

# **Vortioxetine overdose in a suicidal attempt** A case report

Mario Gennaro Mazza, MD<sup>a,\*</sup>, Aurora Rossetti, MD<sup>a</sup>, Eugenia Rossana Botti, MD<sup>b</sup>, Massimo Clerici, MD, PhD<sup>a</sup>

# Abstract

**Rationale:** Vortioxetine is a new multimodal antidepressant approved by the Food and Drug Administration for the treatment of Major Depressive Disorder and recently introduced in Europe. While antidepressant properties of vortioxetine and its tolerability have been demonstrated by preclinical and clinical studies data on the safety of vortioxetine after overdose are still lacking.

Patient concerns: A 50-year-old Caucasian man presenting a severe depressive episode that in a suicide attempt he took vortioxetine at 250 mg.

Diagnoses: Suicide attempt by vortioxetine in a patient affected by Major Depressive Disorder.

**Interventions:** General evaluations and gastric lavage with 2 L of water plus 50 g of activated charcoal was performed. After 12 hours of clinical stability, the patient was discharged from the emergency department and considering the suicidal ideation he was admitted to the inpatients psychiatric department.

**Outcomes:** After vortioxetine overdose the patient displayed no clinical signs or symptoms resulting from the exposure suggesting a good safety in overdose.

**Lesson:** Overdose safety of different antidepressant drugs is a matter of great considering that overdose in individuals affected by Major Depressive Disorder frequently involves prescribed antidepressants. Previous studies showed wide variation in the relative toxicity of different antidepressant drugs with higher toxicity for tricyclic antidepressants, followed by venlafaxine bupropion and mirtazapine and lower for selective serotonin reuptake inhibitors. By now there is limited clinical trial experience regarding human overdose with vortioxetine and the maximum single dose tested was 75 mg in men associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing. Even if there is still limited available evidence and further investigation is needed to better understand the potential risk of vortioxetine overdose; from our case, it seems that vortioxetine overdose at 250 mg (12 times the common daily dose) showed no signs or symptoms resulting from the exposure suggesting a good safety in overdose.

**Abbreviations:** 5-HT = serotonin, DSM-5 = Statistical Manual of Mental Disorders-5, ECG = electrocardiogram, GGT = gamma-glutamyl transpeptidase, MDD = major depressive disorder, SNRI = serotonin–norepinephrine reuptake inhibitor.

Keywords: antidepressant, case report, major depressive disorder, overdose, suicide attempt, vortioxetine

## 1. Introduction

Vortioxetine is a new multimodal antidepressant approved by the Food and Drug Administration for the treatment of Major Depressive Disorder (MDD) and recently introduced in Europe.

In addition to blocking the traditional serotonin (5-HT) transporter, vortioxetine is also an antagonist at 5-HT3A, 5-HT7, and 5-HT1D receptors; is a partial agonist at 5-HT1B receptors and a full agonist at 5-HT1A receptors.<sup>[1-3]</sup> Vortioxetine has a bioavailability of 75% with a mean T-max of 7 hours

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Received: 22 February 2018 / Accepted: 26 April 2018 http://dx.doi.org/10.1097/MD.000000000010788 and mean T1/2 of 66 hours meaning a low risk of discontinuation syndrome. The rate of binding of vortioxetine to plasma protein is 96%; vortioxetine is metabolized by P450 enzymes (especially CYP2D6) with no significant induction or inhibition of P450 and no pharmacologically inactive metabolites.<sup>[2,3]</sup> Antidepressant properties of vortioxetine have been demonstrated by preclinical and clinical studies. Vortioxetine is more effective than placebo in terms of response, remission, and depressive symptoms; when compared with serotonin-norepinephrine reuptake inhibitor (SNRI), there is no advantage or disadvantage for vortioxetine.<sup>[4,5]</sup> A series of short-and long-term studies confirmed the efficacy and safety of vortioxetine in patients with MDD, especially it was found that treatment-emergent sexual dysfunction was not significantly different between vortioxetine and placebo and sleep-related symptoms were low and not doserelated. The main adverse effect of vortioxetine is nausea and vomiting.<sup>[6-10]</sup> Data on the safety of vortioxetine after overdose are still lacking. Here, we report the case of a suicide attempt by vortioxetine overdose committed by a patient affected by MDD.

# 2. Case presentation

A 50-year-old white man outpatient diagnosed as MDD according to Statistical Manual of Mental Disorders-5 criteria (DSM-5). From October 2013, the patient has treated with

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amisulpride 50 mg 1/2 tablet per day and trazodone 150 mg 1 tablet per day. Starting from August 2016, because of a partial efficacy of pharmacological therapy, trazodone was suspended and was introduced vortioxetine 10 mg 1 tablet per day and clonazepam 2 mg per die. This therapy was well tolerated without any adverse reactions. The patient had a previous history of substance use disorder (heroin dependence from 14 to 24 years; cocaine dependence from 31 to 33 years) and a previous history of alcohol use disorder (from 14 to 31 years). He was also diagnosed with hepatitis C when he was 31-year-old and immediately treated with a rapid virological response, in general, good physical health (body height of 180 cm; body weight of 70 kg; body mass index of 22).

At 6:00 AM of June 13, 2017 the patient took about 250 mg of vortioxetine (50 tablets of 5 mg) and approximately 10 mg of clonazepam in a suicide attempt.

At 10:50 AM he presented himself at the emergency department, he was conscious and able to walk. Glasgow Coma Scale score was 15. There was no neck stiffness. Cranial nerves were intact. Muscle power and tendon reflexes were normal. Sensations were intact. He denied any incontinence or biting his tongue. No signs or symptoms of serotonin syndromes were observed. Hearts, lungs, and abdomen showed no abnormalities at physical examination. No abuse of alcohol or other drugs was reported by the patient and it was confirmed by urine drug test. The vital signs were within the normal ranges (Table 1).

At energency department (bit all signs Blood pressure, nm Hg         At psychiatric ward discharge (24 after ingestion)         At psychiatric ward discharge (24 after ingestion)           Blood pressure, nm Hg         110/65         105/65         110/70           Pulse rate (beats per minute)         70         72         65           Saturation of profiberal oxygen, %         98         98         99%           Respiratory rate (breats per minute)         12         13         12           Temperature, °C         36.5.5         36.6         36.8           Bodod cell count, Minmc         4.61         4.75         4.85           Hemoglobin, gdL         15.7         16.5         16.6           Withe blood cell count, Minmc         6.0         7.3         6.8           Patted scell count, Kinmc         2.45         2.77         Normal (07.4           Number blood cell count, %         59         59         50           Basophyle count, %         59         50         50           Storing function frag fu	Vital signs, ECG, and laboratory findings during the observation period after vortioxetine overdose.				
Vital signs         Filte and pressure, nm Hg         110/70         105/65         110/70           Blod pressure, nm Hg         10         70         72         65           Saturation of peripheral oxygen, %         98         98         99%           Respiratory rate breaks per minute)         12         13         12           Temperature, °C         36.5         36.6         96.8           Electrocardogram         Normal (0Tc 413)         Normal (0Tc 420)         12           Laboratory findings         Interview         16.5         16.8           Red blood cell count, Mmmc         4.61         4.75         4.85           Henogobin, g/dL         15.7         16.5         16.8           White blood cell count, K/mmc         6.0         7.3         6.8           Platets cell count, K/mmc         245         278         323           Lymphocytic count, %         0         0         0           Desinophytic count, %         0         0         0           Prothrombin time, (NR)         1.09         Activated cotting time (NR)         1.09           Activated cotting time (NR)         1.02         -         -           Prothrombin time, (NR)         1.09         2.30 <th>Type of analysis</th> <th>At emergency department (5h after ingestion)</th> <th>At psychiatric ward admission (24 h after ingestion)</th> <th>At psychiatric ward discharge (7 d after ingestion)</th>	Type of analysis	At emergency department (5h after ingestion)	At psychiatric ward admission (24 h after ingestion)	At psychiatric ward discharge (7 d after ingestion)	
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Respiratory rate (breaths per minute)         12         13         12           Temperature, "C         36.5         36.6         36.8           Electrocardiogram         Normal (OTc 413)         Normal (OTc 420)           Red blood cell count, K/mmc         4.61         4.75         4.85           Hemoglobin, g/dL         15.7         16.5         16.8           White blood cell count, K/mmc         6.0         7.3         6.8           Platets cell count, K/mmc         2.0         2.7         3.2           Lymphocyte count, %         59         59         59           Essinophyte, %         0         0         7.4         5.4           Protorombin time, \$         12.6         7.8         3.6.8           Protorombin time, \$         37.5         -         -           Activated clotting time, \$         37.5         -         -           Activated clotting time, \$         37.5         -         -         -           Creatine, mg/dL         0.77         0.76         0.84         -           Creatine, incase, U/L         342         60         -         -           Blood sugar level, mg/dL         42         4.1         140         -	Saturation of peripheral oxygen, %	98	98	99%	
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Laboratory findings Platets or local Minima A for A fo	Electrocardiogram	Normal (QTc 413)		Normal (QTc 420)	
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White blood cell count, K/mmc         6.0         7.3         6.8           Plattets cell count, K/mmc         245         278         323           Lymphocyte count, %         27         323           Neutrophyle count, %         59         59           Eosinophyle count, %         4         323           Basophyle, %         0         0           Monocytes, %         0         0           Prothrombin time, s         10         10           Prothrombin time (NR)         1.09         -           Activated clotting time (ratio)         1.17         -           Creatine-inase, U/L         0.77         0.76         0.84           Creatine-inase, U/L         102         -         -           Lactate dehydrogenase, U/L         342         -         -           Blood sugar level, mg/dL         95         82         60           Glomerular Filtration Rate (mL/min/1.73 m <sup>2</sup> )         >90         >90         >90           Sodium, mMo/L         142         141         140           Potassium, mMo/L         2.49         2.44         32           Chioride, Md/L         104         -         -           Calcium, mMo/L         2.	Hemoglobin, g/dL	15.7	16.5	16.8	
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Creatinie, mg/d.       0.77       0.76       0.84         Creatine-kinase, U/L       102       102         Lactate dehydrogenase, U/L       342       60         Blood sugar level, mg/dL       95       82       60         Glomerular Filtration Rate (mL/min/1.73 m <sup>2</sup> )       >90       >90       >90         Sodium, mMo/L       142       141       140         Potassium, mMo/L       4.5       4.8*       4.5         Chloride, mMo/L       104       2.49       2.44         Aspartate aminotransferase, U/L       21       19       23         Alanine aminotransferase, U/L       34       37       38         Gamma-glutamyl transpeptidase, U/L       71*       82*         Total cholesterol, mg/dL       143       131         HDL cholesterol, mg/dL       55       55         LD cholesterol, mg/dL       75.5       58         Triglycerides, mg/dL       75.5       58         Triglycerides mg/dL       75       108         Urine drug testing       51       55	Activated clotting time (ratio)	1.17			
Creatine-kinase, U/L102Lactate dehydrogenase, U/L342Blood sugar level, mg/dL9582Glomerular Filtration Rate (mL/min/1.73 m²)>90>90Sodium, mMol/L142141140Potassium, mMol/L4.54.8*4.5Chloride, mMol/L104104104Calcium, mMol/L1042.4492.44Aspartate aminotransferase, U/L211923Alanine aminotransferase, U/L343738Gamma-glutamyl transpeptidase, U/L71*82*Total cholesterol, mg/dL143131HDL cholesterol, mg/dL5555LDL cholesterol, mg/dL75.558Triglycerides, mg/dL75108Urine drug testing00104	Creatinine. mg/dL	0.77	0.76	0.84	
Lactate dehydrogenase, U/L $342$ Blood sugar level, mg/dL95 $82$ $60$ Glomerular Filtration Rate (mL/min/1.73 m²)>90>90>90Sodium, mMol/L142141140Potassium, mMol/L4.5 $4.8^*$ $4.5$ Chloride, mMol/L104 $2.49$ $2.44$ Aspartate aminotransferase, U/L2119 $23$ Alanine aminotransferase, U/L34 $37$ $38$ Gamma-glutamyl transpeptidase, U/L $71^*$ $82^*$ Total cholesterol, mg/dL5555LDL cholesterol, mg/dL5555LDL cholesterol, mg/dL75.58Triglycerides, mg/dL75108Urine drug testing00	Creatine-kinase. U/L	102			
Blood sugar level, mg/dL       95       82       60         Glomerular Filtration Rate (mL/min/1.73 m <sup>2</sup> )       >90       >90       >90         Sodium, mMol/L       142       141       140         Potassium, mMol/L       4.5       4.8*       4.5         Chloride, mMol/L       104	Lactate dehydrogenase. U/L	342			
Glomerular Filtration Rate (mL/min/1.73 m²)>90>90>90Sodium, mMol/L142141140Potassium, mMol/L4.54.8*4.5Chloride, mMol/L104104104Calcium, mMol/L211923Alanine aminotransferase, U/L343738Gamma-glutamyl transpeptidase, U/L71*82*Total cholesterol, mg/dL143131HDL cholesterol, mg/dL5555LDL cholesterol, mg/dL75.558Triglycerides, mg/dL75108Urine drug testing Ethanol0	Blood sugar level, mg/dL	95	82	60	
Sodium, mMol/L         142         141         140           Potassium, mMol/L         4.5         4.8*         4.5           Chloride, mMol/L         104         104         104           Calcium, mMol/L         104         2.49         2.44           Aspartate aminotransferase, U/L         21         19         23           Alanine aminotransferase, U/L         34         37         38           Gamma-glutamyl transpeptidase, U/L         71*         82*           Total cholesterol, mg/dL         143         131           HDL cholesterol, mg/dL         55         55           LDL cholesterol, mg/dL         75.5         58           Triglycerides, mg/dL         75         108           Urine drug testing         0         104	Glomerular Filtration Rate (mL/min/1.73 $m^2$ )	>90	>90	>90	
Potassium, mMol/L4.54.8*4.5Chloride, mMol/L1041042.492.44Calcium, mMol/L211923Aspartate aminotransferase, U/L343738Gamma-glutamyl transpeptidase, U/L343782*Total cholesterol, mg/dL143131HDL cholesterol, mg/dL5555LDL cholesterol, mg/dL75.558Triglycerides, mg/dL75108Urine drug testing00	Sodium, mMol/L	142	141	140	
Chloride, mMol/L104Calcium, mMol/L104Calcium, mMol/L2.49Aspartate aminotransferase, U/L21Alanine aminotransferase, U/L343738Gamma-glutamyl transpeptidase, U/L71*Total cholesterol, mg/dL143HDL cholesterol, mg/dL55LDL cholesterol, mg/dL55Triglycerides, mg/dL75.5Urine drug testing71Ethanol0	Potassium, mMol/L	4.5	4.8*	4.5	
Calcium, mMo/L2.492.44Aspartate aminotransferase, U/L211923Alanine aminotransferase, U/L343738Gamma-glutamyl transpeptidase, U/L71*82*Total cholesterol, mg/dL143131HDL cholesterol, mg/dL5555LDL cholesterol, mg/dL75.558Triglycerides, mg/dL75108Urine drug testing00	Chloride, mMol/L	104			
Aspartate aminotransferase, U/L211923Alanine aminotransferase, U/L343738Gamma-glutamyl transpeptidase, U/L71*82*Total cholesterol, mg/dL143131HDL cholesterol, mg/dL5555LDL cholesterol, mg/dL75.558Triglycerides, mg/dL75108Urine drug testing0	Calcium, mMol/I		2 49	2.44	
Alanine aminotransferase, U/L343738Gamma-glutamyl transpeptidase, U/L71*82*Total cholesterol, mg/dL143131HDL cholesterol, mg/dL5555LDL cholesterol, mg/dL75.558Triglycerides, mg/dL75108Urine drug testing0	Aspartate aminotransferase. U/L	21	19	23	
Gamma-glutamyl transpeptidase, U/L71*82*Total cholesterol, mg/dL143131HDL cholesterol, mg/dL5555LDL cholesterol, mg/dL75.558Triglycerides, mg/dL75108Urine drug testing Ethanol0	Alanine aminotransferase. U/L	34	37	38	
Total cholesterol, mg/dL143131HDL cholesterol, mg/dL5555LDL cholesterol, mg/dL75.558Triglycerides, mg/dL75108Urine drug testing Ethanol0	Gamma-glutamyl transpeptidase. U/L		71*	82*	
HDL cholesterol, mg/dL 55 55 LDL cholesterol, mg/dL 75.5 58 Triglycerides, mg/dL 75 108 Urine drug testing Ethanol 0	Total cholesterol, mg/dl		143	131	
LDL cholesterol, mg/dL 75.5 58 Triglycerides, mg/dL 75.5 108 Urine drug testing Ethanol 0	HDL cholesterol, mg/dL		55	55	
Triglycerides, mg/dL 75 108 Urine drug testing Ethanol 0	LDL cholesterol, ma/dL		75.5	58	
Urine drug testing Ethanol 0	Trialycerides, ma/dl		75	108	
Ethanol 0	Urine drug testing			100	
	Ethanol	0			

ECG = electrocardiogram.

Barbiturates Benzodiazepines

Opiates

Cocaine

Methadone Marijuana

Point out abnormal values.

0

40 ng/mL<sup>\*</sup>

0

0 0

0

Mental state examination performed by a psychiatrist in the emergency department suggested the diagnosis of severe depressive episode according to DSM-5 criteria. The patient showed depressed mood and congruent affect, diminished interest and pleasure almost all activities most of the day, fatigue and loss of energy, feelings of worthlessness and insomnia for some months now. Investigating the suicidal ideation, the patient acknowledged the suicidal intent of vortioxetine overdose.

The laboratory tests and the electrocardiogram (ECG) made in the emergency department were normal (Table 1). Only urine value of benzodiazepines was positive (40 ng/mL). After general evaluations at 11:20 AM gastric lavage with 2 L of water plus 50 g of activated charcoal was performed. After 12 hours of clinical stability, the patient was discharged from the emergency department and considering the suicidal ideation he was admitted to the inpatients psychiatric department. When admitted to psychiatry ward vital signs were normal such as ECG and laboratory tests apart from a slight hyperkaliemia and increased gamma-glutamyl transpeptidase (GGT) (Table 1).

The patient's condition improved after 1 week of recovery. The psychopharmacology therapy was modified since the lack of efficacy of the previous therapy: vortioxetine was suspended while sertraline 100 mg 1 tablet per day, amisulpride 50 mg 1 tablet per day, flurazepam 30 mg 1 tablet per day, and delorazepam 0.5 mg per day was introduced. The vital parameters were always normal, the patient never showed any organic signs or symptoms resulting from the overdose and he denied of having suicidal ideation any longer. Patient's mood improved such as interest and feelings of worthlessness, he recovered energy and a regular sleep. After 7 days of hospitalization, the patient has discharged from the psychiatry ward in generally good physical health with normal ECG and normal laboratory tests apart from slight increased GGT (Table 1).

After, we contacted our institutional review board; there was no need for ethical approval for this case report article. Informed patient consent was obtained for the publishing of this case report, all in accordance with Declaration of Helsinki.

#### 3. Discussion

Overdose safety of different antidepressant drugs is a matter of great interest given that in patients affected by MDD overdose of prescribed drugs is a frequent method used for suicidal act.<sup>[11-14]</sup> Antidepressants are involved in around 20% of all overdose suicides and in 20% to 30% of nonfatal overdoses.<sup>[15]</sup> Considering that the way used for suicidal attempt is often determined by availability, overdose in individuals affected by MDD frequently involves prescribed antidepressants.<sup>[16]</sup>

In spite of the high risk of antidepressant overdose in patients affected by MDD practitioners have to consider prescribing patterns headed for less toxic antidepressant drugs that are equally efficacious in order to reduce fatality.

Previous studies show wide variation in the relative toxicity of different antidepressants drugs.<sup>[13–17]</sup>. It is known that the toxicity is higher for tricyclic antidepressants, followed by venlafaxine bupropion and mirtazapine and is lower for selective serotonin reuptake inhibitors. Among the selective seroton be associated with the higher case fatality rates in overdose.<sup>[12,13]</sup> An antidepressant is considered safe when a dose 14 times the daily therapeutic dose does not lead to a life-threatening situation. For selective serotonin reuptake inhibitors moderate overdoses (up to

30 times the common daily dose) are associated with minor or no symptoms and very high doses (>75 times the common daily dose) result in more serious adverse events, including seizures, ECG changes, and decreased consciousness may occur. Contrary tricyclic antidepressants can be fatal if ingested in quantities exceeding 10 times the daily dose.<sup>[18]</sup>

To our knowledge, there is limited clinical trial experience regarding human overdose with vortioxetine. In premarketing clinical studies, cases of overdose were limited to patients who accidentally or intentionally consumed up to a maximum dose of 40 mg of vortioxetine and the maximum single dose tested was 75 mg in men (3–4 times the common daily dose). Ingestion of vortioxetine in the dose range of 40 to 75 mg was associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing.<sup>[19]</sup>

Thus in order to improve knowledge about safety in the overdose of this novel antidepressant drug we decided to report this case of vortioxetine overdose. From our case, it seems that vortioxetine overdose at 250 mg (12 times the common daily dose) showed no signs or symptoms resulting from the exposure suggesting a good safety in overdose.

At clinical, laboratory, and ECG assessment, we only find abnormal values of urine benzodiazepines at emergency department evaluation, potassium at psychiatric ward admission evaluation and GGT at psychiatric ward admission and discharge evaluation. A positive value of urine benzodiazepines is explained by the clonazepam use since August 2016 and by its overdose in the suicide attempt.<sup>[20]</sup>

Considering the raised GGT, to exclude the possible effect of the overdose on the liver, we investigated previous evaluation of GGT and found GGT were raised yet before the overdose. Likely previous history of hepatitis C and alcohol use disorder could explain the increased GGT value.<sup>[21]</sup>

Regarding the hyperkaliemia at psychiatric ward admission evaluation, we excluded the most common cause of hyperkalemia such as acute kidney failure, chronic kidney disease, Addison disease (adrenal failure), type 1 diabetes, and use of angiotensinconverting enzyme inhibitors or angiotensin II receptor blockers. Even if it is to underline that it was only a slight and temporary increase, it was not possible to identify a cause and we cannot exclude that hyperkaliemia was induced by vortioxetine overdose.

A great limitation of our case report is that we were not able to test the patient for vortioxetine levels in his blood or urine; thus we cannot be fully accurate about the number of drugs the patient took. The motivation, the setting, and other details of the overdose were investigated by 2 independent psychiatrists during the daily psychiatric interview and the overdose seemed to be really sustained by a suicidal intention. In addiction, the patient carried at emergency department the empty blisters of drugs he took in the overdose to demonstrate his attempt.

Due to the limited available evidence, further investigation is needed to better understand the potential risk of vortioxetine overdose.

### **Author contributions**

Conceptualization: Mario Gennaro Mazza. Data curation: Mario Gennaro Mazza. Formal analysis: Mario Gennaro Mazza. Investigation: Mario Gennaro Mazza. Methodology: Mario Gennaro Mazza. Project administration: Mario Gennaro Mazza. Supervision: Mario Gennaro Mazza, Aurora Rossetti, Eugenia Rossana Botti, Massimo Clerici.

Writing - original draft: Mario Gennaro Mazza.

Writing – review & editing: Mario Gennaro Mazza, Aurora Rossetti, Eugenia Rossana Botti, Massimo Clerici.

## References

- Sanchez C, Asin KE, Artigas F, et al. A novel antidepressant with multimodal activity: review of preclinical and clinical data. Pharmacol Ther 2015;145:43–57.
- [2] Bang-Andersen B, Ruhland T, Jorgensen M, et al. Discovery of 1-[2-(2,4 dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. J Med Chem 2011;54:3206–21.
- [3] Mork A, Pehrson A, Brennum LT, et al. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. J Pharm Exp Ther 2012;340:666–75.
- [4] Alvarez E, Perez V, Dragheim M, et al. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. Int J Neuropsychopharmacol 2012;15: 589–600.
- [5] Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebocontrolled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. Int Clin Psychopharmacol 2012;27:215–23.
- [6] Jacobsen PL, Harper L, Chrones L, et al. Safety and tolerability of vortioxetine (15 and 20 mg) in patients with major depressive disorder: results of an open-label, flexible-dose, 52-week extension study. Int Clin Psychopharmacol 2015;30:255–64.
- [7] Henigsberg N, Mahableshwarkar AR, Jacobsen P, et al. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. J Clin Psychiatry 2012;73:953–9.
- [8] Boulenger JP, Loft H, Olsen CK. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebocontrolled, duloxetine-referenced study in the acute treatment of adult

patients with major depressive disorder. Int Clin Psychopharmacol 2014; 29:138–49.

- [9] Mahableshwarkar AR, Jacobsen PL, Serenko M, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of vortioxetine in adults with major depressive disorder. J Clin Psychiatry 2015;76:583–91.
- [10] McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. Int J Neuropsychopharmacol 2014;17:1557–67.
- [11] Peretti S, Judge R, Hindmarch I. Safety and tolerability considerations: tricyclic antidepressants vs. selective serotonin reuptake inhibitors. Acta Psychiatr Scand Suppl 2000;403:17–25.
- [12] Hawton K, Bergen H, Simkin S, et al. Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. Br J Psychiatry 2010;196:354–8.
- [13] White N, Litovitz T, Clancy C. Suicidal antidepressant overdoses: a comparative analysis by antidepressant type. J Med Toxicol 2008; 4:238–50.
- [14] Wilson E, Lader M. A review of the management of antidepressant discontinuation symptoms. Ther Adv Psychopharmacol 2015;5: 357–68.
- [15] Hawton K, Bergen H, Casey D, et al. Self-harm in England: a tale of three cities. Multicentre study of self-harm. Soc Psychiatr 2007;42: 513-21.
- [16] Tournier M, Grolleau A, Cougnard A, et al. Factors associated with choice of psychotropic drugs used for intentional drug overdose. Eur Arch Psychiatry Clin Neurosci 2009;259:86–91.
- [17] Buckley NA, McManus PR. Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. BMJ 2002;325:1332–3.
- [18] Barbey JT, Roose SP. SSRI safety in overdose. J Clin Psychiatry 1998;59 (suppl 15):42–8.
- [19] NIH; DailyMed. Current Medication Information for Brintellix (Vortioxetine Hydrobromide) Tablet, Film Coated (Updated: July 2014). Available from, as of June 30, 2015.
- [20] Baselt RC. Deposition of Toxic Drugs and Chemicals in Men. Seal Beach, CA: Biomedical Publication 1983.
- [21] Torruellas C, French SW, Medici V. Diagnosis of alcol liver diease. World J Gastroenterol 2014;20:11684–99.