Assessment of the Antidepressant Side Effects Occurrence in Patients Treated in Primary Care

Enisa Ramic¹, Subhija Prasko², Larisa Gavran², Emina Spahic³

ABSTRACT
Introduction: It is an undeniable fact that antidepressants can cause side effects. Antidepressants generally have a similar effect but they differ in their application safety, as well as their side effects. Aim: To determine differences in the frequency and intensity of antidepressant induced side effects in patients treated in primary care. Methods: The research was designed as a prospective, cross-sectional study, conducted on a voluntary and anonymous basis, and it included depression patients treated with antidepressant medications during 2013-2015 in Zenica-Doboj Canton using the Hamilton Depression Rating Scale and Toronto Side Effects Scale. Results: The total sample included 508 subjects. As a significant problem, abdominal pain was felt by 14% of subjects, indigestion by 19% of subjects, nausea by 15% of subjects, diarrhea by 9% of subjects, and constipation by 11% of subjects. 29% of subjects suffered from sweating, 20% suffered from a sudden heat stroke, 10% suffered from swelling, and 23% of them reported suffering from dry mouth as a significant problem. The prevalence of side effects in relation to how do they affect life and daily activities of subjects is statistically significant (P <0.000). Statistically significant side effects of SSRIs antidepressants correlate with the duration of our subject's treatment: perception of increased sleep (0.039) as well as decreased sleep (P = 0.009), sweating (P <0.001), sudden heat stroke (P <0.001), being without orgasm (P = 0.004), decreased libido (P <0.001), weight loss (P = 0.045). Conclusion: It is necessary to educate the patients about the nature and features of the depressive disorder, and to notify the patients of the expected course of recovery, as well as the need to adhere to the recommended therapy and the possible side effects of the medication. Keywords: depression, antidepressants, side effects of antidepressants.

1. INTRODUCTION
Depression is a disease of our modern age and it presents a great challenge not only for mental health professionals, but also for family medicine physicians (1). It is estimated that over 120 millions of people from all over the world suffer from depression, of which twice as many are women. Depression is expected to become the world’s second significant health problem by 2020. Most of the patients who suffer from depression are between 35 and 55 years old (2).

The first step in the treatment of depression is to set a boundary between the domain of family medicine physicians and the domain of psychiatrists (3). According to the experiences of various authors, mild and moderate depression are in the domain of family medicine physicians. Their responsibility is not only the first contact with a patient, but also the monitoring of the patient treated by a psychiatrist.

Antidepressants generally have a similar effect, but they differ in their safety and side effects. A large number of antidepressants side effects is related to their effect on various neurotransmitter systems (4). The adverse reactions of antidepressants and the irrational use of these medicaments may be related to the low level of research in this domain and the lack of awareness among physicians about this problem (5).

In some patients antidepressants have an effective therapeutic effect, in some patients they cause a development of only mild, almost imperceptible side effects, while in some patients who suffer from mild depressive disorders they can cause a development of a severe chronic depression (6, 7). Individual hypersensitivity to the drug; age; sex; type of antidepressant based on its pharmacological effect; duration of the...
therapy; polypragmasia; and other things are also important in the assessment of antidepressant side effects (2).

The main reason for discontinuing the treatment with antidepressants is a development of unwanted side effects. It is an undeniable fact that antidepressants can cause side effects (6). Depression and anxiety are very common symptoms that occur when discontinuing the treatment with antidepressants. In this case of adverse drug reactions the clinical manifestation is more severe. Unfortunately, these symptoms are usually misjudged as a recurrent episode of depression, so a patient continues to take an antidepressant, thereby creating a vicious circle. The group of antidepressants called Selective Serotonin Reuptake Inhibitors (SSRIs) are the most frequently prescribed ones nowadays. Known side effects of treatment with SSRIs that are common are: anxiety, restlessness, insomnia, dry mouth, overweight, nausea, diarrhea, sweating, headaches, dizziness, decreased libido, tremor and sexual difficulties (8, 9, 10). The most commonly noticed side effects of Venlafaxine are: nausea, insomnia, dry mouth, sleepiness, dizziness, constipation, sweating, anxiety, asthenia, sexual difficulties (ejaculation disorder), hypertension and palpitations (9, 10). Tricyclic antidepressants tend to cause more side effects than other antidepressants because of their broad mechanism of action. Drowsiness is a very common side effect, especially in the first few weeks after starting with the treatment. These antidepressants may cause cardiac arrhythmias, obesity, loss of libido, dizziness and nausea, dry mouth, blurred vision, constipation, impaired mycitis, and impaired mystical function with confusion (6, 8). Monoamine oxidase inhibitors (IMAOs) are the oldest group of antidepressants. Common side effects of these medications are dizziness, insomnia, weight gain, headaches, sexual problems, and daytime sleepiness (7, 11).

2. AIM
To determine differences in the frequency and intensity of antidepressant induced side effects in patients treated in primary care. Including factors were diagnosis of depressive disorder without psychotic symptoms or other comorbidities and treatment with antidepressive drugs in duration of minimaly three months.

3. PATIENTS AND METHODS
The research was designed as a prospective, cross-sectional study, conducted on a voluntary and anonymous basis, and it included depression patients treated with antidepressant medications during 2013-2015 in Zenica-Doboj Canton using the Hamilton Depression Rating Scale and Toronto Side Effects Scale.

Questionnaires
Objective screening tests were used in the research: Hamilton Depression Rating Scale (12). The Toronto Side Effects Scale (TSES) which contains 32 items was also used in this research (15). It has been created for a direct evaluation of antidepressants side effects on the central nervous system, gastrointestinal tract and it also relates to sexual difficulties, their frequency and intensity (14, 15). Answers were based on intensity and severity of symptoms.

Statistical Data Analysis
The analysis of results was performed by using the standard Statistical Package for the Social Sciences (SPSS) version 19.0. Standard methods of descriptive statistics were applied in the statistical analysis of results. The χ2-test and the t-test (p <0.05) were used in order to test the statistical significance of the difference of the selected variables. A non-parametric Spearman’s rank correlation test and multivariate regression analysis of variance ANOVA were helpful in multivariate correlation analyzes.

4. RESULTS
A total sample included n = 508 subjects. The average age of the subjects (n = 508) was 48.98 years ± 11.585 years (standard deviation, SD). The highest number of subjects treating an episode of depression were women, 320 out of 508 (63%), and between 41 and 60 years of age (59%). Only 10% patients achieved remission and absence of the depressive disorder as a successful treatment outcome. 20% patients suffered from mild depressive disorder, and 21% patients from moderately severe depression. Serious depression was recorded in 17%, and very serious with treatment in 32% patients.

| Frequency of the symptom | Intensity of the problem | No (%) | P |
|--------------------------|--------------------------|--------|---|
| Nervousness              |                          |        |   |
| never                    | not a problem            | 43 (9) |   |
| rarely                   | insignificant            | 99 (19)|   |
| sometimes                | moderate                 | 168 (33)| 0.001 |
| often                    | significant              | 143 (28)|   |
| daily                    | severe                   | 55 (10)|   |
| Anxiety, fear            |                          |        |   |
| never                    | not a problem            | 47 (9) |   |
| rarely                   | insignificant            | 102 (20)| 0.001 |
| sometimes                | moderate                 | 172 (34)|   |
| often                    | significant              | 131 (26)|   |
| daily                    | severe                   | 56 (11)|   |
| Shaky hands              |                          |        |   |
| never                    | not a problem            | 161 (32)| 0.001 |
| rarely                   | insignificant            | 140 (28)|   |
| sometimes                | moderate                 | 110 (22)|   |
| often                    | significant              | 61 (12)|   |
| daily                    | severe                   | 36 (7)|   |
| Muscle spasm             |                          |        |   |
| never                    | not a problem            | 179 (35)| 0.001 |
| rarely                   | insignificant            | 148 (30)|   |
| sometimes                | moderate                 | 103 (20)|   |
| often                    | significant              | 62 (12)|   |
| daily                    | severe                   | 16 (3)|   |

Table 1. Comparative representation of differences in the incidence of undesirable symptoms of nervousness and anxiety in a relation to the intensity of a problems that these undesirable symptoms present in all subjects, according to the Toronto scale (n = 508)
5. DISCUSSION

A treatment with antidepressants has often a potential risk of side effects and suicidal thoughts (16, 17). Although Selective Serotonin Reuptake Inhibitors (SSRIs) do have better overall safety and tolerability comparing to older antidepressants, experience and clinical trials have shown a significant incidence of their side effects.

Ferguson has investigated the causes of various side effects profiles, especially the causes of sexual dysfunction, weight gain, and sleep disorders. An occurrence of side effects in long-term SSRI therapy is most concerning. Ferguson’s results comply with ours. The statistically significant side effects of SSRI antidepressants in correlation with the duration of the treatment in our subjects are: perception of increased sleep (P < 0.009) as well as decreased sleep (P < 0.001), sudden heat stroke (P < 0.001), being without orgasm (P = 0.004), decreased libido (P < 0.001), weight loss (P = 0.045).

In clinical studies it has been confirmed that SSRIs have significantly less side effects compared to Tricyclic Antidepressants (TCA) (19). They do not cause irregularities in cardiac conduction or rhythm disturbances in case of an overdose (20). As confirmed in our study, Selective Serotonin Reuptake Inhibitors (SSRIs) are currently the first choice of therapy for depression (17).

In a prospective control study which included 1251 patients, in the treatment of depression 659 of them have used sertraline and 592 of others have used SSRIs (paroxetine, fluoxetine, or fluvoxamine) for at least 12 months. A significant side effect in patients treated with Sertraline compared to patients treated with other SSRI antidepressants is diarrhea (14% vs. 6.8%), P < 0.05 (21). Our results are contradictory. In our study, tiredness occurred most commonly in treatment with Paroxetine (50%) and Flusetin (48%), but differences in the prevalence of this side effect among the five most prescribed antidepressants were not significant. Headache most frequently occurs in treatment with Flusetin (39%), just as well as dizziness (30%); blurred vision (26%), and dry mouth occur in treatment with Paroxetine. However, the differences for all known SSRI side effects are not significant.

6. CONCLUSION

It is necessary to educate the patient about the nature and properties of the depressive disorder, and to introduce him to the expected course of recovery, as well as the need to adhere to the recommended therapy and the possible side effects of the drug. The results of our research have shown an important degree of variability in side effects of the most commonly prescribed SSR1 antidepressants compared to those reported in clinical trials, which had been monitored before they were approved.

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• **Authors contribution:** Each author equally participated in preparation of this article. Final proof reading was made by the first author.

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