Risks Associated with Vortioxetine in the Established Therapeutic Indication

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Abstract: Background: Vortioxetine is approved for the treatment of Major Depressive Disorder (MDD). However, the safety of this drug in a large group of populations is still unclear. Thus, we have tried to analyze the risk profile of vortioxetine.

Material and Methods: The data related to the risk profile of vortioxetine has been extracted from Pub-Med from January 2014 to May 2019. The adverse drug reactions (ADRs) have been categorized into listed and unlisted categories as per the Summary of product characteristics (SmPC) of the innovator. Further, unlisted ADRs have been analyzed as per Naranjo Scale.

Results: Galactorrhea, hyperprolactinemia, glycolimia, exacerbation of anxiety, weight gain, edema, excessive itching, petechiae, and ecchymoses have been observed with the use of vortioxetine and falls under the unlisted category. Further, the causality assessment results have shown a probable relation between vortioxetine and galactorrhea, hyperprolactinemia, edema, excessive itching, ecchymoses, and petechiae. Weight gain, glycolimia and exacerbation of anxiety have a possible relationship with vortioxetine. The common ADRs observed with the use of vortioxetine are nausea, diarrhea, constipation, vomiting, pruritus, including pruritus generalized, abnormal dreams, and dizziness.

Conclusion: In conclusion, more data is required to establish a strong relationship between vortioxetine and reported unlisted ADRs.

Keywords: Adverse drug reactions, vortioxetine, major depressive disorder (MDD), marketing authorization holder (MAH), regulatory authorities (RAs), summary of product characteristics (SmPC).

1. INTRODUCTION

Vortioxetine is a new drug under the class of selective serotonin reuptake inhibitors (SSRIs) for Major Depressive Disorder (MDD). The Food and Drug Administration (FDA) has approved this drug for marketing in October 2013 [1]. It shows its therapeutic action through two mechanisms i.e., the inhibition of the serotonin transporters and direct modulation of serotonin receptor activity. The recommended dosage of vortioxetine is 5-20 mg/day [2].

Major Depressive Disorder (MDD) is a heterogeneous mental disorder associated with various cognitive, emotional, and physical symptoms. This disorder is affecting around 350 million people globally and ranked 4th worldwide in overall disease burden [1,3]. Clinically, various classes of antidepressant drugs such as tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs) are available for the treatment of MDD but unfortunately, half of the patients respond to these drugs and some of them have this disease again. Apart from this, the currently used drugs are associated with various adverse drug reactions (ADRs) such as sexual dysfunction, tremors, loss of appetite, insomnia, weight changes, etc [1,4].

Vortioxetine has shown better improvement in adult MDD patients who had poor responses to existing SSRIs and Selective nor-epinephrine Reuptake Inhibitor (SNRI) [5]. The improvement in the cognitive function of adults with recurrent MDD has also been observed after treatment with vortioxetine. Baune et al., (2018) conducted a network meta-analysis to compare the effects of antidepressants on cognitive dysfunction of Patients with Major Depressive Disorder using Digit Symbol Substitution Test (DSST) and found that vortioxetine was the only antidepressant that exerted statistically significant effects [6]. The vortioxetine treatment does not result in any significant adverse effect on the heart and does not cause increases in cQT length. However, emerging reports have indicated various ADRs associated with the use of vortioxetine on other organs. Recently, Report and Ozkan (2018) reported galactorrhea and hyperpro-
lactinemia with the use of vortioxetine [7]. The CYP2D6 plays a major role in the metabolism of vortioxetine. Thus, ADRs as well as the therapeutic efficacy of vortioxetine can be enhanced in poor CYP2D6 metabolizers or in the presence of CYP2D6 inhibitors. The exact role of vortioxetine in the treatment of established therapeutic indication is unclear [8]. Thus, in this article, we analyzed the risk profile of vortioxetine in established therapeutic indication by collecting information from Pubmed.

2. METHODOLOGY

The review was conducted as Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [9]. The study protocol was followed as per a recently published study [10].

2.1. Data Sources and Search Strategy

The data related to the risk profile of vortioxetine has been extracted from Pubmed, from January 2014 to May 2019. The following search strategy was used to retrieve articles “selective serotonin reuptake inhibitors”, “SSRIs”, “vortioxetine”, and “risks”, “ADRs”, “adverse drug reactions”. Both authors have screened all titles and abstracts independently.

2.2. Study Selection

Both the authors screened all titles and abstracts independently. Search terms, as well as inclusion and exclusion criteria, were used to filter for more relevant studies. The below mentioned inclusion and exclusion criteria have been used for screening of studies. Language restrictions were applied to include only English full text. For multiple or duplicate publications of the same data set, we included only the most recent or complete study.

2.2.1. Inclusion and Exclusion Criteria

Articles were included in the study based on inclusion criteria i.e., articles that were available from January 2014 to May 2019 related to vortioxetine. All age groups of patients having confirmed Major Depressive Disorder (MDD) and administered at least vortioxetine. The research articles are only included: the articles in which subject had at least one ADR; the articles were excluded based on exclusion criteria i.e. studies without defined ADR, articles that were published after May 2019 and contained only pharmacokinetic properties, drug development and validation of vortioxetine, articles in which vortioxetine was not used, review articles, meta-analysis, editorials, and expert opinion were also excluded.

2.3. Quality Assessment

The methodological quality of the studies in the systematic review was assessed by both authors using a 15 point checklist adapted from Downs and Black [11]. The quality of each study was evaluated based on external and internal validity, methodology, confounders, and population demographics. Both authors reviewed the articles and assigned a numerical value representative of its quality. The scores were categorized into four groups. Studies with scores between 0 and 3 were classified as “poor quality” studies, 4–7 were deemed “low quality,” 8–11 were “medium quality,” and 12–15 were “good quality” studies.

2.4. Data Extraction

The data (number of patients, age, gender, dose, adverse drug reactions) from the included studies have been extracted by one author, whereas the second author checked the extracted data. The disagreements were resolved by discussion between the two review authors.

2.5. Analysis

The Summary of Product Characteristics (SmPC) of vortioxetine hydrobromide 5, 10, and 20 mg was extracted from Electronic Medicines Compendium (EMC, 2019) [12] and used as Innovator Reference safety information (RSIs) to determine whether the ADRs observed with vortioxetine are “listed” or “unlisted”. The unlisted ADRs were analyzed by using Naranjo probability scales to find the causality relationship between the drug and the ADR.

3. RESULTS

3.1. Selection of Articles

A total number of 360 studies were extracted regarding vortioxetine from Pubmed. Finally, based on inclusion and exclusion criteria, 09 studies have been selected for the safety study of vortioxetine. The sorting of articles as per PRISMA guidelines is presented in (Fig. 1). Study quality was conducted in order to exclude poor-quality studies; however, there were no studies that were of poor quality.

3.2. Analysis of Safety

All valid studies, regulatory authority, and other post-marketing Individual case safety reports (ICSRs) (as applicable) available were analyzed (clinical review) for safety signals. A total of 9 articles with the product containing vortioxetine were reported since the first marketing authorization.

Out of these 09 studies, 05 studies are related to clinical trials, and the remaining 04 studies are case reports. The selected 04 case reports include 11 ADRs. Out of these 11 ADRs, 02 ADRs are listed (hypotension and pruritus) as per the SmPC of the innovator and remaining 09 ADRs (glycemia, weight gain, exacerbation of anxiety, galactorrhea, hyperprolactinemia, pectechiae, ecchymoses, edema, and excessive itching) are unlisted. Further assessment was not done for listed ADRs (01 case report). The unlisted ADRs were further assessed for causality assessment using the Naranjo scale.

The 05 clinical trials reported the various ADRs such as headache, nausea, sedation, upper abdominal pain, fatigue, vomiting, decreased appetite, irritability, sexual dysfunction, depression, anxiety, insomnia, dizziness, pruritus, etc. with the use of vortioxetine.
4. DISCUSSION

Vortioxetine was approved in October 2013 for the treatment of Major Depressive Disorder (MDD). This disorder is a mental disorder having a distinct change of mood, characteristic of sadness, low self-esteem, and loss of interest [13]. It can negatively influence personal life, work-life, or education, as well as sleeping, and eating habits [14]. The etiology of this disease is still unknown, however, various risk factors such as genetics and a history of manic episodes, etc, play an important role in the development of this disease [15].

Currently, various classes of drugs such as levomilnacipran (SSRI, SNRI), vilazodone hydrochloride (SSRI), and vortioxetine (SSRI) are available in the market for treatment of MDD. Vortioxetine belongs to SSRI, which inhibits the serotonin transporter, thus increasing synaptic serotonin, which is decreased in depression, as shown in (Fig. 2). Vortioxetine has shown better efficacy among available SSRIs (sertraline, venlafaxine XR, and bupropion SR) in the treatment of MDD. Apart from this, the withdrawal rate due to AEs was also significantly lower in patients treated with vortioxetine compared with those treated with sertraline, venlafaxine, and bupropion [16]. The common ADRs observed with the use of vortioxetine are nausea, diarrhea, constipation, vomiting, pruritus, including pruritus generalized, abnormal dreams, and dizziness that are compiled in Table (1) as per system organ class (SOC).

Various ADRs have been also observed in various phases of clinical trials. Findling et al., (2017) conducted pharmacokinetics and safety study of vortioxetine on pediatric patients and reported various ADRs such as headache, nausea, sedation, upper abdominal pain, fatigue, vomiting, decreased appetite, and irritability [17]. The sexual dysfunction, nausea, depression, anxiety, insomnia vomiting, nausea, headache, dizziness, pruritus, fatigue, and anxiety were reported with the use of vortioxetine in phase 3 clinical trial.
Nierenberg et al., (2019) also reported the most common ADR nausea with the use of vortioxetine in a clinical trial [19]. Papakostas et al., (2018) also reported nausea, headache, dizziness, and somnolence in 493 patients [5]. The efficacy and safety of vortioxetine in adults with major depressive disorder were assessed by Nishimura et al., (2018) in Randomized, Double-Blind, Placebo-Controlled 8-week Trial [20]. The details of patients who experienced ADRs with the use of vortioxetine in clinical trials are compiled in Table (2).

Postmarketing studies have indicated an increase in the frequency of existing ADRs and the emergence of unknown ADRs. The unknown ADRs were observed due to limitations of clinical trials such as limited population, controlled environment, duration, etc [21, 22]. The ADRs which were observed from post-marketing studies are compiled in Table (2). In the current investigation, we found 4 case reports containing 11 ADRs. Out of these 11 ADRs, 02 ADRs are listed (hyponatraemia and pruritus) as per the SmPC of the innovator and remaining 09 ADRs (glycolimia, weight gain, exacerbation of anxiety, galactorrhea, hyperprolactinemia, petechiae, ecchymoses, edema and excessive itching) are unlisted. Report and Ozkan (2018) reported the galactorrhea and hyperprolactinemia with the use of vortioxetine in a 33-year-old woman after 4 months of treatment [7]. Galactorrhea and hyperprolactinemia are unlisted as per the Innovator's SmPC. The causality assessment of the current investigation has shown a probable relationship between vortioxetine and galactorrhea and hyperprolactinemia. Glycolimia, exacerbation of anxiety, and weight gain are other unlisted ADRs as per the Innovator's SmPC reported with the use of vortioxetine. Recently Reid (2018) has reported glycolimia, exacerbation of anxiety, and weight gain with the use of vortioxetine in a 52-year-old woman for the treatment of depression [23]. The causality assessment in the current investigation has shown a possible relationship between these events and drugs. Edema, excessive itching, and petechiae are also observed with the use of vortioxetine. Recently, a 43-year-old woman suffered from excessive itching, edema, petechiae, and ecchymoses after three months of the treatment. The lab tests indicated no change in the level of complete blood count and hematological parameters. After discontinuation of vortioxetine, these reactions were resolved. The patient’s history indicated that neither she took any medications nor she consumed any food, which might have caused allergies [24]. As per the Naranjo scale, the case falls under the category of probable ADR. Hyponatremia was also observed with the use of vortioxetine in a 72-year-old female patient [25]. The details of cases observed with ADRs with the use of vortioxetine are compiled in Table (3).

Table 1. Common ADRs associated with use of vortioxetine.

| System Organ Class | Frequency | ADRs |
|--------------------|-----------|------|
| Gastrointestinal disorders | Very common | Nausea, Diarrhoea, Constipation, Vomiting |
| Skin and subcutaneous tissue disorders | Common | Pruritus, including pruritus generalised |
| Psychiatric disorders | Common | Abnormal dreams |
| Nervous system disorders | Common | Dizziness |

very common (≥1/10); common (≥1/100 to <1/10).
**Table 2. Name, gender and age of patients experienced ADRs with use of vortioxetine in clinical trials.**

| Adverse Drug Reactions (ADRs)                                                                 | Number of Patients | Age  | Gender          | Dose                | Phase | References |
|--------------------------------------------------------------------------------------------|--------------------|------|-----------------|---------------------|-------|------------|
| Headache, nausea, sedation, upper abdominal pain, fatigue, vomiting, decreased appetite, and irritability | 48                 | 7-17 | Male and female | 5,10,15 or 20 mg/day | Phase III | [16] |
| Sexual dysfunction, nausea, depression, anxiety, insomnia, vomiting, headache, dizziness, pruritus, fatigue, anxiety | 711                | 18-55| Male and female | 10-20 mg/day        | Phase III | [17] |
| Nausea                                                                                       | 151                | 18-65| Male and female | 10-20 mg/day        | Phase III | [18] |
| Nausea, headache, dizziness, somolence                                                       | 493                | 18-75| Male and female | 10-20 mg/day        | Phase III | [19] |
| Nausea, constipation, dry mouth, dizziness, and insomnia                                      | 600                | 20-64| Male and female | 5, 10, or 20 mg/day | Phase III | [20] |

**Table 3. Detail of ADRs reported in case reports of vortioxetine.**

| Adverse Drug Reactions                              | Number of Patients | Age  | Gender | Dose                | References |
|-----------------------------------------------------|--------------------|------|--------|---------------------|------------|
| Glycolimia, weight gain and exacerbation of anxiety  | 1                  | 52   | Female | 5mg every night     | [23] |
| Galactorrhea and hyperprolactinemia                 | 1                  | 33   | female | 20mg/day            | [7]        |
| Petechiae, and ecchymoses, edema, itching           | 1                  | 43   | female | 5mg/day and 10mg/day| [24] |
| Itching and pruritis                                | 1                  | 35   | female | 5mg/day             | [24] |
| Hyponatremia                                        | 1                  | 72   | female | 5mg/day             | [25] |

Vortioxetine may have a safer profile compared with other existing SSRIs and SNRIs, particularly sexual dysfunction and weight gain. Vortioxetine showed low rates of sexual dysfunction and a favorable weight-gain profile. Gonda et al., (2019) reported a negligible effect of vortioxetine on weight gain [26] and Jacobsen et al. (2015) showed beneficial effects of vortioxetine in patients experiencing sexual dysfunction during antidepressant therapy with SSRIs [27]. These effects might be due to multimodal mechanisms (5-HT1A agonist, 5-HT1b partial agonist, SERT inhibitor, and 5-HT, 5-HT, and 5-HT antagonist) of vortioxetine which make it different from SSRIs and SNRIs. The common ADRs observed with vortioxetine are nausea and vomiting. The origin of nausea and vomiting is unknown and this effect is counterintuitive because of the established antiemetic activity of 5-HT3 antagonists. Thus, nausea and vomiting, which are observed with the use of vortioxetine can be due to the full agonist activity of the drug at 5-HT1A receptors, which cannot be excluded but is unlikely [28].

Emerging clinical trial results have also shown significant improvement in the cognitive function of adults with recurrent MDD after treatment with vortioxetine. McIntyre et al., (2014) conducted a randomized, double-blind, placebo-controlled study on the use of vortioxetine (10 and 20 mg/d) in cognitive function in depressed adults and concluded that both doses of vortioxetine significantly improved cognitive function of subjects. The effect of vortioxetine on cognitive function was independent of its effect on improving depressive symptoms [29]. Another clinical trial to study the effect of vortioxetine on the cognitive function of major depressive disorder (MDD) patients conducted by Mahableshwarkar et al., (2015) [30]. The trial was multicenter, randomized, double-blind, placebo-controlled, active-referenced ( duloxetine 60 mg), parallel-group study and results of the trial concluded that vortioxetine (10-20 mg) had significantly improved cognitive function and was well-tolerated in MDD patients (aged 18-65 years). Katona et al., (2012) also reported improvement of cognitive function of major depressive disorder patients after treatment of vortioxetine in a randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study. Overall, the beneficial effect of vortioxetine on the improvement of the cognitive function of MDD patients was independent of its antidepressant effect [31]. The effect of vortioxetine on the 5-HT system might be responsible for the improvement of cognitive function. Thus, based on available data of clinical studies, vortioxetine is a useful treatment option in patients with MDD where impaired cognitive function is apparent.

The treatment with vortioxetine is also simple and cost-effective. Christensen et al., (2018) reported vortioxetine as a cost-effective alternative to duloxetine [32]. Soini et al., (2017) reported vortioxetine as a good alternative in the treatment of MDD after conducting cost-utility analysis (vortioxetine versus venlafaxine XR and sertraline) [33]. Young et al., (2017) reported vortioxetine as a cost-effective treatment option in MDD [34].

**5. LIMITATION OF STUDY**

The current investigation does not include spontaneous data. The articles were extracted from PubMed only. Other search engines such as Cochrane and EMBASE were not used for this study.

**CONCLUSION**

In conclusion, vortioxetine is an antidepressant drug for the treatment of MDD. In addition, it also showed improvement of cognitive dysfunction in patients with MDD. The causality assessment results have shown a probable relation between vortioxetine and galactorrhea, hyperprolactinemia, edema, excessive itching, ecchymoses and petechiae. Weight gain, glycolimia and exacerbation of anxiety have a
possible relationship with vortioxetine. Thus, further studies are required to establish a strong relationship between these ADRs with vortioxetine.

CONSENT FOR PUBLICATION
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CONFICT OF INTEREST
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