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Research Article

Adverse Events of Eye Disorders Related to the Use of Vortioxetine: A Disproportionality Analysis

Nesrin Caglayan Duman

Ordu University, Faculty of Medicine, Department of Medical Pharmacology, Ordu, Türkiye

Abstract

Aim: The present study aims to evaluate the potential risk of ocular adverse events with vortioxetine use by analyzing real-world adverse events reported in the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) database.

Material and Method: The OpenVigil 2.1-MedDRA-v24 disproportionality analysis software package, including the Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) algorithms, was used to determine the potential risk of ocular adverse events associated with vortioxetine and to determine signal strength. Ocular adverse event reports related to the generic name vortioxetine as the primary suspect in the FAERS database between 16 May 2014 and 30 September 2024 were included in this study. Risk signal strength for ROR and PRR were classified as low, medium and strong in line with the signal intensity.

Results: Twenty-nine 'preferred terms' with 3 or more reports were included in this study. Given the results of the disproportionality analysis, 5 adverse events with potential positive signals were found. These were halo vision (ROR=8.205, PRR=8.202; medium signal), angle-closure glaucoma (ROR=5.646, PRR=5.642; medium signal), blepharospasm (ROR=3.408, PRR=3.406; weak signal), oculogyric crisis (ROR=2.394, PRR=2.393; weak signal), and blurred vision (ROR=2.023, PRR=2.011; weak signal).

Conclusion: The disproportionality analysis conducted on the FAERS database revealed possible adverse events associated with vortioxetine in eye disorders and not documented in the drug's package insert (except for angle-closure glaucoma). In conclusion, these findings indicate that continued post-marketing surveillance plays a decisive role in signaling potential new ocular adverse drug events.

Keywords: Vortioxetine, adverse event, eye disorders, disproportionality analysis

INTRODUCTION

Vortioxetine is a new antidepressant with a unique profile as it is an atypical (multimodal) serotoninergic agent (1). It is a second-generation antidepressant approved by the regulatory agencies in America and Europe (2). The marketing authorization for this medicine was approved by the U.S. Food and Drug Administration (FDA) on 30 September 2013 and by the European Medicines Agency (EMA) on 18 December 2013.

Efficacy and tolerability of vortioxetine have been demonstrated in studies (2). The Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 Update on Clinical Guideline recommends vortioxetine, a relatively new antidepressant, as one of the first-line treatments for major depressive disorders due to its unique pharmacodynamic mechanisms and efficacy (3). Therefore, its scientific popularity tends to increase (4).

However, since vortioxetine is a relatively new drug, its safety profile is not clear yet. There are limited adverse drug events (ADEs) data for recently approved antidepressant agents such as vortioxetine. Adverse events (AEs) of vortioxetine also differ from conventional antidepressants, with a low incidence of sexual dysfunction, weight gain, or cardiovascular changes (5). Gastrointestinal symptoms such as nausea and vomiting ranked first among the major AEs associated with the use of new-generation antidepressant drugs, while ophthalmic conditions such as glaucoma and cataract ranked seventeenth (6).

AEs are defined as medically undesirable occurrences resulting from the use of a pharmaceutical product. ADEs

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Corresponding Author: Nesrin Caglayan Duman, Ordu University, Faculty of Medicine, Department of Medical Pharmacology, Ordu, Türkiye

E-mail: nesrincglyndmn@gmail.com

are prevalent and represent a substantial healthcare burden. The most comprehensive database of ADEs is that of the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) (7). The FAERS database is a publicly accessible collection of ADE reports submitted voluntarily by healthcare professionals, patients, and pharmaceutical companies. The database reflects real-world occurrences of ADEs (8). The database includes patient information, adverse reaction data, drug utilization details, report sources, drug indications, and patient outcomes (9).

The FAERS database codes all adverse events using preferred terms (PTs) from the Medical Dictionary of Regulatory Activities (MedDRA). Disproportionality analysis of the data obtained from large databases of spontaneous AE reporting systems such as FAERS has been an important method for drug safety monitoring (10,11). Regarding the pharmacovigilance, proportional reporting ratio (PRR) (12) and reporting odds ratio (ROR) (13) are the most popular methodologies utilized for the detection of ADE signals. The FAERS database contains reports that are either duplicate or incomplete. Consequently, data mining tools such as OpenVigil are employed. OpenVigil, a web interface for the analysis of spontaneous or systematic collections of treatments (drugs) and observed AEs (adverse effects of drugs) (14), is a tool used when analyzing the pharmacovigilance data that calculates ROR and PRR values.

The present study aims to investigate the post-marketing safety profile of vortioxetine by performing a disproportionality analysis for vortioxetine and ocular ADEs using the FAERS database.

MATERIAL AND METHOD

Data Source and Collection

Adverse drug reactions reported in the public version of the FAERS database were used in this observational, retrospective pharmacovigilance study. The present study used OpenVigil 2.1-MedDRA-v24 to query the FAERS database. OpenVigil 2.1 is a software tool designed for the specific purpose of data extraction, cleaning, mining and analysis of AE data from the FAERS database. Ocular adverse event reports for the generic name 'vortioxetine', 'vortioxetine hydrobromide' and 'vortioxetine dl-lactate' submitted between 16 May 2014 and 30 September 2024 were selected and included in this study. The present study included reports of adverse reactions where the reporter indicated vortioxetine as 'Primary Suspect'. Ocular adverse events in the FAERS database were individually inquired by using the OpenVigil analysis tool. The relationship between drug and adverse events was analyzed by choosing 'Frequency' as the analysis method and 'Entire Cases' as the case type on the inquiry tab of this tool.

Data Analysis

A disproportionality analysis was performed using OpenVigil version 2.1. PRR and ROR were employed to detect safety signals. All algorithms are based on 2×2 contingency tables. In this study, PTs with a reported frequency of ≥3 were selected for the initial screening procedure. The risk signal strength assessment criteria for ROR and PRR were signal intensity (assessment criteria) classification as weak (2< ROR or PRR ≤10), medium (10< ROR or PRR ≤50) and strong (ROR or PRR >50) (15). If signals met the criteria of both methods, they were classified as positive signals. It is widely accepted that a chi-square value exceeding 4 is statistically significant (https://openvigil.sourceforge.net/). The analysis was performed using Microsoft Excel 2024 software.

The human-related datasets used in this study are publicly available for any research program. Patient consent was not obtained in this study because of the nature of the data source. This research did not require ethics committee approval since the authors had no knowledge of data collection or the participants in the present study.

RESULTS

ADE Reports and Clinical Information

A total of 29,661,136 ADE reports were recorded in the FAERS database until 30 September 2024. There were 15,448 ADE reports incorporating vortioxetine as the main suspect drug. Of these reports, 771 cases were related to eye disorders. There were more females (430 cases, 55.8%) than males (143 cases, 18.5%), most cases were submitted in 2024 (232 cases, 30%), and the predominant reporting country was USA (428 cases, 55.5%). In 46.3% of cases, the age of the case was not specified, and most cases with age information (42.8%) were aged between 18 and 64 (as shown in Table 1).

Signal Strength Analysis of Vortioxetine-Related Eye Disorder AEs

There were 29 PTs with 3 or more eye disorder reports associated with vortioxetine and 399 reports related to these PTs. The most reported PTs were vision blurred (n=129), visual impairment (n=44), and eye pain (n=36).

In this study, ROR and PRR were used to analyze ADE signals, and 5 potential positive signals were detected between 16 May 2014 and 31 September 2024. Angle-closure glaucoma (8 reports; ROR=5.646, 95% CI 2.818 - 11.311; PRR=5.642, 95% CI 2.818 - 11.298) and halo vision (4 reports; ROR=8.205, 95% CI 3.068 - 21.938; PRR=8.202, 95% CI 3.068 - 21.923) had a medium signal strength, whereas vision blurred (129 reports; ROR=2.023, 95% CI 1.701 - 2.407; PRR=2.011, 95% CI 1.694 - 2.388), blepharospasm (8 reports; ROR=3.408, 95% CI 1.702 - 6.823; PRR=3.406, 95% CI 1.702 - 6.816), and oculogyric crisis (3 reports; ROR=2.394, 95% CI 0.771 - 7.431; PRR=2.393, 95% CI 0.771 - 7.428) had a weak signal strength.

The observed frequency of eye pain (ROR=1.51, PRR=1.508, χ^2=5.668) was statistically significantly higher than the expected frequency but did not meet the assessment criteria for signal intensity in this study. PTs related to eye disorders are presented in Table 2.

Table 1. Basic information on ocular adverse event reports related to vortioxetine*

Category		Number of cases (n)	Percentage (%)
Gender	Male	143	18.5
	Women	430	55.8
	Unknown	198	3.7
Age (years)	<18	11	1.4
	18-64	330	42.8
	65-84	71	9.2
	≥85	2	0.3
	Missing	357	46.3
Report year	2014	17	2.2
	2015	47	6.1
	2016	47	6.1
	2017	133	17.6
	2018	96	12.5
	2019	73	9.5
	2020	57	7.4
	2021	78	10.1
	2022	84	10.9
	2023	94	12.2
	2024	232	30.0
Reported countries	United States of America (USA)	428	55.5
	Non-USA	343	44.5

*FDA Adverse Event Reporting System (FAERS) Public Dashboard was used when preparing this table

Table 2. Signal detection results of ocular adverse event reports related to vortioxetine

PTs	Reports	ROR (95% CI)	PRR (95% CI)	χ2
Vision blurred	129	2.023 (1.701-2.407)	2.011 (1.694-2.388)	64.857
Visual impairment	44	0.714 (0.531-0.961)	0.715 (0.533-0.961)	4.722
Eye pain	36	1.51 (1.088-2.095)	1.508 (1.088-2.09)	5.668
Eye swelling	18	1.086 (0.684-1.724)	1.085 (0.684-1.723)	0.051
Dry eye	13	0.63 (0.366-1.085)	0.63 (0.366-1.085)	2.465
Glaucoma	13	1.47 (0.853-2.531)	1.47 (0.853-2.534)	1.509
Diplopia	11	0.953 (0.528-1.722)	0.953 (0.528-1.721)	0.0
Mydriasis	11	1.701 (0.941-3.074)	1.7 (0.942-3.071)	2.509
Ocular hyperaemia	11	0.512 (0.283-0.925)	0.512 (0.284-0.925)	4.635
Eye pruritus	9	0.616 (0.32-1.183)	0.616 (0.32-1.183)	1.795
Photophobia	8	1.003 (0.502-2.007)	1.003 (0.502-2.006)	0.028
Blepharospasm	8	3.408 (1.702-6.823)	3.406 (1.702-6.816)	11.266
Angle-closure glaucoma	8	5.646 (2.818-11.311)	5.642 (2.818-11.298)	25.968
Eye disorder	8	0.502 (0.251-1.004)	0.502 (0.251-1.004)	3.469
Ocular discomfort	6	1.403 (0.63-3.126)	1.403 (0.63-3.124)	0.35
Blindness	6	0.291 (0.131-0.647)	0.291 (0.131-0.648)	9.679
Lacrimation increased	6	0.454 (0.204-1.011)	0.455 (0.204-1.012)	3.403
Cataract	6	0.244 (0.109-0.543)	0.244 (0.11-0.543)	13.329
Eye haemorrhage	6	0.935 (0.42-2.082)	0.935 (0.42-2.081)	0.001
Miosis	5	1.338 (0.557-3.217)	1.338 (0.557-3.215)	0.155
Eye irritation	5	0.205 (0.085-0.492)	0.205 (0.085-0.492)	14.664
Photopsia	5	1.709 (0.711-4.108)	1.708 (0.711-4.106)	0.844
Vitreous floaters	4	0.897 (0.336-2.39)	0.897 (0.336-2.389)	0.0
Halo vision	4	8.205 (3.068-21.94)	8.202 (3.068-21.923)	18.475
Macular degeneration	4	0.764 (0.287-2.037)	0.764 (0.287-2.036)	0.103
Blindness transient	4	1.102 (0.414-2.939)	1.102 (0.414-2.938)	0.005
Retinal haemorrhage	4	1.165 (0.437-3.107)	1.165 (0.437-3.105)	0.001
Eyelid oedema	4	0.739 (0.277-1.97)	0.739 (0.277-1.97)	0.153
Oculogyric crisis	3	2.394 (0.771-7.431)	2.393 (0.771-7.428)	1.236

PTs: preferred terms, ROR: reporting odds ratio, PRR: proportional reporting ratio; χ^2, Chi-Squared with Yates' correction

DISCUSSION

Drug use is based on a risk-benefit profile. As new medicines are constantly being developed, the physician must stay up to date with potential AEs (16). If all parties (ophthalmologists, psychiatrists, and patients) are aware of the adverse effects of medication, most severe and irreversible eye damage can be avoided. All psychotropic drugs can potentially cause ocular adverse effects such as eyelid and keratoconjunctival disorders, uveal diseases, cataract/pigmentary deposits in the cornea and lens, angle-closure glaucoma, and retinopathy (17). There are very few studies evaluating the ocular adverse effects of medicines. This study provides an assessment of the evidence regarding possible ocular adverse reactions thought to be caused by vortioxetine used in psychiatric treatment.

In the present study, the angle-closure glaucoma (ROR=5.646, PRR=5.642) was found to have a weak signal strength. Considering a study on the FAERS database, drug-induced glaucoma can be caused by drugs such as sulfonamides like topiramate which are well known to cause this adverse effect, as well as lesser-known drugs such as olanzapine and ranibizumab. Of all the drugs associated with angle-closure glaucoma in this study, tropicamide (18 reports; ROR=167.95, PRR=164.263) and acetazolamide (51 reports; ROR=114.782, PRR=113.088) were determined to be the statistically most significant ones (18). In a previous literature review, antidepressants were considered one of the drug classes known to increase the risk of angle-closure glaucoma (19). A study carried out on selective serotonin reuptake inhibitors (SSRIs) provided evidence of an association between various SSRI antidepressants and acute angle-closure glaucoma, particularly within the first week of starting treatment (OR=5.8, 95% CI 1.89 - 17.9) (20). There are two main risk factors for angle-closure glaucoma: anatomically narrow angles and the use of medications that affect intra-ocular pressure (21). The significantly higher incidence of vision disturbances leading to signal formation and eye pain compared to other drugs may be because it is one of the symptoms of acute angle-closure glaucoma.

Blurred vision and halo vision are visual disturbances that can be seen as drug adverse effects (22). Vortioxetine was associated with a lower risk of short-term blurred vision than placebo (OR=0.43; 95% CI 0.19-0.96; p-value=0.04) in a study of neurological adverse effects of antidepressants (23). In the present study, blurred vision (ROR=2.023, PRR=2.011) had a weak signal strength, whereas halo vision (ROR=8.205, PRR=8.202) had a medium signal strength. Considering the comparison between severe and non-severe groups for ocular adverse events associated with a group of drugs and blurred vision was found to be significantly higher in the severe patient group (24). As determined in this study, vision changes that occur as a drug adverse effect can be considered as a factor in determining the course of the disease.

Blepharospasm is one of the possible/rare adverse effects of antidepressants (25). In the present blepharospasm had 8 reports (ROR=3.408, PRR=3.406) and a weak signal strength. A similar FAERS disproportionality analysis study reported 172 reports for blepharospasm in adverse events of atypical antipsychotics associated with ocular neuromuscular disorders, and 54 of them reported strong signal for aripiprazole (26). In a case report, discontinuing psychotropic medication ameliorated blepharospasm in 67% of patients (27). As can be seen in these studies, blepharospasm caused by the drugs used in psychiatry and the recovery of blepharospasm upon discontinuation of those drugs indicate the importance of evaluating adverse events in patients follow-up.

Especially the use of antipsychotic drugs (e.g. neuroleptic drugs) is a risk factor for oculogyric crisis. Therefore, it is important to determine the causative drug for the diagnosis of drug-induced oculogyric crisis (28). In the present study, the oculogyric crisis had 3 reports (ROR=2.394, PRR=2.393) and a weak signal strength. In a FAERS database study comparable the present study, cariprazine used in the treatment of schizophrenia was found to have a high risk of causing possible oculogyric crisis (12 reports; ROR=45.95, PRR=45.88) (29).

In the package insert of for vortioxetine, the manufacturer only mentioned angle-closure glaucoma as an ocular adverse event (30). In November 2017, there were additions and/or revisions to the product information of vortioxetine regarding angle-closure glaucoma. In other words, this change was included in the product information approximately 4 years after the product was released (31). AEs associated with blurred vision, blepharospasm, halo vision, and oculogyric crisis are not explicitly mentioned in the product information, indicating the presence of novel ADE signals. In late 2013, vortioxetine was introduced to the market, and it was determined in the present study carried out 10 years after the introduction to the market that there may be various possible adverse effects on eyes.

Study Limitations

This research has several limitations. The study was limited to AEs in which vortioxetine was the primary suspect. Information on concomitant drug use, reporter type, drug indication, and outcome were not included in this study because of lack of data or inaccessibility. A weakness of the study is that in the spontaneous reports in the FAERS database, some case reporters were not healthcare professionals and self-identified the primary suspected drugs. Due to the nature of the study, a causal relationship between AEs and drugs could not be established. OpenVigil lacks information on the effect of comorbidity, dose and duration of use on the occurrence of AEs. Despite these limitations inherent in clinical trials, spontaneous reporting systems are valuable because they allow large amounts of data to be used for the safety

assessment of suspected AEs. It is recommended that future prospective studies be conducted to validate the findings of this investigation.

CONCLUSION

Patients are exposed to new and sometimes unexpected toxicities when using new-generation antidepressants prescribed by psychiatrists. Rare ocular adverse events may develop during antidepressant treatment. Ophthalmologists should be aware of such ophthalmic adverse events and their potential severity for better management and diagnosis, both in daily practice and clinical trials.

In the present study, FAERS disproportionality analysis was performed to investigate vortioxetine-related AEs and to identify possible ocular AE signals. The results achieved in this study provide an important reference point to ensure the safe use of vortioxetine in the treatment of depression. The available evidence obtained in this study suggests that initial and follow-up ophthalmic consultations may be necessary for patients receiving vortioxetine due to the risk of blepharospasm, blurred vision, angle-closure glaucoma, oculogyric crisis, halo vision, etc. Moreover, these results highlight the importance of ongoing post-marketing surveillance to detect potential new ADEs.

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