Frequency and characteristics of side effects associated with antidepressant drugs

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Apstrakt

Depresija je jedno od najčešćih hroničnih oboljenja, za koje se procjenjuje da će do 2020. god., biti vodeći uzročnik radne nesposobnosti i drugih životnih tegoba. Depresivni sindrom se zbog toga mora ozbiljno shvatiti i liječiti.

Tretman depresije podrazumjeva postizanje potpune remisije, što nije jednostavno postići, jer većina pacijenata prekida primjenu lijeka prije vremena. Jedan od najvećih razloga za prijevremeni prekid terapije je pojava neugodnih neželjenih efekata.
Cilj studije je bio istražiti dinamiku, incidencu i karakteristike najčešćih neželjenih efekata antidepresivnih lijekova primjenjenih u pacijenata sa depresijom, tokom hospitalizacije na ženskom odjeljenju Psihijatrijske klinike Kliničkog centra u Sarajevu.
Rezultati su pokazali da je tretman bio efikasan u većine pacijenata. Inhibitori ponovnog preuzimanja serotonina (SSRI) su imali manje izražene neželjene efekte u odnosu na triciklične antidepresive (TCA). Najčešći neželjeni efekti TCA (amitriptilin) su bili poremećaj akomodacije, tahikardija, suhoća usta, tremor i sedacija, a najjače izraženi suhoća usta, tremor i tahikardija. Neželjeni efekti SSRI (fluoksetin, fluvoksamin) su bili blagog intenziteta, najčešće u vidu mučnine, tahikardije, znojenja i suhoće usta.

Abstract

Depression is among the most common of chronic health problems. WHO report predicts that depression will be the leading cause of disability in the industrial world by the year 2020.

To be successful, treatment for the patients suffering from depression must be continued until complete recovery, but most patients do not stay on their antidepressant medication long enough. One of the most frequent reasons for break down is appearance of unpleasant side effects.
In this study we followed up dynamics of the characteristic side effects of antidepressant therapy, with the major goal to assess their frequency and characteristics. The sample was all female patients taking antidepressant drugs in the Department of Psychiatry of Clinical Centre of University in Sarajevo.
The treatment with antidepressants was efficient in most of the patients. A major advantage of SSRI over TCA was less pronounced side effects. The most intensive side effects of TCA (amitriptyline) were dry mouth, tremor and tachycardia while the most frequent side effects included blurred vision, tachycardia, dry mouth, tremor and sedation. Side effects of SSRI (fluoxetine/fluvoxamine) were mild, and the most frequent were nausea, tachycardia, swelling, dry mouth.

Introduction

Depression is an affective disorder, known from antic period. It is characterized by the mood changes as primary clinical manifestation, which can lead to the other serious mental health changes.
Depression is among the most common of chronic health problems, also associated with societal costs higher than any other chronic diseases, especially in terms of patients' severe limitations in daily functioning and well-being[1].
It is estimated that one in five women and one in fifteen men can expect to develop depression during their lifetime.

Without treatment, 10 to 15% of people suffering from severe depressive disorder commit suicide. With treatment, the majority of patients with this illness will recover.

Depression high morbidity rate can also be seen in a fact that, antidepressant Prozac® is on the 3rd place of the top selling 200 drugs in 1999[2].
A recent World Health Organization report predicts that depression will be the leading cause of disability and premature death in the industrial world by the year 2020[3].

The American Psychiatric Association has published standardised criteria for the depressive disorders diagnosing (table 1).

Table 1 Criteria for major depressive episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. 1. Depressed mood most of the day, nearly every day; 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day; 3. Significant weight loss (when not dieting) or weight gain, or decrease or increase in appetite nearly every day; 4. Insomnia or hypersomnia nearly every day; 5. Psychomotor agitation or retardation nearly every day (not merely subjective feelings of restlessness or being slowed down) 6. Fatigue or loss of energy nearly every day; 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or feelings of guilt about being sick); 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day; 9. Recurrent thoughts of death (not merely fear of dying), recurrent suicidal ideation, or a suicide attempt.
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The symptoms are not due to the direct physiologic effects of a substance or a general medical condition.
D. The symptoms do not meet criteria for a mixed episode and are not better accounted for by bereavement.

There are several approaches to the treatment of depression depending on the severity of the condition and the risks to the patients, but in any cases it includes psychotherapy and antidepressive therapeutic agents. Untreated depression recovers within 6-12 months, with very high relapse rates. The use of antidepressants approximately doubles the chance that a depressed patient will recover within 2-4 months.

The best way to evaluate scientifically the effectiveness of therapy is to conduct a randomised controlled clinical trial. Here are the results of the few randomised controlled clinical trials that have been done (table 2). For the less severely depressed patients antidepressant drug, placebo pill with supportive visits to a physician, interpersonal and cognitive behavioural therapy were equally effective; for the severely depressed patients antidepressive therapy was highly effective while cognitive therapy was ineffective.

There is a surprising lack of any scientific research done on the effectiveness of psychoanalysis and psychotherapy in the treatment of major depression[3].

Table 2 Result of the clinical trials on the therapies of severe major depression

Treatment	***Effectiveness***
Antidepressive drug[5]	good
Interpersonal psychotherapy[5]	fair
Cognitive therapy[5]	unknown
Electroconvulsive therapy[6]	good
Anticonvulsant therapy, lithium (for prevention)[7]	good
Antianxiety medication[8]	poor
Antipsychotic medication[3]	unknown
Psychoanalytic psychotherapy[3]	unknown
Family therapy[3]	unknown
Group therapy[3]	unknown

Table 3 Common duration of antidepressive therapy

1. month	2. month	3. month	4. month	5. month	6. month	7. month	8. month	9. month	10. month

Various drugs have been developed and used in depression treatment. As the neurobiology of mood disorders and the mechanism of action of antidepressants continue to be elucidated, there has been a shift in emphasis from changes in neurotransmitter release and metabolism to the regulation of gene expression and neuroprotection[9].
Antidepressive therapy usually takes 2-4 weeks before any significant improvement is obtained, and 2-6 month before maximal improvement appears.
To be successful, treatment for the patients suffering from depression must aim not to the partial improvement of illness but to the complete remission (virtual elimination of symptoms) and recovery of life quality, according to an expert panel comprised of guidelines U.S. Mental Health Association (NMHA), Nov. 30th, 2001, in New York City. Antidepressant therapy should not be withdrawn before there have been 4 -5 symptom-free month (table 3).

Most patients do not stay on their antidepressants long enough for it to be effective. One study found that only 25% of patients started on antidepressants by their family physician stayed on it longer than one month[10]. One of the greater reasons for break down is appearance of the unpleasant side effects. They occur early in the treatment (while improvement is often delayed), produce bed compliance and patients refuse the drug therapy before complete recovery[11]. Most frequently side effects are related to their mechanism of action. Antidepressants interfere with activity of many neurotransmitters, on peripheral and central site of receptors[12]. But, individual classes of antidepressants are distinguished by their side-effect profiles.

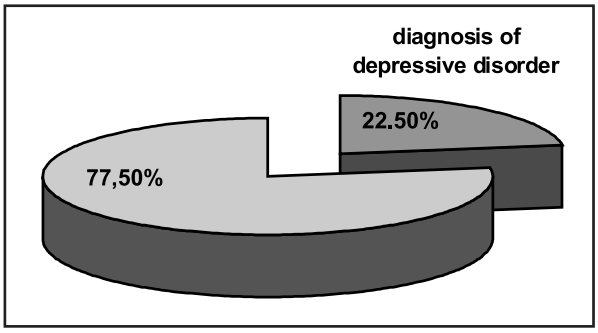
Method

Study was epidemiological, prospective, and randomised.
In this study we followed up dynamics of 16 different symptoms (dry mouth, constipation, dizziness, tremor, blurred vision, anxiety, sedation, nausea, dyspepsia, vomiting, headache, urinary disturbances, palpitations, sweating, myalgia, skin rashes), which are the characteristic side effects of antidepressive therapy, with major goal to asses their frequency and characteristics.
The sample was all female patients taking antidepressive drugs in the Department of Psychiatry of Clinical Centre of University in Sarajevo, during the period of five months.
The was done evaluation is done by the measuring of body weight, pulse rate in sitting and standing position, blood pressure in sitting and standing position, HAMD scale, scale of appetite, carbon hydrate needs scale and adverse effects scale.
All parameters were taken one day before the antidepressive therapy introduction, than every following week and on the last hospitalisation day.

Results and discussion

The sample was 27 patients who meet criteria ICD-10 for severe depressive episode, among 120 patients hospitalised in the Department of Psychiatry during the five month-period.

Graph 1 Diagnosis of depressive disorder



Patients were divided into two groups depending on antidepressants.
Average daily dose of amitriptyline was 75 mg (18 patients), fluoxetine 30 mg (8) and one patient was taking fluvoxamine in daily dose of 300 mg (table 4).

Table 4 Antidepressants and average daily dosage

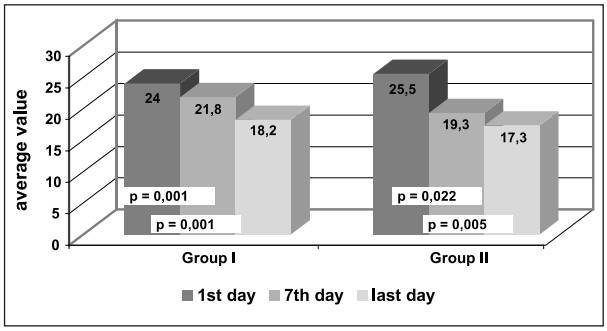
	Group of antidepressants	Antidepressants	Average daily dose	Number of patients
Group I	Tricyclic antidepressants (TCA)	Amitriptyline	75 mg	18
Group II	Selective serotonin reuptake inhibitors (SSRI)	Fluoxetine Fluvoxamine	30 mg 300 mg	8 1

Amitriptyline was effective in 72.3% patients, and fluoxetine/fluvoxamine was effective in 78% patients. Lonnqvist and Armstrong reported similar results of antidepressive effective treatment in 65-75% of all patients with depression[13, 4].

Hamilton Rating Scale for Depression (HAM-D_{17}) has been used for 4 decades as the "gold standard" instrument to assess the severity of depression and response to therapy in clinical researches. The maximum possible score for HAM-D is 52, in practice very few patients' core is above 35. Most people have depression score 14 or more[14, 15].

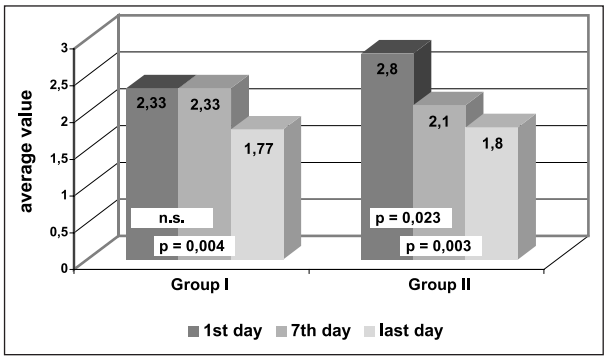
In group I on the first day Hamilton scale score was 24, after seven days 21. 8 (t-test p-0.001) and on the last day it was 18. 2 (t-test p=<0.001). In group II on the first day Hamilton scale was 25. 5, after seven days 19.3 (t-test p-0.022) and on the last day it was 17. 3 (t-test p=<0.005) (graph 2).
Significant difference was seen in both groups after seven days of the therapy.

Graph 2 HAMD score



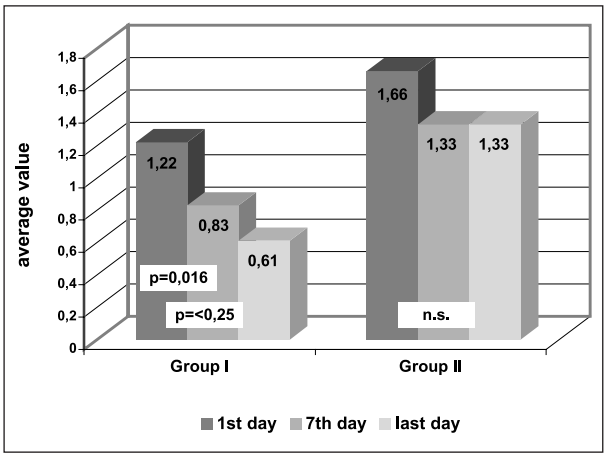
On the first day was recorded: depressive symptoms that caused clinically significant impairment in social, occupational and other functioning areas. Patients had feelings of worthlessness and inappropriate guilt and thought of death. Depressive feeling was significantly decreased, but still was there on the last hospitalisation day (scale 0-3; graph 3)

Graph 3 Depressive feeling

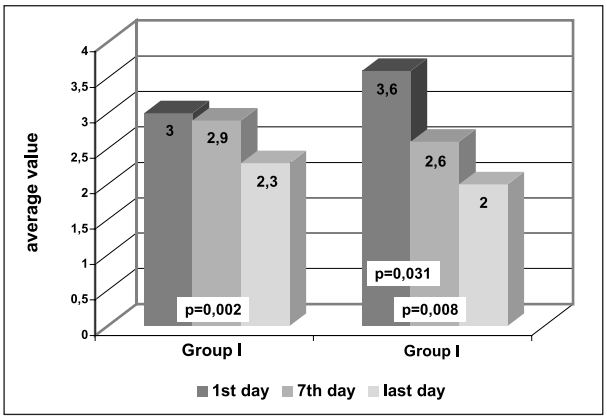


The first improved symptom (item on the HAM-D), after seven days of amitriptyline treatment, was insomnia (delayed) (scale 0-2) and in SSRI group that was depression feeling, work capacity/interests (scale 0-4) and retardation (scale 0-3). The improvement in insomnia, work capacity and interests, retardation, anxiety and appetite in TCA group was obtained -on the last hospitalisation day (graph 4, 5, 6).

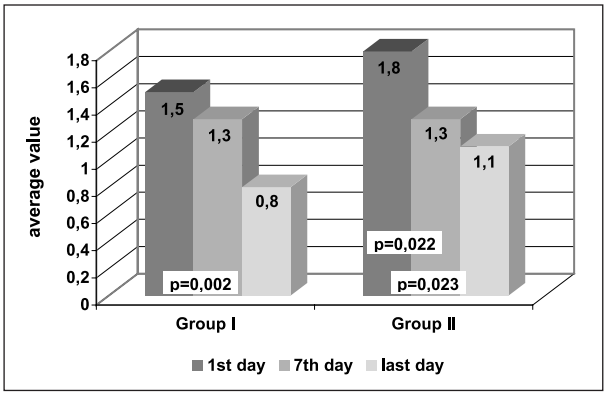
Graph 4 Insomnia (delayed)



Graph 5 Work capacity/interests



Graph 6 Retardation



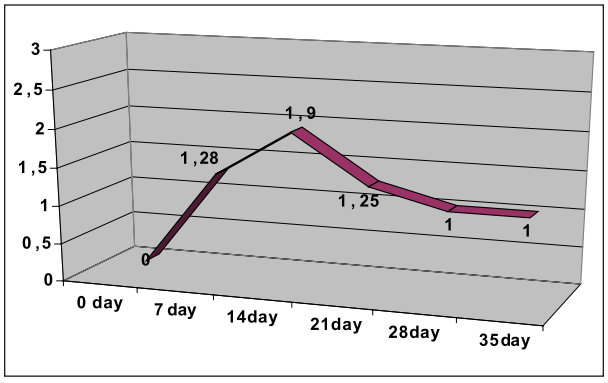
Antidepressants express an influence on the body weight. Patients in group I had significant increase of appetite (p=0.009) and weight gain (average value 0. 83 kg), and in group II patients experienced weight loss (average

value 0.67kg). Anorexia has also occurred during fluoxetine therapy according literature data, and it is most likely associated with the weight loss observed in several studies. Anorexia has occurred in 9-15% of patients treated, and occurs more frequently with fluoxetine than with other antidepressants; however, it is rarely a cause of the drug discontinuation[16, 17, 18].

In this study, all patients developed side effects. Incidence of side effects in TCA group was 7.4 on patient (7.4/) and 4 on patient (4/) in SARI group. This high incidence of side effect can be explained with mechanism of action of antidepressants. Tricyclic antidepressants interfere with the activity of at least five putative neurotransmitters by several different potential mechanisms at both central and peripheral sites, which results with adverse effects[12]. There is also a wide range of inter-individual sensitivity and susceptibility between patients, and very little consistent correlation between plasma concentration and particular adverse effects.

Side effects were the most intensive (range 0 till 3) during the second week of therapy, and reduced within the third week (graph 7).

Graph 7 Intensity of side effects

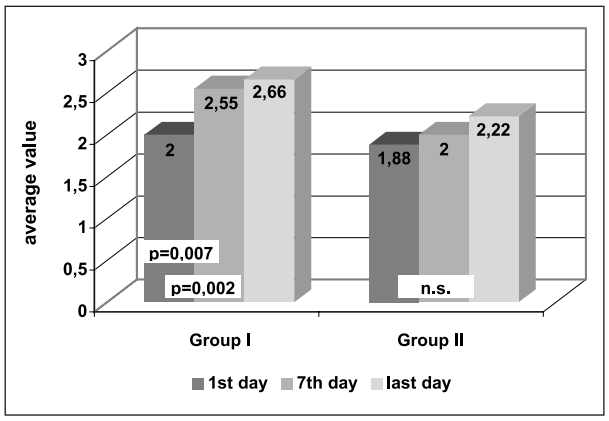


Patients in TCA group (group I), after seven days of therapy, experienced significantly different severity of all following symptoms (p=< 0.001), and it was lasted through the whole period. A significant difference in intensity (range 0-3) was found for dry mouth (p=0.007; p=0.002), blurred vision and sedation after seven days of therapy,, while for tachycardia (p=0.014) and tremor (p=0.002) on the last day (graph 8, 9, 10, 11, 12). None of the side effects where reported to necessitate additional pharmacotherapy. Only one patient with tachycardia needed a dose reduction.

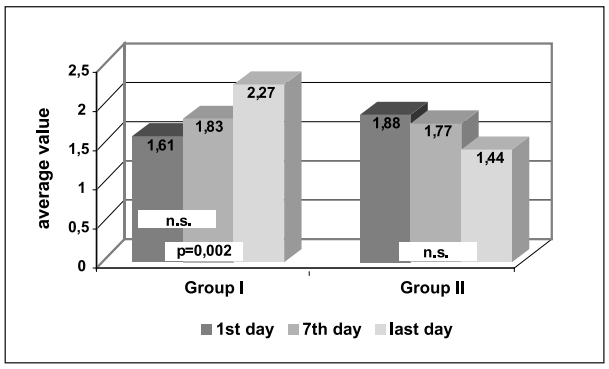
It is well known that all tricyclic antidepressants have a spectrum of anticholinergic activity, presenting as troublesome adverse effects such as dry mouth, sweating, confusion, constipation and blurred vision. The most serious adverse effects relate to the cardiovascular system[11, 12, and 19]. Elderly patients are more sensitive to anticholinergic effects of TCAs and may develop confusion or delirium even at moderate doses or with concurrent use of other anticholinergic drugs; orthostatic hypotension in the elderly can lead to padovi, particularly in patients with heart disease; TCAs lower the threshold for bundle branch block and complete heart block. Tricyclic antidepressants have sedative effects too, and this may be desirable and undesirable depending on particular patient's state of apathy or agitation.

Change in intensity of the following symptoms vs. pretreatment throughout the whole period in SSRI group (group II) was not significant, probably because of the low affinity to muscarinic and histaminic receptors (graph. 8, 9, 10, 11, 12).

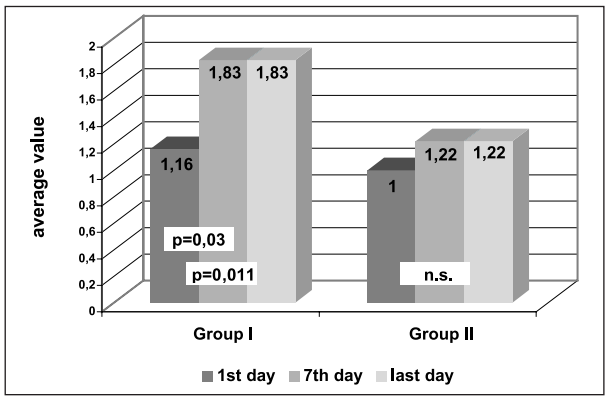
Graph 8 Dry mouth



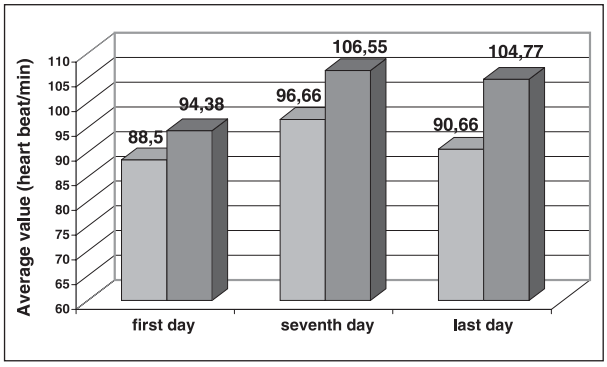
Graph 9 Tremor



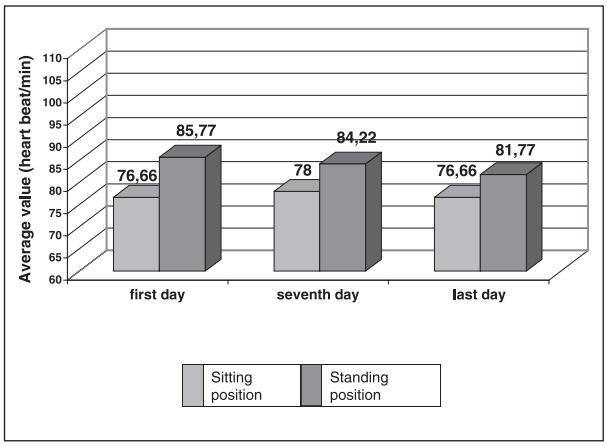
Graph 10 Blurred vision



Graph 11
Pulse rate in sitting and standing position (group I)

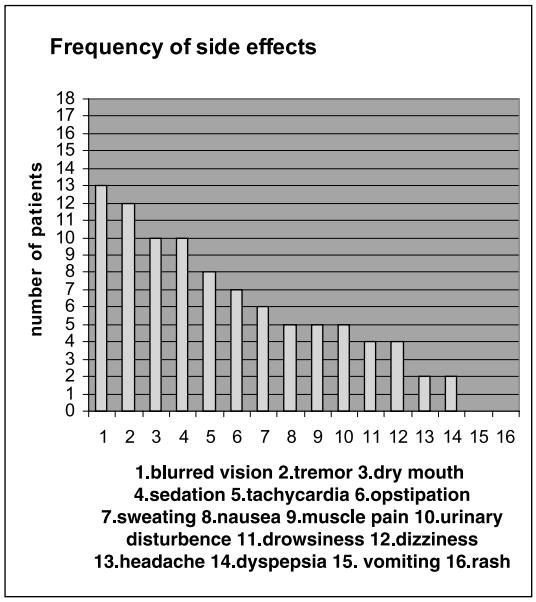


Graph 12 Pulse rate in sitting and standing position (group II)



The most frequent side effects, observed in group I, were blurred vision (13/18) and tachycardia (9/18) after seven days, and dry mouth (10/18), tremor (12/18) and sedation (10/18) on the last day (graph13).

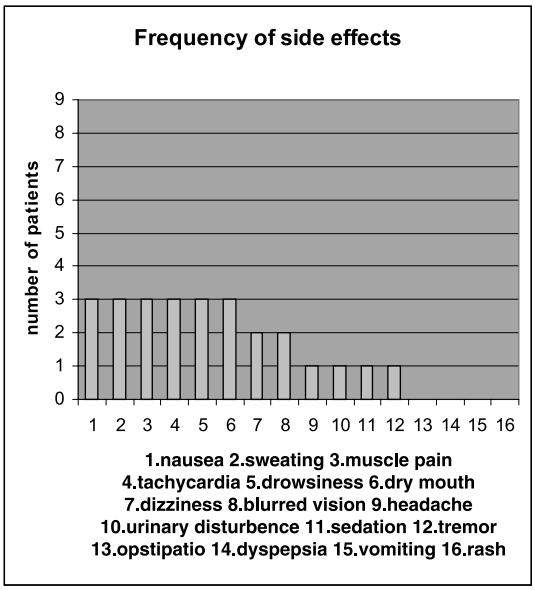
Graph 13 Frequency of side effects (group I)



Selective serotonin re-uptake inhibitors (SSRIs), compared with tricyclic drugs, have less pronounced anticholinergic effects and cause less severe cardiotoxicity. Gastrointestinal side effects are one of the major disadvantages of SSRIs. Wernicke, Cohn and Wilcox published that the most frequent side effects, which occurred in 10-25% of the patients, were nausea (25%), nervousness, insomnia, headache, tremor, anxiety, drowsiness, dry mouth (14%), sweating (30%) and diarrhea[17, 20]. Most of these side effects occurred early in the treatment and seldom led to the drug withdrawal.

The most frequent side effect in group II after seven days of therapy was nausea (30%), than sweating and dry mouth seen on the last day. Only one patient had intensive nausea, but the patient continued with the application of the same dose. None of side effects necessitated additional pharmacotherapy or dose reduction.

Graph 14 Frequency of side effects (group II)



Conclusion

Antidepressant's treatment is efficient in most of the patients. Side effects are common during the treatments. A major advantage of fluoxetine over amitriptyline is less pronounced side effects. Every patient in amitriptyline group had average 7.4 side effects and 4 in fluoxetine group. The most intensive amitriptyline side effects were dry mouth, tremor and tachycardia whilethe most frequent side effects included blurred vision, tachycardia, dry mouth, tremor and sedation. The most frequent fluoxetine side effects were nausea, tachycardia, swellingand dry mouth.

We can conclude that SSRIs and TCAs are equal in efficacy in the treatment of depression, but SSRIs are toler-

ated better (lack the significant anticholinergic, cardiovascular and sedative effects of TCAs), so SSRIs should be considered as first-line agents especially in the treatment of older adults.

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