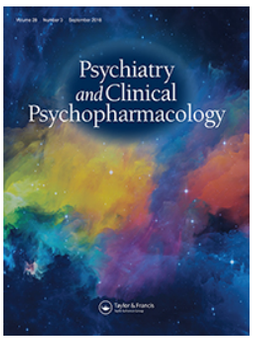

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Mesut Cetin & Samet Kose

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CASE REPORT

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Serious dermatological adverse effects of vortioxetine: two cases

Mesut Cetin [a] and Samet Kose [b]

[a]Editor-In-Chief, Psychiatry & Clinical Psychopharmacology and Psychiatry and Behavioral Sciences, Istanbul, Turkey; [b]Associate Professor. of Psychiatry, Franklin, TN, USA

ABSTRACT

In this case report, we present two patients who developed serious dermatological adverse reactions following vortioxetine use. Dermatological signs and symptoms disappeared following discontinuation of vortioxetine. These two cases can be useful in routine clinical practice to recall the parameters that need to be systematically addressed in cases of suspected adverse drug reactions with vortioxetine use in depressed patients.

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KEYWORDS
Vortioxetine; adverse reaction; edema; petechiae; ecchymoses

Major depressive disorder (MDD) is a highly prevalent psychiatric disorder and is reported as one of the most leading cause of disabilities and markedly contributes to a significant global burden of the disease worldwide. Newer generation antidepressant drugs (ADs) such as vortioxetine are widely used as the first line of treatment for major depressive disorders. Vortioxetine is an antidepressant that has been approved by the US Food and Drug Administration (FDA) for the treatment of MDD. Vortioxetine has a multimodal activity that combines two pharmacologic modes of action: direct modulation of serotonin (5-HT) receptor activity and inhibition of the 5-HT transporter. Also, vortioxetine is a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist; a 5-HT1B receptor partial agonist; a 5-HT1A receptor agonist; and an inhibitor of the 5-HT transporter In vivo non-clinical studies also demonstrated that vortioxetine enhanced levels of 5-HT, NE, DA, Ach, and Hist in specific areas of the brain. However, complete pharmacodynamic profile of vortioxetine is unknown. The recommended dosage of vortioxetine for the treatment of MDD is 5–20 mg/day. Suitable starting dose is usually 5–10 mg/day. Many multicenter trials have evaluated the treatment effects of 10 mg vortioxetine in the treatment of MDD; however, these trials have shown inconsistent results. While GI side effects (nausea, vomiting), dizziness, sweating, headache, dry mouth, hyponatremia, and sleep disturbances have been reported with the use of vortioxetine, no significant weight gain, lower sexual dysfunction (20–30 percent) compared to other SSRIs were considered as advantages in the management of MDD patients [1].

Adverse drug reactions are major cause of morbidity, emergency service presentations, and hospital admissions. Early recognition of adverse drug reactions is crucial in the medication management of psychiatric disorders. In this case report, we aim to report serious dermatological adverse effects such as severe pruritis or excessive itching, edema, petechiae, and ecchymoses in the legs and spread to other part of bodies in two MDD patients with 10 mg/day vortioxetine treatment. These side effects disappeared when the use of vortioxetine was discontinued in both patients. When we review the literature; we have seen that only pruritis has been reported as a dermatologic side effect in 1–5% patients with vortioxetine treatment and severe dermatologic adverse effects such as edema, petechiae, and ecchymosis have not been reported. Therefore, to the best of our knowledge, these two cases will be the first in which dermatological adverse effects due to vortioxetine treatment in MDD to be reported.

Case presentations

Case 1: A 43-year-old woman, single, living with her parents, works as financial advisor to a private company. Her psychiatric complaints were depressed mood, anhedonia, pessimism about future, fear and distrust, inability to make decisions, irritability, and occasional distress. Patient had a dysthymic and vulnerable premorbid personality. She presented to several psychiatrists and was prescribed various antidepressants, most recently partially treated with fluoxetine 20 mg/day. Since her complaints were still present, we discontinued fluoxetine and started vortioxetine 5 mg/ day and increased dosage of vortioxetine to 10 mg/day at the second week of her treatment. In the third month of vortioxetine therapy, patient started complaining from excessive itching in her legs and other parts f her body and edema, petechiae, and ecchymoses at her legs. No significant lab abnormalities (including CBC and hematological panel) have

CONTACT Samet Kose sametkose@gmail.com Franklin, TN, USA

Table 1. Laboratory values of Case 1.

WBC	7.31 [4.0–10.6]
Neutrophils (%)	46.5 [44.0–76.0]
Lymphocytes (%)	42.4 [15.0–43.0]
Monocytes (%)	9.6 [4.0–10.0]
Eosinophils (%)	1.1 [0.0–7.0]
Basophiles (%)	0.4 [0.0–2.0]
Neutrophils (number)	3.40 [2.0–7.0]
Lymphocytes (number)	3.10 [0.9–4.0]
Monocytes (number)	0.70 [0.3–1.0]
Eosinophils (number)	0.08 [0.00–8.00]
Basophils (number)	0.03 [0.0–0.2]
RBC	4.4 [3.5–5.5]
Hb	12.4 [12.1–15.9]
Hct	38.4 [34.3–46.6]
MCV	87.3 [77.8–94.0]
MCH	28.2 [26.5–32.6]
RDW-SD	45.1 [35.0–46.3]
Platelets	204 [150–400]
aPTT	23.8 [21–36]
Prothrombin time (PT)	9.9 [10.0–14.0]
Active PT	130 [70.0–130.0]
INR	0.9 [0.8–1.25]

Table 2. Laboratory values of Case 2.

WBC	4.68 [4.0–10.6]
Neutrophils (%)	44.6 [44.0–76.0]
Lymphocytes (%)	44.9 [15.0–43.0]
Monocytes (%)	8.8 [4.0–10.0]
Eosinophils (%)	1.3 [0.0–7.0]
Basophiles (%)	0.4 [0.0–2.0]
Neutrophils (number)	2.09 [2.0–7.0]
Lymphocytes (number)	2.10 [0.9–4.0]
Monocytes (number)	0.41 [0.3–1.0]
Eosinophils (number)	0.06 [0.00–8.00]
Basophils (number)	0.02 [0.0–0.2]
RBC	4.6 [3.5–5.5]
Hb	11.3 [12.1–15.9]
Hct	36.2 [34.3–46.6]
MCV	78.9 [77.8–94.0]
MCH	24.6 [26.5–32.6]
RDW-SD	45.7 [35.0–46.3]
Platelets	271 [150–400]
BUN	8.0 [6.0–20.0]
Creatinine	0.63 [0.55–1.02]
Alanine aminotransferase (ALT)	39.0 [12.0–59.0]
Aspartate aminotransferase (AST)	2.3 [10.0–37.0]
Specific IgE	0.22 [< 0.3]

been found (Table 1). The patient was not taking any other medications, nor consumed any foods which might have caused any allergies. Patient was consulted with a dermatologist and the formal diagnosis was drug-induced allergy. Vortioxetine was discontinued immediately and in her next follow-up examination, it was replaced with 30 mg/day of duloxetine. Patient's complaints were resolved following this. The patient had a score of 6 on the Naranjo Adverse Drug Reaction Probability Scale (NSDRPS) [2,3], which indicated a probable relationship between the dermatologic adverse effects observed and use of vortioxetine.

Case 2: A 35-year-old woman, married, mother of 6-year-old twin daughters. She owns a kindergarten school programme. Her psychiatric complaints included depressed mood, anhedonia, pessimism about future, anxiety, fear of illness, insomnia and loss of appetite. Previously, she presented to several psychiatrists and used various antidepressants, the last one was escitalopram 10 mg/day, and partially benefited. We gradually decreased and discontinued escitalopram in two weeks and started vortioxetine 5 mg/day. During the third week of vortioxetine 5 mg/day treatment, an excessive itching and pruritis developed in the skin all of over her body. No significant lab abnormalities were found in her lab work (Table 2). The patient did not take any other medication, but recently he had not consumed food-drug intolerance or any other food that could cause allergies. In the dermatology consultation made, the formal diagnosis of the dermatologist was drug-induced allergy. Therapy of vortioxetine was then discontinued. Vortioxetine was discontinued and escitalopram was started again at 5 mg/day and increased to 10 mg/day in two weeks. Patient's skin complaints improved and disappeared. The patient had a score of 6 on the Naranjo Adverse Drug Reaction Probability Scale (NSDRPS) [2,3], which indicated a probable relationship between the dermatologic adverse effects observed and use of vortioxetine.

Written informed consents have been obtained from both patients and available in patients' charts that these reports will be published including the photos.

Discussion

In the last two decades, psychotropic drugs, including antipsychotics given to the new market on the pipeline are not more than a dozen. In such an environment, vortioxetine was given to the market with great hopes. While the efficacy is as good as compared to other SSRI antidepressants, only itching has been reported in the drug's website and product monograph of the drug. In the abovementioned two cases, signs of severe dermatologic adverse effects such as edema, petechiae, and ecchymosis were observed and reported. Drug-induced allergic reaction diagnosis was made in both cases by the dermatologists and confirmed by both physical exam and lab results. When the vortioxetine was discontinued, the skin conditions were improved within a couple of weeks.

It is widely known that long and intensive studies and steps are needed in order for a molecule to become a drug. These steps are: (a) the discovery of the molecule, (b) the preclinical phase: the in vitro studies are the period during which the animals are made on animals, and (c) clinical research phase: involves clinical trials in healthy volunteers and patients. This stage consists of following four phases [4]:

Phase I: A series of experiments to assess the tolerance and pharmacokinetic properties of the molecule and drug-related safety data collection, purpose, and dose range, usually 20–100 individuals.

Phase II: Once it has been demonstrated that a candidate compound can be safely studied in human subjects, phase II clinical trials can be initiated. This phase identifies the efficacy and safety of the candidate

compound and also aims to determine if the candidate compound has the potential to safely improve the lives of patients; 100–300 patients with the target disorder are tested to determine the efficacy of the drug, side effect profile, and the collection of dose–response data. The data of these studies are usually applied with clear and very strict protocols.

Phase III: This process generally requires 1000–3000 patients, possibly more, multiple clinical sites, an institutional review board (IRB) and they can last from 2.5 years to 5 years, depending on the nature of the disease and the patient population. In order to be considered a success, a phase III clinical programme must produce at least two "adequate and well-controlled studies" that demonstrate both the safety and efficacy of the candidate compound. In the United States, the "New Drug Application" (NDA) must be submitted to the FDA. In the European Union countries, a similar application is made to the European Medicines Evaluation Agency (EMEA). Apart from these, it is necessary for each country to obtain approval by making the necessary application for the legally responsible organization. Once the product is approved, it can be started to be used as a medication.

Phase IV: Once a candidate compound has successfully completed two adequate and well-controlled studies, a new drug application can be prepared and submitted to the appropriate regulatory body. Objective of postmarketing surveillance studies include the identification of low-frequency adverse events, continued safety monitoring to better characterize known risks, gauging the potential for drug–drug interactions, establishing treatment guidelines for pediatric and geriatric populations, and determining the real-world efficacy of the candidate compound. Side effects that do not occur during the clinical trials can be reported during this phase. Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in clinical practice and should not be compared to the rates in the clinical trials of another psychotropic drug. The drug development process lasts for the entire patent lifetime. Studies conducted for use in new indications after drug use has been accepted as Phase III trials and are performed in accordance with the same rules. The development of new doses and formulations should also be examined afterwards. In the pharmaceutical industry, when brand-name companies patent new inventions that might be in fact just slight modifications of old drugs, it is called "evergreening."

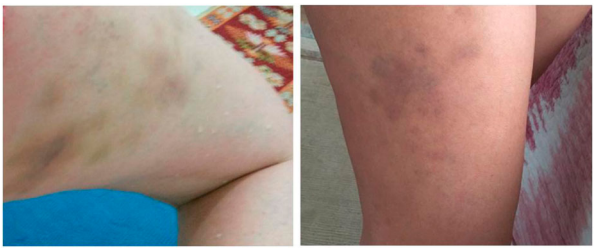

Figure 1. Edema, petechiae, and ecchymosis observed in Case 1 and Case 2.

In the light of the above information, vortioxetine is an antidepressant approved for the treatment of MDD in 2013. Vortioxetine entered the market in Turkey recently. The serious dermatologic adverse reactions such as seen in our two cases would be instrumental for prescribing clinicians to be aware of vulnerability to such adverse effects of vortioxetine treatment and availability of other pharmacological options and would also provide valuable data for the phase IV period. Furthermore, our cases can be useful in routine clinical practice to recall the parameters that need to be systematically addressed in cases of suspected adverse drug reactions so that clinical judgement can be improved and become more consistent (Figure 1).

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Mesut Cetin http://orcid.org/0000-0002-6378-5701
Samet Kose http://orcid.org/0000-0003-0841-004X

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