Efficacy and Safety of Duloxetine (Dulsevia®) in the Dose of 90 mg in Patients with Major Depressive Disorder or Generalized Anxiety Disorder in Clinical Practice

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Abstract

BACKGROUND The remission rate for patients on antidepressant therapy is under 50%. When in a remission, almost all patients have at least one residual symptom, which can be attributed to inappropriate selection of an antidepressant and undertreatment. Duloxetine has a dual mechanism of action and therefore effectively relieves a broad range of symptoms including painful physical symptoms of depression. The efficacy of duloxetine increases with the dose resulting in fewer residual symptoms and higher remission rates. The purpose of the non-interventional study was to monitor clinical efficacy and safety of duloxetine (Dulsevia®), in particular the 90 mg daily dose, in clinical practice.

METHODS The non-interventional study included 527 patients with depression and (or) generalized anxiety disorder. Each patient was monitored for two months and, during that time, the patient was scheduled for three visits in compliance with the regular clinical practice. More than 50% of previously treated patients had already received duloxetine at the 64.7 mg mean daily dose. At their first visit, 48.0% of patients were prescribed 90 mg of duloxetine and, after two months, 76.2% of patients were receiving 90 mg duloxetine. The investigators used the Clinical Global Impression Rating Scale for Severity (CGI-S), the Clinical Global Impression Rating Scale for Improvement (CGI-I), and the Numerical Rating Scale (NRS) to assess therapeutic efficacy. Satisfaction of investigators with efficacy as regards concentration, daily functioning and fatigue, and adverse reactions was also recorded.

RESULTS After the two-month therapy, all monitored efficacy parameters (CGI-S, CGI-I, NRS) presented statistically important improvement. After eight weeks, the clinical state improved in 91.0% of the patients on therapy, while the disease improved much to very much in 79.7% of the patients. At the third visit, 66.3% of the patients reported no pain or mild pain, and 43.9% of the patients were normal, not at all ill, or were borderline mentally ill. At the end of the study, approximately 80% of investigators were satisfied or very satisfied with the therapeutic effect of Dulsevia® on concentration, daily functioning, and decreased fatigue. Patients whose doses were titrated during the observation period from 60 mg at the first visit to 90 mg at the second visit presented statistically more significant CGI-S reduction compared

to patients whose doses remained the same over the entire non-interventional observation period, and investigators were satisfied with therapeutic effect of duloxetine on concentration, daily functioning, and reduction of fatigue. Patients tolerated the duloxetine therapy well as 86.7% of patients did not experience any adverse reactions during the study. At the end of the observational period, causally related adverse reactions occurred only in 5.1% of patients.

CONCLUSIONS The non-interventional study demonstrated efficacy and safety of duloxetine (Dulsevia®), in particular at the 90 mg daily dose, in clinical practice. Improvement of some clinical outcomes of the therapy can be achieved by increasing the dose.

Introduction

Depression is one of the most common mental disorders in Europe. According to the statistical data, it is also the most common reason for persistent incapacity or disability. (1, 2) The remission rate for patients on antidepressant therapy is only 20–40%. When in a remission, almost all patients have at least one residual symptom. (3) The most common residual symptoms include pain, fatigue, insomnia and concentration disorder. These increase the severity of the disease and the risk for the disease recurrence as well as the risk of suicide, and significantly reduce the patients' quality of life. (3, 4, 5) The fact that one in two patients with depression in Europe is still treated with a selective serotonin reuptake inhibitor (SSRI), which acts only on the symptoms of depression related to serotonin, and prescribing too low doses contribute to the lower efficacy of treatment of depression. (6, 7)

Duloxetine is an antidepressant from the group of serotonin-norepinephrine reuptake inhibitors (SNRI). Owing to its dual mechanism of action, it is effective in relieving a broad range of symptoms, including painful symptoms of depression. The medicine has a balanced effect on both systems even with low doses. By duloxetine dose titration, in addition to the effect on the serotonergic system its effect on the noradrenergic system is increased; therefore, its effect on the pain and other noradrenergic symptoms is greater with high doses. High doses of duloxetine also act on the dopaminergic system. Fewer residual symptoms and higher remission rate may therefore be expected when the dose is increased. (5, 8, 9, 10, 11) Despite this, one in two patients in Europe taking duloxetine is treated with a dose of 30 mg, which is according to the Summary of product characteristics suitable only for the initial treatment of anxiety. (6, 12)

The plasma concentrations of duloxetine may be affected by the patient's enzyme status, as enzymes CYP1A2 and CYP2D6 are involved in the metabolism of duloxetine in liver. Patients that concomitantly take the inducers of the above-mentioned enzymes (carbamazepine, omeprazole, dexamethasone, etc.) or smoke have even by 50% lower plasma concentrations of duloxetine. They therefore need a higher dose to reach the desired therapeutic response. (12, 13, 14)

Krka, d. d., Novo mesto is the first and the only pharmaceutical company in Europe to place on the market duloxetine 90 mg strength in addition to duloxetine 30 mg and 60 mg strengths. (15) The dose of 90 mg of duloxetine allows for optimisation of treatment in the patients who do not achieve complete remission with lower doses or have residual symptoms despite the remission. The dose of 90 mg in one tablet is also a simpler choice for treating patients that need to take two tablets. The non-interventional follow-up of the safety and efficacy of one dose of Dulsevia® 90 mg per day has given the first more detailed results and experience obtained in the normal clinical treatment of patients with depression or generalized anxiety disorder. (6, 12)

Methods

The non-interventional study of the safety and efficacy of duloxetine used in clinical practice for the treatment of patients with a major depressive disorder or generalized anxiety disorder, focussed on the one dose of 90 mg, was conducted from November 2018 until July 2019. It was carried out in compliance with the Declaration of Helsinki and the Slovenian Code of Medical Ethics. The study was approved by the Committee for Medical Ethics of the Republic of Slovenia and was notified to the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia.

The study included male and female patients aged over 18 with a diagnosis of major depressive disorder and/or generalized anxiety disorder. The study also included patients already treated with duloxetine but requiring higher doses, patients already treated with other antidepressants but the therapy was not effective or the patients did not tolerate it, and patients treated with a daily dose of 90 mg of duloxetine given in two different doses (30 mg and 60 mg). Each patient was monitored for two months and during that time the patient was scheduled for three visits in compliance with the regular clinical practice: visit 1 at the inclusion in the study, visit 2 (optional) one month after inclusion, and visit 3 two months after inclusion in the study.

The investigators assessed the severity of the disease based on the Clinical Global Impression Rating Scale – Severity (CGI-S) at all three visits, and the efficacy of treatment based on the Clinical Global Impression Rating Scale – Improvement (CGI-I) at visit 2 and visit 3. CGI-S is a 7-point scale, where 1 is used for 'not ill' and 7 for 'very ill'. CGI-I is used to assess improvement. It is also a 7-point scale, where 1 means 'markedly improved' and 7 'markedly worsened'.

At all three visits, each patient also assessed the severity of pain using the Numeric Rating Scale (NRS). Value 0 on the NRS indicates 'no pain', 1 means that the pain is very mild and hardly noticeable, and 10 indicates that the pain is very severe. Based on the assessed score on the numeric scale, the patients were categorised into three groups: 0–3 (patients without pain or with mild pain), 4–7 (patients with moderate pain), 8–10 (patients with severe pain).

At visit 2 and visit 3, investigators assessed their level of satisfaction with the effect of Dulsevia® on concentration, daily functioning and fatigue based on the 5-point scale, where 1 means 'very dissatisfied' and 5 'very satisfied'.

Separately, also the group of patients receiving 60 mg of duloxetine daily during the entire course of the study and the group of patients who received 60 mg of duloxetine daily at visit 1 and were increased the dose to 90 mg of duloxetine daily at visit 2 were analysed with respect to the efficacy of treatment.

The safety of treatment with Dulsevia® was evaluated based on all adverse reactions observed during the entire course of the non-interventional study.

Results

Patients

The non-interventional study included 527 patients with depression or generalized anxiety disorder (GAD). Their mean age was 53.6 years; the youngest patient was 22 and the oldest one was 89 years old. Two thirds of the patients involved were women and one third was men.

The highest percentages of patients suffered from depression (64.3%) and from depression and concomitant GAD (25.2%).

Most patients (78.9%) had already been treated with one or several medicines acting on the central nervous system. Of these, most had been receiving treatment with serotonin-norepinephrine reuptake inhibitors (54.6%), antipsychotics (28.1%) and selective serotonin reuptake inhibitors (25.0%). With regard to the active substance used, the highest percentage of patients had been previously treated with duloxetine (51.9%) at a mean daily dose of 64.7 mg, with quetiapine (15.4%) at a mean daily dose of 66.1 mg and with sertraline (10.1%) at a mean daily dose of 92.5 mg.

At visit 1, in 21.3% of the patients treatment with one or several other medicines with effect on the central nervous system was initiated concomitantly with duloxetine. Of these, the greatest percentage received an antipsychotic (45.5%) or anxiolytic (22.3%). The concomitantly initiated therapy was practically not changed at control visits.

Dosage

At visit 1, the dose of 90 mg of duloxetine daily was initiated in almost 50% of the patients. The percentage of the patients treated with this dose was further increased at next visits (to 72.4% of the patients at visit 2 and to 76.2% of the patients at visit 3). During the course of the study, an increase in the percentage of the patients receiving duloxetine in the dose of 120 mg was observed and a reduction in the percentage of the patients receiving the 30 mg or 60 dose (Figure 1). The average dose of duloxetine initiated at visit 1 was 71.8 mg, 86.9 mg at visit 2 and 93.4 mg at visit 3.

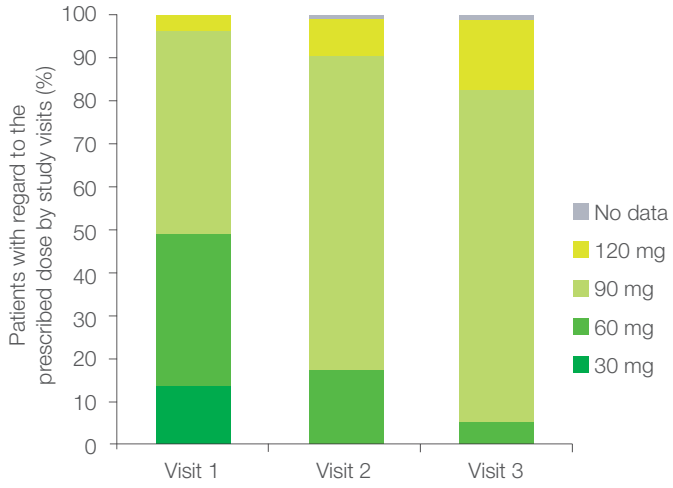

Figure 1. Distribution of the percentage of patients with regard to the prescribed dose of Dulsevia® by study visits.

At visit 1, treatment with Dulsevia® was initiated in 21.1% of newly diagnosed patients. The highest percentage of the patients started treatment with a dose of 60 mg of duloxetine (56.8%). At visit 2 and visit 3, most of these patients were receiving a dose of 90 mg (69.1% at visit 2 and 79.1% at visit 3).

Efficacy

After eight weeks of treatment with duloxetine, a statistically significant reduction in the severity of the disease assessed according to the score on the CGI-S scale was observed ($p < 0.0001$), i.e. from 4.28 ± 0.80 at visit 1 to 3.46 ± 0.88 at visit 2 and 2.63 ± 0.99 at visit 3. In relative terms, the severity of the disease was reduced by 38% until visit 3. At visit 1, the percentage of the patients that were moderately ill to among the most severely ill was 88.6%, after one month of the treatment 50.4%,

and after two months of the treatment 19.7%. As regards the patients that were mildly or borderline ill and those that were normal, not at all ill, their percentage increased to 78.2% after two months of treatment (Figure 2).

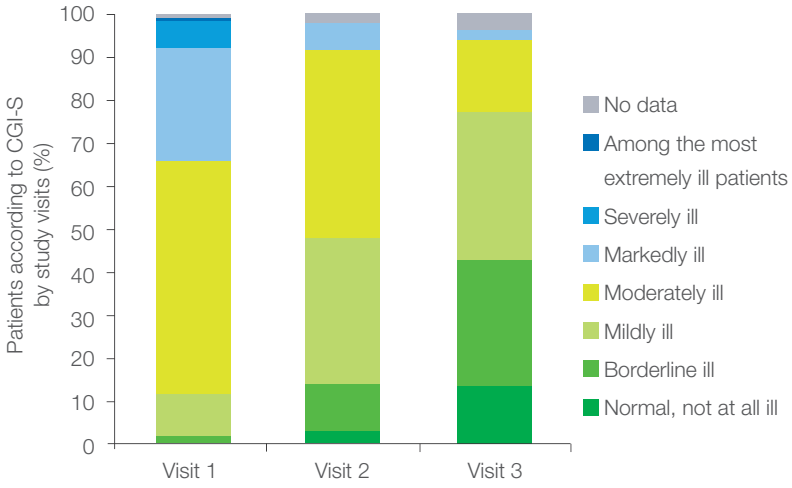

Figure 2. Percentage of patients according to CGI-S by study visits.

After two months of treatment with duloxetine, statistically significant improvement ($p < 0.0001$) in the clinical state of patients assessed according to the CGI-I scale was observed. The mean CGI-I score after one month of treatment was 2.41 ± 0.82; after two months, the score was 1.92 ± 0.90. After one month of treatment, patients' clinical state improved much to very much in 59.6% of the patients; after two months, the percentage was even 79.7% (Figure 3).

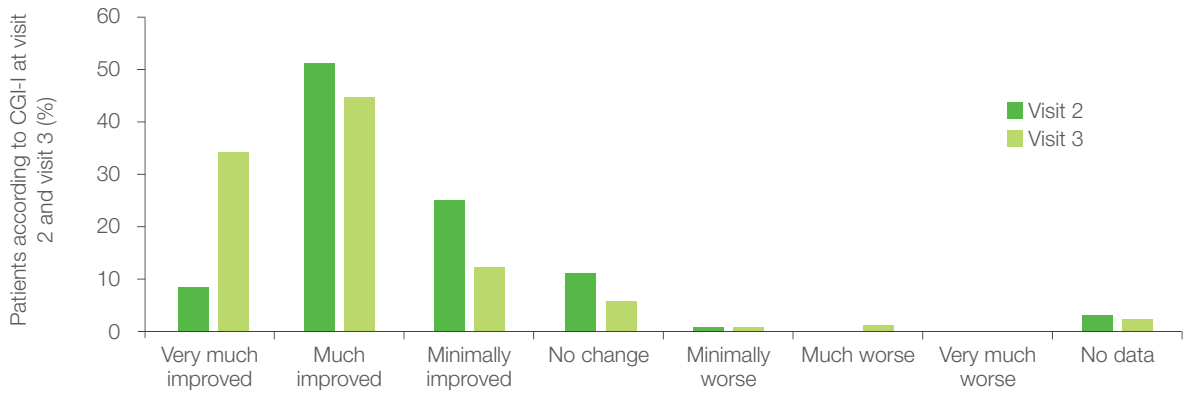

Figure 3. Percentage of patients with regard to the improvement of the patients' clinical state according to CGI-I at visit 2 and visit 3.

After eight weeks of monitoring, a statistically significant reduction in the severity of pain assessed based on the numeric rating scale was observed ($p < 0.0001$). The mean score for the severity of pain was 4.59 ± 3.00 at visit 1; 3.47 ± 2.52 at visit 2; and 2.45 ± 2.19 at visit 3.

The efficacy of the treatment with duloxetine was also confirmed by the percentage of the patients without pain or with a mild pain (Figure 4).

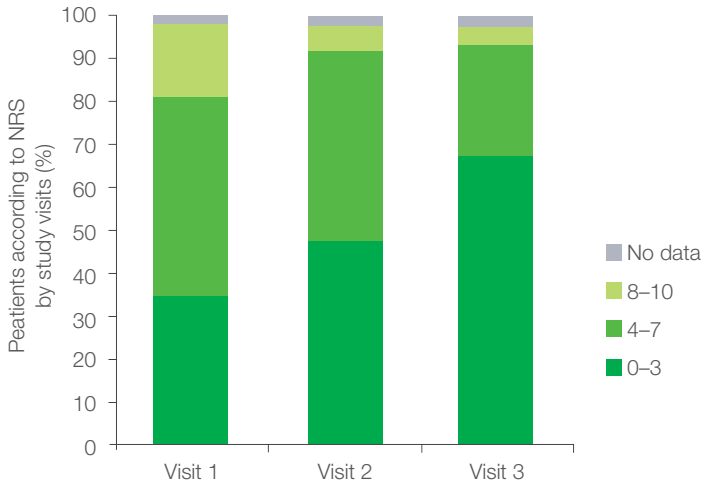

Figure 4. Percentage of patients with regard to pain severity according to NRS by study visits.

The comparison of pain severity rated using a numerical scale with the severity of disease rated using the CGI-S scale showed they are proportionally dependent on each other. The patients with the lower pain score on the numeric rating scale also have a lower score on the CGI-S scale, which means a reduction in the severity of disease. After two months of treatment with Dulsevia®, an increase in the percentage of those with lower CGI-S scores with regard to the pain severity score was observed in all three groups of patients (Figure 5). In the period from visit 2 to visit 3, clinical improvement of the disease was observed irrespective of the pain severity rating at the previous visit.

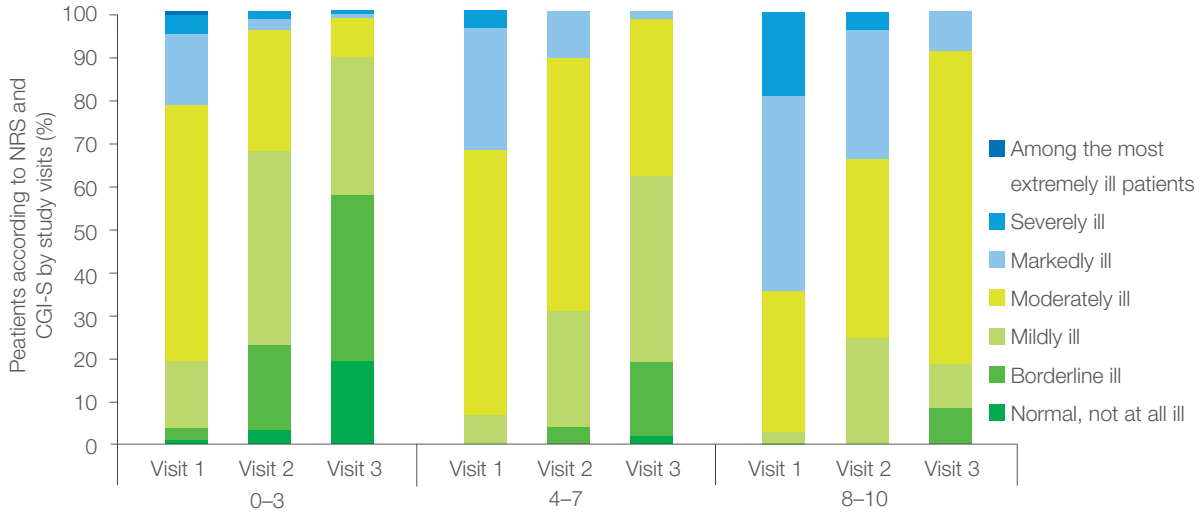

Figure 5. Distribution of patients with regard to the severity of pain according to NRS and the severity of the disease according to CGI-S by study visits.

A separate analysis of the patients that received duloxetine in the dose of 60 mg at visit 1 and were increased the dose to 90 mg at visit 2 was carried out. After two months of treatment, a statistically significant reduction in the severity of the disease was observed also in this group of patients; a reduction in the CGI-S score by an average absolute value of 1.9 was observed. In the group of patients that continued on duloxetine 60 mg, i.e. with no change in the dose, the score was reduced by an average absolute value of 1.5 points. In the patients whose dose was increased from 60 mg to 90 mg,

a statistically significantly greater reduction in the CGI-S score ($0.01 < p < 0.05$) was observed than in the patients that were receiving the 60 mg dose through the entire course of the study. After two months of treatment with duloxetine, the group of patients that were increased the dose from 60 mg to 90 mg at visit 2 showed a statistically significant improvement in the patients' clinical state ($p < 0.0001$). In relative terms, there was 20% improvement in CGI-I score. In addition, statistically significant reduction in pain severity ($p < 0.0001$) according to the numeric rating scale was observed in these patients, i.e. by the average absolute value of 2.3 points.

Assessment of satisfaction with the effect of the medicinal product on concentration, daily functioning and reduction of fatigue

As early as after one month of the treatment with Dulsevia®, more than 60% of investigators were satisfied or very satisfied with its effect on the improvement of concentration and daily functioning, and reduction of fatigue. Until visit 3, a statistically significant increase in this percentage was observed. At the end of the study, 79.5% of investigators were satisfied or very satisfied with the effect of Dulsevia® on concentration; with the effect on daily functioning 86.5% of investigators; and with the effect on the reduction of fatigue 82.5% of investigators. The mean score for satisfaction with the efficacy of Dulsevia® at visit 3 was 4.09 ± 0.77 as regards concentration; 4.24 ± 0.70 as regards daily functioning; and 4.17 ± 0.74 as regards fatigue. Patient distribution with regard to satisfaction score is shown in Figure 6.

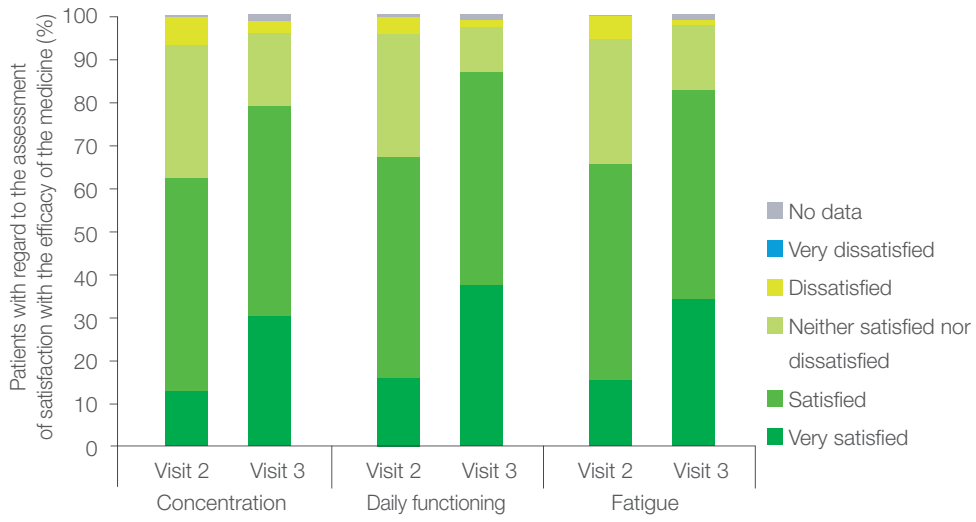

Figure 6. Percentage of patients with regard to the assessment of satisfaction with the effect of Dulsevia® on concentration, daily functioning and fatigue at visit 2 and visit 3.

In the group of patients, who were increased the dose of duloxetine from 60 mg to 90 mg at visit 2, greater satisfaction of investigators with the effect of the medicinal product on concentration, daily functioning and reduction of fatigue was observed in comparison to the group of patients who were treated with the 60 mg dose through the entire course of the study (Table 1).

Parameter	Subgroup of patients	Number of patients	Relative increase in satisfaction
Concentration	60 mg	35	11.3% ± 18.0%
	60 mg → 90 mg	141	19.7% ± 27.7%
Daily functioning	60 mg	35	8.8% ± 13.4%
	60 mg → 90 mg	140	21.5% ± 28.9%
Fatigue	60 mg	35	7.0% ± 18.6%
	60 mg → 90 mg	141	21.1% ± 32.5%

Table 1. Relative increase in investigators' satisfaction with the effect of Dulsevia® on concentration, daily functioning and reduction of fatigue from visit 2 to visit 3 by subgroups of patients (60 mg: the group of patients receiving the 60 mg dose through the entire course of the study; 60 mg → 90 mg: the group of patients that were increased the dose from 60 mg to 90 mg at visit 2).

Tolerability

At the end of the study, there were 86.7% of the patients without adverse reactions. In only 12.0% of the patients, causally related adverse reactions were observed, which were mild in most of them. In patients treated with an individual dose, the percentage of those with adverse reaction (AR) after one month or two months of treatment did not increase by increasing the dose (Table 2).

Dose of Dulsevia®	Percentage of the patients experiencing AR after one month of treatment with regard to all the patients treated with this dose	Percentage of the patients experiencing AR after two months of treatment with regard to all the patients treated with this dose
30 mg	21.1%	0.0%
60 mg	10.0%	6.3%
90 mg	8.7%	5.3%
120 mg	15.4%	2.3%

Table 2. Frequency of AR after one month and two months of treatment with regard to the dose initiated at the previous visit

The most frequently reported adverse reactions include nausea, observed in 3.2% of the patients, dry mouth and headache in 2.7% of the patients, insomnia in 2.5% of the patients, and constipation in 2.1% of the patients. The reported severe adverse reactions include nausea, dizziness, headache, anxiety, vomiting, constipation, insomnia, urinary retention, palpitations, and sweating. The majority of severe adverse reactions resolved without taking actions, such as discontinuation of the study medicine or dose reduction. The most causally related adverse reactions occurred during the first month of treatment (in 10.8% of the patients); their frequency decreased to 5.1% in continued treatment. In 1.3% of the patients, the treatment was discontinued due to adverse reactions. Figure 7 shows the percentage of the patients with adverse reactions at visit 2 and visit 3.

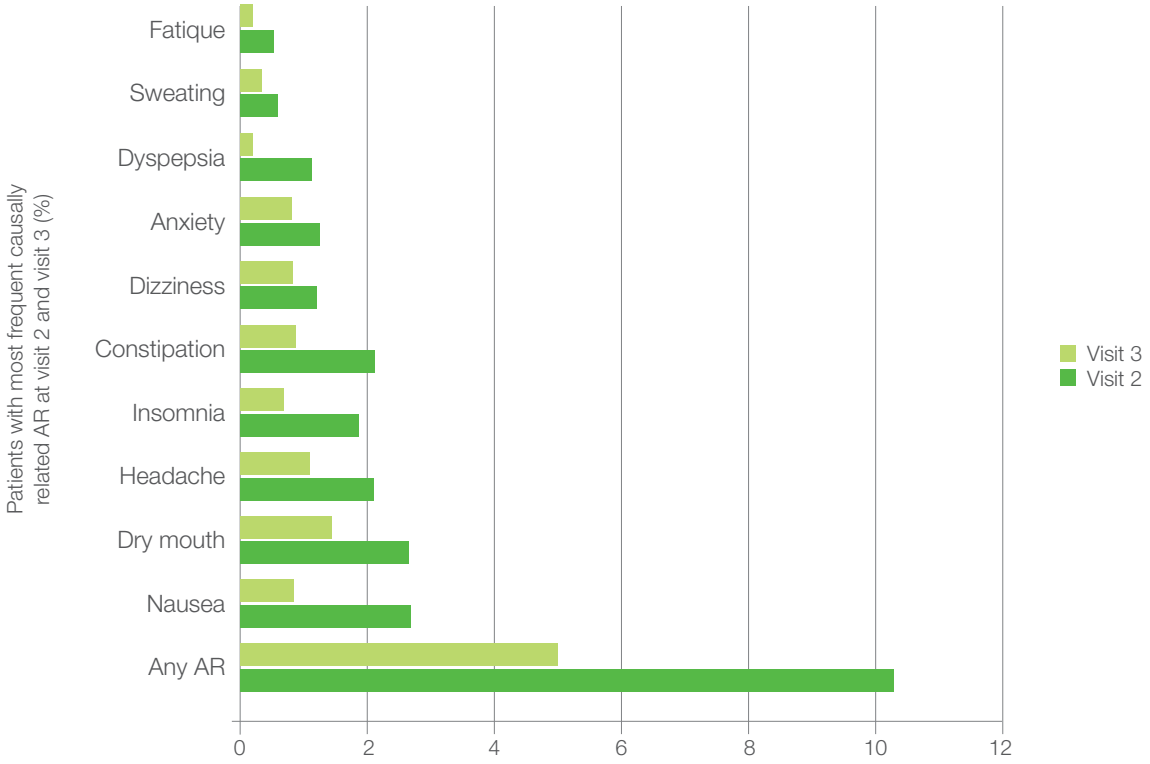

Figure 7. Percentage of patients with most frequent causally related AR at visit 2 and visit 3

Discussion

The non-interventional study of the safety and efficacy of duloxetine (Dulsevia®), in particular the 90 mg daily dose, in clinical practice in the treatment of patients with a major depressive disorder or GAD is the first clinical study in Europe conducted with a 90 mg dose of duloxetine in a single tablet. Use of duloxetine in average daily doses higher than 60 mg has been reported in the literature but it refers to taking duloxetine in daily doses of 90 mg or 120 mg composed of several tablets of different strengths. A single daily dose of 90 mg would facilitate administration to such patients and, consequently, improve their adherence to the treatment. (16, 17) The average daily dose of 90 mg was used in most of the studies as a dose to prevent the recurrence of the disease or for long-term treatment. (18, 19)

The majority of the patients included in the non-interventional study had previously been treated with medicines acting on the central nervous system. Of these, 51.9% had already been treated with duloxetine at an average daily dose of 64.7 mg. Almost one half of the patients were prescribed duloxetine in a daily dose of 90 mg at the first visit. By the end of the study, the percentage of the patients treated with the 90 mg dose increased to 76.2%. Although most patients had previously been treated with a relatively high daily dose of duloxetine, statistically significant reduction was observed for all three parameters used for assessing the efficacy of treatment (CGI-S, CGI-I, numeric rating scale). This confirms that titration of duloxetine to a dose of 90 mg or higher is effective. After eight weeks, the clinical state improved in 91.0% of the patients on therapy, while the disease improved much to very much in 79.7% of the patients. At the last visit, there were 66.3% of the patients with no pain or with mild pain, and as many as 43.9% of the patients were not ill or were borderline ill according to CGI-S. The reasonableness and effectiveness of duloxetine titration to high doses was further supported by an additional analysis of the subgroups of patients. The results of the present study demonstrated a statistically significantly greater reduction on the CGI-S scale in the patients that were

increased the dose from 60 mg prescribed at visit 1 to 90 mg at visit 2 than in the patients receiving the 60 mg dose through the entire course of the study. The optimisation of treatment by increasing the dose contributes to a greater efficacy of the treatment with duloxetine, which is important in particular for the patients who do not achieve remission and/or have residual symptoms. (16, 20)

The results of the study are comparable with the results of the previous study with Dulsevia®, which included 993 patients with depression, GAD and painful diabetic peripheral neuropathy. Compared to our study, almost one half of the included patients were newly diagnosed and untreated. At visit 1, duloxetine was most frequently initiated with a dose of 30 mg daily; after the final visit, the average daily dose was 62.2 mg. After eight weeks, the clinical state improved in 82% of the patients on therapy and a 30% reduction in severity of the disease was achieved. Although the present study included patients that had been previously treated with an average dose of duloxetine that was higher than the dose received by the patients in the previous study at their final visit, a comparable improvement of the disease was confirmed. (16, 21) The results of the present study are also comparable with the results from other clinical studies. (22, 23, 24) In one of the comparable studies, in which patients with depression were treated with duloxetine in an average dose of 93 mg, the clinical state measured with the 17-item Hamilton depression rating scale (HAM-D-17) improved after approximately seven weeks of treatment in 68% of the patients. (22)

During the study, improvement was observed in the average score for satisfaction with the effect of Dulsevia® on concentration, daily functioning and reduction in fatigue, which are most common residual symptoms of depression. After two months, approximately 80% of investigators were satisfied or very satisfied with the therapeutic effect of the medicinal product as regards concentration and daily functioning, and reduction of fatigue. In the group of patients who were increased the dose from 60 mg at visit 1 to 90 mg at visit 2, greater relative improvement in the investigators' satisfaction between the visits was observed compared to the group of patients treated with the 60 mg dose through the entire course of the study. This indicates that increasing the dose of duloxetine could relieve the residual symptoms. (5, 10, 16) Our results supported the results from the already published randomised clinical trials, which demonstrated the positive effect of duloxetine on concentration and lack of energy in depressive patients. In young and adult patients suffering from depression, concentration disorder and reduced decision-making capacity, 70% improvement was observed after 12 weeks of treatment with duloxetine; as early as after one week of treatment, improvement of symptoms as regards the lack of energy was also observed. (25, 26)

Although the average dose of duloxetine was increased during the course of the study, the patients tolerated the treatment well as no adverse reactions were observed in 86.7% of the patients. The frequency of adverse reactions did not increase with the increased dose of Dulsevia®. The majority of causally related adverse reactions were mild or moderate; they occurred more frequently in the first month of treatment. At the end of the study, only 5.1% of the patients had causally related adverse reactions. The safety of Dulsevia® in the average daily dose of 62.2 mg was already confirmed in the previous non-interventional study. The treatment was well tolerated as in 85.5% of the patients no adverse reactions were recorded. At the end of the treatment, only 3.5% of patients had causally related adverse reactions. In the present study, similar results as regards the safety of the medicinal product have been obtained although the patients received duloxetine in a dose that was on average by more than 30% higher. (16, 21) It has been confirmed in a number of other clinical studies that duloxetine is a safe medicinal product up to the dose of 120 mg daily. The randomised clinical trials in which the safety of treatment with duloxetine in a daily dose of 60 mg was compared with the safety of the 120 mg daily dose showed no significant difference in the frequency of adverse reactions between the two groups. (23, 27, 28, 29, 30)

Conclusion

The non-interventional study demonstrated the clinical efficacy and safety of the treatment with duloxetine (Dulsevia®), in particular with the dose of 90 mg, in the patients with depression or generalized anxiety disorder. The treatment of the patients receiving duloxetine in high doses was effective as a statistically significant reduction in the severity of the disease was observed, clinical state of the patients was improved and reduction in pain severity was observed. The investigators were satisfied with the effect of Dulsevia® on concentration, daily functioning and reduction of fatigue. These results were additionally supported by the analysis of the subgroups of patients. In the patients whose doses were titrated from 60 mg to 90 mg at visit 2, the reduction in CGI-S was statistically significantly greater than in the patients receiving the 60 mg dose through the entire course of the study. The investigators' satisfaction with the efficacy of the medicinal product on concentration, daily functioning and reduction of fatigue in these patients was also greater.

Although higher doses of duloxetine were used during the course of the study, no adverse reactions were recorded in 86.7% of the patients. Their frequency also decreased. The results demonstrate that Dulsevia® is an effective and safe antidepressant and that improvement of clinical outcomes of treatment can be achieved by increasing the dose.

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