antidepressant drugs like Duloxetine, in psychiatric patients. More specifically, the thesis supported by the authors would appear to be corroborated: a massive intake of Duloxetine drug can increase considerably the medication's side effects of sedation and immobilisation causing a venous thrombosis. Considering possible increases in the prevalence of Duloxetine prescriptions, further investigations are required to gain a better understanding of the postmortem behaviour of this drug and its potential role in causing death.

The authors, aware that important information pertinent to the development of thromboembolism is not known in this patient, believe that the value of this article is not so much in proving any causal link between thromboembolism and Cymbalta (Duloxetine), but in reinforcing the need for awareness of the possibility of thromboembolism complicating overdose with Duloxetine.

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