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EDITORIAL

Vortioxetine: a comprehensive update on a new-generation antidepressant

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Major depressive disorder (MDD) is a chronic disease defined by one or more major depressive episodes lasting at least two weeks and no history of manic episodes (1). MDD affects approximately 6% of the world's adult population each year and is about twice as common in women than men (2). This disorder increases suicide and some important medical illnesses such as diabetes (3). According to the World Health Organization (WHO), depressive disorders are the single largest contributor to non-fatal health loss (7.5% of Years Lived with Disability) (4).

Although psychotherapy and electroconvulsive therapy are used, pharmacotherapy is still typically a primary form of treatment for MDD (5). Tricyclic antidepressants (TSA) and monoamine oxidase inhibitors (MAOIs) were the first antidepressant drugs, introduced in the 1950s (5). Second-generation antidepressants, such as selective serotonin reuptake inhibitors (SSRIs); selective serotonin and noradrenaline reuptake inhibitors (SNRIs); atypical antidepressants, such as bupropion; serotonin antagonist reuptake inhibitors, such as nefazodone; and agents with indirect noradrenergic and serotonergic effects, such as mirtazapine, are the most commonly used treatments for MDD, and are recommended as preferred treatments by most treatment guidelines (5-7).

However, the results of antidepressant treatment have not been completely satisfactory. The results of the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) clinical trial indicated that fewer than 30% of depressive patients had a sufficient response to a single antidepressant (8) and that remission was lower in patients with two failed treatments (9). Approximately half of patients respond poorly to first-line antidepressant treatment (10). Moreover, current treatments often have side effects (11). A recent systematic review and meta-analysis investigated the efficacy and safety of pharmacological and non-pharmacological treatments for MDD (12). According to the results, with the exception of probiotics, all of the treatments studied (acupuncture, mirtazapine, herbal medicine, venlafaxine, physical exercise, cognitive-behavioral therapy, bupropion, fluoxetine, and vortioxetine) appeared to be significantly more effective than placebo. In terms of safety, herbal medicine and mirtazapine demonstrated no significant difference in the overall risk of adverse events compared with placebo. Many patients with depression decide to discontinue treatment after their first antidepressant trial (13).

Patients who cannot tolerate an antidepressant medication or for whom it proves to be ineffective may benefit from another antidepressant drug with a different mechanism of action. Vortioxetine, desvenlafaxine, levomilnacipran, and vilazodone are examples of new-generation antidepressants. These new drugs may become the first choice of antidepressant medication for first-time users as well as a new option for patients whose treatment with older drugs has not been successful. Depression may

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not be due merely to a lack of serotonin in the brain, but a result of complex interactions of various neurotransmitters, including serotonin, norepinephrine, glutamate, and histamine. The combined mechanisms of action of new-generation antidepressants may provide greater therapeutic benefits (14).

New-generation antidepressants were designed with the goal of optimizing treatment efficacy and tolerability. Vortioxetine is one of the new antidepressants with multimodal activity (10). It is the first mixed serotonin agonist and antagonist antidepressant (7). It has been approved for the treatment of MDD in many countries, including European nations (15) and the United States (16). The antidepressant mechanism of action of vortioxetine combines serotonin transporter (5-HTT) inhibition and direct modulation of serotonin receptor activity; it is a 5-HT1A receptor agonist; a 5-HT1B receptor partial agonist; a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist; and a 5-HTT inhibitor (14,17,18). These additional serotonin receptor targets distinguish vortioxetine from other SSRIs and SNRIs, and this activity may provide unique clinical benefits for symptomatic recovery in MDD patients (7). Vortioxetine increases the extracellular concentration of various neurotransmitters, such as dopamine, histamine, noradrenaline, and acetylcholine, in addition to providing a regulatory effect on serotonin receptors and 5-HTT (14,18). The serotonin system has a positive effect on mood, affect, and cognition. Vortioxetine also modulates key neurotransmitters involved in cognitive regulation, such as glutamate, acetylcholine, histamine, dopamine, and noradrenaline (17).

Dose and Pharmacokinetics

Vortioxetine is available in 5-, 10-, and 20-mg tablets. Vortioxetine was found to be less effective at low doses of 2.5-5 mg, while a dose range of 5-20 mg is effective (17). The maximum dose of 20 mg vortioxetine has demonstrated a better clinical response than lower doses (19-22). However, the 20-mg dose has also been associated with a higher risk of side effects (14). An initial 10-mg dose once a day may be increased to 20 mg according to tolerability and clinical response (14). The pharmacokinetics of vortioxetine are linear and dose-proportional (23). Since the binding rate of vortioxetine to plasma proteins is 80-90%, it has a wide distribution volume (steady-state distribution volume of approximately 2600 L) (14,23). It has been reported that vortioxetine at higher doses (20 mg) was significantly superior to a placebo (14). It takes 3-16 hours to reach the maximum plasma concentration after ingesting the drug, and the terminal half-life is about 60-70 hours in multiple doses (14,23). Steady-state plasma concentrations are generally obtained within two weeks (23).

Factors such as age, sex, race/ethnicity, body weight, and liver or kidney impairment had no clinically significant effects on vortioxetine exposure (23). For example, no clinically meaningful difference in the pharmacokinetics of vortioxetine was observed between the data obtained from a study conducted in the Chinese population and previous data of a non-Chinese population (24).

Vortioxetine is largely metabolized trough oxidation and is a substrate for many CYP450 isoforms, primarily cytochrome P450 (CYP450) and 2D6 (CYP2D6) (14,17). Vortioxetine is metabolized by CYP450 enzymes and glucuronic conjugation via uridine diphosphate glucuronosyltransferase. The main metabolite is pharmacologically inactive, and the minor pharmacologically active metabolite is not expected to cross the blood-brain barrier, indicating that the main compound is primarily responsible for in vivo activity (23). Dose adjustment is recommended only for poor 2D6 metabolizers based on polymorphism of the cytochrome P450 enzymes involved (23). Concomitant use of vortioxetine and drugs other than bupropion, a potent CYP2D6 inhibitor, and rifampin, a broad CYP450 inducer, did not significantly affect the safety profile (23). For example, the use of vortioxetine with ethanol, diazepam, or lithium revealed no significant pharmacodynamic (i.e. psychomotor) effects and the combination was well tolerated (25).

Safety and Tolerance

Though generally mild, side effects have been reported to lead to greater discontinuation of vortioxetine treatment (3-11%) than placebo (1-8%) (18,19). The most common side effects reported in at least 5% of patients are nausea, headache, diarrhea, and dry mouth (20). Interestingly, it has been reported that side effects such as abnormal orgasm, ejaculation disorder, decreased libido, and erectile dysfunction have been noted not with the lowest commercially available dose of 5 mg (26), but with the 2.5 mg dose (26). Another interesting point is that the risk of side effects is greater in men than in women (18). Although a high rate of pruritus (56% overall) was observed in a phase I pharmacokinetic study conducted in Chinese patients with MDD, the rate was very low in the phase III study (0.8%) (24).

Baldwin et al. (27) observed that the common side effects (≥5% and >2x placebo) associated with the use of vortioxetine (5-20 mg/day) were nausea (20.9-31.2%) and vomiting (2.9-6.5%). The authors noted that the nausea was temporary, with a median duration of 9-16 days. Insomnia was recorded at a rate of 2.0-5.1% vs. 4.0% for the placebo, and sexual dysfunction 1.6-1.8% vs. 1.0% for the placebo. Symptoms occurring after abrupt discontinuation of treatment in the first and second weeks were similar to those with the placebo. Vortioxetine did not significantly affect clinical laboratory parameters, body weight, heart rate or blood pressure relative to the placebo, or demonstrate a clinically significant effect on electrocardiographic parameters, including the QTcF interval. No new side effects were seen in long-term treatment, and the average weight gain was 0.7-0.8 kg. The data indicate that vortioxetine (5-20 mg/day) is safe and generally well-tolerated in the treatment of MDD (7,27).

Efficacy and Tolerability

- Short-term Clinical Trials

Several randomized, double-blind, placebo-controlled (RDBPC) studies of patients diagnosed with MDD have evaluated the efficacy of multiple vortioxetine doses (5, 10, 15, or 20 mg/day) for different short periods (6, 8, or 12 weeks). In most of these studies, drug-treated MDD patients showed significant improvement compared with a placebo (19,28-32). The findings suggest that vortioxetine at clinically effective doses of 5-20 mg/day provides clinical efficacy for moderate to severe MDD (28). A randomized, double-blind (RDB) study using the atypical antidepressant agomelatine as an active comparator revealed statistically significant superiority with 10 or 20 mg/day vortioxetine treatment (33), while an eight-week RDBPC study with venlafaxine XR found that vortioxetine was at least as effective as venlafaxine XR and was better tolerated (34). The results of two previously conducted RDBPC phase III trials of vortioxetine for MDD in Japan did not suggest superior efficacy to a placebo (35,36). In another recent eight-week phase III study, patients were randomized to dosage groups of 10 mg (n=165) or 20 mg (n=163) vortioxetine or a placebo (n=161). The findings indicated that vortioxetine at both 10 mg/day and 20 mg/day doses demonstrated strong antidepressant efficacy in Japanese patients with MDD and was well tolerated (37). Kishi et al. (38) also conducted a systematic review and meta-analysis to investigate the benefits and effectiveness of vortioxetine in Japanese patients with MDD due to the different results seen in these phase III studies. The results of the meta-analysis showed that vortioxetine at both 10 mg and 20 mg doses provided a significant benefit for the treatment of MDD in Japanese patients, as reported by Inoue et al. (37). This result is consistent with a multinational review and network meta-analysis finding that vortioxetine was an effective antidepressant (39). The results of the first two studies (35,36) investigating the effectiveness of vortioxetine for MDD in Japanese patients may have been due to a type II error (i.e., low statistical strength). These two studies (35,36) showed a greater placebo response and a similar drug response when compared with the Inoue et al. (37) study.

A recent open study examined the efficacy of vortioxetine (daily dose 12.90±5.65 mg) in 66 outpatients with MDD and found a significant improvement on specific psychometric scales, and only a nonsignificant trend of association between higher dosage and effectiveness (40). In the total sample, 51.5% was classified as responding and 36.4% were classified as remitters. While two-thirds of the participants in this study did not report any side effects, among those who did, gastrointestinal side effects (72.7%) were most common. Almost two-thirds of the sample completed the follow-up process, while 36.4% discontinued treatment due to side effects (37.5%) and lack of efficacy (29.2%). Although this study provides an insight into the real-world efficacy and tolerability of vortioxetine, studies with larger samples are needed.

- Long-term Clinical Trials

The clinical efficacy of vortioxetine has also been assessed in long-term clinical trials. An open-label, 52-week study reported a 60% response rate and 61% remission rate in 834 MDD patients taking vortioxetine 5 mg/day for the first week, with subsequent dose adjustments from 2.5, 5 and 10 mg/day on the basis of response and tolerability, found that vortioxetine was effective in preventing the relapse of depressive symptoms (41). An analysis of data collected from five long-term, open-label extension studies noted higher response and remission rates over time, with a total response rate of 65% and a total remission rate of 60% over 52 weeks (42). Another RDPBC of 396 MDD patients in remission after acute treatment received open-label, fixed-dose vortioxetine (5-10 mg) or placebo found that vortioxetine significantly prolonged the time until relapse and the relapse rates decreased (13% vs. 26%) (22). These studies indicate that vortioxetine may help to prevent MDD relapse.

- Comparison of Vortioxetine with Other Antidepressants

Llorca et al. (43) indirectly compared vortioxetine with seven other antidepressants with different mechanisms of action in terms of efficacy and tolerability using meta-regression analysis. They found that vortioxetine was not significantly different from agomelatine, desvenlafaxine, duloxetine, escitalopram, sertraline, venlafaxine, or vilazodone in terms of efficacy. The authors also reported that vortioxetine was tolerated better than venlafaxine but not as well as agomelatine.

There have been few one-to-one comparisons between vortioxetine and other antidepressants. A systematic review by Li et al. (44) suggested that duloxetine was more effective than vortioxetine. However, patients treated with vortioxetine had a lower risk of developing side effects (e.g., nausea, diarrhea, hyperhidrosis, constipation, dry mouth, and decreased appetite). An RDPBC study comparing vortioxetine with venlafaxine resulted in no cross-group difference in functional remission, while vortioxetine was found to be superior in terms of minimal tolerance problems as well as symptomatic improvements (34).

Montgomery et al. (33) found that vortioxetine may be more effective than agomelatine in patients who did not have an adequate response to SSRI or SNRI treatment. Another 12-week RDB of a similar structure aimed to evaluate whether the efficacy and tolerability of vortioxetine were independent of previous SSRI (citalopram, escitalopram, paroxetine, sertraline) or SNRI (duloxetine, venlafaxine) treatment (10). The patients were randomized to vortioxetine (n=252, 10-20 mg/day) or agomelatine (n=241, 25-50 mg/day). Vortioxetine demonstrated superior performance to agomelatine and was well tolerated in poor responders to SSRI, while there were smaller, insignificant improvements in the SNRI subgroup.

- Meta-Analyses on Vortioxetine

A meta-analysis of 11 RDBPC studies with a treatment period of 6 to 8 weeks investigating the efficacy and safety of vortioxetine in patients with MDD concluded that vortioxetine 5, 10, or 20 mg/day was associated with significant decreases in the Montgomery-Asberg Depression Rating Scale (MADRS) total score compared with a placebo (-2.27, -3.57 and -4.57, respectively; p <0.01) (45). Patients receiving vortioxetine 10 or 20 mg/day had significant decreases in the scores of 9 of 10 MADRS individual items. Vortioxetine treatment was also associated with a significantly higher response rate (50% reduction compared with the initial MADRS score), significant improvements in remission (MADRS score ≤10), and other depression-related scores compared with a placebo. The authors reported that the results of this meta-analysis supported the efficacy of vortioxetine (5-20 mg/day) in adults with MDD and that the treatment effect of vortioxetine increased with the dosage.

Koesters et al. (46) included 15 studies (7746 participants; seven placebo-controlled studies, eight studies comparing vortioxetine with SNRI) in a Cochrane review. Vortioxetine was found to be more effective than a placebo in response (Mantel-Haenszel risk ratio [RR]: 1.35, 95% confidence interval [CI]: 1.22-1.49; 14 studies with 6220 participants), remission (RR: 1.32, 95% CI: 1.15-1.53; 14 studies with 6220 participants), and depressive symptoms (mean difference [MD]: -2.94, 95% CI: -4.07 to -1.80; 14 studies, 5566 participants) measured using the MADRS. There was no significant difference in the rate of treatment termination. (RR: 1.05, 95% CI: 0.93-1.19; 14 studies with 6220 participants). More participants discontinued use of vortioxetine (moderate evidence) compared with a placebo due to side effects (RR: 1.41, 95% CI: 1.09-1.81; 14 studies with 6220 participants), than due to ineffectiveness (RR: 0.56, 95% CI: 0.34-0.90; 14 studies with 6220 participants). Low-quality evidence from eight studies demonstrated no clinically significant difference in response or remission between vortioxetine and SNRIs.

Zheng et al. (47) analyzed eight RDBPC studies (n=2354) of vortioxetine 10 mg/day in adult patients with MDD in a meta-analysis. The results demonstrated that the response rates (odds ratio [OR]: 1.88, 95% CI: 1.40-2.53; p<0.0001) and remission rates (OR: 1.54, 95% CI: 1.27-1.86; p<0.00001) of vortioxetine 10 mg/day users were significantly higher from those of placebo users. The positive score change in the MADRS and other scales (MD: -3.50, 95% CI: -4.83 to -2.17; p<0.00001) was found to be statistically significant. However, vortioxetine users reported more nausea (OR: 4.18, 95% CI: 3.21-5.44; p<0.00001) and constipation (OR: 1.88, 95% CI: 1.14-3.09; p=0.01).

Cipriani et al. (39) compared the efficacy and acceptability of 21 antidepressant drugs in a systematic review and network meta-analysis and reported that vortioxetine was more effective than plasebo (OR: 1.65, 95% CI: 1.44-1.88) and was equivalent to a placebo in terms of discontinuation of treatment (OR: 1.01, 95% CI: 0.86-1.19). Agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were found to be the most effective

(OR: 1.19-1.96), while agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and other antidepressants were better in terms of less termination of treatment (OR: 0.43-0.77).

Another review reported that vortioxetine was effective as an antidepressant, tolerable in terms of both short- and long-term side effects, including fewer sexual function side effects, and had a direct therapeutic effect on cognitive function (48). Two other systemic reviews and meta-analyses noted that although vortioxetine was significantly more effective than a placebo for the acute treatment of MDD, it may not be more effective than an SNRI and was generally equally effective (49,50).

Efficacy in Specific Symptoms or Groups

- Effect of Vortioxetine on Anhedonia

Anhedonia is defined as the impairment of the capacity to experience pleasure or gratification. Anhedonia is a common symptom of MDD and has been reported in approximately 75% of patients (51). This is important because anhedonia and impaired reward learning have been associated with a poorer disease prognosis and treatment response (52). A recent study showed that vortioxetine significantly improved anhedonia (53). The unmet need in depression treatment is to improve the patient's functionality and other patient-reported negative outcomes such as quality of life. Antidepressants that can alleviate anhedonia and cognitive dysfunction can help in this regard, since improvement in these areas is associated with improvement in psychosocial function and quality of life.

- The Effect of Vortioxetine on Emotional Blunting

Almost half of patients treated with SSRIs/SNRIs reported limitations in the full spectrum of emotion that they would normally experience even during remission, or in other words, emotional blunting (54). The COMPLETE study evaluated the efficacy of 10 or 20 mg of vortioxetine per day in patients receiving outpatient treatment for MDD who had a previously inadequate response to an SSRI or SNRI and who were emotionally blunted (55). About half of the patients reported no emotional blunting after just eight weeks of treatment. Similarly, patients showed improvement in all other variables evaluated, including motivation and energy, cognitive performance, depressive symptoms, and general functionality. The authors reported that improvement in emotional blunting was associated with improvement in functionality, as well as energy and motivation, regardless of improvement in depressive symptoms.

-The Effect of Vortioxetine in the Treatment of MDD in the Elderly

Depression is more common in the elderly and individuals with chronic medical problems or cognitive impairments, and depression can exacerbate the course of these problems or cognitive impairments (56). Depression in the elderly may have atypical features and may not meet the depressive disorder criteria. Some 15% of the elderly have symptoms of depression but not MDD, so treatment of elderly patients requires special attention and experience (1,57). Vortioxetine demonstrated greater efficacy than a placebo in a pairwise meta-analysis of studies conducted in patients over 65 years of age (58). A recent RDB study compared 60 patients diagnosed with MDD and a Hamilton Depression Rating Scale score of ≥19 classified into two groups that received vortioxetine (15 mg/day) or sertraline (75 mg/day) for six weeks (59). There was no significant difference between the groups in terms of response rate, remission rate, response time, time to remission, or side effects. The results of this study indicated that vortioxetine was as effective and reliable as sertraline in the treatment of elderly patients with MDD.

- The Effect of Vortioxetine on Physical Symptoms

Only patients treated with 5 or 10 mg of vortioxetine (therapeutic doses) or placebo were included in a meta-analysis to evaluate the effect of vortioxetine on physical symptoms using data from five RDBPC studies (60). The results showed that vortioxetine treatment of MDD patients, including those with high levels of anxiety symptoms, led to significant improvements in MDD-related physical symptoms.

- The Effect of Vortioxetine on Cognitive Impairment

Preliminary evidence suggests that cognitive dysfunction in individuals with MDD is a major cause of general functionality impairment (e.g., workplace performance) (61). Moreover, it has been suggested that improvement in cognitive function significantly affects functional recovery from an MDD episode (62). Cognitive impairment is increasingly acknowledged as a fundamental deficiency in patients with MDD and treatment-resistant depression (TRD) (7). Evidence suggests that clinically significant deficiencies in execution, attention, and memory function occur in many MDD patients during a depressive episode (63,64). In some MDD patients, these impairments in cognitive function persist independently even after recovery from depressive

symptoms (65). Although some studies suggest that dysfunction in the rostral anterior cingulate cortex may contribute to the development of cognitive impairment, further research is needed to understand the precise relationship between impairments in cognitive function and MDD (66). In addition, the ability of antidepressant treatments to improve cognitive impairment in MDD and TRD patients is limited (67,68). Approximately 30% of patients successfully treated with SSRIs continue to report significant impairment in cognitive function (69).

Vortioxetine has been reported to have positive effects on cognition in patients with MDD. A systematic review by Rosenblat et al. (70) suggested that vortioxetine can improve psychomotor speed, executive function, and delayed recall fields (standardized MD [SMD]: 0.2-0.3), possibly due to its antagonistic effect on 5-HT7 receptors. In an eight-week study, McIntyre et al. (32) evaluated the cognitive function of MDD patients and found that executive function, processing speed, attention, learning, and memory results using objective neuropsychological tests and subjective measurements were superior to a placebo with 10 or 20 mg/day vortioxetine use. It was reported that these positive effects on cognition were not secondary, indirect effects of the relief of depressive symptoms with medication, but were direct, positive effects of vortioxetine on cognition. Another study also noted positive improvements in all areas of cognitive function in elderly patients treated with similar doses of vortioxetine compared with patients treated with a placebo (31).

In a multicenter RDBPC and actively referenced (duloxetine 60 mg) parallel-group study, vortioxetine (10-20 mg) achieved significantly greater improvement in cognitive function, depression, and overall functioning than a placebo in adults (18-65 years) with MDD, and was reported to be well tolerated (71). Duloxetine treatment yielded better results compared with a placebo on subjective measures of cognitive function but did not demonstrate significant superiority in the results of two objective neuropsychological tests. This study also revealed that the beneficial effect of vortioxetine on cognitive function was a direct therapeutic effect rather a result of a reduction in depressive symptoms.

The FOCUS study, which is an efficacy study of vortioxetine on cognitive dysfunction in adult patients with MDD, evaluated changes in cognitive function in 602 patients with MDD who received vortioxetine (10 or 20 mg) or a placebo and it was observed that vortioxetine was effective in improving cognitive function (72). The positive improvement in cognitive function appeared independently of the alleviation of depressive symptoms.

The results of an RDBPC and active referenced study showed that treatment with vortioxetine (10 mg/day) or paroxetine (20 mg/day) significantly improved overall cognitive performance and clinician-assessed functionality compared with a placebo (73). Furthermore, the improvements in depressive symptoms were found to be similar in the vortioxetine and paroxetine groups, while Digit Symbol Substitution Test (DSST) results indicated that neuropsychological improvement was greater in the vortioxetine group. Baune et. al. (74) subsequently reported that vortioxetine (SMD: 0.325, 95% CI: 0.120-0.529; p=0.009) was more effective than escitalopram, nortriptyline, SSRI, or TSA antidepressants in improving DSST performance. Another eight-week RDBPC study that investigated the effect of vortioxetine on cognitive function in MDD patients divided the participants into three groups (first group: SSRI+placebo, second group: SSRI+vortioxetine [10-20 mg/day], and third group: vortioxetine [10-20 mg/day]+placebo) (75). An improvement in cognitive performance was found in patients with MDD in remission without significant difference between treatments. Secondary results showed that vortioxetine monotherapy demonstrated benefits in cognitive performance and depressive symptoms, although not of statistical significance.

Impairment in cognitive function is thought to lead to impairment in general functionality. A study conducted among actively working patients using vortioxetine for MDD revealed a strong association between cognitive function and real-world functionality and long-term benefits of vortioxetine treatment (76). Finally, a review also reported that vortioxetine appeared to be a useful and promising treatment option in MDD patients with cognitive dysfunction, but its role in treatment needs to be further clarified (77).

- Effect of Vortioxetine on the General Functionality

The functionality level during the index depressive episode appears to be a better predictive for recovery than the severity of symptoms. Therefore, the level of functionality should be taken into consideration when assessing depression recovery (78). In an 8-week duloxetine (60 mg/day) referenced RDBPC study of 529 patients with moderate to severe MDD, once-daily vortioxetine (10 or 20 mg/day) treatment was found to provide better functionality results than a placebo (MD:

5.9, 95% CI: 1.5-10.4), while no significant effect was observed with duloxetine (79). This study also found that 96.9% of the vortioxetine effect on functionality was directly attributable to a treatment effect, and improvements in depressive symptoms did not mediate this effect. Symptomatic remission and functional recovery should be considered overarching treatment goals of antidepressant therapy. Three groups (vortioxetine [10 or 20 mg], duloxetine [60 mg], and placebo) were formed for an eight-week multinational, RDBPC, duloxetine-referenced study evaluating the effect of vortioxetine in adult outpatients with moderate to severe MDD (n=602) (80). Vortioxetine exerted a strong dual effect on depressive symptoms and functional capacity, whereas duloxetine did not.

There are also studies linking improvement in functionality with improvement in cognitive function. Levada and Troyan (81) conducted a study in Ukraine and reported that the improvement in cognitive function was the most important determinant of improvement in general functionality and that it was among the key contributors to the improvement of workplace performance. In the AtWoRC (Assessment in Work Productivity and the Relationship with Cognitive Symptoms) study, which evaluated vortioxetine treatment in terms of cost and benefit, it was found that after 52 weeks of treatment with vortioxetine, patient absenteeism decreased, productivity increased, and drug treatment represented a savings, depending on the improvement in MDD symptoms (82). The authors reported that workplace productivity gains as a result of vortioxetine treatment would lead to significant cost savings for the Canadian economy.

- Effect of Vortioxetine with Comorbid Alcohol Use Disorder

Despite the high prevalence of alcohol use disorder (AUD) and MDD comorbidity, and the severity and adverse consequences of both diseases, the available evidence is still inadequate to even outline the treatment strategies for these patients, and the treatment guidelines have failed to reach consensus on the issue (83). Systematic reviews have reported that SSRIs, SNRIs, and TSAs show some efficacy in improving both depressive symptoms and some AUD-related traits, including the number of drinks per drinking days and the number of patients who abstained from alcohol use (84-86). However, in depression secondary to alcohol use, the antidepressant effect remains even more modest than the effect on independent primary depression (85). Treatment of this clinical population is further complicated by the frequent occurrence of alcohol-related medical comorbidities that may limit the range of drugs available for use (83). A recent study evaluated the therapeutic effect of vortioxetine (10-20 mg/day, flexible-dose) with psychosocial support in patients with MDD and comorbid AUD (n=57) and patients with MDD alone (n=56) paired for baseline features (83). Vortioxetine significantly improved depression in patients with comorbid MDD and AUD, and a significant proportion of participants (45.6%) achieved clinical remission for depression. Additionally, baseline to endpoint improvements on all secondary outcomes (anxiety, anhedonia, cognitive functions, functionality, quality of life, and severity of general clinical symptoms) ($p<0.001$) were observed, with no significant difference between groups. Given the response seen in depression symptoms, cognitive function, and general functionality; its good reliability and tolerability profile; and its low potential for abuse, vortioxetine may be an appropriate drug therapy for patients with comorbid MDD and AUD as part of an integrated therapeutic rehabilitation program.

-The Effect of Vortioxetine with Comorbid Generalized Anxiety Disorder

The effects of vortioxetine on generalized anxiety disorder (GAD) have also been studied. Preliminary data from preclinical studies suggest that vortioxetine has the potential to be an effective treatment for MDD with GAD (87). Several RDBPC studies of the efficacy of vortioxetine for GAD were included in the meta-analysis conducted by Pae et al. (88). The results showed that vortioxetine was more effective than a placebo and provided a modest effect, with an SMD of -0.118. Vortioxetine performed better in a sample of patients with severe GAD (SMD: 0.338). The most common side effects associated with vortioxetine in all four studies included in the research were nausea, headache, dizziness, and dry mouth. A more recent meta-analysis revealed that although multiple doses of vortioxetine (2.5, 5, or 10 mg/day) provided improvement when compared with a placebo, it did not reach a statistically significant level (89). In addition, no statistically significant difference was found between multiple dose administrations in terms of remission rates, discontinuation for any reason, side effect rates, quality of life or disability scores. The authors stated that vortioxetine was safe and well-tolerated, and that the data should be interpreted carefully, as the research was based on a limited number of RDBPC studies.

- The Effect of Vortioxetine with Comorbid Anxiety Disorder

Comorbid anxiety is common in MDD, and the presence of both is more difficult to treat than MDD alone. In a meta-analysis of 10 RDBPC trials of 6 to 8 weeks' duration in adults (18-75 years), vortioxetine treatment (5-20 mg/day) demonstrated significant superiority over a placebo in MADRS scores (vortioxetine 5 mg/day: n=415, MD:-2.68, p=0.005; 10 mg/day: n=373, MD: -3.59, p<0.001; 20 mg/day: n=207, MD:-4.30, p=0.005) and the Hamilton Anxiety Rating Scale (HAM-A) (5 mg/day: n=419, MD:-1.64, p=0.022; 10 mg/day: n=373, MD:-2.04, p=0.003; 20 mg/day, n=207, MD:-2.19, p=0.027) scores (90). Significantly greater improvement was found in the HAM-A psychic subscale for all doses compared with a placebo. The most common side effects (5.0%) were nausea, headache, dizziness, dry mouth, diarrhea, nasopharyngitis, constipation, and vomiting. The authors noted that vortioxetine reduced the symptoms of depression and anxiety in patients with MDD and severe anxiety. In a 52-week flexible-dose (15 or 20 mg/day) open extension study, Jacobsen et al. (91) analyzed three 8-week RDBPC studies of patients who completed vortioxetine treatment and found that the vortioxetine treatments were safe and well-tolerated, and that the patients continued to show improvement in depression and anxiety symptoms and general functionality throughout their treatment period. The results of these two studies indicate that vortioxetine may be a good choice to treat MDD with comorbid anxiety.

- Effect of Vortioxetine in Patients with a History of Trauma

A history of trauma is common in patients with MDD and can have a substantial impact on treatment. In a study analyzing data from four RDBPC studies investigating the effectiveness of vortioxetine (5-20 mg/day) and a placebo in MDD patients (18-75 years of age), 61% (1113/1811) of the participants had no history of trauma (in childhood and/or recently) (92). Vortioxetine was found to have significant short- and long-term efficacy on depression and anxiety symptoms as well as general functionality of MDD patients with a history of trauma, and also reduced the risk of relapse (RR: 2.8) compared with a placebo.

- Effect of Vortioxetine on Sexual Dysfunction, Weight, and Sleep

In a thought-provoking study by Jacobsen et al. (93), participants with MDD who had been treated with citalopram, paroxetine, or sertraline and responded to treatment but suffered from sexual dysfunction were randomized to receive vortioxetine (10 or 20 mg; n=225) or escitalopram (10 or 20 mg; n=222) for eight weeks. Antidepressant efficacy was similar and continuous in both groups, and the safety profiles were similar to those in previous studies. The authors found that switching to vortioxetine provided a significant advantage to patients with SSRI-induced sexual dysfunction. In another sample, vortioxetine demonstrated a positive profile in terms of sexual side effects with no significant difference in side effects for different doses (40). No weight gain was observed in placebo-controlled studies and in open-label extension studies with vortioxetine (27,40). A low incidence of sexual dysfunction and sleep disturbance with vortioxetine treatment were attributed to receptor modulation (28).

- Switching from Other Antidepressant Therapies to Vortioxetine Therapy

Two studies have evaluated the effects of initiating vortioxetine treatment following an unsatisfactory response to SSRI or SNRI monotherapy (94). In a study of vortioxetine (Lu AA21004) in comparison to agomelatine in adults suffering from MDD with inadequate response to previous medication (REVIVE), 493 MDD patients with an inadequate response to SSRI or SNRI monotherapy were randomized to receive vortioxetine or agomelatine for 12 weeks (33). Vortioxetine patients recorded lower scores on depression scales and had better response and remission rates. Moreover, the proportion of patients who discontinued treatment due to side effects of vortioxetine was lower (9.5% vs. 5.9%). Common side effects (5%) were nausea, headache, dizziness, and drowsiness. Vortioxetine was determined to be safe and well-tolerated. In the second study, 252 MDD patients with an inadequate response to SSRI or SNRI monotherapy were similarly randomized to 12-week double-blind treatment with either 10-20 mg of vortioxetine or 25-50 mg of agomelatine. Vortioxetine was found to be significantly more effective than agomelatine in terms of improving depressive symptoms in those who did not respond to SSRIs, but the superiority of vortioxetine was not evident in those who did not respond to SNRIs (10).

A study conducted in Finland assessed the cost-benefit of switching to vortioxetine treatment in MDD patients with an inadequate response to SSRIs or SNRIs

in a comparison with other replacement drugs (agomelatine, bupropion SR, sertraline, and venlafaxine XR) (95). Vortioxetine cost less, both directly and indirectly, and was found to be more effective than all compared drug therapies. The average annual direct cost of vortioxetine was 4% less than venlafaxine XR and 8% less than sertraline. The higher efficacy associated with vortioxetine treatment resulted in a higher percentage of patients in remission and recovery. The cost-benefit analysis demonstrated that vortioxetine could be a good alternative for MDD patients. In the PREDDICT (a study investigating the efficacy of augmenting vortioxetine with celecoxib) trial, 80 patients who had previously used an antidepressant other than vortioxetine (SSRI, SNRI, mirtazapine, or agomelatine) initiated vortioxetine treatment (96). The side effects observed were generally mild. There was a decrease in the mean total MADRS score from the baseline to week two of 2.5 (SD=6.0) and an additional 2.5 (SD=5.9) from week two to the week four. The research indicates that switching from other antidepressants to vortioxetine can be done safely and is generally well tolerated.

CONCLUSION

Vortioxetine is a novel multi-modal antidepressant. The combination of inhibition of the serotonin transporter and serotonin receptor subtypes (5-HT1A, 5-HT1B, 5-HT1D, 5-HT3, 5-HT7) appears to offer clinical advantages to the existing, more selective antidepressants (7). RDB studies have examined and affirmed the efficacy of vortioxetine in the treatment of MDD at a dose range of 5-20 mg in adults (14). In studies with patients with an inadequate response to SSRI or SNRI monotherapy who switched to vortioxetine or agomelatine, vortioxetine was found to be superior, with lower depression scale scores and improved response and remission rates. The research also indicates that switching from SSRI or SNGI treatment to vortioxetine treatment was achieved without any problems.

Clinical trials have provided evidence that vortioxetine significantly improved cognitive impairment as well as depressive symptoms in MDD patients (7). Vortioxetine (10 or 20 mg/day) improved attention, processing speed, executive function, learning, and memory measures in MDD patients. These gains were attributed to the direct effect of the drug on cognitive function, not as an indirect effect of the alleviation of depressive symptoms (7). This feature distinguishes the clinical benefits of vortioxetine from those of other antidepressants. Data from clinical trials has revealed that vortioxetine improved information processing speed, which is an important aspect of cognitive dysfunction observed in MDD patients. The data were sufficient for the US Food and Drug Administration to update the label of vortioxetine and include this new information with the drug's therapeutic benefits (7). In the future, it will be important to investigate the effectiveness and tolerability of vortioxetine in the treatment of depression associated with neurodegenerative disorders such as multiple sclerosis, dementia, or Parkinson's disease, where cognitive dysfunction is a significant problem.

Improvements in general functionality, quality of life, and anxiety have also been reported with vortioxetine (14). The data of vortioxetine use in cases of comorbid AUD and MDD are limited, but the results also appear to be promising (83).

The most common side effect is nausea, particularly at the beginning of treatment. Vortioxetine is one of the most tolerable antidepressants and has low treatment discontinuation rates (39). The receptor modulation activity of vortioxetine is likely responsible for the low incidence of weight change, sexual dysfunction, and sleep disorders.

The studies included in this review suggest that vortioxetine can be an effective treatment for MDD as a first treatment option or in instances of an inadequate response to other antidepressants. Switching from other antidepressant therapies to vortioxetine has been shown to be successful and uncomplicated. Vortioxetine also appears to significantly lower the risk of relapse of MDD. It is also noteworthy that the results of studies conducted in countries such as China and Japan support the findings of research conducted in North America and Europe.

It has been demonstrated that vortioxetine had a direct positive effect on cognitive impairment in patients with MDD, and improved overall functionality and quality of life. Preliminary data have also indicated that vortioxetine may be a promising treatment option in cases of MDD with comorbid AUD or anxiety disorder. Reports suggest that vortioxetine may be effective on anhedonia, a symptom of MDD, and emotional blunting, which can occur with SSRI drugs. Furthermore, vortioxetine has a low rate of treatment discontinuation and is considered to be safe and tolerable in terms of side effects. Vortioxetine appears to be a valuable option in MDD treatment.

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