According to the World Health Organization data, more than 350 million people suffered from depression in 2012 (1), which was up to 52 million people more than in 2010 (2). The disease is twice as common in women as in men (3), has a chronic course with a tendency to recur and is an important cause of considerable limitations in social functioning, which is significantly related to cognitive impairment, common in depression. In view of the worrying trends towards increased incidence of depressive disorders, there is a need to bring to market new drugs for a more effective therapeutic intervention. Implementation of antidepressant treatment in hospital and outpatient practice is continuously growing. In the United States, antidepressants are the most commonly prescribed class of drugs, and the use of antidepressants increased by 4.28% in the period between 1996 and 2005 (4).

Pharmacological treatment of depression is based on the still popular monoamine hypothesis of the disease, related to the mechanism of action of most currently registered antidepressants (5). The recommended first-line drugs usually include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (6-8). Despite many commercially available antidepressants, therapeutic effects are still unsatisfactory. One of the recent studies, confirming the incomplete effectiveness of currently used antidepressants, is the STAR*D study (9). Given the above limitations of therapy, new solutions to improve the healing process are being sought. One alternative is to search for new antidepressants that can significantly improve the effectiveness of pharmacotherapy of depressive disorders.

Levomilnacipran is the newest antidepressant belonging to selective SNRIs. The drug was approved by the US Food and Drug Agency (FDA) on 25 July 2013, and registered in the United States as a new antidepressant. Levomilnacipran (Fetzima) is currently available in the form of prolonged release capsules, used once daily in the recommended dosage range of 40 to 120 mg (10).

The purpose of this article is an overview of the most important data on the pharmacological and clinical properties of the newest antidepressant – levomilnacipran.

Keywords: levomilnacipran, antidepressant, milnacipran
noted that levomilnacipran has twofold greater selectivity for norepinephrine relative to serotonin reuptake inhibition (11). In vitro studies have demonstrated a strong affinity of levomilnacipran to serotonin and norepinephrine transporters, with a minimal impact on the dopamine transporter. The drug did not show any significant binding forces with other receptors, transporters or ion channels. The relative strength of binding to specific transporters is as follows:
- for human recombinant serotonin transporter (SERT) – Ki = 11 nM
- for human recombinant norepinephrine transporter (NET) – Ki = 71-90 nM (12).

Auclair et al. showed that pharmacological activity of levomilnacipran greatly exceeded the activity of both the racemate and the dextrorotatory enantiomer of milnacipran. The comparative analysis revealed that Ki values for the levorotatory enantiomer of human recombinant form of NET and SERT were 92.2 nM and 11.2 nM, respectively, which substantially exceeded the binding force of the racemate as well as the dextrorotatory enantiomer (13). Compared to other SNRIs - venlafaxine and duloxetine, levomilnacipran is ten times more selective for NET than SERT transporter (13). The selectivity ratio of 5-HT/NE for levomilnacipran is 1.7, while for venlafaxine or duloxetine it is 0.1 and 0.07, respectively (14).

Following oral administration, levomilnacipran bioavailability is 92% and the degree of plasma protein binding is 22%, in the concentration range of 10-1000 ng/mL. Food has no significant impact on the concentrations of the drug substance in the body. The average time to obtain the maximum drug concentration (Cmax) after oral administration is approx. 6-8 h (15). The pharmacokinetic profile of levomilnacipran was evaluated in three randomized phase 1 studies in healthy subjects 18-45 years of age (16). Levomilnacipran showed a dose dependent increase in the maximum blood concentration and biological half-life of 12.4-12.9 h. The internal conversion between levomilnacipran and its stereoisomers does not occur in humans, and drug concentration does not change significantly when administered with food (16).

Levomilnacipran is mainly metabolized in the liver, through a variety of pathways involving cytochrome P450 enzymes, primarily CYP3A4, and to a lesser extent CYP2C8, 2C19, 2D6 and 2J2 (15). The resultant metabolites do not show pharmacological activity. Following the oral administration of levomilnacipran solution, nearly 58% of the drug is eliminated unchanged, primarily by renal excretion in the urine (17).

**Efficacy**

Five short-term randomized trials with placebo were carried out to evaluate the effectiveness of levomilnacipran versus placebo. The studies included adults with a confirmed diagnosis of MDD and a current depressive episode lasting for at least 4 weeks. Patients resistant to treatment and those with other coexisting psychiatric disorders and with significant somatic disorders were excluded from the study.

In phase II clinical trials, the drug was used in the dose range of 75-100 mg during a 10-week randomized, double-blind, placebo controlled study. In the study, all included patients met DSM-IV criteria for a major depressive episode lasting for at least a month; they scored more than 22 points in the Hamilton Depression Rating Scale (HDRS17) and at least 10 points in the Sheehan Disability Scale (SDS). The levomilnacipran dose was titrated up to 100 mg over 12 days, and then the patients were evaluated during a 10 week treatment period, using the Montgomery-Asberg Depression Rating Scale (MADRS). In the further observation period, the condition of patients was assessed using the HDRS17 and SDS scales. The results of the study showed a significant advantage of levomilnacipran over placebo in relation to the points scored in MADRS, HDRS, and SDS scales (18).

| Table 1. A comparison of activity between both drugs on norepinephrine and serotonin systems. |
|---------------------------------------------|---------------------------------------------|
| Levomilnacipran | Milnacipran |
| hSERT [nM] | 11.2 ± 0.3 | 16.9 ± 1.3 |
| hNET [nM] | 92.2 ± 11.9 | 139 ± 24 |
| 5-HT : NE reuptake effects | 1 : 2 | 1 : 1 |

In a 8-week, phase III study, Asnis et al. demonstrated a significant superiority of levomilnacipran over placebo in all treatment groups with respect to changes in the total score in the MADRS scale. The doses of levomilnacipran ER in each group were 40, 80 and 120 mg, respectively. In the dose range of 80-120 mg, levomilnacipran was significantly more effective than placebo, based on the SDS score (19).

Bakish et al. carried out an 8-week randomized, phase III study that evaluated the efficacy of levomilnacipran in the dose range of 40-80 mg in the treatment of major depression. For both doses, i.e., 40 and 80 mg, the drug demonstrated a significant superiority over placebo. The first effects were observed 4 weeks after the initiation of levomilnacipran therapy in each study group, which was confirmed by the MADRS score. Levomilnacipran was also more effective than placebo in reducing the SDS score (20).

Similar findings have been reported by Sambunaris et al. in an 8-week, randomized, placebo-controlled phase III study, the authors evaluated the efficacy of levomilnacipran in the treatment of Major Depressive Disorder (MDD). Statistically, the study drug was significantly more effective than placebo in respect of the MADRS total score (21).

Superiority of levomilnacipran over placebo was not confirmed by Gommoll et al., who evaluated 355 patients receiving the levorotatory enantiomer of milnacipran, using the MADRS scale. The study enrolled patients aged 18-80 years who met the diagnostic criteria for MDD according to the DSM-IV. MDD diagnosis was confirmed on the basis of additional criteria, according to the Mini-International Psychiatric Interview (22). All patients were enrolled in the study during a current episode of depression lasting for at least 4 weeks, and were further evaluated in the MADRS scale, where the necessary condition for inclusion in the study was the score of no less than 30 points. Response to treatment and remission were numerically more frequent in the levomilnacipran than placebo group, but no statistically significant differences were observed in this regard. The effectiveness of reduction in the MADRS total score (minimum 50% reduction in the baseline threshold) was 38.5% for levomilnacipran vs. 34.8% for placebo. Remission - the MADRS score equal to or less than 10 points, was obtained in 25.3% for levomilnacipran compared to 23.8% for placebo. Despite a slight superiority of levomilnacipran over placebo, no statistically significant differences were observed in this study (23).

Shiovitz et al. demonstrated that the time to relapse was longer in the case of levomilnacipran than placebo; however, a statistically significant superiority of the drug in relation to the MADRS total score was not confirmed. Severity of depression assessed in the MADRS scale was significantly associated with a considerably higher reduction in the risk of recurrence for levomilnacipran compared to placebo (24).

Safety
Like other selective serotonin reuptake inhibitors, levomilnacipran can cause relevant side effects. According to a clinical review of the prolonged-release drug available on the market under the name Fetzima, the most common undesirable effects of levomilnacipran are gastrointestinal symptoms; the most frequently reported disorders are nausea and dry mouth: 17.1% and 10.1% of cases, respectively. The other, common side effects are: constipation (8.5%), increased sweating (8.5%), erectile dysfunction (5.7%), increased heart rate (5.7%), tachycardia (4.9%), vomiting (4.8%), and palpitations (4.7%).

The most common reasons for discontinuation of therapy were nausea and vomiting. Asnis and Henderson in their review paper have presented the statistics of undesirable effects related to levomilnacipran, referring to five previous randomized trials evaluating the efficacy of the drug. The study, carried out on 1583 patients, demonstrated that the most frequent side effects were nausea and headaches, which occurred in 17% of patients receiving levomilnacipran. A common symptom was also dry mouth, which occurred in 10% of patients. In the present statistical analysis, the frequencies of other, frequent adverse reactions were: 9% increased sweating, 9% constipation, 8% dizziness, 6% increased heart rate, 6% erectile dysfunction, 5% insomnia, 5% vomiting, 5% tachycardia, and 5% palpitations (25).

Serious adverse drug reactions only occurred in a few cases. In the study carried out by Shiovitz et al., for an average daily dose of 90 mg, there were single incidents of hypertension, chest pain with elevated troponin I levels and creatine kinase MB, acute pancreatitis and suicidal thoughts (24). Bakish et al. reported in three patients a non-cardiac chest pain, asthma and intussusception (20). In the randomized study, Mago et al. reported angina pectoris, convulsions, a manic episode and severe arrhythmias (26).

Is levomilnacipran a worthy successor of milnacipran?
Milnacipran is a racemate which is a mixture of both enantiomers - dextrorotatory 1S, 2R and lev-
orotary 1R, 2S. In the United States, it has been registered as a drug intended for the treatment of fibromyalgia - a disease characterized by chronic pain within the musculo-articular system. In 2009, milnacipran was approved by the FDA as an effective therapeutic agent – the drug was registered under the trade name Savella.

As a selective serotonin-norepinephrine reuptake inhibitor, milnacipran has also antidepressant potential. It is now used as an antidepressant in the European Union and Japan. In a randomized, multicenter, double-blind study, the efficacy of milnacipran was comparable to that of venlafaxine. In the long-term treatment of adults with MDD, comparable results concerning the effectiveness and tolerability of both drugs at doses up to 200 mg were obtained (27). Studies conducted in Europe and the US supported the efficacy of milnacipran in the treatment of depression (28). Kamijima et al. evaluated the efficacy and safety of milnacipran as equivalent to paroxetine. In depressive patients, the effectiveness of both antidepressants was evaluated on the basis of the Hamilton Rating Scale for Depression - HAM-D (29).

The adverse event profiles of both drugs are similar; however, in the case of milnacipran undesirable effects are much more frequent. Among gastrointestinal symptoms, the most commonly reported disorder was nausea, which occurred in 37% of all respondents. Constipation and vomiting occurred in 16% and 7% of patients, respectively (30). Milnacipran also increased both systolic and diastolic blood pressure (31).

Levomilnacipran is a new antidepressant, approved for the treatment of MDD in the United States. The effectiveness of levomilnacipran in the treatment of depression was confirmed on the basis of clinical trials. The drug also prolonged the periods of remission, which was confirmed in several randomized trials with placebo. Enantiomers are usually superior to a racemate due to a higher selectivity of the pharmacokinetic profile, less complicated chemical structure, reduced potential for drug-drug interactions, and improved therapeutic index. The activity of enantiomer 1S, 2R is also higher than that of the dextrorotatory form, which has been confirmed in clinical studies. The biological half-life of milnacipran is 8 h, and is shorter than the half-life of the levorotary enantiomer (32), which may result in clinical effects of both drugs. The dosage of levomilnacipran is also beneficial for patients, since the drug is administered once daily. Levomilnacipran is the most selective for the norepinephrine transporter of all SNRIs. Such dependence can have a beneficial therapeutic effect on certain symptoms of depression, because some of the symptoms are more associated with the NET transporter (working memory, attention, concentration, alertness, energy and social functioning). Unfavorable aspects of a high noradrenergic selectivity, however, include undesirable effects, mainly within the cardiovascular system. Hypertension and arrhythmias may occur during therapy, thus, patient’s physical health should always be taken into account prior to initiation of the treatment.

REFERENCES

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