ORIGINAL ARTICLE

Observational multicenter study of efficacy of paroxetine film-coated tablet in the treatment of anxiety disorder

Alma Džubur Kulenović[1], Amra Memić Serdarević[1], Zehra Halilović[2], Haris Mašnić[3], Amra Bahto[4], Belma Kapo[5], Daniela Delić[5], Amila Hadžimuratović[6]

[1]Clinical Center University of Sarajevo, Sarajevo, [2]General Hospital Konjic, Konjic, [3]Cantonal Hospital Goražde, Goražde, [4]Health Care Centre of Canton Sarajevo, Sarajevo, [5]''Bosnalijek'' d.d., Sarajevo, [6]School of Medicine University of Sarajevo, Sarajevo; Bosnia and Herzegovina

ABSTRACT

Aim To examine the efficiency of paroxetine treatment of anxiety disorders in adult patients over the period of 12 months and the improvement of symptoms of anxiety disorder during this period, as well as to examine the tolerability of the administered treatment and patient compliance during the study.

Methods This observational, multicenter, cohort, clinical study included 171 patients with diagnosed anxiety disorder who were administrated paroxetine film-coated tablets 20 mg and followed up during the next 12 months. Patients were observed at 6 points, baseline and five additional assessments. The Beck Anxiety Inventory was used to determine the baseline severity of anxiety and Patients Health Questionnaire module GAD-7 was used to determine the severity of anxious symptoms and to follow up patients during the additional observations. Tolerability and patient compliance were followed throughout the study.

Results Statistically significant decline in severity of anxiety disorder over the observation period (p=0.001) was found. At the beginning of the study, 64 (45.7%) patients had severe anxiety symptoms, 43 (30.7%) moderate, 25 (17.9%) mild and eight (5.7%) had none to minimal symptoms. At the end of the study, there were no more patients with severe anxiety, while four (3.4%) had moderate symptoms. On the other hand, 26 (22.2%) had mild symptoms and 87 (74.4%) had none to minimal symptoms of anxiety disorder.

Conclusion The results of this study provide further evidence for paroxetine's efficacy and tolerability in the treatment of anxiety disorders with good patient compliance.

Key words: anxiety disorder, drug tolerance, treatment outcome, paroxetine

Corresponding author:
Amila Hadžimuratović
School of Medicine,
University of Sarajevo
Čekaluša 90, 71000 Sarajevo,
Bosnia and Herzegovina
Phone: +387 33 642 750;
Fax: +398 33 81 42 50;
E-mail: amilahadzimuratovic@gmail.com
ORCID ID: https://orcid.org/0000-0001-7607-5429

Original submission:
29 January 2018;
Revised submission:
03 April 2018;
Accepted:
04 May 2018.
doi: 10.17392/947-18

Med Glas (Zenica) 2018; 15(2):186-191

INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV) (1) and International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) (2) classification define anxiety disorder as a prominent tension and worry about every-day events and problems, occurring on more days than not for at least six months and it is associated with symptoms such as restlessness, fatigue, difficulty concentrating, irritability, muscle tension and sleep disturbance (3). The four most common anxiety disorders are generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD) and posttraumatic stress disorder (PTSD) (4). However, despite the substantial disability associated with each anxiety disorder and the availability of effective treatments, only a minority of patients (15% to 36%) with anxiety are recognized in primary care (4). Likely factors in this sub-optimal management include the range of different anxiety disorders, their co-morbidity with other disorders (particularly mood disorders), a widespread lack of awareness of anxiety disorders by affected individuals and health practitioners and the low confidence of many practitioners in their management (5). Epidemiological surveys indicate that GAD is the second most frequent psychiatric disorder, after major depression, in the primary care setting and that nearly three fourths of the general population report at least one or more unreasonable fears, episodes of sudden panic, or generalized nervousness (6,7). There is also a convergence in studies showing that anxiety disorder accounts for at least 35% of all disability and sick leave days, with high persistence, chronic nature and increasing number of complications (8). High comorbidity is found between anxiety and depression, which increases the risk of suicide, disability and psychiatric hospitalization with the decrease of the treatment compliance. Patients with depression/anxiety comorbidity tend to have more chronic and recurrent forms of illness that require long-term treatment (9,10).

Current guidelines for the pharmacological management of GAD tend to recommend first line treatment with selective serotonin reuptake inhibitor (SSRIs) or pregabalin (11). Paroxetine is widely used and generally well tolerated antidepressant in adults, elderly individuals and patients with comorbid illness (12). Notably, paroxetine is the only SSRI currently approved for the treatment of all five anxiety disorders in addition to major depressive disorder (12). Paroxetine does not significantly affect psychomotor function in healthy volunteers, patients with depression or elderly patients. As with other SSRIs, paroxetine is not associated with any clinically significant hemodynamic or electrophysiological cardiovascular effects in healthy volunteers and it appears to be well tolerated in patients with depression with or without ischemic heart disease (13).

The aim of this study was to examine the efficiency of paroxetine treatment of anxiety disorders in adult patients over the period of 12 months and the improvement of symptoms of anxiety disorder during this period, as well as the tolerability of the administered treatment and patient compliance during the study.

PATIENTS AND METHODS

Patients and study design

The study was designed as an observational, multicenter, cohort, clinical study that included a total of 171 subjects of both genders who were diagnosed with anxiety disorder. Patients were administered paroxetine film-coated tablets 20 mg and followed up in medical centers from January 2015 until January 2016 (12 months).

The study was conducted by 52 doctors in 33 medical centers from major cities of Bosnia and Herzegovina including Sarajevo, Banja Luka, Teslić, Modriča, Gradiška, Cazin, Velika Kladuša, Ključ, Bosanski Petrovac, Goražde, Bugojno, Travnik, Jajce, Gornji Vakuf, Vitez, Zvornik, Srebrenik, Banovići, Živinice, Lukavac, Tuzla, Gradačac, Konjic, Mostar and Tomislavgrad.

Inclusion criteria were age older than 18 years and the diagnosis of anxiety disorder using the Beck Anxiety Inventory (BAI) (14). Exclusion criteria were hypersensitivity to paroxetine or other supportive components of the medicine, administration of concomitant treatment with monoamine oxidase inhibitors and associated clinical conditions that may affect the pharmacokinetics of paroxetine. Patients who showed deterioration of the underlying disease, developed serious adverse reactions that required discontinuation of therapy or developed diseases that affected the course of research were excluded from the further study.

The study was submitted to and approved by the Agency for Medical Products and Medical Devices of Bosnia and Herzegovina, according to the Law on Medicines of Bosnia and Herzegovina.

Methods

Patients were observed at six points: baseline and five additional assessments. During the baseline observation BAI was used to determine the baseline severity and to assess the inclusion criteria and Patients Health Questionnaire (PHQ-SADS) anxiety module GAD-7 (15) was used to determine the severity of anxiety symptoms and to follow up patients during the five additional observations (16,17). Based on the GAD-7 and the severity of symptoms patients were divided into four categories: minimally to none expressed symptoms, mild symptoms, moderate symptoms and severe symptoms. After the first, bassline, observation subjects began the treatment. The second observation was performed in the second week from the baseline observation, the third observation was performed in the fourth week of the study, the fourth observation was performed in the sixth week of the study, the fifth observation was performed in the twelfth week of the study and they all included an assessment of the efficacy and safety of treatment with the drug dose adjustments depending on the assessment of the effectiveness of therapy. The final, sixth observation was performed in the 36th week of research and it included a final overall evaluation of the efficacy and safety of the therapy. The researches followed the participants' flow by using the CONSORT diagram.

The sample size was calculated on the following basis: a pilot study was designed using a sample of 40 subjects who were assessed by using GAD-7, before the treatment and two weeks after the treatment. The calculated effect size was 0.279. Total calculated sample size was 140 subjects. The calculation was performed using G power software version 3.1 (18).

The drug effectiveness was assessed on the basis of physician's examination of the patients and using the GAD-7 anxiety model. The safety of the study was provided by monitoring the incidence of adverse reactions of the drug with the assessment of the link between drug application and reporting adverse reactions (certain, probable, possible, not probable, unclassified relation and non-classifiable) and the adherence to the basis of assessment in the application of therapy (number of tablets).

Statistical analysis

Sample size estimation was based on the assumption of the efficiency of the drug in earlier studies that were performed on SSRIs (80% efficacy of paroxetine vs. 65% efficacy of comparators). Calculation was done by $\chi 2$ test with the level of significance of 95% (p=0.05). Ratio between the groups was 2:1.

Distribution of data from the study were tested for normality by Kolmogorov-Smirnoff test and then described by measures of central tendency and variability (median and interquartile range). Friedman test for repeated measures was used to present ordinal variables (observing the anxiety reduction trend) and the Wilcoxon signed-rank test was used to present differences between two measurements.

RESULTS

This study included 171 patients who were diagnosed with anxiety disorder and who met all inclusion criteria. Out of 171 patients, 108 (63%) were females and 63 (37%) were males (p=0.001). The average age of patients was 48.9±14.6 years. Out of 171 patients, 73 (43%) had generalized anxiety disorder, 36 (21%) had panic disorder with or without agoraphobia, 29 (17%) had social-anxiety disorder, 24 (14%) had posttraumatic stress disorder and 9 (5%) patients had obsessive-compulsive disorder. A total of 111 (65%) patients had received previous treatment and 60 (35%) were newly discovered patients. Out of patients who had used concomitant therapy, 42 (36.2%) used alprazolam, 24 (20.7%) used bromazepam, 23 (19.8%) used diazepam, six (5.2%) used sulpiride and five (5%) patients used some other drug treatment.

The BAI showed the average score of patients was 31.93±11.08, with the maximal score being 53 and minimal score being 5. Categorization of patients' symptoms showed that 7 (4%) had minimal anxiety, 15 (9%) had mild anxiety, 38 (22%) had moderate anxiety and 111 (65%) had severe anxiety disorder.

Based on the exclusion criteria 31 subjects were excluded from the study. During the course of the

study, 23 patients were further excluded from the study. Out of total patients included in this study (n=171), 102 (60%) patients were present during all six observations. Friedman test showed a statistically significant decline in severity of anxiety disorder over the observation period, validated by GAD 7 (p=0.0001). During the first observation mean value of GAD 7 was 14, while during the last (sixth) observations the mean value of GAD 7 was 3 (Figure 1).

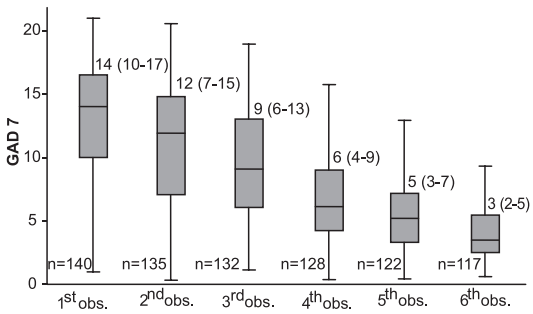

Figure 1. Mean values of severity of anxiety disorder over the observational (obs.) period
GAD 7, Generalized Anxiety Disorder 7; p=0.0001

Examining the results of the GAD 7 during the first and last observation (36 weeks) showed a significant reduction in the expression of symptoms (p=0.001). During the first observation, 64 (45.7%) patients had severe symptoms, while 8 (5.7 %) patients had none to minimal symptoms of anxiety. During the last observation, there were no patients with severe symptoms, while 87 (74.4 %) patients had none to minimal symptoms of anxiety (Table 1).

Table 1. Decline of severity of anxiety symptoms over the observational period

		No (%) of patients during observational period					
Anxiety symptoms		**First**	**Second**	**Third**	**Fourth**	**Fifth**	**Sixth**
GAD 7	**None to minimal**	8 (5.7)	14 (10.4)	24 (18.2)	41 (32.0)	59 (48.4)	87 (74.4)
	Mild	25 (17.9)	35 (25.9)	50 (37.9)	62 (48.4)	53 (43.4)	26 (22.2)
	Moderate	43 (30.7)	44 (32.6)	39 (29.5)	21 (16.4)	8 (6.6)	4 (3.4)
	Severe	64 (45.7)	42 (31.1)	19 (14.4)	4 (3.1)	2 (1.6)	-
	Overall	140 (100)	135 (100)	132 (100)	128 (100)	122 (100)	117 (100)

GAD 7, Generalized Anxiety Disorder 7;

During the first observation, 60 (35.1%) patients were administered 10 mg of paroxetine film-coated tablets and 111 (64.9%) patients were administered 20 mg of paroxetine. Further along in the study the dosage of paroxetine has changed according to GAD 7 questionnaire so that at the end of the study 13 (11.3%) patients were administered 40 mg of paroxetine, 11 (9.3%) were administered 30 mg of paroxetine, 84 (70.9%) were administered 20 mg of paroxetine and six (8.6%) patients were administered 10 mg of paroxetine film-coated tablets.

Out of 171 patients, 84 (49.1%) presented with adverse reactions during the observation period. In 80 (95%) patients the observed adverse reactions were related to the expected side effects of paroxetine and in four (5%) the adverse reactions were correlated with the concomitant therapy.

The patient assessment of the effectiveness of paroxetine has shown that 106 (64.6%) assessed the drug as "very good", 54 (32.9%) as "good" and four (2.4%) patients assessed the drug as "unsatisfactory". The assessment of tolerability of the administered treatment showed that 118 (70.2%) patients had a very good response to treatment, 46 (27.4%) had a good response to the treatment and four (2.4%) patients had unsatisfactory response to the treatment. When it comes to patient compliance, 122 (73.9%) patients had a very good treatment adherence, 38 (23%) had a good treatment adherence and only five (3%) patients assessed the collaboration with researches/doctors as unsatisfactory (Figure 2).

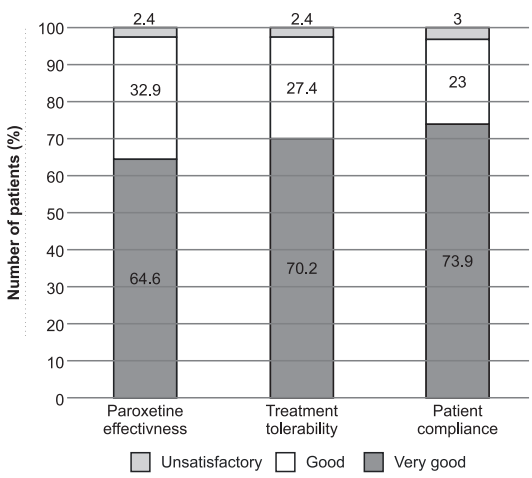

Figure 2. Assessment of therapy effectiveness, treatment tolerability and patient compliance

DISCUSSION

Our study showed that the administration of paroxetine was effective in reducing anxiety disorder symptoms. These results were demonstrated

by a significant decrease in mean value of the total GAD-7 score from the first to the last observation. There was also a significant reduction in expression of anxiety symptoms from the first to the last observation, validated with GAD-7. These results are clinically significant since the symptoms that were moderate to severe at the beginning of the treatment were, on average, of mild intensity after 12 months of the treatment with paroxetine. The significance of the observed change in GAD-7 scores was related to high rates of response and remission. Full remission, with none to minimal expression of symptoms, in which anxiety patients are essentially indistinguishable from healthy counterparts was achieved by 36.1% of the paroxetine patients that completed the study. For patients who completed the study, the patient's compliance was as high as 95%.

Other studies conducted to assess the efficacy and safety of paroxetine obtained similar results. A review study from 2000 describing three trials show that paroxetine (20–50 mg/ day) is an effective and well-tolerated treatment for social anxiety disorder. Paroxetine produced overall improvement in addition to providing more specific benefits with respect to anxiety and avoidance symptoms and social anxiety-related disability (19). A study comparing the efficacy of paroxetine vs. benzodiazepines in the treatment of generalized anxiety disorder showed that paroxetine was effective in the treatment of GAD as well as safer and better tolerated (20). Post-hoc analyses in a study of remission status of patients with GAD have demonstrated that approximately twice as many paroxetine treated patients compared with placebo-treated patients can be classified as being in remission following 24 weeks of double-blind treatment (20).

Results of the presented study have shown that paroxetine was generally well tolerated. The dropout rate due to adverse events was 15%. This rate is consistent with the results of other studies investigating paroxetine treatment of depression and other anxiety disorders and lower than 26% reported in generalized anxiety disorder studies of extended-release venlafaxine (6).

The patients lost to follow-up in our study probably have associated with characteristics of the patient population under study and the nature of the anxiety disorder.

The percentage of 70.9% of patients were administered 20 mg/day of paroxetine at the end of this study indicating that this dosage may be effective for the majority of anxiety disorder patients.

Although SSRIs are prevalently used in the treatment of anxiety disorder, there are still concerns regarding those medications (21). Common side effects of SSRIs such as nausea, dizziness, headaches, jitteriness, and both sleep and gastrointestinal disturbances can be mistaken for symptoms that are commonly experienced as part of the anxiety disorder. This can lead to misinterpretation of side effects as the worsening of anxiety (21). Consequently, it is necessary to start with lower than usual doses, gradual titrate the doses and have an ongoing psychoeducation about side effects when using these medications in the anxiety disorder population (21).

In conclusion, results presented in this study provide further evidence for the findings that paroxetine in the dose of 20 mg/day can significantly contribute to the reduction of anxiety symptoms in patients with anxiety disorder. The results of our study also indicate that paroxetine has good effectiveness and tolerability in adult patients with anxiety disorder.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATION

Competing interests: none to declare

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association, 2000.
2. World Health Organization. The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization, 1992.
3. Barton S, Karner C, Salih F, Baldwin DS, Edwards SJ. Clinical effectiveness of interventions for treatment-resistant anxiety in older people: a systematic review. Health Technol Assess 2014; 18:1366.
4. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med 2007; 146:317-25.

5. Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, Christmas DM, Davies S, Fineberg N, Lidbetter N, Malizia A, McCrone P, Nabarro D, O'Neill C, Scott J, van der Wee N, Wittchen HU. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol 2014; 28: 403-39. Rickels K, Zaninelli R, McCafferty J, Bellew K, Iyengar M, Sheehan D. Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study Am J Psychiatry 2003; 160:749-56.
6. Gorman JM. Comorbid depression and anxiety spectrum disorders. Depress Anxiety 1996-1997; 4:160-8.
7. Sobockia PA, Wittchen HU. Cost of anxiety disorders in Europe. Eur J Neurol 2005; 12:39–44.
8. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci 2015; 17:327–35.
9. Hirschfeld RMA. The comorbidity of major depression and anxiety disorders: recognition and management in primary care Prim Care Companion J Clin Psychiatry 2001; 3:244–54.
10. Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalized anxiety disorder: systematic review and meta-analysis. BMJ 2011; 342:d1199.
11. Tang SW, Helmeste D. Paroxetine. Expert Opin Pharmacother 2008; 9:787-94.
12. Wagstaff AJ, Cheer SM, Matheson AJ, Ormrod D, Goa KL. Paroxetine: an update of its use in psychiatric disorders in adults. Drugs 2002; 62:655-703.
13. Julian LJ. Measures of Anxiety. Arthritis Care Res (Hoboken). 2011; 63:467-72.
14. Kroenke K, Spitzer RL, Williams JB, Lowe B. The Patient Health Questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. Gen Hosp Psychiatry 2010; 32:345–59.
15. Kabacoff RI, Segal DL, Hersen M, Van Hasselt VB. Psychometric properties and diagnostic utility of the Beck Anxiety Inventory and the State-Trait Anxiety Inventory with older adult psychiatric outpatients. J Anxiety Disord 1997; 11:33-47.
16. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988; 56: 893-7.
17. Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods 2009; 41:1149-60.
18. Lydiard RB, Bobes J. Therapeutic advances: paroxetine for the treatment of social anxiety disorder. Depress Anxiety 2000; 11:99-104.
19. Rocca P, Fonzo V, Scotta M, Zanalda E, Ravizza L. Paroxetine efficacy in the treatment of generalized anxiety disorder. Acta Psychiatr Scand 1997; 95:444-50.
20. Rickels K, Zaninelli R, McCafferty J, Bellew K, Iyengar M, Sheehan D. Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. Am J Psychiatry 2003; 160:749-56.
21. Ravindran LN, Stein MB. The pharmacologic treatment of anxiety disorders: a review of progress. J Clin Psychiatry 2010; 71:839–54.