The efficacy and safety of duloxetine in the treatment of depression, generalised anxiety disorder and diabetic peripheral neuropathic pain

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Abstract

BACKGROUND Duloxetine is a dual-action antidepressant from the group of serotonin and noradrenaline reuptake inhibitors. It is approved for indications including depression, generalised anxiety disorder (GAD) and diabetic peripheral neuropathic pain (DPNP). This article reports on a non-interventional study conducted with the aim of demonstrating the safety and efficacy of duloxetine (Dulsevia®) in clinical practice, and on an epidemiological study that provided an insight into the use of duloxetine in daily clinical practice.

METHODS At the end of the non-interventional study (after eight weeks of treatment) in 993 patients, the mean daily dose of duloxetine was 62.2 mg. 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 visual analogue scale (VAS) to assess therapeutic efficacy, and they monitored the safety of the treatment.

RESULTS The clinical state improved in 82% of the patients in eight weeks. Disease severity decreased by 30%. Moreover, the treatment reduced pain intensity, as demonstrated by a mean absolute reduction of the VAS score of 3 (out of 10) at the end of the treatment. Duloxetine was well tolerated by most of the patients. No adverse events were reported in 852 (85.8%) of the patients. Only 3.5% of the patients still had causally related adverse events at the end of the treatment.

CONCLUSIONS The results of the study demonstrated that duloxetine was safe and effective in daily clinical practice.

Introduction

Duloxetine is approved in the EU for treating major depressive disorder, generalised anxiety disorder (GAD) and diabetic peripheral neuropathic pain (DPNP)[1, 2]. In the USA it is also approved for other indications (fibromyalgia, chronic musculoskeletal pain)[3]. Guidelines include recommendations to use duloxetine in other types of neuropathic pain as well[2, 4, 5].

Depression is among the most common mental health problems. It profoundly affects the quality of life, outcomes of treatment of comorbid conditions and treatment costs as well as morbidity and

mortality. It is estimated that depression affects more than 300 million people around the world, which is 4.4% of the world population. A similar number of people, 264 million, are globally affected by anxiety disorder. The annual prevalence of depression in Europe is estimated to be about 7% and that of anxiety about 14%[6, 7].

Depression and anxiety often present together in clinical practice. It is estimated that about two thirds of patients with GAD also have symptoms of depression and that somewhat less than a third of patients with depression also have symptoms of GAD[8]. Many patients with depression also experience pain symptoms. Some studies have shown that 7 in 10 patients with depression report only pain symptoms[9]. Pain is found in three quarters of patients with depression and its presence predicts poorer treatment outcome and lower probability to attain remission[10].

Diabetic neuropathy is a blanket term referring to different clinical or subclinical changes to the nervous system that are associated with diabetes. DPNP is experienced by 16–26% of diabetic patients[2]. It is a chronic pain that patients usually assess with an average score of 5 on the visual analogue scale (VAS) and that reduces their quality of life by affecting their physical and emotional life, sleep and work[10, 11]. It is therefore not surprising that two thirds of DPNP patients suffer from depression with moderately severe or severe symptoms or from anxiety disorder[12, 13]. In addition, DPNP is a stronger predictor of depression than other complications of diabetes[14].

Duloxetine is a dual-action antidepressant from the group of serotonin and noradrenaline reuptake inhibitors. To a lesser extent it also inhibits the reuptake of dopamine into the presynaptic neurons. The mechanism of the analgesic action of antidepressants is linked to the serotonin and dopamine system. Duloxetine reduces pain symptoms by potentiating descending pain inhibitory pathways in the central nervous system.[9, 15]

Duloxetine has been available on the Slovenian market since 2005. Dulsevia®, Krka's duloxetine, has been available since 2015. In this article we report on an epidemiological study of the use of duloxetine in Slovenia and a non-interventional study of its safety and efficacy conducted with the aim to gain a broader insight into everyday clinical use of duloxetine and to demonstrate the safety and efficacy of Dulsevia® in clinical practice.

Methods

The non-interventional study of the safety and efficacy of duloxetine in patients with major depressive disorder, GAD or DPNP was carried out from March do December 2016 in Slovenia. The study followed the principles of the Declaration of Helsinki and was approved by The National Medical Ethics Committee of Slovenia (NMEC) on 25 August 2015 (No 0120-364/2015-2). A notification application to the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP) was submitted on 23 December 2015.[16]

The purpose of conducting the study was to demonstrate the safety and efficacy of duloxetine in the treatment of major depressive disorder, GAD and DPNP in clinical practice. Each patient was scheduled to have three study visits during a two-month study period, including the inclusion visit, a visit one month after inclusion and a visit after 2 months of treatment. All patients were included in the statistical analysis of the efficacy and safety of the treatment.[16]

Monitoring of efficacy

Physicians measured disease severity based on Clinical Global Impression-Severity (CGI-S) rating scale scores obtained during the three study visits and treatment efficacy based on Clinical Global Impression-Improvement (CGI-I) rating scale scores obtained during the second and third study visit. CGI-S is a seven-point scale with 1 = normal and 7 = among the most extremely ill patients. CGI-I is a seven-point scale with 1 = very much improved and 7 = very much worse. Patients assessed the intensity of their pain on a visual analogue scale (VAS) during the first, second and third study visit (VAS: 0 = no pain, 1 = very mild and hardly noticeable, 10 = worst pain imaginable).[16]

Monitoring of safety

Adverse event monitoring was carried out by recording spontaneous reports on adverse events or reports obtained in response to indirect questioning. The investigators assessed the severity of adverse reactions (mild, moderate, severe), their frequency (single occurrence, uncommon, persisting), their outcomes and their possible relatedness to duloxetine, and actions taken for adverse events (none, discontinuation of the medicine, dose reduction, symptomatic treatment or hospitalisation). They reported in writing on every serious, medically significant or unexpected adverse event or adverse interaction with other medications.[16]

Statistical analysis

Efficacy variables were treated as ordinal random variables. Pain intensity (VAS) was considered a discretised ratio random variable. Statistical significance of differences between two mean measurements obtained in the same population was set at 0.05. The asymptotic z-test was used and the interval means were determined using the asymptotic 95% confidence interval. Calculations were done in Microsoft Office Excel 2013©.[16]

In the same period, between February 2016 and May 2017, an epidemiological study was conducted in Slovenia with the purpose to investigate duloxetine prescribing habits in patients with major depressive disorder, GAD or DPNP. Sixty-eight physicians (psychiatrists, neurologists, diabetologists) from across Slovenia participated in the study. The study was approved by the Republic of Slovenia National Medical Ethics Committee (NMEC) on 23 June 2015, No 34/06/15. Participating physicians were using a plain questionnaire to gather data on patient history (age, sex, indication at the time of initiation of duloxetine, previous treatment), prescribed daily doses of duloxetine and reasons for initiating duloxetine, and on concomitant medications. Calculations were done in Microsoft Office Excel 2010©.[17]

Results

Patients

The patient population in the non-interventional study consisted of 993 patients with depression, GAD or DPNP. All were above 18 years of age and required treatment for indications as detailed in the Dulsevia® Summary of Product Characteristics. The second study visit was attended by 982 patients and the third study visit by 909 patients. The mean age of the patients was 63.1±14.05 years. Sixty-eight per cent of them were women and 31% were men.[16]

The epidemiological study population (501 patients) was similar in that the mean age of the patients was 56±14.38 years and more women (64%) were included than men.[17]

In the non-interventional study, duloxetine was most commonly initiated in patients with depression (42%), followed by DPNP (24%) and GAD (22%). Other patients (11%) had combinations of these disorders and in 10 patients (1%) the diagnoses were unknown (Table 1).[16]

In the epidemiological study, duloxetine was initiated for similar reasons, as 41% of the patients were treated for depression, 24% for GAD and 10% for DPNP. Different combinations of these disorders were found in 16% of the patients and 9% of them were treated with duloxetine for other indications (Table 1).

The most common of these were other types of anxiety disorder and different types of pain. Depressive disorder and anxiety disorder were reported as a single or an additional indication in as many as 85% of the patients treated with duloxetine. An indication associated with pain was reported in 28% of the patients.[17]

	Non-interventional study		Epidemiological study	
Indication	**N**	**%**	**N**	**%**
Depression	413	41,6	205	41
DPNP	240	24,2	48	10
GAD	218	22	121	24
Depression and GAD	49	4,9	54	11
Depression and DPNP	36	3,6	19	4
GAD and DPNP	21	2,1	7	1
Depression and GAD and DPNP	6	0,6	2	0
No data	10	1		
Other indications			45	9
	993	**100**	**501**	**100**

Table 1. Indications for initiating duloxetine in the non-interventional study (n=993) and in the epidemiological study (n = 501)

No previous psychiatric therapy had been received by 45% of the non-interventional study population and 55% of the patients had been treated previously. Previously treated patients were most frequently treated with escitalopram (170 patients; 17.1%), sertraline (94; 9.5%), alprazolam (75; 7.6%), duloxetine (62; 6.2%), paroxetine (47; 4.7%), bromazepam (40; 4%) and mirtazapine (30; 3%). More than one active substance may have been used concomitantly by a single patient.[16]

Somewhat more than half of the epidemiological study population (57%) had been taking other medicines before duloxetine was introduced and in 43% of them duloxetine was initiated as the first medicine in the investigated indications. Most of the previously treated patients had been taking a single medicine (75%). One fourth of them had been taking different combinations of medicines. The greatest number of them had used antidepressants (88%), mostly selective serotonin reuptake inhibitors (67% of those treated with an antidepressant), 11% of them with antiepileptics, 4% with antipsychotics, 3% with anxiolytics and 2% with analgesics. The greatest number of patients included in the study (58%) started taking duloxetine in the last month of the study, and were thus in the treatment initiation phase, and 32% of the patients were taking duloxetine for more than one month.

At least 6 patients were taking duloxetine for more than one year. The longest duration of treatment was 30 months.[17]

Doses

The most common initial daily doses of duloxetine in the non-interventional study were 30 mg (48%) and 60 mg (48%). A daily dose of 90 mg was prescribed in 2% of the patients and a daily dose of 120 mg in 1% of the patients. The total mean total daily dose at the first visit was 47.2 mg. The mean daily dose of duloxetine increased during the study to 59.4 mg at the second visit and to 62.2 mg at the third visit (Figure 1).[16]

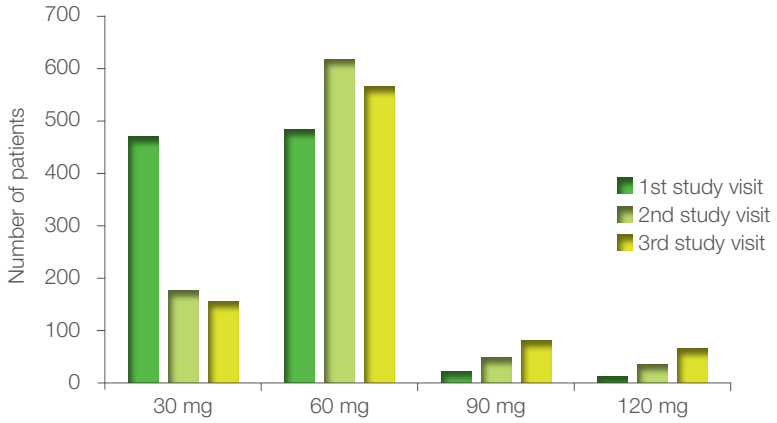

Figure 1. Total daily dose of duloxetine in the non-interventional study

The epidemiological study demonstrated that most often physicians prescribed duloxetine in a daily dose of 60 mg (55%), mostly (in 93% of cases) administered as one 60 mg capsule and rarely (in 7% of cases) as 30 mg administered twice daily. One fourth (27%) of the patients were prescribed 30 mg of duloxetine daily and 18% of them more than 60 mg of duloxetine daily. The mean daily dose was 59.6 mg. Interestingly, the mean dose of duloxetine in patients starting treatment in the last month of the study (the mean initial dose was 58.5 mg) was similar to the mean dose in patients treated for more than one month (the mean therapeutic dose was 63.2 mg). If patients taking therapeutic doses are considered, there was an increase in the number of those treated with the 120 mg daily dose and a decrease in the number of those treated with the 30 mg daily dose (Figure 2).[17]

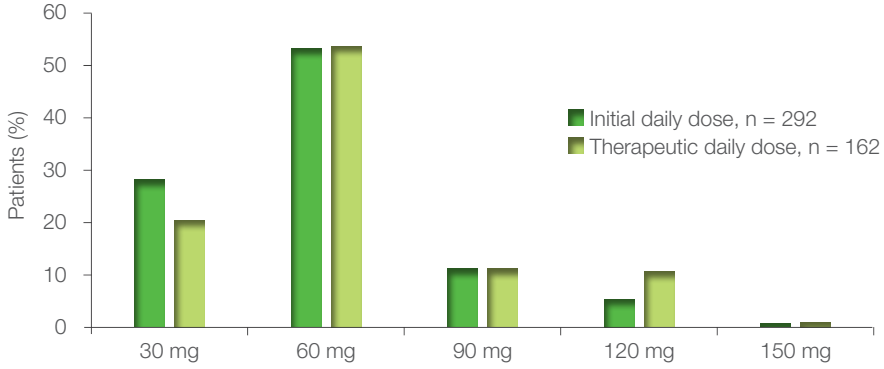

Figure 2. Percentages of patients treated with different initial and therapeutic daily doses of duloxetine

According to physicians, duloxetine has a simple dosage scheme, which was given as the reason to use duloxetine in as many as 42% of the patients (Table 2).[17]

Reasons for using duloxetine	%
Efficacy of therapy	79
Safety of therapy	54
Simple dosage	42
Failure of previous therapy	44
Hypersensitivity to other medicines	3
Other	6

Table 2. Reasons for using duloxetine (in percentages calculated for total study population, N = 501)

Efficacy

The results of the non-interventional study demonstrated a significant ($p < 0.0001$) reduction in disease severity, as demonstrated by improvement in the CGI-S scores after eight weeks of duloxetine therapy. The mean CGI-S score was 4.18 ± 0.95 at the first visit, 3.47 ± 1.02 at the second visit and 2.86 ± 1.13 at the third visit. The mean absolute reduction of the CGI-S scores between the first and the second visit was 0.74 ± 0.91 and their relative reduction was 16% ± 22%. In the period between the first and the third visit, the absolute CGI-S score reduction was 1.35 ± 1.16 and the relative CGI-S score reduction was 30% ± 26%. Change in disease severity is shown in Figure 3. The clinical state of the patients was assessed as 'not at all ill' or 'borderline mentally ill' in 5.4% of the patients at the first visit and in 36.0% of the patients at the third visit. An assessment 'severely' or 'most extremely ill' was made in 5.7% of the patients at the first visit and in 0.5% of the patients at the third visit.[16]

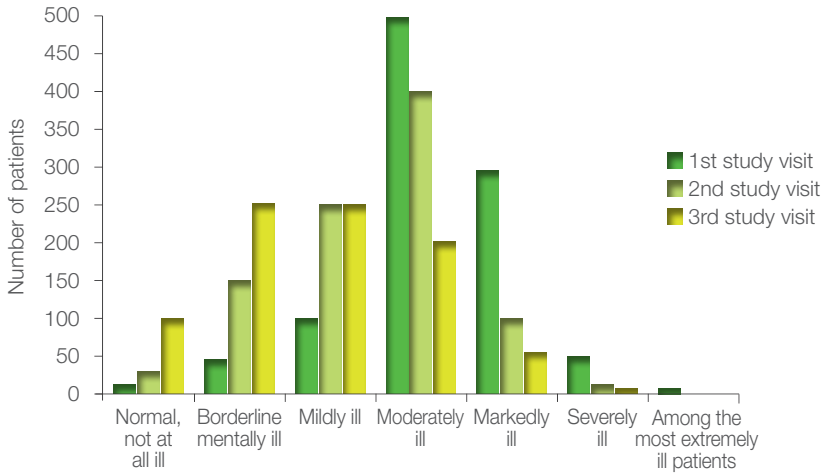

Figure 3. Change in disease severity (CGI-S) between study visits

There was a statistically significant ($p < 0.0001$) improvement of the patients' clinical state after eight weeks of duloxetine therapy, as demonstrated by the CGI-I scores. The mean CGI-I score decreased from 2.36 ± 0.93 at the second visit to 1.78 ± 0.83 at the third visit. It decreased absolutely by 0.51 ± 0.79 and relatively by 18% ± 31%. The clinical state was assessed as improved in 82% of the patients at the second and the third visit. At the third visit, an at least moderate improvement of the clinical state was observed in 75% of the patients. Figure 4 shows improvement in the CGI-I scores at the second and the third visit.[16]

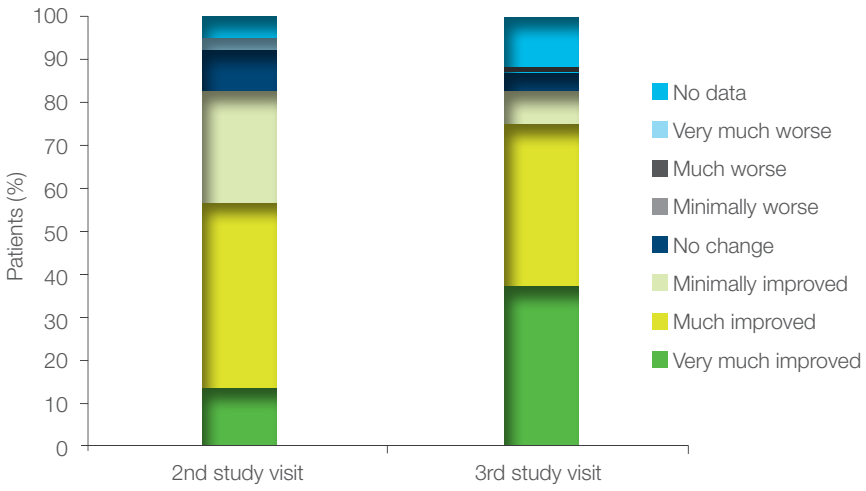

Figure 4. Clinical efficacy (CGI-I) at the second and the third visit

Pain intensity decreased statistically significantly ($p < 0.0001$) after eight weeks, as demonstrated by changes in the VAS score. The mean VAS score decreased from 5.78 ± 2.40 at the first visit to 3.88 ± 2.15 at the second visit and to 2.70 ± 1.85 at the third visit. The mean absolute reduction in the VAS score between the first and the third visit was 3.09 ± 2.08. VAS scores between study visits are shown in Figure 5.

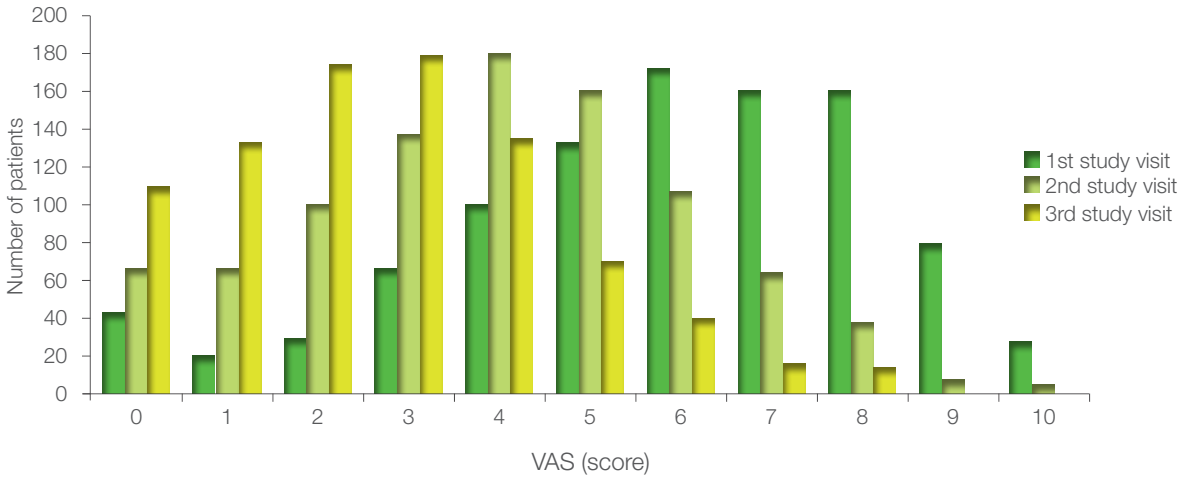

Figure 5. Pain intensity VAS scores during study visits

Although the mean VAS score at the first visit was higher in patients with DPNP than in those with depressive disorder or GAD (6.83 ± 1.55 vs 5.38 ± 2.59), pain was rather intense in both groups. The greatest reduction in pain was observed in the period between the first and the second visit in both groups, and at the end the VAS score was below 3 (2.98 ± 1.68 vs 2.58 ± 2.58) in both groups. In patients with DPNP this indicates a 56% relative improvement from baseline, and a 50% improvement from baseline in patients with depressive disorder and/or GAD.[16]

The results of the epidemiological study also demonstrated that, in the opinion of physicians, duloxetine is an effective medicine, since in eight patients out of ten they stated duloxetine efficacy as the reason for initiating duloxetine therapy and in four out of ten failure of previous therapy (Table 2). There are several other reasons why physicians prescribe duloxetine, as more than one reason for its prescribing was given in more than half (70%) of the patients.[17]

Safety

Duloxetine was well tolerated by most patients. No adverse events were reported in 852 (85.8%) of them. Eight hundred and seven (81.3%) patients did not experience adverse events and in 45 (4.5%) patients data on adverse events were insufficient and provided no conclusive evidence on the occurrence of adverse events. Adverse events were experienced by 141 patients (14.2%). Those that were in the opinion of the physicians causally related to duloxetine treatment were reported in 134 patients (13.5%). Most of them occurred in the period between the first and the second study visit (in 12.3% of the patients). Their occurrence was lower in the period between the second and the third visit, when they were reported in only 3.5% of the patients. Causally related adverse events were mostly nausea (7.4%), dizziness (4.4%), headache (2.8%), dry mouth (2.7%), insomnia (2.1%), anxiety (1.9%), fatigue (1.9%), somnolence (1.8%) and dyspepsia (1%). Other adverse events were experienced by less than 1% of the patients (Figure 6).[16]

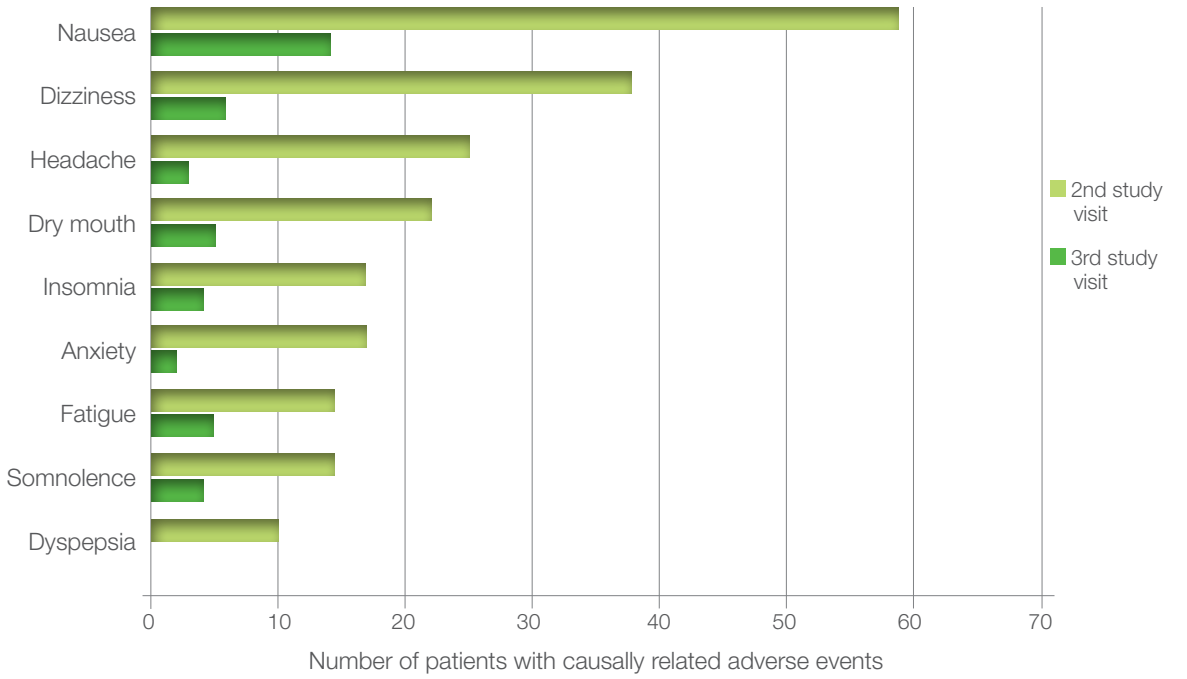

Figure 6: Number of patients with most frequent causally related adverse events

Adverse events were mild in the greatest percentage of patients with causally related adverse events (68 patients; 6.8%). Forty-four (4.4%) patients had moderate adverse events and 21 (2.1%) had severe adverse events, and in one (0.1%) patient data on the severity of adverse event were missing.[16] Seventy-nine (7.9%) patients with causally related adverse events continued treatment without any actions taken for adverse events. Treatment discontinuation was required in 42 (4.2%) patients with causally related adverse events. Symptomatic treatment was introduced in 0.9% of the patients, the dose was reduced in 0.5% of the patients, one (0.1%) patient was hospitalised for a serious adverse event (diarrhea), and in one (0.1%) patient the action taken for adverse event was unknown.[16]

Safety monitoring revealed two serious adverse events. One patient committed suicide between the second and the third study visit. In this case, a causal relation between the event and treatment with duloxetine could be neither excluded nor confirmed (CIOMS form: SI2016K6690). In the other patient the serious adverse event was diarrhea, which was unlikely to be causally related to duloxetine (CIOMS form: SI2017K8473STU) in the opinion of the physician.[16]

As shown by the results of the epidemiological study, the reason why physicians prescribed duloxetine was its safety in more than one half (54%) of the patients (Table 2).[17]

Concomitant medication

Most of the patients participating in the non-interventional study were using concomitant medications. The percentage of patients on concomitant medication was 78% at the first visit, 76% at the second visit and 71% at the third visit. They were most often treated with acetylsalicylic acid, antidiabetics (metformin, insulin, gliclazide), pantoprazole, bisoprolol, statins, alprazolam, analgesics (tramadol combined with paracetamol, naproxen, diclofenac), perindopril and combinations containing perindopril, zolpidem and levothyroxine.[16]

Similarly, concomitant medications were used by nearly three quarters (74.3%) of patients included in the epidemiological study. More than one half (57.9%) of all patients were taking CNS medicines, one in ten (9.6%) patients was taking an analgesic and one in three (33.9%) patients was taking a medicine for treating other diseases. The most common concomitant CNS medicines were antipsychotics (37.9% of the patients), anxiolytics (35.5% of the patients), antidepressants (27.9% of the patients) and antiepileptics (22.1% of the patients). One third of the patients on CNS medication (35.5%) were taking more than one CNS medicine.[17]

Discussion

The therapeutic effect of duloxetine on emotional symptoms and pain in patients with major depressive disorder, GAD or DPNP has been demonstrated in several placebo-controlled and randomised studies.[9, 18–25]

The here presented study confirmed that duloxetine improves the clinical state and reduces pain without regard to the reason of initiating duloxetine therapy. The study results demonstrated the efficacy of duloxetine 60 mg to 120 mg daily. The mean reduction in disease severity between the first and the third study visit was 1.35 on the CGI-S scale, or 30%. Thirty-six per cent of the patients were assessed at the third study visit as ‘not ill’ or ‘borderline mentally ill’ and only 0.5% of them as ‘severely ill’. These results are comparable to those reported in international clinical studies mentioned further in this chapter.

Another comparable result relates to the improvement scores (CGI-I) at the third study visit, as at least a score of ‘much improved’ clinical state was observed in 75% of the patients and the mean CGI-I score was 1.78.[16]

In a double-blind, placebo-controlled study of the efficacy of duloxetine in patients with major depressive disorder, duloxetine statistically significantly reduced disease severity (by 1.67 on the CGI-S scale) in 8 weeks of treatment (baseline 4.2; $p = 0.007$) compared to placebo (by 1.07 on the CGI-S scale). The CGI-I scores reported after eight weeks of treatment were 2.69 in patients taking placebo and 2.10 in patients taking duloxetine. The patients were taking daily doses of 120 mg duloxetine if tolerated, which could explain the greater improvement if compared to our non-interventional study.[18] A statistically significant difference between duloxetine and placebo, as assessed by investigators, was also found in a 10-week, double-blind, placebo controlled study where a rating of ‘very much improved or ‘much improved’ (CGI-I) was reported in 62.2% of patients treated with duloxetine and 42.1% of patients taking placebo. The CGI-S score indicated ‘not ill’ or ‘moderately mentally ill’ in 46.1% of the patients treated with duloxetine for eight weeks (compared to 27.7% of patients in the placebo group) and ‘severely ill’ in only 3.9% of patients on duloxetine therapy, as compared to 6.9% of patients taking placebo.[19]

In a 52-week randomised study investigating the risk of relapse in patients with GAD, the treatment result was assessed using the CGI-I scale. Duloxetine was administered in daily doses of 60 mg to 120 mg during the first, 26-week period of the study. Patients with good response to duloxetine therapy, that is, rated 'much/very much improved' (CGI-I) during the first 26 weeks, were then included in the second study period. A statistically significant reduction in the risk of relapse was observed during the continuation of treatment with 60 mg to 120 mg of duloxetine daily in the second period of the study compared with placebo.[20]

The efficacy and safety of duloxetine in doses of 60 mg to 120 mg administered for pain relief were investigated in a 12-week, double-blind, randomised, placebo controlled study in patients with DPNP. Improvement of the CGI-S scores was used as a secondary efficacy measure. A greater improvement compared to placebo was found in both the group taking 60 mg of duloxetine and the group taking 120 mg of duloxetine.[21]

A similar 12-week, double-blind, placebo-controlled study included patients with DPNP with or without depressive disorder. Treatment with duloxetine doses of 60 mg or 120 mg daily was found effective compared to placebo, which was demonstrated by an improvement in the CGI-S score (-1.37; $sp < 0.05$ or -1.47; $sp < 0.01$).[22]

Pain symptoms improved in our non-interventional study by a mean VAS score of 3.09. Two hundred and fifty-six patients assessed their pain with a VAS score of 8 or more at the first study visit. Their number was reduced to 13 at the third visit, and as many as 600 of them assessed their pain with a score of 3 or lower. Pain intensity was reduced between the first and the third visit by 50% in patients with depressive disorder and/or GAD and by 56% in patients with DPNP.[16]

Duloxetine doses of 80 mg daily resulted in a statistically significantly greater reduction in overall pain intensity compared with placebo in international studies assessing the effect of duloxetine on pain symptoms in depressive disorder with the VAS scale. An 8-week duloxetine therapy reduced pain intensity by 47%.[23]

The results of another randomised, double-blind study in patients with depressive disorder and pain symptoms demonstrated that in 9 weeks daily doses of 60 mg duloxetine reduced pain symptoms measured with VAS statistically significantly when compared to placebo. Moreover, a statistically significant reduction in item 13 (general somatic symptoms such as backaches, headaches, muscle aches) of the Hamilton Rating Scale for Depression (HAM-D17) was found in patients taking duloxetine.[9]

Study data have shown that there is a correlation between improvement in pain symptoms and a greater likelihood of remission in depression.[10] An analysis of two randomised, double-blind, placebo-controlled studies carried out in patients with GAD demonstrated that 60 mg to 120 mg of duloxetine daily results in a statistically significantly ($p < 0.001$) greater reduction in overall pain intensity measured with VAS than placebo. In patients treated with duloxetine, pain intensity was reduced by 42–48.7%, compared to 26–31.1% in those taking placebo. Patients with lower CGI-I scores (indicating greater improvement in the clinical state) had a greater reduction in pain severity (VAS) at the end of the treatment. In patients with a rating 'very much improved' in clinical state (CGI-I = 1), the overall pain was reduced by 77.4%. For comparison, overall pain in patients with an unchanged clinical state (CGI-I = 4) was reduced by 15.4%.[24]

Studies on duloxetine efficacy in reducing pain in patients with DPNP more often used the 11-item Likert scale for measuring pain*. The primary efficacy measure was weekly change in the mean 24-hour average pain intensity. Despite the use of different measuring scales as those used in our non-interventional study, the authors found that duloxetine in daily doses of 60 mg to 120 mg resulted

* Likert Pain Scale: 0 – no pain, 10 – worst pain ever experienced

in statistically significantly greater improvement in pain symptoms (24-hour average pain intensity) than placebo.[21] Duloxetine improves the pain assessment score by a direct analgesic effect, which is independent of an improvement of mood symptoms (measured with a depression rating scale; Beck Depression Inventory, BDI).[25]
Duloxetine was well tolerated in our non-interventional study. In 85.8% of the patients no adverse events were reported (81.3% of the patients did not experience adverse events and in 4.5% of them data on adverse events were insufficient and provided no conclusive evidence on the occurrence of adverse events). The frequency of adverse events was the highest during the first month of the treatment and fell during the continuation of the treatment. Adverse events were most often mild (51%) or moderate (33%).[16]

International studies have also demonstrated that the incidence of adverse events experienced by patients treated with duloxetine (80 mg daily) is not statistically significantly greater than that observed with placebo.[19] In a study where duloxetine was used in daily doses of 60 mg, the investigators assessed most adverse events as mild or moderate. The most common adverse event was nausea, which mostly occurred in the first week of the treatment and later occurred less often.[9]

A study was recently published in the USA, which compared the suicide rate in the period from January 1997 to December 2007 in untreated patients with depression and patients treated with antidepressants. The authors found that the likelihood of suicide attempts is the greatest in the period preceding diagnosis and slowly falls during the following six months. The likelihood of suicide attempts in untreated patients was the greatest during the second month after diagnosis. Patients treated with antidepressants were not exposed to a higher risk of suicide than untreated patients and there were no noticeable differences that could be attributed to the use of different classes of antidepressants, such as SNRIs or SSRIs. In contrast, patients with depression had an increased risk for suicide relative to the general population, without regard to treatment, which shows that depression increases the risk of suicidal behaviour.[26] A conclusion that the use of antidepressants is not associated with an increased risk for suicide has also been reached by a group of American investigators from five centres, who conducted a 27-year longitudinal observation study to monitor 757 psychiatric patients. The likelihood of antidepressant medication use was greater in patients with more serious symptoms. In these patients antidepressant therapy statistically significantly reduced the risk for suicide.[27] A relation between an increased risk for suicide and the use of duloxetine was also rejected in a 2006 meta-analysis that showed that duloxetine therapy, compared to placebo, improved HAM-D item 3 scores used to assess suicidal ideation.[28]

Conclusions

The results of the reported Slovenian non-interventional study of duloxetine (Dulsevia®) in 993 patients with major depressive disorder, GAD or DPNP, support the clinical efficacy and safety of Dulsevia®. The mean initial daily dose of duloxetine was 47.2 mg and its final dose was 62.2 mg. The obtained epidemiological data revealed a similar dosage, as the most commonly prescribed duloxetine dosage was 1 capsule of 60 mg daily, which indicates that simple dosage is an important factor in the treatment of the above disorders. Duloxetine is most commonly used for treating patients with depressive disorder. However, one patient out of ten has more than one diagnosis. Most patients included in the non-interventional study and in the epidemiological study were taking other medications from different therapeutic classes in addition to duloxetine. Treatment with Dulsevia® resulted in a statistically significant reduction of disease severity and improvement of the clinical state, as demonstrated by an improvement in the CGI-S scores and the CGI-I scores as well as a reduction in pain intensity (VAS).

No adverse events were reported in relation to the use of Dulsevia® in 85.8% of the patients and causally related adverse events mainly occurred during the initial period of the treatment.

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