

## THE EFFECT OF MEBEVERINE ON THE QUALITY OF LIFE OF PATIENTS WITH IRRITABLE BOWEL SYNDROME IN THE TUZLA CANTON

Dino Crnkić, Ervin Alibegović, Fahir Bečić, Mensura Aščerić, Sadat Kurtalić, Admir Kurtćehajić

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**Authors:**  
Dino Crnkić, Ervin Alibegović<sup>1</sup>,  
Fahir Bečić<sup>2</sup>, Mensura Aščerić<sup>3</sup>,  
Sadat Kurtalić<sup>4</sup>, Admir Kurtćehajić<sup>5</sup>

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**Affiliations:**  
Faculty of Pharmacy of the University  
of Tuzla, University Clinical Center  
Tuzla, <sup>2</sup>Faculty of Pharmacy of the  
University of Sarajevo, <sup>3</sup>Faculty of  
Pharmacy of the University of Tuzla,  
<sup>4</sup>Cantonal hospital „Irfan Ljubijankić“  
Bihać, <sup>5</sup>Plava poliklinika Tuzla, 75000  
Tuzla, Bosna i Hercegovina

**Corresponding author:**  
Dino Crnkić

**Email:**  
dino.crnkic@viatris.com

By definition, irritable bowel syndrome (IBS) is a chronic disorder of the gastrointestinal tract, characterised by abdominal pain and changes in the bowel movement, without any detectable organic disease (no histological, morphological, biochemical, or microbiological abnormality). The study included 200 patients with irritable bowel syndrome who had a colonoscopy performed and were diagnosed with irritable bowel syndrome using the Rome IV criteria. From January to April of 2018, the study was conducted as a prospective cohort study at the University Clinical Center Tuzla (UCC). The participants were surveyed during the initial exam and on week four and eight after the administered therapeutic protocol. The aim of the study was to determine the most commonly used medicine for treatment of symptoms of irritable bowel syndrome in the Tuzla Canton. Results: The most commonly prescribed medicine after the diagnosis of irritable bowel syndrome was mebeverine as monotherapy or mebeverine in combination with an antidepressant. Discussion: Even though there are more than 50 registered medicines for the treatment of irritable bowel syndrome in the Tuzla Canton, probably due to its availability most often mebeverine was the medicine of choice.

**Conclusion:** After the colonoscopy and the diagnosis of irritable bowel syndrome, regardless of the age, sex, or the subtype of irritable bowel syndrome, mebeverine was the first choice of medicine.

**Key words:** the most commonly used medicines, patients with irritable bowel syndrome, mebeverine

**Introduction:** By definition, irritable bowel syndrome is a chronic disorder of the gastrointestinal tract, characterized by abdominal pain and changes in bowel emptying, in the absence of detectable organic disease (no histological, morphological, biochemical, or microbiological abnormalities). The study included 200 patients with irritable bowel syndrome who underwent colonoscopy and were diagnosed with irritable bowel syndrome based on ROMA IV criteria. The study was conducted according to the type of longitudinal prospective study in UKC Tuzla in the period from January to April 2018. Respondents were interviewed on the day of examination, and 4 and 8 weeks after the therapeutic protocol. The aim of the study was to determine the most commonly used drug in the treatment of irritable bowel syndrome in Tuzla Canton.

**Result:** The most commonly prescribed drug after the diagnosis of irritable bowel syndrome was mebeverine as monotherapy or mebeverine in combination with an antidepressant. Discussion: Although in the area of Tuzla Canton for the treatment of irritable bowel syndrome there are more than 50 registered drugs, probably due to its affordability, mebeverine is the most common drug of choice. Conclusion: After colonoscopy and diagnosis of irritable bowel syndrome regardless of age and gender and subtype of irritable bowel syndrome, mebeverine is the drug of choice.

**Key words:** the most commonly used drug, patients with irritable bowel syndrome, mebeverine

### INTRODUCTION

By definition, irritable bowel syndrome is a chronic disorder of the gastrointestinal tract, characterised by abdominal pain and changes in the bowel movement<sup>1</sup>, without any detectable organic disease (no histological, morphological, biochemical, or microbiological abnormality). Irritable bowel syndrome is a set of medical symptoms which occur together; it is not a disease<sup>2</sup>. It manifests as abdominal pain, disorder of the bowel movement,

and bloating, without any organic disease. Patients with the irritable bowel syndrome often visit family medicine clinics. Irritable bowel syndrome is a chronic, recurrent, often even lifelong disease, which has its onset at an early age, and it is an important health problem worldwide<sup>3</sup>. Irritable bowel syndrome has great effect on the quality of life, but the efficiency of the therapy after the conducted treatment is not known<sup>4</sup>. Many different preparations were used for the treatment of the symptoms of irritable bowel

syndrome, but after the initial enthusiasm often caused by the placebo effect, they would stop being used. Nowadays the most commonly used medicines are from the following classes: antispasmodics, antidepressants, and from other classes of medications; also in use are medicines with prokinetic effect, anxiolytics, antiflatulants, gonadotropin releasing hormone analogues and mast cell degranulation inhibitors. Another possibility is the use of some of the medicines which would affect neurotransmitter receptors, such as beta-adrenergic antagonists and agonists, diphenylhydantoin. The use of these medicines is still in the experimental phase. Spasmolytics are medicines that have a spasmolytic effect. Anticholinergics, calcium channel blockers, and some other medicines, whose effect is exerted by mechanisms different from the abovementioned groups, are used. Particular attention is devoted to the use of mebeverine hydrochloride which decreases the intensity of the abdominal pain and distension while regulating the frequency of defecation and stool consistency in patients with irritable bowel syndrome regardless of their predominant symptoms and improves the overall condition of the patient. According to anatomical therapeutic chemical (ATC) classification system, mebeverine belongs to the group of medicines which act on the alimentary tract and metabolism. They act in a way that they occupy the stress-sensitive sodium channels in the smooth muscles, which reduces the sodium and thus calcium flow. Mebeverine is the most commonly used medicine for treatment of irritable bowel syndrome. In Bosnia and Herzegovina (BiH), mebeverine is registered in two forms - coated tablets taken 3 times a day and prolonged-release capsules taken twice a day<sup>5</sup>. Functional disorders of the digestive tract are some of the most common diseases, and they affect high percentage of adults<sup>6</sup>. The most common are functional dyspepsia in the upper and irritable bowel syndrome in the lower gastrointestinal tract. The cost of treatment of functional diseases of the gastrointestinal tract is high and has an important role in creating social and health system of any country. There are 4 types of irritable bowel syndrome based on the predominant type of change of the rhythm and stool type: irritable bowel syndrome with diarrhea, irritable bowel syndrome with constipation, irritable bowel syndrome with mixed bowel habits, and the undetermined type of irritable bowel syndrome. The best way to diagnose irritable bowel syndrome is to combine looking at signs and symptoms, excluding other gastrointestinal diseases, and positive biomarkers<sup>7</sup>. Diagnosis of irritable bowel syndrome is made based on the Roma IV criteria which are: Recurring stomach ache which has occurred at least once a week in the last three months in connection with two or more of the following symptoms: in connection with defecation, change in the stool frequency, change in the type of the stool. The criteria have to be met in the previous three months. These symptoms should be accompanied by at least two out of three listed symptoms: change in stool passage (incomplete passage, urgent need to have a bowel movement, straining), bloating (abdominal wall distension), and discovering mucus in stool<sup>8</sup>. Research shows that geographical location, social order, development of the country, economic parameters, and the organization of the healthcare system have a significant, sometimes decisive, influence on the incidence,

character, type and level of therapeutic response in patients with irritable bowel syndrome<sup>7</sup>. The incidence, frequency, and character of irritable bowel syndrome is influenced by social standard, sex, high BMI, stress, work habits, level of development of the healthcare system, and can vary in different countries, even significantly vary within one organized and developed whole. Literature shows different efficiency of therapeutic protocols which can be explained by different types and characteristics of the ailment in different regions. Within Bosnia and Herzegovina, there is no clear data on the effectiveness of therapeutic protocols in the treatment of irritable bowel syndrome. Much research was conducted around the world and therapeutic protocols were defined, but in BiH, especially in the Tuzla Canton, there is no research about the use of medicines in the treatment of patients with irritable bowel syndrome. The aim of this study is to determine the quality of life of participants with irritable bowel syndrome before and after therapeutic protocol with mebeverine as monotherapy or combined with antidepressants.

## STUDY PARTICIPANTS AND RESEARCH METHODS

Study included 200 adult study participants of both sexes who were treated in outpatient clinics at the UCC Tuzla between January and April of 2018. Study participants and group forming Prospective cohort study included 200 study participants, 138 female patients (69%) and 62 male patients (31%), with irritable bowel syndrome, who had a colonoscopy and were diagnosed with irritable bowel syndrome using Roma IV criteria. Based on the type of irritable bowel syndrome, the participants were divided into three groups: IBS with diarrhea (N=70), IBS with constipation (N=80) and IBS with mixed bowel habits (N=50).

## Methods

Participants filled in a survey during the examination, and four and eight weeks after the administered therapeutic protocol, using Irritable Bowel Syndrome-Quality of Life Measure (IBSQoL) questionnaire<sup>9</sup>. Participants themselves filled in the questionnaire and rated their quality of life on the following scale from 1 to 5:

- 1 - quality of life is not impaired at all
- 2 - quality of life is slightly impaired
- 3 - quality of life is moderately impaired
- 4 - quality of life is quite impaired
- 5 - quality of life is significantly

Colonoscopy was performed on all participants using the standard procedure for colonoscopies in outpatient clinics, and video colonoscope CF-Q160, video colonoscope CF-Q165, and video colonoscope CF-Q160DL were used. All adverse effects and side-effects were reported in accordance with existing procedures (Adverse Reaction Reporting Form)<sup>10</sup>.

## RESULTS

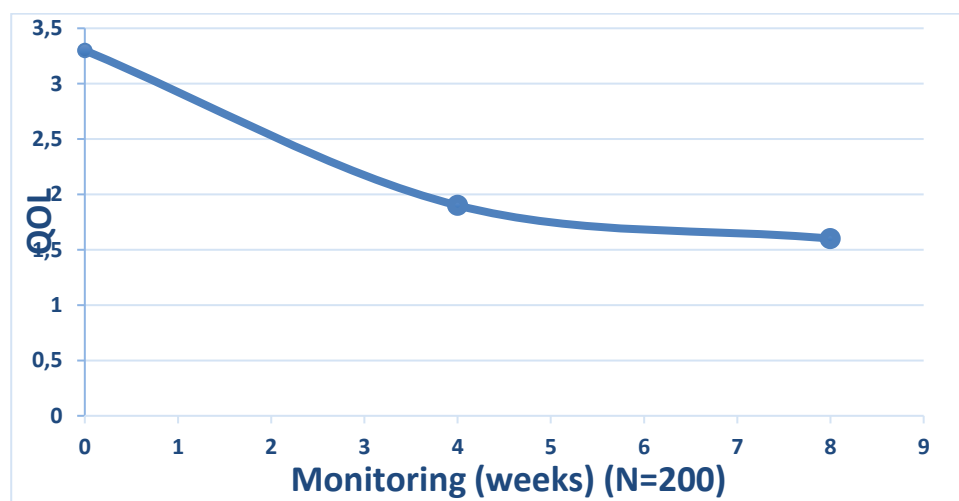
Average age of participants was 47 years (SD=13.37), more precisely average age of female participants was 46.2 years (SD=13.74) and of male participants was 48.8 (SD=12.55). According to the type of irritable bowel, participants were divided into the following three groups: IBS with diarrhea (IBD-D), IBS with constipation (IBS-C) and IBS with mixed bowel habits (IBSM) (Table 1).

**Table 1** Distribution of participants based on the type of irritable bowel syndrome and sex (N=200)

IBS Type	Total	Male	Female
IBS-C	80	22	58
IBS-D	70	30	40
IBS-M	50	10	30

Mebeverine was administered in the therapeutic protocol; 150 participants, 98 female participants (65.33%) and 52 male participants (34.67%), received mebeverine as monotherapy. Fifty participants, 40 female participants (80%) and 10 male participants (20%), received mebeverine with an antidepressant. Based on the doctor's report after week four and eight, it was determined that all of the participants carried out the therapeutic protocol, i.e. used the prescribed therapy after week four and eight. Through quality of life assessment questionnaire, the

reason for administration of mebeverine was tracked using Irritable Bowel Syndrome-Quality of Life Measure. Based on the Irritable Bowel Syndrome-Quality of Life Measure questionnaire, values measured on a scale from 0 to 5 were collected before therapy administration, after four weeks of using the therapy (first check-up), and eight weeks after the start of therapeutic protocol (second check-up). Average score before the therapeutic protocol in all patients was 3.3, while after the first check-up it was 1.9 and after the second 1.6 (Image 1).



**Figure 1.** Scores of all participants before therapy, and after the first and second check-up. To track the change in quality of life of the participants using typical IBS-QoL questionnaire, we performed analysis of variance on repeated samples, where the questionnaire score

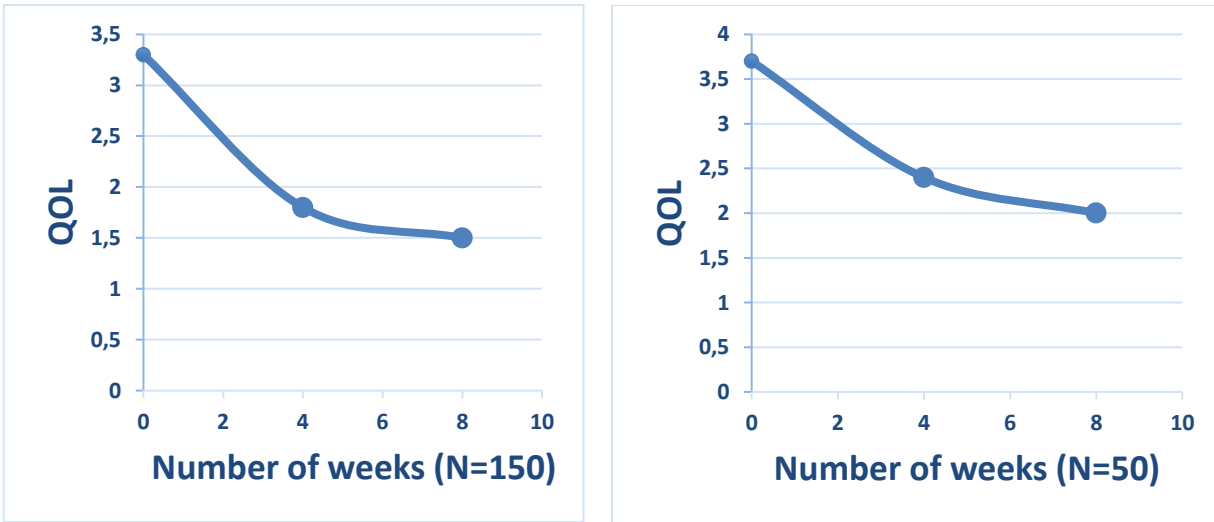
was the dependent variable, while independent variables were sex (male-female), IBS type (C, D, or M), and therapy type (monotherapy or combination therapy). The age of participants was used as a covariable of the model (Table 2).

**Table 2:** Effect of independent variables on the quality of life score in the IBS-QoL questionnaire

	df	F	Sig.	Effect Size (ES)
Age	1	9.567	.002	.048
Sex	1	1.597	.208	.008
IBS type	2	4.591	.011	.047
Therapy	1	8.278	.004	.042

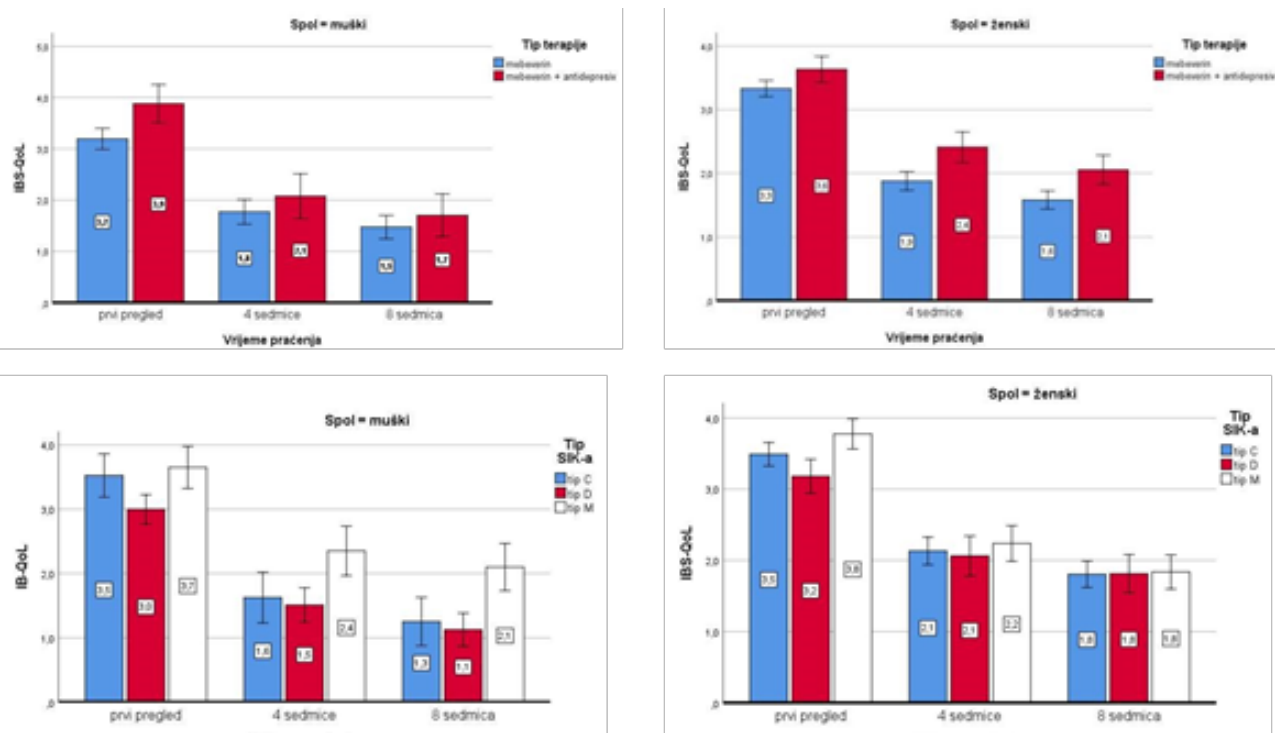
Table 2 shows that quality of life of all participants in the three time periods was affected by the age of participants ( $p=0.002$ ), which supports our decision to check the effect of the independent variable, while also controlling the age of participants. The independent variables which affect quality of life of participants were IBS type ( $p=0.011$ ) and therapy type ( $p=0.004$ ). Using the Irritable Bowel Syndrome-Quality of Life Measure questionnaire results, values measured on a scale from 0 to 5 were collected for participants, who used mebeverine as monotherapy, before therapy administration, after four weeks of using therapy (first check-up), and eight weeks after the

start of therapeutic protocol (second check-up). Average score before therapeutic protocol in patients who used mebeverine as monotherapy was 3.2. For those patients who used combination therapy, the score was 3.7 after the first check-up. After the second check-up (week 4), patients who used mebeverine as monotherapy rated their quality of life with 1.8, while patients who used combination therapy rated with 2.4. Then after the second check-up (week 8), score of patients who used mebeverine as monotherapy was 1.5, while for those who used combination therapy, it was 2.0 (Image 2).



**Figure 2.** Scores of all participants who used mebeverine as monotherapy and combination therapy before treatment, and after the first and second check-up. According to the Irritable Bowel Syndrome-Quality of Life Measure questionnaire results, during the initial check-up there were statistically significant differences in scores of quality of life between groups of men using mono and combination therapy, as it was expected. Combination therapy was prescribed to patients of poorer clinical status. Quality of life significantly improved in both groups after weeks four and eight, regardless of the therapy

type. It was not the same for women, because for them quality of life was significantly better in patients who used monotherapy, and it was the case both in the fourth and eighth week of monitoring. Despite the differences, generally sex did not affect the quality of life. Regarding the type of irritable bowel syndrome, it can be observed that in men there was bigger improvement in quality of life in IBS-C and IBS-D. For women, the improvement was of smaller intensity and without particular differences between IBS types (Image 3).



**Figure 3** Effect of therapy and IBS type on IBS-QoL questionnaire results

**DISCUSSION**

Irritable bowel syndrome is a functional disorder of the bowels which is a significant burden for the healthcare system and can seriously jeopardize the quality of life; it is also the most commonly diagnosed gastrointestinal condition. Numerous studies were conducted around the world and allowed the creation of therapeutic protocols,

but in BiH, especially the Tuzla Canton, there were no studies regarding effect of mebeverine on the quality of life of patients with irritable bowel syndrome. Diagnostic tests were performed on 200 study participants from the Tuzla Canton who were diagnosed with irritable bowel syndrome. 69% of the participants were female, and 31% male. It is know that the prevalence of the irritable bowel

syndrome, regardless of the type, is higher in women than men. The incidence of the disease in women compared to men is 1.5 to 3 times higher. International prevalence study shows the ration 67% to 23% of women and men with IBS respectively<sup>9</sup> and it can be seen that the sample examined in the Tuzla Canton shows results similar to the mentioned study. Having taken this into consideration, it can be concluded that in the examined Tuzla Canton, as in other parts of the world, irritable bowel syndrome is a disease of sex-specific prevalence. Average age of the study participants from the Tuzla Canton was 47 years. One should take into consideration the fact that persons under the age of 18 did not participate in the study due to the specific organization of the healthcare system. According to the studies conducted around the world, more than one quarter of the patients are younger than 50. In our study in the Tuzla Canton, the youngest participant was 18 years old, while the oldest was 74. Studies around the world show that patients between the age of 35 and 55 seek medical attention most often, which is also the case with the participants of our study. According to results of our study, more than two thirds of participant had constipation (IBS-C) or diarrhea (IBS-D) type of irritable bowel syndrome, while one third of participants predominantly had irritable bowel syndrome with mixed bowel habits (IBS-M). There is statistically significant predominance of IBS-C in women compared to men, while statistical difference in sex was not observed for IBS-D and IBS-M. In the study, which included 191 participants, conducted in 2011, complete predominance of irritable bowel syndrome with constipation, as well as that with diarrhea, was determined. Possible effect of female hormones on the motility of the gastrointestinal tract is taken as the possible reason for the predominance of irritable bowel syndrome with constipation in women. Functional disorders of the upper gastrointestinal tract have also been reported in the same persons<sup>11</sup>. Through comparison of the gathered data, it can be concluded that our groups of participants display similar distribution of subtypes of irritable bowel syndrome as other Euroasian countries which published the results of their epidemiological studies. All two hundred participants accepted the use of mebeverine as monotherapy or in combination with other medication, which shows their motivation for treatment. Mebeverine monotherapy was administered to all patients regardless of their age, sex, and irritable bowel syndrome subtype. The main criterion for administration of combination therapy was the concomitant lack of sleep in participants and the duration of symptoms longer than a year before going for a check-up. Based on the study with Cailleri and Ford in 2017, antispasmodic medications are most commonly used in the treatment of irritable bowel syndrome, allowing for the fact that mebeverine is not available in the USA<sup>12</sup>. In the world, there are 81 medicines used for treatment of irritable bowel syndrome. In the Tuzla Canton, mebeverine is the most available, commonly prescribed and used medicine. The fact that it is on the List of Medicines of the Compulsory Health Insurance of the Tuzla Canton makes it more accessible to patients; there are even reported cases of self-prescription of mebeverine. In the Tuzla Canton, there are two registered forms of mebeverine: coated tablets (135 mg) taken 3 times a day and prolonged-release

capsules (200 mg) taken twice a day. This availability of the medication made the study more relevant because patients took it regularly and without interruption. Anxiolytics were used according to established criteria, and similar studies used the same criteria, one of the biggest being the study of Merat et al. in 2010<sup>13</sup>. Given the fact that mebeverine is very available in the researched area, our study can be considered a bigger regional study on the efficiency of this medication as PubMed search on February 2, 2020 did not show the same or bigger published research on the use of mebeverine as monotherapy or combined with other medications. That gives this study importance, and given the characteristics of the participant groups, we can conclude that the results of our study can be used in other countries of the region and broader. Irritable Bowel Syndrome-Quality of Life Measure questionnaire is a questionnaire for irritable bowel syndrome assessment and is specifically used for respondents with irritable bowel syndrome. The research of Andraee et al. from 2013 with 754 participants in a randomized clinical trial has shown this questionnaire as having high sensitivity and as a valid instrument not only for tracking the assessment of the quality of life, but also for tracking the effect of the therapy<sup>14</sup>. Impaired quality of life was shown by a score above 3. Average score before the therapeutic protocol in our study was 3.30 according to the Irritable Bowel Syndrome-Quality of Life Measure questionnaire. This goes to prove that the quality of life of our participants was significantly impaired. Through comparative analysis, it can be noticed that the study used one questionnaire typical for irritable bowel syndrome and one atypical questionnaire as tools for measuring the quality of life of participants with irritable bowel syndrome. Both separately distributed questionnaires have shown that the quality of life of our participants with irritable bowel syndrome in the Tuzla Canton was significantly impaired regardless of age, sex, and subtype of irritable bowel syndrome. Upon therapeutic protocol administration, after 28 days, participants were administered mebeverine as monotherapy or mebeverine in combination with anxiolytics. Average score of the typical questionnaire was 1.9 after 4 weeks, while it was 1.85 according to the atypical. This can lead to the conclusion that the quality of life was improved 42.6% for all participants no matter the age, sex, subtype of irritable bowel syndrome, and the use of mebeverine as monotherapy or combined with anxiolytics. The criterion for the administration of antidepressants was doctor's assessment that mebeverine as monotherapy cannot yield adequate results. Since the doctors were gastroenterologist with more than 10 years of work experience and clinical practice in treatment of irritable bowel syndrome, there was ethical and professional justification for such approach. Subsequent analysis of the questionnaire lead to the conclusion that all participants who use combination therapy had questionnaire scores over 3.5. This shows that typical and atypical questionnaire can be used not only for determining the efficiency of the treatment, but also as parameter for administering the therapy, mebeverine as monotherapy or combination therapy. The recommendation would be to administer combination therapy to participants whose score during the first check-up is above 3.5 (based on any questionnaire), while participants with scores below 3.5 are candidates for

mebeverine as monotherapy. For all participants, according to both questionnaires, during the first check-up, after four weeks, there was already a decrease in the scores from 3.8 to 2.45, i.e. the quality of life improved 36.5% in comparison to the first scores. Based on the typical and atypical questionnaire, second check-up showed additional improvement in the quality of life, from 1.8 to 1.5 (16.7%) or from 1.7 to 1.4 (17.65%). After two months, stagnation occurs and there is no additional improvement in the quality of life. Statistical results showed that mebeverine as monotherapy leads to additional improvement in the quality of life after eight weeks, according to both questionnaires. Mebeverine, when used as monotherapy, in this timespan did not show any side effects in treatment of irritable bowel syndrome. Studies show that the efficiency of mebeverine is over 80% regardless of age, sex, and subtype of irritable bowel syndrome and that it has got high tolerance in used dosage, twice a day 200 mg over the course of eight weeks.

Additionally, the studies show that there is no need for an increase in this dosage<sup>15</sup>. The statistical results do not show any statistically significant differences in the effect of mebeverine on men and women regardless of the age and subtype of irritable bowel syndrome. Similar results were gathered by Lu et al in 2000<sup>16</sup>. After eight weeks, the efficiency of combination therapy, mebeverine and anxiolytics, was analysed and it was noted that scores improved from 2.4 to 2.0, i.e. quality of life improved 16.7%, or from 2.45 to 1.95, i.e. quality of life improved 20.5%. Stagnation in the improvement of the quality of life occurs after eight weeks. Literature data shows similar results in the improvement of the quality of life, and the biggest study with relevant results, which was published in 2008, shows overall efficiency in more than two thirds of participants<sup>17</sup>. Statistically significant difference was not observed in the efficiency of combination therapy regardless of age, sex, and subtype of irritable bowel syndrome.

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