Depression is a devastating, widespread condition affecting 15–20% of the population. It may cause significant functional impairment. In spite of variety of available antidepressant drugs, more than 30% of the patients with major depressive disorder (MDD) still cannot achieve neither adequate response nor remission (1).

Both DSM-5 and ICD-10 diagnostic criteria underline the significance of symptoms resulting from cognitive impairment. DSM-5 specify: diminished ability to think or concentrate or more indecisiveness present nearly every day (indicated by either subjective report or observation made by others), psychomotor agitation or retardation (non-subjective, reported by others) (2). In turn, ICD-10 – indicate poor concentration, substantial psychomotor retardation or agitation (3). Nonetheless, the role of cognitive dysfunctions seem to remain underestimated in case of depressive disorders, thus they are rarely perceived as therapeutic target. Vortioxetine is a relatively new, multi-functional agent. With its unique properties and strong affinity towards serotonin transporter (5-HTT), vortioxetine is a modulator and stimulator of serotonergic transmission. Vortioxetine is an antidepressant drug suitable for therapy in various types of depression: severe, anxiety-associated, and of elders. It acts equally strong as SNRIs or agomelatine and has favorable effects on cognitive functioning. Although vortioxetine has not undergone comprehensive preclinical testing, the available data indicate that this particular agent may be more advantageous in terms of its procognitive effects, as compared to other drugs – which often seemed to be analogous in preclinical and clinical testing. In vitro examination of hippocampal pyramidal cells revealed that vortioxetine improves both synaptic transmission and neuroplasticity responsible for memory and learning patterns. Contrary to fluoxetine, the long-term treatment with use of vortioxetine on mice resulted in enhanced visual and spatial memory, along with reduced occurrence of typical depressive behavior. In addition, vortioxetine is a very first drug efficiently augmenting cognitive function in adults diagnosed with severe depressive episode, irrespective of its curative potential on the affective sphere. It may exert even stronger direct effect (assessed with DSST) on cognitive functions than duloxetine. With its supplementary capacity of acting directly on several subtypes of serotonin receptors, vortioxetine is certainly more than just a SSRI. It has been proved that it is as effective as venlafaxine and more efficient than agomelatine in MDD treatment, additionally exerting procognitive effects. In addition, vortioxetine may be beneficial in overcoming sexual dysfunction in patients, who have been suffering from such condition as a result of treatment with other antidepressant agents. The drug is generally well tolerated with the most prevalent side effects being mild to moderate nausea along with (mostly transient) headaches. Vortioxetine may significantly improve the quality of life in patients suffering from depression.

Keywords: vortioxetine, depression, cognitive dysfunction
Pharmacodynamic and pharmacokinetic properties of vortioxetine

Vortioxetine is, in terms of chemistry, a derivative of arylpiperazine: 1-[(2-(4-dimethyl-phenyl)-sulfanyl)-phenyl]-piperazine (6). The molecular weight and molecular formula of vortioxetine are: 298.45 g/mol and C_{18}H_{22}N_{2}S, respectively. The bioavailability after oral administration amounts to 75% and the mean half-life equals 57 h (6, 7). The peak plasma concentration of 9-33 ng/mL is reached after 7-11 h, under assumption of administering 5-10 mg daily doses (9). Vortioxetine is metabolized by several liver P450 cytochromes: CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 in particular (9, 10).

With its unique properties and having strong affinity towards serotonin transporter (5-HTT), vortioxetine is a modulator and stimulator of serotonergic transmission. Additionally, it inhibits – Ki = 1.6 nM, serotonin transporter (SERT).

Vortioxetine presents agonistic effect towards 5-HT\textsubscript{1A} receptor (Ki = 15 nM), with high levels of intrinsic activity (IA = 80%) (6, 11). The compound is a partial agonist of 5-HT\textsubscript{1B} receptor (Ki = 33 nM) (9, 11) and the antagonist of 5-HT\textsubscript{3A}, 5-HT\textsubscript{7} and 5-HT\textsubscript{1D} receptors (Ki = 19 nM) (8, 11). Distribution of the 5-HT\textsubscript{7} receptors in central nervous system indicates for their regulatory role in cognitive functioning, attitude, perception of pain, circadian rhythm and sleep (12). Serotonin is an evolutionary transmitter, which modulates numerous functions of the central nervous system, e.g.: mood, anxiety, stress, aggression, feeding, cognition or sexual behavior (13).

Previously described effect of vortioxetine on serotonin transmission may underlie the concept of exerting impact on neural pathways controlled by other modulators, responsible for attitude and cognitive capacity, including norepinephrine (NE), acetylcholine (ACh) and glutamate. In preclinical studies, vortioxetine increased the extracellular levels of 5-hydroxytryptamine, NE, ACh, HA and dopamine in cerebral regions involved in both mood modulation and cognitive functioning (9).

As far as potential side effects are concerned, the vortioxetine’s affinity towards β1 adrenergic receptor (Ki = 46 nM) should be considered (6).

Clinical application of vortioxetine

Compared to placebo, vortioxetine proved to be more effective in treatment of the Major Depressive Disorder with use of HDRS (The Hamiltonian Depression Rating Scale) or MADRS (The Montgomery Asberg Depression Rating Scale), as was visible while comparing scores achieved at the beginning, after response to therapy and at the remission, respectively (14, 15).

Alvarez et al. determined the antidepressant efficacy of vortioxetine in contrast to venlafaxine and placebo, in a randomized, controlled, double-blind clinical trial. Initially, all the patients in the study presented with min. 30 MADRS points depression. Drug tolerance for 5 mg dose of vortioxetine and placebo were comparable, and 10 mg dose was even better tolerated than the 225 mg dose of venlafaxine (6).

The effectiveness of vortioxetine in depression treatment was further evaluated by Baldwin et al. (16). The 8-week-long multicentre randomized clinical trial was designed to confront 2.5, 5 and 10 mg vortioxetine doses with placebo and 60 mg-dose of duloxetine. The mixed model repeated measures analysis proved higher efficacy of 5 and 10 mg vortioxetine and 60 mg duloxetine, as compared to placebo (6, 15, 16).

Furthermore, Henigsberg et al. compared antidepressant potential of 1, 5 and 10 mg doses of vortioxetine with placebo. Ten mg dose of vortioxetine proved to be an effective treatment of depression in terms of primary endpoint of the study – improvement in the Hamiltonian scale. A global assessment with use of HDRS, clinical global impression – CGI-I and MADRS demonstrated higher efficacy of vortioxetine over placebo, at all of the examined doses (9, 17). In addition, Boulenger et al. showed the efficiency of vortioxetine in prevention of recurrent episodes of depression (18).

Furthermore, vortioxetine has positive effects on anxiety reduction (5). A trial conducted in Europe and Africa by Bidzan et al. aimed to assess the curative potential of vortioxetine in generalized anxiety disorder (GAD). Three hundred and one patients diagnosed with GAD were included in the study, all of them having > 20 points in HAM-A and placebo, in a randomized, controlled, double-blind clinical trial. Initially, all of them in the study presented with min. 30 MADRS points depression. The MMRM analysis indicated a significant advantage of vortioxetine in contrast to placebo and at the remission, respectively (14, 15).

Analogous studies were carried by Rothschild et al. in USA. Patients were randomized into 2 groups, receiving: 5 mg of vortioxetine or placebo. Anxiety levels were measured with use of HAM-A scale. After 8 weeks of treatment regimen, no differences were observed between tested drug and placebo with reference to primary endpoints of the study. Such discrepancies between the results obtained by Rothschild and Bidzan may resulted...
from: higher mean anxiety level and greater percent of previously treated patients in Bidzan’s study, smaller percent of untimely patient resiginations in the same study, and the majority of patients enrolled in Bidzan’s trial being Caucasian – thus, according to STAR*D study, having greater probability of achieving remission. In turn, Baldwin et al. evaluated the role of vortioxetine in prevention of recurrent GAD. Introducing vortioxetine was linked to significantly lower risk of recurrent episodes (6, 20).

**Vortioxetine procognitive potential in preclinical**

Although vortioxetine has not undergone comprehensive preclinical testing, the available data indicate that this particular agent may be more advantageous in terms of its procognitive effects, as compared to other drugs – which often seemed to be analogous in preclinical and clinical testing (21). Procognitive properties of vortioxetine have been depicted by various preclinical trials. *In vitro* examination of hippocampal pyramidal cells revealed that vortioxetine improves/increases both synaptic transmission and neuroplasticity responsible for memory and learning patterns, whereas escitalopram presented no such procognitive potential. Using the cognitive-behavioral models (new object recognition tests), vortioxetine caused memory improvement in rats. Additionally, it increased the levels of acetylcholine and histamine in medial prefrontal cortex. This finding is of particular importance considering cognitive capacity, as acetylcholine is responsible for memory and learning, while histamine plays role in attention, alertness and memory (9, 22).

Westrich et al. dedicated their trial to assess vortioxetine’s modulatory potential on various 5-HT receptors in terms of its influence on circadian rhythm and memory in rats. Object Recognition Test was among exploited methods. The study revealed that vortioxetine exerts substantial effects on circadian rhythm and episodic memory correction in rats, mainly due to its antagonistic properties towards 5-HT7 receptors (23).

Yan Li et al. compared the effect of fluoxetine and vortioxetine action on cognitive functioning, affective behavior, cerebral stem cell proliferation, growth factor levels and gene expression in middle-aged mice. The visual-spatial skills are age-related not only in human, but also in animal models. The study indicated the existence of age-related visual-spatial memory dysfunction in healthy middle aged mice. Contrary to fluoxetine, the long-term treatment with vortioxetine resulted in enhanced visual-spatial memory skills, along with reduced occurrence of typical depressive behavior in mice (24).

**Procognitive effects presented in clinical trials**

Vortioxetine is a very first drug that efficiently augments cognitive function in adults diagnosed with severe depressive episode, irrespective of its curative potential on the affective sphere (9).

In a randomized, placebo-controlled trial on 24 healthy volunteers, neither short nor long-term treatment with 10 mg of vortioxetine hindered psychomotor or cognitive functions. At the same time, even single administration of 30 mg of mirtazapine distorted such abilities. These results clearly prove that vortioxetine has no negative effect on cognitive functions (9).

Several clinical trials were dedicated to verify the independent procognitive properties of vortioxetine. One of them was a randomized, placebo-controlled, double-blind study concerning adult patients diagnosed with depression and MDE and MDRS score ≥ 26. They received placebo, or either 10 or 20 mg of vortioxetine over 8-week period. The primary endpoint comprised change in combined score from two neuropsychological tests: DSST (the Digit Symbol Substitution Test – which assessed the rate of processing information, executive function and alertness) and RAVLT (the Rey Auditory Verbal Learning Test – assessing memory and learning capacity), achieved after 8 weeks of treatment – as compared to initial state. This particular study included 193, 204 and 194 patients receiving 10 or 20 mg of vortioxetine or placebo, respectively. As compared to placebo, both prescribed doses of vortioxetine presented statistically significant outcome in comparison with the initial point. Further analysis based on individual neuropsychological tests revealed the advantage of both doses of vortioxetine over placebo (6, 9).

A randomized, placebo-controlled study on vortioxetine and duloxetine had been conducted by Mahableshwarkar et al. It assessed vortioxetine’s potential effect on cognitive functioning in patients with depression, who reported deterioration of such skills. The trial outcome indicated the advantage of vortioxetine in 10-20 mg daily doses over placebo, with reference to initial DSST, PDQ and CGI-I scores. The results of University of San Diego Performance-Based Skills Assessment as well stressed the substantial improvement of functions in patients treated with vortioxetine. The most often compared agent – duloxetine, exhibited no significant difference from placebo in terms of DSST and San Diego Performance-Based Skills Assessment. However, it considerably improved in PDQ and CGI-I (9, 20).

Theuniessen et al. focused on determining the effect of vortioxetine on cognitive and psychomotor
abilities. The study revealed no unfavorable response in terms of driving as well as cognitive and psychomotor capacity, after either short or long-term treatment with vortioxetine (25).

Katona et al. assessed the antidepressant potential and safety of administering vortioxetine in population of elder patients. In a 8-week, randomized clinical trial, the drug had been compared to placebo and 60 mg of duloxetine in patients (mean age of 70.6 years) with recurrent depressive episodes. Both agents showed to be more effective than placebo, and vortioxetine was better tolerated than duloxetine. Vortioxetine also proved to be more efficient than placebo in terms of improving memory, information processing and verbal learning (26). Katona et al. evaluated the effects of vortioxetine on cognitive functions in elderly patients diagnosed with MDD. Vortioxetine significantly outranked the placebo, resulting in substantial improvement of DSST and RAVLT. In comparison, duloxetine improved RAVLT, but not DSST. This indicates that vortioxetine may exert greater direct effect on cognitive function enhancement (measured with DSST) than duloxetine (26).

While analyzing cognitive dysfunction in depression, current classification should be recalled, which distinguished cold (independent of emotion) and hot (emotion-dependent) cognitive impairments. It is commonly believed that cold cognitive deficits do not retreat in remission state, and in persistent form they may cause poor response to treatment with antidepressants (4).

Safety of medication administration
The side-effect profile of vortioxetine is similar to other SSRIs. It comprises nausea, vomiting, diarrhea, headache and vertigos (6). The most prevalent adverse events were linked to gastrointestinal system. Nausea was the most often reported side effect, and it seemed to be dose dependent. Nearly 32% of patients receiving 20 mg dose of vortioxetine suffered from nausea (9). Vortioxetine neither had effect on weight gain, nor caused ECG deviations (6). Furthermore, 2-week randomized study confronting placebo and moxifloxacin with 10 and 40 mg of vortioxetine revealed no significant increase in the QTc (9). Sexual dysfunctions occurred less often than in case of venlafaxine (6). The number of spontaneously reported sexual dysfunctions from patients who were on vortioxetine therapy was low both in randomized and open studies. Vortioxetine was compared to escitalopram (10-20 mg doses) in an 8-week, randomized, double-blind study including 447 MDD patients, who had been previously treated with SSRIs causing sexual dysfunction. Vortioxetine showed a substantial improvement in CSFQ-14 (Changes in Sexual Functioning Questionnaire Short-Form) in comparison with the initial results (9, 27).

Exerting additional impact on certain serotonin receptors, vortioxetine is certainly more than just a SSRI. It acts equally strong as SNRIs or agomelatine and has favorable effects on cognitive functioning. Furthermore, it may reduce sexual dysfunction in patients who reported such problems during treatment with other antidepressants. The medication is generally well tolerated, with the most prevalent side effect being mild to moderate nausea along with mostly transient headaches (28).

Vortioxetine may significantly improve the quality of life in patients suffering from depression. Florea et al. explored its effect on the quality of life in such patients. Health Related Quality of Life (HRQoL) had been assessed in adult patients with MDD during 6-8-week long randomized studies of vortioxetine versus placebo, with use of: 36-point Short-Form Health Survey, the Quality of Life Enjoyment and Satisfaction Questionnaire short-form, the EuroQol 5-Dimension Questionnaire and 12-point Health Status Questionnaire (in one trial). Patients had been administered 5, 10, 15 or 20 mg doses. Vortioxetine therapy lead to significant improvement in HRQoL in these patients (29).

It is possible that this up-and-coming medication will change the future of psychiatric patients by substantially improving their quality of life and cognitive functioning.

REFERENCES

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