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The use of vortioxetine in the treatment of depression following the failure of therapy with a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor

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Summary

Up to 40% of patients with depression do not respond to first-line treatment and among those who do respond, only about half achieve remission. For this reason, guidelines for treating depression mainly focus on how to proceed in cases of treatment failure or only partial response. The aim of this review paper is to present studies evaluating the effectiveness of vortioxetine in treatment of patients with depression following treatment failure with an SSRI/SNRI drug.

Vortioxetine is an effective antidepressant that, after treatment failure with an SSRI/SNRI drug, allows 32–55% of patients to achieve remission. However, the assessed dosing regimen of vortioxetine deviated from that used in the initial therapy of depression, i.e. by the second week (8th day) of therapy the dose was increased to the maximum – 20 mg/day and the period for treatment effectiveness assessment was 8–12 weeks. This dosing regimen more closely resembles the pharmacological approach utilised in the treatment of obsessive-compulsive disorder rather than depression. The administration of a high dose of vortioxetine did not negatively impact the tolerability of the treatment, even among patient groups at high risk of adverse events (elderly patients, co-existence of anxiety). The most common adverse effect was nausea; however, it was not observed that rapid dose escalation intensified this effect. This is most likely attributable to the receptor profile of vortioxetine.

Key words: vortioxetine, dosage regimen, efficacy

Introduction

Advancements in pharmacological treatment mean that an increasing number of patients suffering from depression can be effectively and safely treated in primary health care setting [1]. However, this does not imply that treating depression has become an easy task. Up to 40% of patients with depression do not respond to the first-line

drug, and among those who do respond, only about half achieve remission [2, 3]. This means that nearly 70% of individuals affected by depression either do not respond to treatment or experience residual symptoms of depression, the persistence of which significantly worsens the prognosis by increasing the risk of relapse and shortening the time to relapse [4].

For these reasons, guidelines on depression treatment focus largely not only on how to diagnose and initiate treatment, but also on what to do in cases of treatment failure or only partial success [5]. The first step should always be the analysis of its possible reasons. This includes verification of the diagnosis, assessment of treatment adherence, the dose of the medication used and the treatment duration. In the differential diagnosis, besides excluding somatic causes and the use of psychoactive substances, particular attention should be given to whether resistance to antidepressant treatment is attributable to unrecognised bipolarity. A common issue explaining the lack of full improvement is the limitation of treatment solely to pharmacotherapy. This may result in a lack of improvement in factors perpetuating depression. These include, among others, negative thought patterns, low self-esteem, lack of stress coping skills, social isolation, interpersonal difficulties, traumatic experiences, lack of daily routine and life goals, and unfavourable habits such as lifestyle-related factors [6]. Failure to consider these factors and the lack of educational, supportive and therapeutic interventions in the treatment plan are among the reasons explaining the lower efficacy of depression treatment protocols based solely on pharmacotherapy compared to coordinated and integrated care. In the latter, a general practitioner, supported by other healthcare system specialists, provides comprehensive support to patients with depression [7], including psychological interventions [8]. These observations also explain why antidepressants, which are highly effective in psychiatric setting, sometimes do not show the expected antidepressive effect during a 6-week therapy in general practice [9].

Depression treatment guidelines clearly describe how to conduct pharmacological treatment after the failure of first-line therapy. Available options include increasing the dose, switching the antidepressant to another, potentiating the antidepressant with a drug from another group, combination therapy, using other biological interventions, particularly electroconvulsive therapy and other methods of brain activity stimulation or modulation [5]. In clinical practice, treatment often begins with drugs from the selective serotonin reuptake inhibitors (SSRIs) group, and if unsuccessful, the treatment is changed to a drug from the serotonin and norepinephrine reuptake inhibitors (SNRIs) group or combined treatment with two antidepressants is used, e.g. an SSRI and bupropion. An alternative approach is the use of a receptor-acting drug, such as vortioxetine. Other drugs where the mechanism of action significantly involves activating or blocking specific receptors include trazodone, mirtazapine and agomelatine [5]. Switching to these drugs or adding them to SSRI/SNRI treatment is often chosen when SSRIs/SNRIs are poorly tolerated, leading to side effects such as nausea, sexual dysfunction, anhedonia, anxiety, or sleep disturbances. In certain patient populations, receptor-acting drugs may surpass the efficacy of SSRIs/SNRIs and should be preferred,

e.g. when insomnia is present (trazodone, mirtazapine, agomelatine). Moreover, in a naturalistic study, it was found that switching of patients with unsatisfactory response to SSRIs to trazodone in the XR formulation was associated with an improvement in depressive, anxiety and anhedonia symptoms. Additionally, male patients also showed improvements in sexual function [10]. In the case of vortioxetine, this superiority is particularly evident in cognitive function disorders [5, 11]. Data published in recent years, however, indicate much broader indications for the use of this drug.

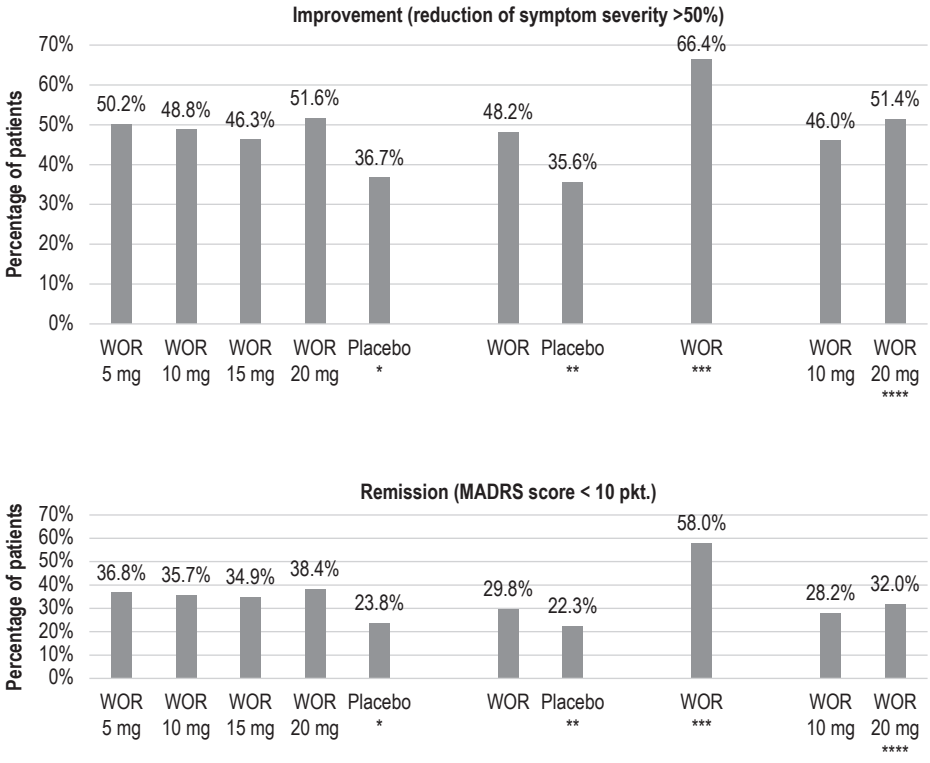
The aim of the article is to present research evaluating the effectiveness of vortioxetine in treating patients with depression after the failure of treatment with an SSRI/SNRI drug, with particular attention to the necessity of using a high dose, its swift increase, and the tolerance of high doses of vortioxetine, including in patient populations with a higher risk of adverse effects.

Antidepressant effectiveness of vortioxetine in clinical practice

One of the significant limitations in treating depression, but also in treating other mental disorders, is the often described lower effectiveness of drugs in everyday clinical practice compared to data from randomised clinical trials (RCT) [12]. In the case of vortioxetine, randomised clinical trials have shown that the percentage of patients with significant improvement (a decrease in symptom severity by at least 50%) is around 50% (50.2% at a 5 mg dose, 48.8% for a 10 mg dose, 46.3% for a 15 mg dose, and 51.6% for a 20 mg dose), compared to 36.7% of patients in the placebo group (Figure 1). The percentage of patients achieving remission is around 36% (36.8% at a 5 mg dose, 35.7% at a 10 mg dose, 34.9% at a 15 mg dose, 38.4% at a 20 mg dose), compared to 23.8% in the placebo group [13].

In a more recent meta-analysis of clinical trials, it was shown that vortioxetine surpasses placebo in achieving improvement (48.2%, vs. 35.6%) and remission (29.8% vs. 22.3%). On average, 5.3% of patients treated with vortioxetine and 3.6% of patients taking placebo discontinue treatment due to adverse effects. This analysis also includes a comparison of the efficacy and tolerance of vortioxetine to SNRI and SSRI drugs. Treatment with vortioxetine compared to venlafaxine was associated with almost the same effectiveness (relative risk – RR for improvement = 1.03, for remission = 0.99), with better treatment tolerance (RR for adverse effects = 0.91 and 0.42 for discontinuation of therapy due to adverse effects). Vortioxetine was inferior to duloxetine in achieving improvement (RR 0.86) and remission (RR 0.85). However, it was better tolerated (RR for adverse effects = 0.89), although it did not significantly differ from duloxetine in discontinuations of therapy due to adverse effects (RR = 0.92). No significant differences in effectiveness and treatment tolerance were found in comparisons of vortioxetine with SSRI drugs [14].

In a meta-analysis that included both retrospective and prospective observational studies without randomisation and control groups, the percentage of patients with improvement during vortioxetine treatment was determined to be 66.4% and the per-



WOR – vortioxetine
Based on: * [13]; ** [14]; *** [15]; **** [17].

Figure 1. **Effectiveness of vortioxetine, represented as the percentage of patients achieving improvement and remission of depressive symptoms**

centage of patients achieving remission to be 58.0% [15]. These values are therefore higher than those described in RCTs.

The effectiveness of vortioxetine in everyday clinical practice was described, among others, in the RELIEVE study in a group of 737 patients over a 24-week treatment period. This study indicates that in the absence of reimbursement restrictions, vortioxetine was used as the first-choice treatment in 43% of patients. Among patients who had previously taken other antidepressants, the main reason for switching to vortioxetine was the lack of efficacy of the previous treatment. This situation applied to 80% of patients, and only in 10.8% of cases the change was due to poor tolerance of the previous drug. The treatment usually started with a dose of 10 mg/day (53.9% of patients), the initial dose of 5 mg was used in 31.6% of patients, 15 mg/day in 5.5%, and 20 mg/day in 9.0% of patients. Adverse effects were observed in 21.2% of patients, the most common being nausea (8.2%). Treatment was discontinued due to adverse effects by 6.8% of patients [16].

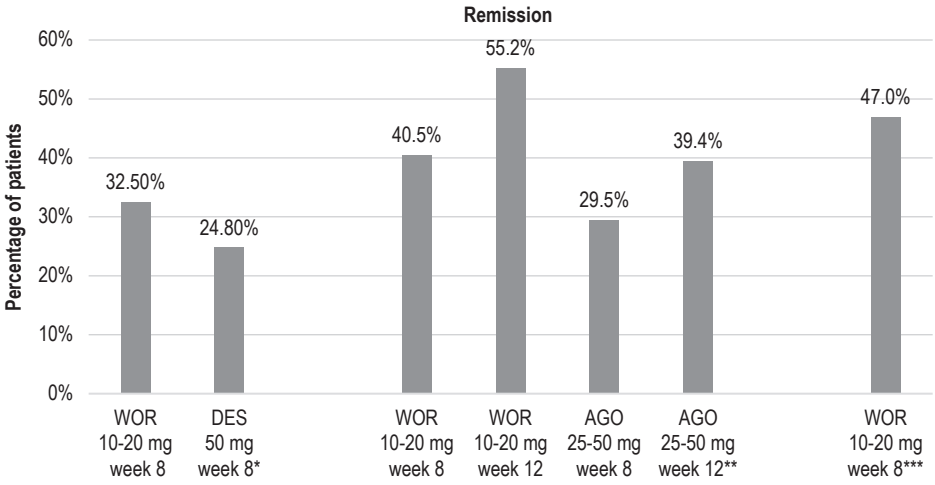
In 2023, an additional analysis of data from six RCTs on short-term (up to 8 weeks) treatment with vortioxetine was published. It demonstrated that patients treated with a dose of 20 mg/day were significantly more likely to achieve improvement than patients treated with a dose of 10 mg/day – 51.4% vs. 46%. Remission of symptoms was observed in 32% and 28.2% of patients respectively. The percentage of patients experiencing adverse effects did not differ significantly between the compared groups. The novel approach in the conducted studies was principally the timing of dose escalation, which transpired after the first week of therapy, on the eighth day of treatment. This resulted in a significant improvement in depressive symptoms, as assessed by the *Montgomery-Asberg Depression Rating Scale* (MADRS), in the second and fourth weeks of treatment [17].

In the context of the clinical effectiveness of vortioxetine, data indicating that the improvement and remission of depressive symptoms during the use of this drug, as well as the improvement of cognitive functions that translate into improved functioning at work, are also noteworthy. In a study evaluating various areas of workplace functioning, improvement was found in all assessed areas after 12 and 52 weeks of vortioxetine treatment, including reduced presenteeism and absenteeism [18]. An interesting method of assessing the antidepressant effectiveness of vortioxetine was also presented in the study by McCue et al. [19]. It relied on determining what percentage of patients, who switched to vortioxetine due to the ineffectiveness of the previously used drug, achieved the goals set by the patient. These included activities such as spending time with family or friends at least 3 times a week, cleaning the house for at least 2 hours a week, going for walks at least 3 times a week. At 12th week of vortioxetine treatment such improvement was determined in 57.8% of patients [19].

Effectiveness of vortioxetine in treating depression after SSRI/SNRI therapy failure

The effectiveness of vortioxetine at a dose of 10–20 mg after SSRI treatment failure was evaluated in the VIVRE study [20]. The control group consisted of patients who switched from SSRIs to desvenlafaxine 50 mg (drug not available in Poland). The duration of the treatment was 8 weeks. Desvenlafaxine is an active metabolite of venlafaxine. In addition to exhibiting reduced variability in drug metabolism, it offers more balanced effects on the noradrenergic and serotonergic systems compared to venlafaxine. The recommended dose is 50 mg/d, as doses up to 400 mg used in clinical studies did not show higher effectiveness than treatment with a dose of 50 mg/d. It was found that in the vortioxetine-treated group, more patients achieved remission (32.5% vs. 24.8%) as assessed by the CGI-S scale (Figure 2), which was also accompanied by greater improvement in social functioning.

The most common adverse effect in both groups was nausea, occurring in 20% of patients treated with vortioxetine and 9% of patients treated with desvenlafaxine. Treatment was discontinued by 1.9% of patients treated with vortioxetine and 1% of



WOR – vortioxetine; DES – desvenlafaxine; AGO – agomelatine
Based on: * [20] – assessment with CGI-S, ** [21] – assessment with MADRS, *** [22] – assessment with MADRS

Figure 2. **Effectiveness of vortioxetine treatment in patients with prior SSRI or SNRI failure, indicated by the percentage of patients achieving remission of depressive symptoms**

patients treated with desvenlafaxine. Except for one patient, the dose of vortioxetine was increased to 20 mg after the first week. 89% continued treatment at this dose until the end of the study, in 10% of patients the dose was reduced to 10 mg/d between weeks 1 and 4 of treatment. Based on these data, it was concluded that treatment with 20 mg of vortioxetine is a safe and effective option following SSRI therapy failure and should be considered prior the use of SNRIs in depression treatment protocols [20].

An earlier study assessing the effectiveness of vortioxetine at a dose of 10–20 mg following SSRI and SNRI therapy failure was the REVIVE study. The control group in this study was treated with agomelatine at a dose of 25–50 mg. The treatment period was 12 weeks. Treatment started with 10 mg of vortioxetine, and the dose could be increased to 20 mg within 1 to 4 weeks of treatment. For agomelatine, the initial dose was 25 mg and could be increased to 50 mg/d after 14 days. With vortioxetine treatment, improvement was observed in 61.5% of patients after 8 weeks and in 69.8% of patients after 12 weeks, compared to 47.4% and 56% during agomelatine treatment. Remission was achieved in 40.5% and 55.2% of patients treated with vortioxetine and 29.5% and 39.4% of patients treated with agomelatine. After 4 weeks of treatment, a higher dose of vortioxetine (20 mg/d) was used in 64.7% of patients, while in the agomelatine-treated group, a higher dose was taken by 71.7% of patients. The percentage of patients with adverse effects was 54.2% during vortioxetine treatment and 52.5% in the agomelatine-treated group. For vortioxetine, the most common adverse effect was nausea (16.2% of patients), while in the agomelatine-treated group it was reported by 9.1% of individuals [21].

The effectiveness of vortioxetine after SSRI/SNRI therapy failure was also assessed in a group of 150 patients experiencing emotional blunting as a side effect of antidepressant treatment. SSRI/SNRI drugs were used at adequate doses for at least 6 weeks. 82% of patients had previously been treated with SSRIs, 11.3% with venlafaxine and 6.7% with duloxetine. Vortioxetine treatment was started at a dose of 10 mg/d, which could be adjusted to a range of 10–20 mg/d from day 8 onwards. At week 8, a dose of 20 mg/d was used in 51.4% of patients. Remission was achieved in 47% of patients, emotional blunting resolved in 50% of patients [22].

Effectiveness and tolerance of vortioxetine in special patient populations

The RECONNECT randomised study evaluated the effectiveness of 8-week treatment with vortioxetine in patients with depression and co-existing generalised anxiety disorder. The study was conducted in a group of 100 people. Treatment began with a dose of 10 mg/day and was increased to 20 mg/day after the first week. Subsequently, the dose was adjusted based on treatment effectiveness and tolerance. 23% of patients received vortioxetine as the first antidepressant and in 77% of patients treatment was switched from another medication. At week 8 an improvement in depressive symptoms was achieved in 61%, remission in 35% of individuals, according to the MADRS; anxiety symptoms improved in 55% and remission was achieved in 42% of patients, according to the *Hamilton Anxiety Scale* (HAM-A). A response to treatment according to both scales (MADRS and HAM-A) was achieved in 52% and remission in 31% of patients. Treatment with a dose of 20 mg/day was continued until the end of the treatment period in 86% of patients, and increasing the dose was not associated with decline in treatment tolerance [23].

In an analysis involving patients from 4 clinical trials in which depression co-existed with moderate to severe anxiety (score ≥20 points) assessed by the HAM-A, 8-week treatment with vortioxetine at doses of 10–20 mg led to significant improvement of depressive symptoms assessed by the MADRS. For doses of 15 mg and 20 mg improvement occurred after 4 weeks of treatment, while for the 10 mg dose significant change occurred only in the 6th week. Additionally, only higher doses of vortioxetine led to improvement in anxiety symptoms assessed by the HAM-A scale. At week 8 improvement in depressive symptoms on the MADRS scale was observed in 32.8% of patients treated with placebo, 41.1% of patients treated with vortioxetine 10 mg/day and 46.8% of patients treated with vortioxetine 20 mg/day. The percentages of patients achieving remission were 18.4%, 23.4% and 27.0%, respectively. For anxiety symptoms assessed by the HAM-A scale, improvement was observed in 37.4% treated with placebo, 39.5% of patients treated with vortioxetine 10 mg and 46.4% treated with 20 mg/day; remission was observed in 29.5%, 34.7% and 39.1% individuals, respectively. Besides the dependency of clinical response to treatment on dose, this study also showed that higher doses did not cause more adverse effects or treatment discontinuation than the 10 mg/day dose [24].

Similar conclusions, dependency of treatment response on using a high dose of vortioxetine, result from an analysis based on data from 4 RCTs that included a separate group of 61% of patients who, in addition to suffering from depression, also had a history of traumatic events. In both patients with childhood traumas and those with recent traumas, treatment with vortioxetine 20 mg led to greater improvement than treatment with 10 mg/day compared to placebo (in the group with childhood trauma – 1.8 vs. – 3.7, for recent trauma – 1.8 vs. – 5.0) [25].

An assessment for the subgroup of patients with generalised anxiety symptoms was also performed for the RELIVE study [16]. These symptoms occurred in 56% of the 737 patients evaluated in this study. Diagnostic criteria for generalised anxiety disorder were met for 180 (24.4%) individuals. The analysis confirmed that in this group, treatment with vortioxetine also leads to clinical improvement, accompanied by a reduction in disability assessed by the *Sheehan Disability Scale* and an improvement in quality of life [26].

In the RELIVE [27] study, a subgroup of patients aged 65 and older was also evaluated. It was found that in terms of effectiveness and tolerance, treatment with vortioxetine is associated with significant benefits in terms of symptom relief, improved functioning and quality of life in older adults [27]. In the context of treating the elderly, data regarding individuals with cognitive impairment is also important, especially since higher doses of antidepressants are often required to achieve mood improvement and irritability, frequently associated with neurocognitive disorders. In the MEMORY study the effectiveness and tolerability of vortioxetine in a group of 82 patients aged 55–85 years suffering from depression co-existing with mild dementia (*Mini–Mental State Examination* score 20–24) diagnosed within the last 6 months was evaluated. Treatment with vortioxetine was initiated at a dose of 5 mg/d, on the 8th day the dose was increased to 10 mg/d, and then a dose in the range of 5–10 mg was used until the end of the 12-week treatment period. During this time 36% of patients achieved improvement and 17% achieved remission. The treatment was well tolerated, from the 4th week of treatment over 50% of patients received a dose of 20 mg/d. Adverse effects occurred in 46% of patients, the most common of which was nausea (11%). Discontinuation of treatment due to adverse effects was necessary in 7% of treated individuals [28].

In addition to the above data on the treatment of depression overlapping with dementia, particularly important are studies and observations highlighting the efficacy and safety of vortioxetine in treating depression in patients with comorbid somatic conditions – such as cardiovascular diseases, diabetes, chronic obstructive pulmonary disease (COPD) [29], Parkinson's disease [30, 31], and epilepsy [32].

Discussion

The presented results indicate that vortioxetine is an effective and well-tolerated antidepressant, which is confirmed not only by the described RCT studies and meta-

analyses concerning this drug but also by large meta-analyses that include various antidepressants [33].

Based on these meta-analyses, the guidelines of the Polish Psychiatric Association and the National Consultant for Adult Psychiatry on the pharmacological treatment of depressive episodes and recurrent depressive disorders indicate that vortioxetine belongs to a group of 5–7 antidepressants with higher efficacy and better tolerability compared to other antidepressants. An additional advantage of vortioxetine among antidepressants is its beneficial effect on cognitive functions impaired by depression. Furthermore, it is metabolically safe and therefore is recommended for the treatment of depression accompanied by increased appetite and weight gain. It is also characterised by high safety in somatic diseases and is recommended for treating depression coexisting with somatic conditions and in elderly patients [5].

The data also confirm a clear relationship between the administered dose of vortioxetine and the treatment response within the entire registered dosing range from 5 to 20 mg/d, indicating that a dose of 20 mg/d should particularly be used in groups of patients at high risk of treatment failure. The superiority of the high dose of vortioxetine over the 10 mg/d dose was demonstrated, among others, in the treatment of patients after the failure of SSRI/SNRI therapy, patients with co-existing anxiety symptoms, e.g. in the course of generalised anxiety disorder, patients over the age of 65 or with coexisting dementia and patients with a history of traumatic experiences. In treating these patient groups, vortioxetine at a dose of 20 mg/d was used in over 50% of patients.

The vortioxetine dosing regimen utilised in clinical trials constitutes significant information. The dose of the drug was increased from 10 mg/d to 20 mg/d as early as on the 8th day of treatment. This was associated not only with a greater degree of improvement after 8 weeks of treatment but also with a faster onset of improvement, as early as the second week instead of the fourth week of treatment. This is a significant observation because an extended period to achieve improvement may result in patients losing motivation to continue treatment and subsequently discontinuing it [34]. However, this approach deviates from the typical dosing regimen of antidepressants in psychiatry. Dose increases are generally advised after 4–6 weeks of treatment, with an emphasis on the lack of reason for hesitation in escalating the dose to the maximum [5]. This is confirmed by the presented data for vortioxetine. Importantly, increasing the dose to 20 mg/d did not lead to a deterioration in treatment tolerance. Vortioxetine is one of the best-tolerated antidepressants due to its combination of serotonin reuptake inhibition and receptor action (blocking of serotonin receptors 5-HT3, 5-HT7 and 5-HT1D as well as partial agonistic action on serotonin receptors 5-HT1B and agonistic action on receptors 5-HT1A [11]. In a meta-analysis indicating the Number Needed to Harm (NNH) for treatment discontinuation due to adverse events, vortioxetine with an NNH = 36 had a significantly lower risk of treatment discontinuation than venlafaxine at a dose of 225 mg/d NNH = 10 and duloxetine at a dose of 60 mg/d NNH = 20 [35].

The most common adverse reactions to vortioxetine, affecting up to several percent of treated patients, include nausea and vomiting. These are adverse reactions typical for many antidepressants [36]. To minimise them, antidepressant therapy is usually started with a subtherapeutic dose, which is then gradually increased. However, in the context of the presented data, this approach delays the drug's effect. Additionally, it may extend the duration of nausea due to the need for multiple dose increases of vortioxetine and the lack of rapid saturation of the 5-HT3 serotonin receptors by the drug. The blockade of these receptors has an antiemetic effect and may reduce the severity of nausea and vomiting [37].

The risk of other adverse events typical of SSRI/SNRI antidepressants, such as emotional blunting, sexual dysfunctions, exacerbation of insomnia and anxiety was not observed in studies using high doses of vortioxetine [17]. The use of a 20 mg/d dose, however, led to greater improvement and a higher percentage of patients with remission of depressive symptoms. Additionally, the resolution of depressive symptoms was accompanied by an improvement of generalised anxiety symptoms [23, 24, 26], cognitive functions and work functioning [18], and other important areas indicated by the patients themselves [19].

In summary, the studies discussed in this paper question several commonly used principles of pharmacotherapy, which originate from the use of tricyclic antidepressants in the treatment of depression, i.e. drugs with a high risk of adverse effects. The first principle, "start low, go slow," indicates the necessity of starting treatment with a low dose of the drug and gradually increasing it. Data from studies on vortioxetine indicate the feasibility of initiating treatment immediately with an effective dose (10 mg) and the advisability of promptly increasing it to 20 mg/day as early as the 8th day of treatment. This is particularly important in patient groups at high risk of lower treatment effectiveness.

Data from clinical studies using vortioxetine is not entirely consistent with another frequently applied pharmacological treatment principle, which is to use the lowest effective dose of the drug. The presented study results suggest that it is more advisable to use the maximum well-tolerated dose of vortioxetine. In studies involving groups at risk of non-improvement, such as the treatment of patients following the failure of SSRI/SNRI therapy [20–22], but also in groups at increased risk of adverse drug reactions, e.g. in elderly individuals [28] or patients with anxiety [23], over 50% of patients received the maximum registered dose of vortioxetine 20 mg/day.

The presented studies also contradict the typical depression treatment protocol, which suggests changing the treatment, e.g. to a drug with dual mechanism of action (SNRI) or augmenting SSRI with, e.g. bupropion, after SSRI treatment failure. In the STAR*D study this approach led to remission in 20% and 28% of patients, respectively as assessed by the *Hamilton Depression Rating Scale* (HRSD17) [38]. In studies evaluating the effectiveness of vortioxetine, after changing treatment from SSRI/SNRI, at a dose of 10 mg in the first week and 20 mg from the second week of treatment, the

observed remission rate was 32.5–47% after 8 weeks of treatment [20–22] and 55.2% after 12 weeks of treatment [21]. These results indicate that, besides swift dose escalation and using the maximum dose, for patients with prior SSRI/SNRI treatment failure, it is also advisable to maintain treatment with vortioxetine for a period of 8–12 weeks. This treatment regimen is thereby more similar to therapy for obsessive-compulsive disorder than depression (a 12-week treatment period, including at least 6 weeks at the maximum well-tolerated dose), with the distinction that the dose is escalated to the maximum already in the second week of treatment.

Declaration of Conflict of Interest

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