The efficacy and safety of aripiprazole in patients with schizophrenia or bipolar mania

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Abstract
Schizophrenia and bipolar disorder are severe mental illnesses, which impair the patient's everyday functioning. A non-interventional study was conducted to demonstrate the safety and efficacy of aripiprazole (Aryzalera®) in clinical practice and to assess patient satisfaction with the treatment. The study included 321 patients aged 41.8 ± 13.3 years. After eight weeks of treatment, a significant clinical improvement in schizophrenia and bipolar disorder was observed ($p < 0.0001$), as demonstrated by the Clinical Global Impression-Improvement (CGI-I) scale score. At the end of the study, clinical improvement (very much, much or minimally improved on the CGI-I scale) was observed in 78.2% of the patients. One third of the patients met the criterion of 'very much improved'. In addition, a significant clinical improvement was observed in patients previously treated with newer atypical antipsychotics as well as in patients to whom aripiprazole was prescribed in combination with another antipsychotic and were treated with both antipsychotics for at least two months. At the end of the study, 76.5% of the patients were satisfied or very satisfied with the treatment with aripiprazole. The patients tolerated the treatment very well and 78% of them were without adverse events. The results of the study have demonstrated that Aryzalera® is an effective and safe medicine for the treatment of schizophrenia and bipolar mania.

Introduction

Schizophrenia and bipolar disorder are some of the most severe mental illnesses as they have a significant and long-lasting effect on a person's thinking and emotions, perception of self and their surroundings. The person's day-to-day functioning is also restricted. These two illnesses cause significant disability. Several interacting factors, such as prompt and accurate recognition of symptoms, correct diagnosis and immediate treatment, have an important impact on the result of treatment. The effectiveness of treatment also significantly depends on patient adherence to treatment and medication tolerability.[1, 2, 3]

Bipolar disorder is a mood disorder. In the last decade mood disorders have been given considerable attention, especially after research studies demonstrated that they were more frequent than previously thought. Bipolar disorder is twice more frequent than schizophrenia, but nevertheless poorly identified and thus, often less effectively treated.[4]

Several studies have demonstrated the efficacy of antipsychotics in the treatment of schizophrenia and bipolar disorder during episodes of mania as well as depression. In the treatment of schizophrenia, atypical antipsychotics that have gradually been replacing other, more traditional antipsychotics, have an advantage. In comparison with typical antipsychotics, atypical antipsychotics have a lower affinity for dopamine D2-receptors and a higher affinity for serotonin 5-HT2A-receptors. Therefore, in addition to treating positive symptoms they also effectively treat negative symptoms, and improve cognitive functioning and tolerability.[5, 6]

Aripiprazole is the first atypical antipsychotic that acts as a partial dopamine D2-receptor agonist and partial serotonin 5-HT1A-receptor agonist. As a partial agonist it may act as an antagonist or agonist at these receptors, depending on the concentration of endogenous dopamine. The ability of stabilising the dopamine-serotonin system is a special characteristic of aripiprazole in the treatment of patients with mental disorders. In clinical studies, the usefulness of aripiprazole was demonstrated in monotherapy and in combination with other antipsychotics in the treatment of patients with schizophrenia.[6, 7, 8]

This non-interventional study investigated the efficacy and safety of Aryzalera® (aripiprazole) in the treatment of patients with schizophrenia or bipolar mania.

Methods

The study was conducted in Slovenia from October 2015 to September 2016.

The purpose of the study was to demonstrate the efficacy and safety of treating schizophrenia and bipolar mania with aripiprazole in clinical practice and to examine patient satisfaction with the treatment. Female and male patients with schizophrenia or a moderate to severe manic episode of bipolar disorder, older than 18 years, were included in the study. The patients received the usual medical care provided in routine clinical practice. They had three study visits: initial visit at the initiation of the medicine (first visit), control visit (second visit) after one month and final visit (third visit) after two months. A total of 321 patients were included.

At the first visit, the severity of illness was assessed with the Clinical Global Impression-Severity Scale (CGI-S). At the second and third visit the patient's clinical condition was assessed with the Clinical Global Impression-Improvement (CGI-I) scale. At the third visit patient satisfaction with the treatment was recorded. Adverse events were recorded at the control and final visit.

The efficacy endpoint was treated as a cardinal variable. Due to the large sample the asymptotic z-test was used for establishing statistical significance of differences between the means of two measurements within the same population. An asymptotic 95% confidence interval (CI) was used for all interval assessments of the means.

Results

A sample of 321 patients, consisting of 151(47.5%) women and 167 (52.5%) men, were included in the statistical analysis. Ten patients did not appear at the third visit, but because there were not enough data we included them in the results analysis. The mean age of the patients was 41.8 ± 13.3 years. Two hundred and thirty-three (72.6%) patients had been diagnosed with schizophrenia, and 79 (24.6%) with bipolar mania. For 9 (2.8%) patients there were no data on their diagnosis. Sixty-three (19.6%) newly diagnosed patients were included in the study and 258 (80.4%) patients who had previously received antipsychotics therapy.

In addition, we conducted two sub-analyses; an analysis of patients who had previously (before the first visit) been taking an atypical antipsychotic and an analysis of patients with schizophrenia who, when aripiprazole was introduced, had already been taking another antipsychotic and who were taking at least two antipsychotics until the end of the treatment.
The first sub-analysis included 239 (74.5%) patients. Of them, 37.6% were treated with olanzapine, 20.9% with risperidone, 14.7% with clozapine and 13.2% with quetiapine. The patients could be treated with several antipsychotics concurrently.

The second sub-analysis included 59 patients with schizophrenia who were concurrently most often prescribed olanzapine (19 patients, 32.2%) in a mean daily dose of 12.5 mg; clozapine (15 patients, 25.4%) in a mean daily dose of 196.4 mg, quetiapine (10 patients, 16.9%) in a mean daily dose of 245 mg and risperidone (7 patients, 11.9%) in a mean daily dose of 5.1 mg. Other antipsychotics were less frequently prescribed.

Of all the patients with bipolar mania, 29 (36.7%) patients were prescribed aripiprazole for monotherapy. Fifty (63.3%) patients were prescribed aripiprazole in addition to a mood stabiliser at the first visit. Among the patients with bipolar disorder who were prescribed aripiprazole in combination with a mood stabiliser, lamotrigine was prescribed to 14 (17.8%) patients, valproic acid to 11 (13.8%) patients and lithium to 4 (5.1%) patients.

As the reason for prescribing aripiprazole, physicians cited efficacy in 208 (64.8%) patients, safety in 154 (48%) patients, improvement of negative symptoms in 120 (37.4%) patients, improved cognition in 117 (36.4%) patients and once-daily administration in 112 (34.9%) patients. Physicians also cited several reasons simultaneously. In both additional sub-analyses, physicians most often cited efficacy as the reason for their choice of medication; in the first subanalysis in 58.2% of the patients and in the second subanalysis in 50.8% of the patients.

Figure 1 shows what aripiprazole doses patients were taking at each visit. More than half of the patients (54.7%) were prescribed aripiprazole 10 mg, while 30% of the patients were prescribed aripiprazole 15 mg. Fourteen (4.4%) patients were prescribed a daily dose of aripiprazole of 30 mg. The mean dose at first visit was 12.5 mg, at the second visit 15.45 mg and at the third visit 16.53 mg. As expected, the total mean daily dose of aripiprazole was increasing during the study due to up-titration of the medicines.

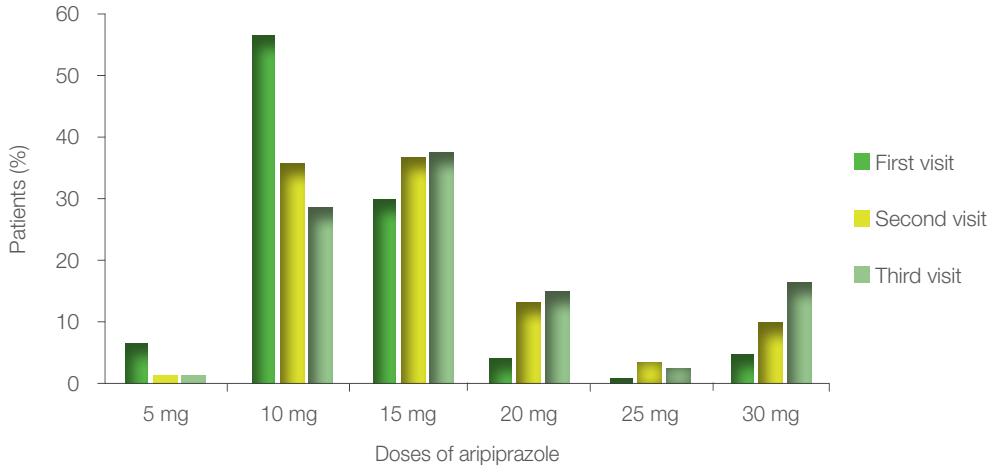

Figure 1. The percentage of patients who were treated with aripiprazole at first, second and third visit; in 84.7% of the patients the initial dose of aripiprazole was 10 mg or 15 mg.

In the subanalysis of the patients with schizophrenia who were taking another antypsychotic when they were prescribed aripiprazole and were taking two antypsychotics for at least two months, aripiprazole was most often prescribed in the dose of 10 mg. The 10 mg dose was prescribed to 31 (52.5%) patients, while 17 (28.8%) patients were prescribed aripiprazole 15 mg.

The CGI-S scale was used to assess the severity of illness. Physicians assessed it with a score from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). At the first visit physicians assessed the severity of illness on the CGI-S scale with a mean severity score of 4.56 ± 1.14 (CI 4.43–4.69). Distribution of patients by illness severity score on the CGI-S scale at first visit is shown in Figure 2. One hundred and eighty (56.1%) patients were among the most extremely ill, severely ill or markedly ill, 99 (30.8%) patients were moderately ill and 24 (7.5%) patients were mildly ill. Eighteen (5.6%) patients were assessed as borderline or they were not at all ill as they had already been treated with antipsychotics. The main reasons for a change of therapy in the latter group of patients were lower efficacy, adverse reactions to previous therapy and easier administration. In 2% of the patients the physicians' assessment was not at all ill and in 4% borderline.

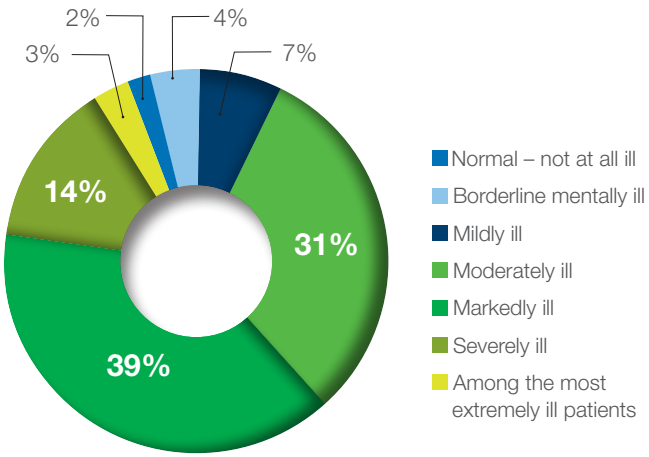

Figure 2. Distribution of patients by CGI-S score at first visit; 56.1% of the patients were assessed as 'among the most extremely ill patients', 'severely ill' or 'markedly ill'

To assess the clinical efficacy of the treatment the physicians used the CGI-I scale and assessed the change in the patient's clinical condition during treatment with a score from 1 (very much improved) through 4 for no change to 7 (very much worse). Distribution of patients by the CGI-I score at the second and third visit is shown in Figure 3. By the end of the study, a clinical improvement was observed (very much improved, much improved and minimally improved on the CGI-I scale) in 78.2% of the patients. Between the second and third visit there was a substantial increase (from 34 to 101) in the number of patients with a markedly improved condition. The CGI-I score statistically significantly improved ($p < 0.0001$) (mean improvement from 2.6 to 2.19), absolutely by 0.38 ± 0.92 (CI 0.28–0.48) and relatively by 10.04% ± 54.17% (CI 4.01–16.07%).

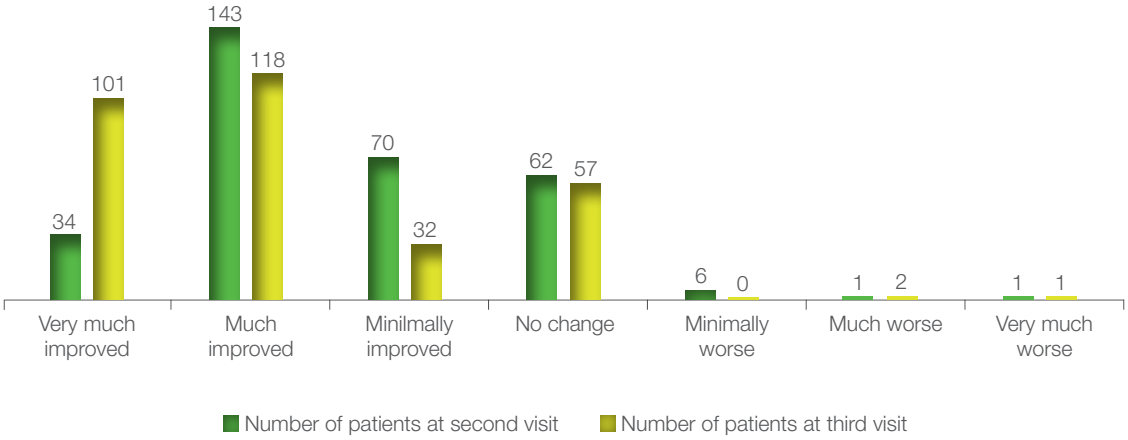

Figure 3. Distribution of patients by CGI-I score for change in the patient's clinical condition at second and third visit. By the end of the study the clinical condition improved in 78.2% of the patients.

In patients that had previously received atypical antipsychotics, we also observed a statistically significant ($p < 0.0001$) clinical improvement after eight weeks of treatment, demonstrated by the CGI-I score, similarly as with the all patient analysis. Between the second and third visit the mean CGI-I score improved statistically significantly ($p < 0.0001$) (mean score improvement from 2.73 to 2.35), absolutely by 0.35 ± 0.95 (CI 0.22–0.47) and relatively by 7.58% ± 59.82% (CI 0.15–15.31%). By the end of the study, the clinical condition of the patients improved (very much improved, much improved and minimally improved on the CGI-I scale) in 174 (72.8%) patients. Similarly to the results of the all patient analysis after the third visit, the number of patients with a very much improved condition, as demonstrated by the CGI-I score, increased significantly (from 20 to 66 patients) compared with the results at second visit.

Also, the sub-analysis of patients with schizophrenia who at initiation of aripiprazole had already been taking another antipsychotic and were taking two antipsychotics for at least two months, showed a statistically significant ($p < 0.0001$) improvement of the patients' clinical condition, as demonstrated by the CGI-I score. Between the second and third visit the mean CGI-I score improved statistically significantly ($p < 0.0001$) (from 2.75 to 2.34), absolutely by 0.41 ± 0.97 (CI 0.16–0.66%) and relatively by 9.58% ± 52.76% (CI –3.88–23.04%). By the end of the study, the clinical condition improved (very much improved, much improved and minimally improved on the CGI-I scale) in 43 (72.9%) patients.

Satisfaction with the treatment was assessed by patients from 1 to 5, whereby 1 was very unsatisfactory and 5 was very satisfactory. Distribution of patients by satisfaction level is shown in Figure 4. After two months of treatment 222 (76.5%) patients were satisfied with the treatment or very satisfied, and from these 112 (34.9%) patients were very satisfied with the treatment. For 31 patients there was no data about their satisfaction with the treatment.

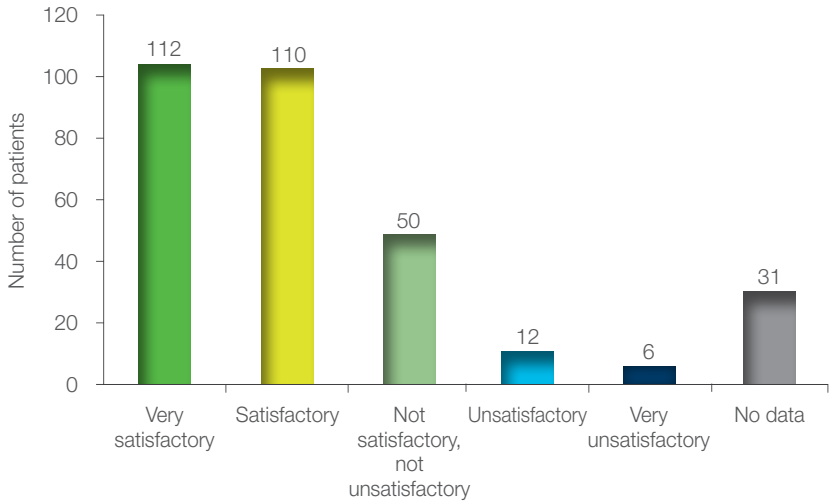

Figure 4. CGI-I scores for satisfaction with the treatment. After two months of treatment 76.5% of the patients were satisfied or very satisfied with the treatment.

In the subanalysis of the group of patients who had previously been treated with atypical antipsychotics, 157 (65.7%) patients were satisfied or very satisfied with the treatment after two months and of these 75 (31.4%) were very satisfied with the treatment. For 23 (9.7%) patients there were no data about their satisfaction levels. Similar results were obtained in the group of patients who were at initiation of aripiprazole already taking another antipsychotic and were taking two antipsychotics for at least two months. At the third visit 32 (55.9%) patients cited that they were very satisfied or satisfied with the treatment. Eighteen (30.5%) patients from this subanalysis were very satisfied with the treatment. For 4 (6.8%) patients there were no data about their satisfaction.

The safety of aripiprazole was assessed by following and assessing adverse events. Treatment with Aryzalera® showed good tolerability as 250 (77.9%) patients had no adverse events. For 5 patients there were no data on adverse events. Adverse events were reported in 66 (20.6%) patients. Of these 62 (19.3%) had causally related adverse events (related to treatment with aripiprazole). Most common in patients with causally related adverse effects were restlessness (7.8%), insomnia (5.9%), sleepiness (5.3%), anxiety (4.4%), tiredness (3.4%) and akathisia (3.1%). Ten (3.1%) patients discontinued the treatment due to causally related adverse events.

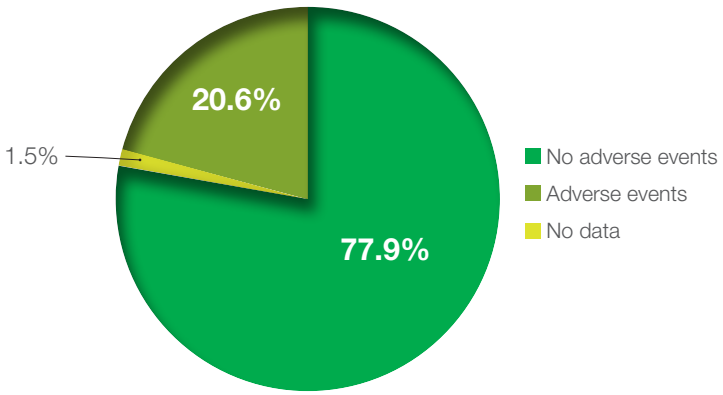

Figure 5. Tolerability of aripiprazole. Tolerability was good since as many as 78% of the patients had no adverse events.

Discussion

Aripiprazole is indicated for the treatment of schizophrenia and bipolar mania in adults and adolescents aged 15 years or over.[9] Three hundred and twenty-one patients aged 18 and over participated in the non-interventional efficacy and safety study. A relatively young population with a mean age of 41.8 ± 13.3 years was included.

The recommended initial daily dose of Aryzalera® in the summary of product characteristics is 10 mg or 15 mg and the recommended maintenance daily dose is 15 mg.[9] In nearly 85% of the patients Aryzalera® was initiated in doses recommended in the summary of product characteristics. The remaining patients were treated with higher doses (up to 30 mg daily). At the third study visit the greatest percentage of patients were still taking 15 mg daily (38.3%) and, as expected, 25 mg and 30 mg were the most commonly prescribed doses (4.7% of the patients at initial visit and 16.3% at the final visit). The percentage shares of prescribed doses show that titration of aripiprazole in adult patients is often not necessary.

The patients received the usual medical care provided in routine clinical practice. Schizophrenia was diagnosed in significantly more included patients (> 70%) than bipolar mania. Aryzalera® was effective in the treatment of patients with schizophrenia or bipolar mania, including those that had previously been treated with a different antipsychotic and in patients with schizophrenia who were taking another antipsychotic at initiation of aripiprazole. The results of the study are consistent with the results of previous studies where it had been shown that aripiprazole is effective in the treatment of patients with schizophrenia, schizoaffective disorder and bipolar disorder.[10, 11]

Although more than 75% of the patients had previously received antipsychotic therapy, the physicians assessed 56% of the patients as among the most extremely ill patients, severely ill or markedly ill on the CGI-S scale. According to data from the literature antipsychotics effectively improve the psychopathology in schizophrenia and bipolar mania, decrease the frequency of relapses and improve the functioning of the patient; however, patients' compliance to treatment remains a problem. It has been estimated that up to 50% of patients with schizophrenia and more than 40% of patients with bipolar disorder do not adhere to treatment. Patients who are treated with atypical antipsychotics should, due to a better safety profile, adhere to treatment better than patients who are treated with conventional antipsychotics. As a third generation antipsychotic aripiprazole improves the clinical condition in patients with schizophrenia or bipolar mania in monotherapy and in combination with another antipsychotic or mood stabiliser.[3, 12, 13]

The efficacy and safety of the treatment with aripiprazole was supported by data on the patients' satisfaction with the treatment. After two months of treatment more than 75% of the patients were satisfied or very satisfied with the treatment. We also demonstrated that patients who had previously been treated with an atypical antipsychotic as well as patients who were taking a different antipsychotic at the initiation of aripiprazole were satisfied with the treatment with aripiprazole. Good tolerability of aripiprazole contributed to their satisfaction as 78% of the patients had no adverse events and only 3% of the patients discontinued the treatment due to causally related adverse events.

Conclusion

The results of this non-interventional study have confirmed the clinical efficacy of Aryzalera®, which was demonstrated as improvement of the mean CGI-I score. After eight weeks of treatment the clinical condition improved with most patients and they were satisfied with the treatment. The tolerability of Aryzalera® was good. In conclusion, Aryzalera® is an effective and safe medicine for the treatment of schizophrenia and bipolar mania.

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