Treatment of depression, anxiety and depression with anxiety with Krka`s antidepressants – a wide choice for different types of patients

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Key words
Depression, anxiety, efficacy, safety, escitalopram, sertraline, venlafaxine, mirtazapine

Abstract
Depression is a disabling illness affecting a large part of population. It is still neither sufficiently recognized nor adequately treated. In most patients with depression or/and anxiety disorders, antidepressants are the first-choice medicines. Guidelines and reviews do not determine a specific class or molecule to be preferred as the first choice. Choosing the right antidepressant is a complex process and based on patients' symptoms, comorbidities and preferences. With the studies' findings described in this article, we would like to add pieces to the mosaic of existing evidence in order to make the choice of an antidepressant easier. Four Krka's antidepressants offer safety, efficacy and high quality, and since they come from three different classes of antidepressants, they also offer appropriate first-choice treatment for a wide variety of patients.

Introduction

Each year 6% of adults will experience an episode of depression; over the course of a person's lifetime more than 15% of the population will experience an episode of depression. Depression is the leading cause of suicide and currently the fourth highest disease burden on society in terms of treatment costs, effect on family and caregivers, and impact on productivity in the workplace.[1] The 2010 global burden of disease study revealed that major depressive disorder (MDD) was the second leading cause of global disability and the eleventh leading cause of global burden. The study additionally confirmed that depressive disorders are the leading direct cause of the global disease burden and contributor to the burden of suicide and the ischemic heart disease.[2]

Nearly three fourths (72.1%) of patients with lifetime MDD also met the criteria for at least one of the other disorders assessed in the US national comorbidity survey replication, including 59.2% with anxiety disorder.[3] The occurrence of depression and anxiety symptoms together is associated with a greater severity of symptoms, greater impairment, a more chronic course of illness, poorer outcome and higher incidence of suicide.[4]

MDD is about two to three times more common in people with chronic physical health problems than in people who are in good physical health. Chronic physical health problems can precipitate and exacerbate depression, but depression can also adversely affect the outcomes of co-existing physical illnesses, including increased mortality.[1] Patients with a depressed mood often report somatic complaints or have medically unexplained symptoms, especially pain.[5] The prevalence of co-morbid pain and depression is between 50–100%.[6, 7]

On the other hand, the risk of endorsing depressed mood in patients with chronic pain shows a 2–3 fold increase.[6] Chronic pain syndromes, such as headache, back pain, joint pain and others, often accompany major depression and anxiety disorders.[8] Up to 90% of patients with depression also have sleep problems[9] and in these patients improved sleep significantly contributes to better treatment compliance.[10]

Depression can be disabling and distressing and can become a chronic disorder, especially if inadequately treated.[1]

Pharmacotherapy is the primary choice for medical management of MDD.[11] As the obvious first-line treatment of major depression there is no single antidepressant from any class. However, newer generation antidepressants, with improvements in safety and tolerability, have replaced tricyclic antidepressants as first-line treatment of depressive illness.[12] Newer or second-generation antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other medicines with related mechanisms of action that selectively target neurotransmitters.[11] Several systematic reviews have assessed the comparative efficacy and safety of second-generation antidepressants. Two recent comparative effectiveness reviews provide the most comprehensive, albeit contradictory, assessments to date.[13, 14] One review concluded that efficacy does not differ substantially among second-generation antidepressants;[14] conversely, the MANGA (Multiple meta-analyses of new generation antidepressants) study group reported that escitalopram and sertraline have the best efficacy-acceptability ratio compared with other second-generation antidepressants.[13] Possible side effects, convenience of dosing regimens, and costs may best guide the choice of a second-generation antidepressant for treating major depression in adults.

The most common factors that psychiatrists consider when prescribing antidepressants are: avoidance of specific side effects, the presence of comorbid psychiatric disorders, and the presence of specific clinical symptoms. Prior treatment history, including prior positive or failed response to a medicine, is the next most frequently endorsed factor influencing medication choice. For more than half of the prescriptions, the presence of specific clinical features influenced antidepressant choice. The presence of insomnia, high levels of anxiety, and fatigue most frequently are reported to influence medication selection. With regard to the influence of diagnostic comorbidity, the presence of comorbid anxiety disorders, particularly panic disorder (PD) and generalized anxiety disorder (GAD), most frequently influenced antidepressant selection. Concern about the occurrence of sexual dysfunction and weight gain are the side effects that had the greatest impact upon medication selection.[15]

Studies of Krka's antidepressants

In Krka we have performed clinical studies with four antidepressants: Krka's escitalopram (Ecytara[A]), Krka's sertraline (Asentra) both from the SSRI class, Krka's venlafaxine (Alventa[B]) from the SNRI class and Krka's mirtazapine (Mirzaten[C]) from the noradrenergic and specific serotonergic antidepressant class. Outcome data are included from five studies, four of which had already been published in independent publications;[16–19] two of them were performed with Asentra. All studies were post-marketing and non-interventional, except the study with Mirzaten, which was post-marketing and interventional. Studies with Ecytara and Asentra (on patients with depression and/or anxiety disorders) were conducted mostly by general practitioners; on the other hand in studies with Asentra (on social anxiety disorder (SAD) patients), Alventa and Mirzaten investigators were psychiatrists. The number of included patients was 2,229. Women represented almost 70% of the included patients. The study with Krka's escitalopram was conducted on 389 patients, most of them with a diagnosis of depression (64%), depression and anxiety (19%) and anxiety (15%). The majority of patients was not treated before (83%); some of them received antidepressants or anxiolytics therapy (17%). Most of the patients included in the study received 10 mg of Ecytara from the beginning of treatment and were also maintained on this dose. The average dosage after 8 weeks was 11.6 mg of escitalopram daily.

[A] The product is marketed under different brand names in different countries (Elicea, Ecytara, Elicea Q-Tab, Escitalex, Anxila).
[B] The product is marketed under different brand names in different countries (Alventa, Olwexya).
[C] The product is marketed under different brand names in different countries (Mirzaten, Mirzaten Q-tab).

The study with Krka's sertraline included 1,526 patients, which were followed during 6 months of treatment. Most of the patients suffered from depression (over 75%) and others from comorbid depression and anxiety disorder. Most of the patients started with 50 mg of Asentra and after 6 months a majority of them (69.1%) was still receiving 50 mg of Asentra daily. The average dosage was 69.5 mg of sertraline daily.

The study with Krka's venlafaxine included 171 patients with a depressive episode. The biggest group of patients (41.6%) suffered from their first depressive disorder episode; others had experienced one or more previous depressive episodes and had already been on therapy for their current depressive episode. The mean prescribed baseline dose of Alventa in the entire sample was 75 mg and was statistically significantly increased ($p < 0.0001$) by the end of the 8-week treatment to a mean of 172 mg/day. The largest number of patients (50%) received 150 mg of venlafaxine daily.

The trial with Krka's mirtazapine included 113 patients with a diagnosis of major depressive episode. For 40% of patients this was their first episode of depression; others had one or more episodes of depression prior to the existing episode. Before being included in the trial, 48% of patients had been receiving treatment with another antidepressant, most frequently SSRIs. The most common reason for the change of the previous antidepressant with mirtazapine was inefficacy. Patients started their therapy with 15 mg of Mirzaten and after 3 days most of them received a dosage of 30 mg. The daily dose at the end of the trial was 45 mg in 41% of patients, 30 mg in 56% of patients, and 15 mg in 3% of patients. The average dose after 8 weeks of therapy was 35.7 mg of mirtazapine daily.

In the study with Asentra on SAD, 30 patients, diagnosed for the first time according to DSM-IV: SAD in the whole spectrum of severity, were included in the study. Patients were treated with 100 or 150 mg of sertraline daily.

The antidepressant efficacy of medicines was proved with different measurements: Clinical Global Impression Rating Scale – Severity (CGI-S) and Improvement (CGI-I), Hamilton Rating Scale for Depression (HAM-D 17) and Beck Depression Inventory-II (BDI-II) Scale. According to HAM-D 17, *response to treatment* was defined as the HAM-D 17 *score* improving by 50% compared to the baseline score and *remission* as HAM-D 17 *score* ≤ 7 at the end of treatment. The anxiolytic effect of a medicine was measured with the HAM-D factor I, Liebowitz Social Anxiety Scale (LASA) or indirectly as a change of co-administrated anxiolytics during the study period. Safety was assessed as the percentage of patients with any adverse reaction and the number of patients who discontinued treatment. Improvement of sleep was measured with the HAM-D factor VI and indirectly as a change in the number of co-administrated hypnotics during the study period. Pain syndrome was measured with the Depression and Somatic Symptom Scale (DSSS). Satisfaction with treatment was assessed from the patients' and doctors' perspectives.

Results

In the studies with Krka's antidepressants, efficacy and safety were assessed in the treatment of depression or/and anxiety, as well as the effect of a selected medicine on pain syndromes and sleep.

Antidepressant efficacy

In the studies with Krka's antidepressants, the patient's condition was improved (markedly or moderately) in almost all patients. According to the CGI-I scale, the condition was improved in 95% (treatment with Ecytara, Asentra and Alventa) or 94% (in case of Mirzaten treatment) of patients. Additionally, in all the studies in which the CGI-S scale was used, the trend moved in the direction of absence of depression or towards milder depression severity.

According to all measured parameters (BDI-II and CGI-S and CGI-I scales), Ecytara was proved as an effective therapy for depressed or/and anxious patients. The average value of BDI-II during the first visit was 32.7; after 8 weeks of treatment (after the fourth visit) it was 12.3. The absolute value of improvement expressed with BDI-II during treatment was 20.4. In relative terms, BDI-II score improved by 62.3% in 8 weeks. The improvement of depression based on BDI-II was statistically significant at all control visits (Figure 1).

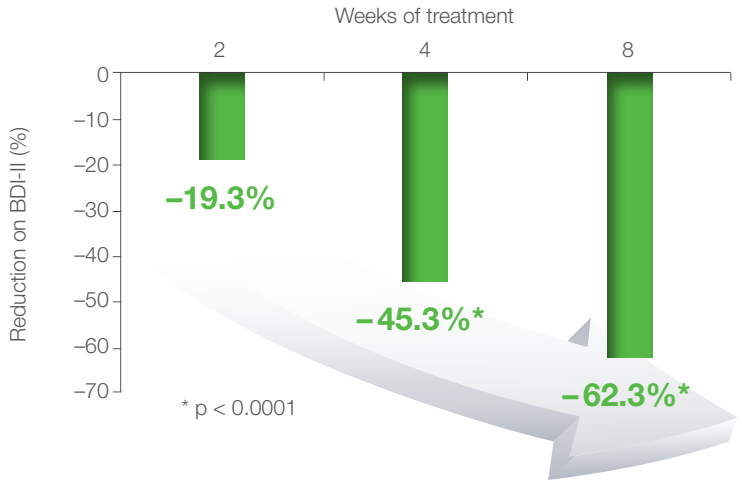


Figure 1. Reduction in symptoms with Beck Depression Inventory-II (BDI-II).

Symptom expression according to CGI-S at the first visit was assessed with the average score of 4.5, and at the fourth visit with 2.2. The absolute value of improvement between the first and the fourth visit was 2.3. In relative terms, CGI-S improved by 51% in 8 weeks. Due to symptom improvement, 63% of patients were borderline ill or without symptoms of the disease.

In the study with Krka's sertraline, the condition was improved in 97.3% of patients. The highest percentage of recovery or improvement was shown in the group of patients with PD without any comorbidities (98.3%) and the lowest in patients with obsessive compulsive disorder (OCD), though the percentage was still very high (95.9%). Interestingly, the highest recovery after 6 months of therapy with Asentra was achieved in patients with PD with comorbid depression (33.3%). Depressed patients with or without comorbidities improved or recovered in 97.2% of cases (Figure 2).

Figure 2. Efficacy at the end of the study – comparison across diagnoses.

The efficacy of Asentra was high across all diagnoses and comparable also in the case of comorbidities of depression with anxiety disorders.

Patients treated with Krka's venlafaxine had the total mean baseline HAM-D 17 score at the first visit of 23.8 points, which was statistically significantly reduced to 8.5 points ($p < 0.0001$) at the fourth visit (after 8 weeks). A statistically significant reduction was registered also in-between individual visits (Figure 3).

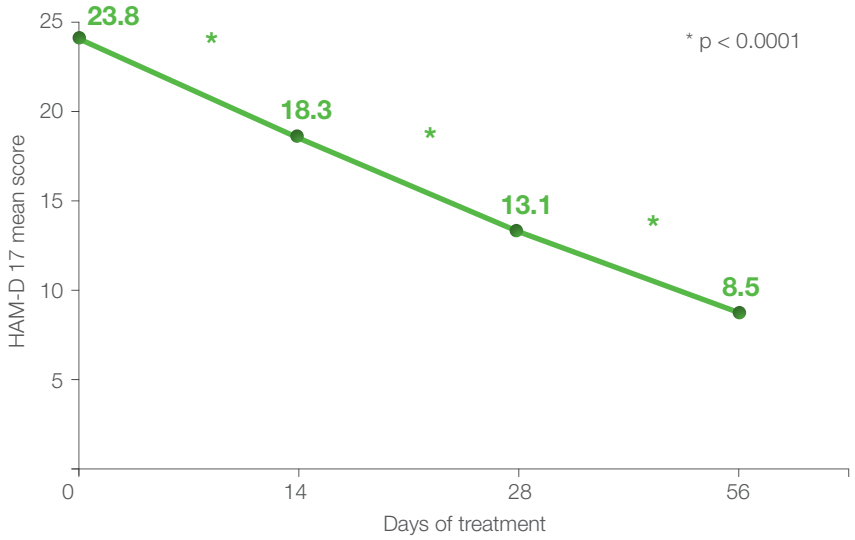


Figure 3. HAM-D 17 score: graph showing changes according to visits in the entire sample

Ninety-three percent of patients responded to treatment and 45% achieved remission at the end of the 8-week treatment. The mean baseline score of 4.8 points on the CGI-S scale (serious to severe illness) was statistically significantly reduced ($p < 0.0001$) at the end of the 8-week treatment to 2.5 points (borderline to slightly ill). The mean CGI-I score at the second visit was 2.9 points (moderate to slight improvement) and was statistically significantly ($p < 0.0001$) reduced by the end of the 8-week treatment to 1.7 points (marked to moderate improvement).

Mirzaten significantly reduced depressive symptoms, which was of statistical significance at all control visits. The difference between the start of the treatment with Mirzaten and the end of the trial was 19.6 points (71% reduction) according to HAM-D 17 score (Figure 4).

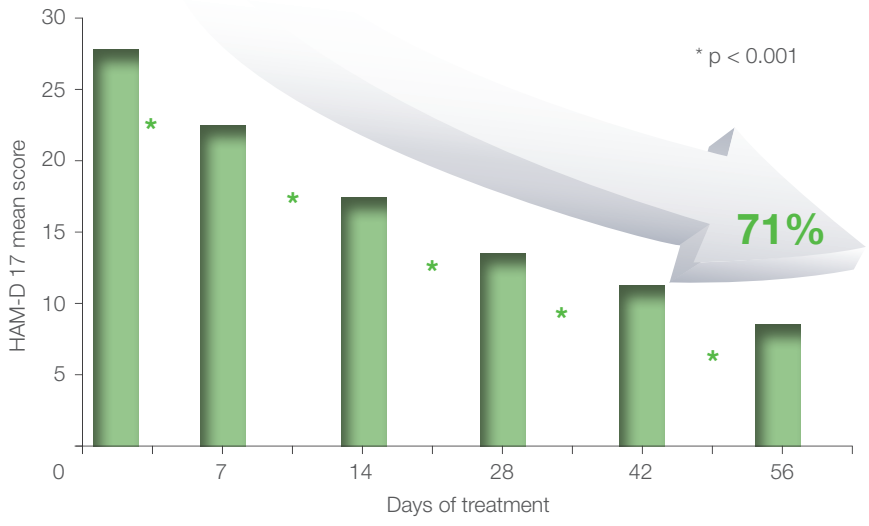


Figure 4. Improvement of depression according to HAM-D 17. Patients per protocol, n = 69.

The clinical significance of the improvement in depression in this trial was further confirmed by the use of CGI-S and CGI-I ($p < 0.001$). Improvement was assessed as marked or moderate compared to baseline in as many as 90% of patients (according to CGI-I). Thus, more than 65% of patients were assessed as "not ill" or "borderline" according to the results obtained with the CGI-S scale at the end of the trial. The percentage of patients responding to the treatment with Mirzaten was exceptionally high, since it reached 97.1% in the period of 8 weeks. Remission of depression by the end of treatment was reported in more than half of patients (51.5%).

Anxiolytic efficacy

The anxiolytic effect of the medicine was detected in all the studies in which it was measured (study with Ecytara, Asentra and Mirzaten).

The anxiolytic effect of Ecytara was measured indirectly as the number of patients receiving concomitant treatment with alprazolam. The number of patients decreased between visits from 61 to 20 (Figure 5).

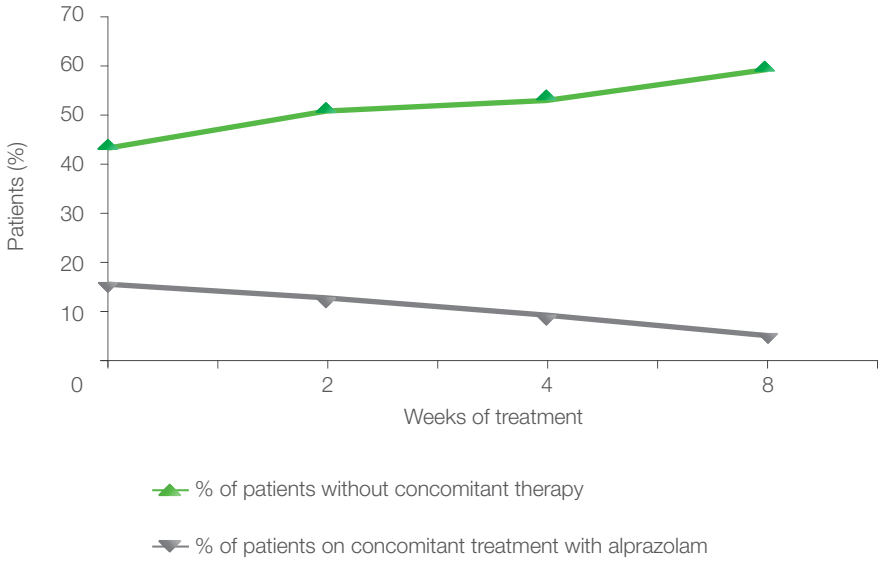


Figure 5. Use of concomitant therapy (anxiolytic-alprazolam)

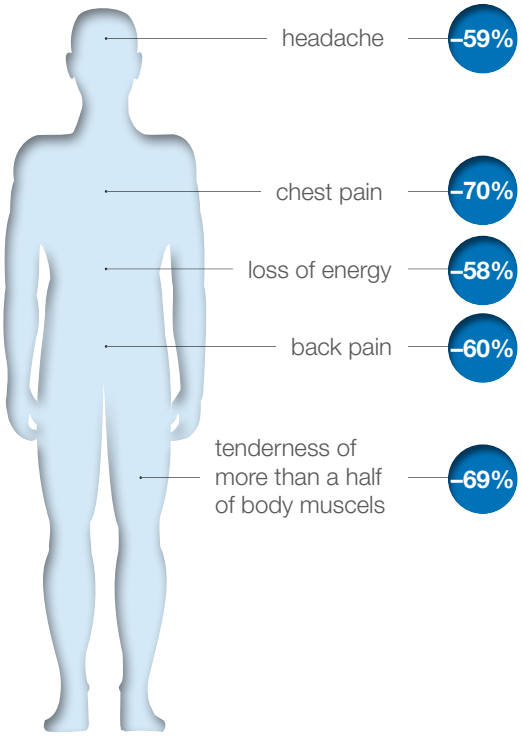
Mirzaten reduced the symptoms of anxiety by 64.4% (measured as HAM-D factor I) during the course of treatment (8 weeks). Additionally, the anxiolytic effect of Mirzaten was reflected in the fact that the number of patients requiring an anxiolytic prior to the start of Mirzaten treatment was reduced during the trial period. Among the patients taking alprazolam, 35% of them discontinued its intake during the trial period.

Sixty-three percent of patients experienced marked or moderate improvement (according to the CGI-I scale: score 1 or 2) in SAD with Asentra therapy. The average severity of illness declined significantly also according to the CGI-S scale (from 4.0 to 3.1 in 12 weeks of therapy).

The LASA score showed linear reduction in anxiety and additionally in the avoidance of social situations. The anxiolytic effect of Asentra, already at 100 mg per day, successfully covered the symptoms of the initial stage of SAD as a monotherapy.

Covering of pain symptoms

Pain symptoms were assessed in the study with Alventa. The baseline score on the DSSS was 33.6 points and underwent a statistically significant reduction to 12.4 points ($p < 0.0001$) by the end of the study. For different types of pain, the results were:



The severity of headache symptoms within the preceding 7 days: statistically significantly reduction – from 27.7% to 62.1% of patients without headache ($p < 0.0001$).

Chest pain showed a statistically significant fall in the entire sample by the end of the 8-week treatment ($p < 0.0001$). At the first visit, 22 out of 148 patients and at the end of the treatment 90 out of 148 patients had no chest pain.

Fatigue or loss of energy in the entire sample was 2.2 points and underwent a statistically significant fall to 0.9 points ($p < 0.0001$) after 8 weeks of treatment.

Absence of back pain in the entire sample was reported by 37 and at the end of the treatment by 83 out of 148 patients. By the end of treatment, the proportion of patients in the groups with different degrees of back pain severity was statistically significantly changed in favour of those with milder pain ($p < 0.0001$).

Similar reduction was also noted regarding the tenderness of more than one half of muscles and also neck and shoulder pain.

Figure 6. Pain symptoms assessed in the study with Alventa

Beneficial effect on sleep

In the Mirzaten study, sleep improvement was measured independently from depression improvement. Mirzaten reduced the mean HAM-D factor VI score – improvement in sleep – (from 3.6 to 0.6) by as much as 83.3% by the end of the trial. The biggest improvement was in the first and second week of the trial (Figure 7). An indirect evidence of the efficacy of Mirzaten's beneficial effect on sleep is provided by the fact that the number of patients requiring a sleeping agent prior to the start of the Mirzaten treatment was reduced during the trial period. Among the patients taking zolpidem, 11% of them discontinued its intake during the trial period.

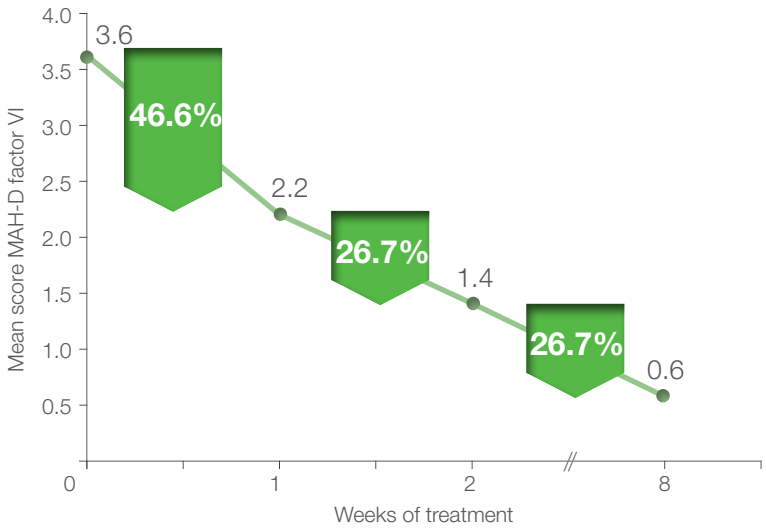


Figure 7. Improvement in sleep (HAM-D factor VI – insomnia) by treatment periods: in the first week, in the second week, and in the last six weeks of treatment. The total improvement was 3.0 points (= 83,3% improvement). Patients per protocol, n = 69.

Safety

All four Krka's antidepressants were very well tolerated, the best tolerated were SSRIs Ecytara and Asentra. A minimal number of patients discontinued treatment due to adverse reactions (ARs) connected to the medicines. The most common ARs were, as expected, typical for each medicine.

Patients tolerated Ecytara well since 89.3% of patients experienced no ARs; ARs assessed as escitalopram-related represented 1.1%. The three most common ARs were nausea (4.1%), headache (2.1%) and insomnia (0.8%). Excellent results were shown for the tolerability of Asentra. Some patients reported an adverse event and only a minimal percentage (0.5%) of patients discontinued the study due to adverse events.

When treated with Alventa, 72% of patients were without any ARs. The most common ARs reported by patients were nausea (3.7%), dry mouth (3.7%) and dizziness (1.9%). Treatment was discontinued in 9.3% of patients; in none of the cases was the correlation between ARs as a response to an increase in the dose or to the absolute size of the dose.

In the therapy with Mirzaten, 39.2% of patients experienced at least one adverse reaction; however, only 2.9% had to discontinue treatment due to ARs. The most frequent ARs were increase in body weight (8.8%), dizziness and increased appetite (each 6.9%). The average body weight increased during the course of the trial by 2.8 kg ($p < 0.0001$). The body mass index increased by 1 (from 25.7 to 26.7; $p < 0.0001$).

Satisfaction with the therapy

Patients treated with Krka's antidepresants were very satisfied with the therapy from the patients' and doctors' points of view. Treatment was evaluated as excellent or good in most of the cases. Patients evaluated the therapy with Ecytara, Alventa, Mirzaten as excellent or good in 95%, 89% and 95.7% of cases respectively, and doctors in 96%, 94% and 98.6% of cases respectively.

Discussion

Therapy selection for depressed patients is a complex process and is based on individual patient's condition, including specific clinical symptoms (insomnia, anxiety, fatigue), comorbid disorders and also specific ARs of the medicine. Krka's antidepressants from different classes offer a solution to a wide majority of depressed patients. The adequate/right selection of the first antidepressant and appropriate therapeutic dose is crucial for a successful recovery. In the studies with Krka's antidepressants, a very high percentage (95% on average) of patients improved their condition according to the CGI-I scale. CGI-S is hard to compare as patients included in different studies on baseline had different severity of illness; nevertheless in all studies the trend was towards absence of illness or milder illness severity. BDI-II rating scale was used only in the Ecytara study and has confirmed a very good efficacy of Ecytara, which is in compliance with the previously published meta-analysis[13] and studies with escitalopram.[20, 21] Alventa demonstrated a high rate of response and remission nevertheless comparable with other studies with venlafaxine.[22–24] Mirzaten confirmed very high efficacy and satisfaction of patients even as the patients included in the study had higher CGI-S in comparison to other studies included in this review. Comparable efficacy was seen also in the previously published studies with mirtazapine.[25, 26]

In the study with Ecytara, a relatively high percentage of patients with anxiety or accompanying anxiety were included. The lower amount of the anxiolytic used indirectly confirmed Ecytara's anxiolytic efficacy, which complies with the studies published on escitalopram.[27, 28] Both studies on

Asentra confirmed its efficacy not only in depressed patients with comorbidities, but also in patients with PD, OCD and SAD. As shown in previous studies, sertraline has similar efficacy as other SSRIs in the treatment of depression and anxiety disorders.[29] In the study on Mirzaten its anxiolytic effect was confirmed directly (measured as HAM-D factor I) and indirectly (reduced number of patients requiring anxiolytic therapy), which is supported also by the previously published articles.[25, 26]

Apart from being effective in the treatment of depressive symptoms, Alventa has demonstrated its efficacy in the treatment of painful somatic symptoms of depression. There is significant evidence that supports venlafaxine as an effective therapy of various chronic pain syndromes (i.e. neuropathic pain, fibromyalgia, chronic back pain, in the prophylaxis of migraine, in tension-type headache).[30–34]

Mirzaten has proven very high efficacy on sleep disturbance syndromes, with the biggest improvement in the first week of therapy, which is in accordance with the previously published study with mirtazapine.[35]

The tolerability of all four Krka's antidepressants was very high; the highest among SSRIs are Ecytara and Asentra. A minimal number of patients discontinued treatment due to ARs connected to medicines. The most common ARs were the expected ones. The tolerability of Ecytara confirmed by the study included in this review is in accordance with the previous studies in which escitalopram's adverse events were seen as generally mild to moderate and transient[36] and escitalopram as safe and well tolerated in short- and long-term treatment of MDD and anxiety disorders (moderate to severe GAD or SAD, PD (with or without agoraphobia) as well as OCD).[37, 38] In the study with Asentra, excellent tolerability was noted with practically no discontinuations from the study due to adverse events. Sertraline in general has very high tolerability,[39, 40] and in comparison with other SSRIs appears to be at least as well tolerated as others and may even have a more favourable side effect profile.[41] Adverse events with Alventa were the expected ones; what is more, the dose increase did not trigger any adverse event that would lead to the discontinuation of therapy. The incidence of adverse events with venlafaxine in other studies is similar to that in patients receiving treatment with well-established SSRIs.[42] In the study with Mirzaten, some discontinuations of treatment due to ARs were noticed. The most frequent AR was weight gain in the beginning of the therapy, which was seen also in other studies with mirtazapine;[43, 44] nevertheless in one of the two studies weight gain was lower than with tricyclic antidepressants.[43] In cases where patients unintentionally lost weight in the course of depression, gaining appetite and weight can be beneficial. Mirtazapine is generally well tolerated in patients with depression and has no ARs on the sexual function. What is more, switching patients with SSRI-induced sexual dysfunction to mirtazapine improved the sexual function.[45, 46]

In studies with SSRIs where investigators were mainly general practitioners, dosages of Ecytara and Asentra were at the lower interval of the recommended dose,[47, 48] while the studies with Asentra in SAD patients, Mirzaten and Alventa conducted by psychiatrists, the doses were higher – in the middle of the recommended dose interval.[48–50] Recommendations are to up-titrate the antidepressant which is well tolerated until sufficient efficacy is achieved.[51] Some studies conducted in primary care general practitioners prove our observation regarding lower doses of antidepressants prescribed to the patients.[52–54]

Conclusions

Krka's studies with Ecytara, Asentra, Mirzaten and Alventa have confirmed the results of many previous published clinical studies conducted in clinical practice. They contribute to the evidence pool of Krka's antidepressants in terms of their safety, efficacy and overall quality. All four Krka's antidepressants assure high quality, safety, efficacy and tolerability, yet their different mechanisms of action allow doctors to choose the most appropriate one according to the patients' symptoms and needs.

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