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The Effects of Fluoxetine Usage on the Concentration of Testosterone Hormone

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ABSTRACT

Depression is the most common mental disease, and yet the best method of its cure is to use SSRIs like fluoxetine. But apart from the effects of fluoxetine on the depression treatment, its side effects on different biological system of the body. In this paper we have tested 45 male patients in 3 groups each of which contained 15 persons. The first group used fluoxetine (20 mg/kl per day) for a period less than 6 months, and the second group used the same doze of fluoxetine for a period more than 6 months. The third group known as the control group contained 15 healthy men who were quite normal in the studied factors of the research. The findings of the research imply that the comparison between the first group and the control group showed no significant change. But in comparison between the second group and the control group it was shown that the fluoxetine leads to the reduction of testosterone (1±14.44 vs. 1±5.26). According to the results of this research, time-dependent fluoxetine usage is effective on the scale of sexual hormone so that the increase in the duration of the usage will lead to more sensible changes.
KEY WORDS*:* Fluoxetine, Depression, Testosterone.

1. INTRODUCTION

The increase of the human wants, and the failure in the fulfillment of such wishes and wants all make the people apt to suffer from the mental problems. We can observe some very undesirable side effects of the medicines on the patients; thus the study of the effects of a drug on the textures, organs, and the structures of the body is as valuable as the discovery of that drug itself. One of the most common medicines for the patients with mental problems is the class of Selective Serotonin Reuptake Inhibitors (SSRIs) among which the fluoxetine is the most commonly used drug. Being used daily with the dosage of 10 or 20 mg/kl per day, this drug has been effective leading to the reduction of the depression, anxiety, fear, and obsession. The studies on the effects of the fluoxetine on the hormones, blood components, sexual behaviors, period pains, diabetes, changes of the ions, and the weight of the body have offered interesting results for the researchers. These findings have resulted in some suggestions for those people who use fluoxetine [5]. Such suggestions and advices aim to decrease the risks of the subjected medicine. It is necessary for the patients in general and cardiovascular and diabetes patients in particular to be aware of the effects and consequences of it. In this research we have tried to study the effects of the fluoxetine usage on the testosterone hormone of the men and its relationship with the duration of the drug usage and its subsequent changes of the testosterone.

2. LITERATURE REVIEW

2.1. Fluoxetine

Fluoxetine is anantidepressant of the selective serotonin reuptake inhibitors (SSRI) class. This medicine is prescribed for the reduction of the symptoms of the major depression, obsessive-compulsive disorder, bulimia nervosa and panic disorder, dysautonomia, postpartum depression, and premature ejaculation. Moreover, it is used in treating panic, fibromyalgia, trichotillomania, etc. Moreover, fluoxetine is used for the treatment of bulimia nervosa, premenstrual dysphoricdisorder, agitated depression and bipolar disorder depression. SSRIs in general and fluoxetine in particular are used in treating the autistic symptoms that is usually faces higher than 7 years old children [1, 7]. Fluoxetine was first documented in 1974 by scientists from Eli Lilly and Company.[1] It was presented to the U.S. Food and Drug Administration in February 1977, with Eli Lilly receiving final approval to market the drug in December 1987.. Despite of the introduction of new medicines in this class, fluoxetine is still a popular drug so that more than 22 million fluoxetine prescriptions were issued in the United States in 2007 [17, 31].

Since the half- life of fluoxetine is long (it longs 4 to 6 days to exit from the body) and so, it increases the possibility of medicine intervention even after leaving the drug. On the other hand, this long half- life of the drug minimizes the possibility of medicine post- withdrawal syndrome [2].

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Table 1. Antidepressant Drugs of SSRI class		
Class	**Drug Trademark**	**Drug Name**
SSRI	Prozac	Fluoxtine
	Seroxat	Paroxetine
	Cipramil	Citalopram
	Lustral	Sertraline

2.1.1. Effectiveness way of the drug

Fluoxetine shows its effects in the neurotransmitters and chemicals that do the communication in the central nervous system, including serotonin that is secreted in the central nervous system. After being spread in the inter-nervous space, serotonin is reuptake by the nervous system and participates in the next activities of the nervous system. The reuptake action is controlled by the presence of fluoxetine. Many researchers believe that the imbalance between the nervous transmitters will lead to the depression. Fluoxetine prevents serotonin reuptake and thus prevents the emergence of depression symptoms [1]. Fluoxetine controls the chemicals and supports the performance of the brain to help reducing the depression, stress, anxiety, and muscle strain. Moreover, fluoxetine prevents the over- aggregation of the electrical energy in the brain and controls hyperactivity [16, 28].

Fluoxetine helps reuptaking the serotonin and hence, the scale of the serotonin increases in the brain. Depression occurs when the scale of serotonin is reduced in the brain. Thus the possible action of the fluoxetine is that it increases the level of serotonin in the brain and restores the normal performance of the brain regions [28]. The duration of the treatment depends on the mental situation of the patient and his/ her family, but the common antidepressant drugs alone are effective in 60 to 75% of the treatment. It usually takes 6 months to reduce the symptoms of the depression, anxiety, or panic in the patient [29]. Besides, fluoxetine is used for the treatment of the premature ejaculation and masturbation with the doctor's prescription [30].

2.1.2. Adverse effects of the fluoxetine

Sexual dysfunction, increase of the tendency to suicide, premature birth, and preterm labor are all among the adverse effects with fluoxetine [24]. In case of occurrence of each of the following rare symptoms the patient has to leave using fluoxetine immediately: Fever, chills, muscle or joint pain, difficulty in breathing, seizures, and low blood sugar symptoms. Besides, the following symptoms may occur but their risks are lower: Agitation, anxiety, drowsiness, dry mouth, nausea, diarrhea, fast or irregular heartbeat, increased sweating, feeling of warmth or heat, flushing or redness of the skin, increased appetite, stomach cramps, abdominal pain or bloating, menstrual problems and insomnia [16, 19]. There are many drugs that increase the possibility of osteoporosis among which one can refer to fluoxetine, paroxetine, and sertraline [20]. Regarding the mentioned effects, once more this drug was approved by FDA in 2003 for the treatment of the bipolar depression [17]. Through increasing the level of the neural transmitters of appetite reducers such as norepinephrine, serotonin and dopamine, the fluoxetine leads to the loss of appetite and thus to the loss of weight [18, 20].

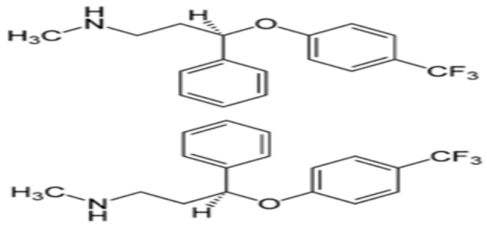

Figure 1. Molecular structure of the fluoxetine

2.2. Testosterone

Testosterone is one of the sexual steroid hormones from the androgen group secreted in testicles and its main constructing component is the cholesterol. The production of the testosterone begins in the eighth fetal week and its secretion is controlled by another hormone, namely LE that is secreted in the anterior pituitary cells.

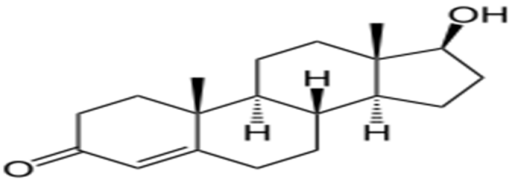

Figure 2. Molecular structure of the testosterone

Testosterone is produced in women as well, but in average, the body of men produces testosterone 20 t0 40 times more than the women [11, 12]. In fetal stage, testosterone forms and develops the penis and scrotum and

cause the formation of the constructs that are involved in the sperm production. The production of testosterone is increased at the time of sexual maturation and it is the main responsible for physical changes of the body. The growth of testicle, the growth of body hairs, the growth of muscles and bones, and the sexual maturation and bass voice are all among these changes. Testosterone and Dihydrotestostetone (DHT) are the main male hormones in the blood. The amount of the testosterone is more than dihydrotestosterone, but the testosterone is changed to the dihydrotestosterone after affecting the targeted texture. To be effective in the targeted texture and preventing the reduction of its own effect, testosterone combines to some proteins that are made in the liver and then, after being transmitted to the targeted organs, it combines to the available transmitters there and then passes the cell walls to make its effects [13].

Different factors cause the reduction of the testosterone in men. One of the most common reasons of this reduction is the aging. Among the other factors one can refer to the smoking, alcohol, some medicines, radiotherapy, heat and using hot bathes and saunas, diabetes, surgical removal of the testis, testicular tumors, liver tumors, varicocele, and pituitary tumors. The sexual dysfunction is one of the most common symptoms of the reduction of testosterone. Other symptoms include depression, changes in the ability of detecting persons, decreased energy, decreased libido, decreased mobility, aggression, lack of concentration, muscle pain, hot flashes, andinsomnia after eating [15].

2.3. Reviewing previous studies

Rabkin, et al (2004) treated 123 HIV+ men with testosterone (400 mg/kl, twice a week) and with fluoxetine (60 mg/kl per day) for 8 weeks. Their results showed that the fluoxetine (54%), testosterone (47%) and placebo (44%) have been effective on the treatment of the fatigue and depression of the AIDS patients. This findings show that although testosterone is a good option for the treatment of fatigue and depression disorders, but fluoxetine is the best option for treating the depression [26].

Bel, et al, (2006) studied 14 depressed patients with health disorder, and besides, 4 persons were studied as the control group. The patients first used 10 mg/kl of fluoxetine daily for seven days, and then they used 20 mg/kl of fluoxetine for 23 days. The results of this research showed that there is no significant relationship between the levels of testosterone with the usage level of fluoxetine [27].

JhimlySarkra, et al, (2008) injected 10 mg/kl fluoxetine to the female healthy or decease- carrying mice in a daily cycle for 10 days. Then they put the fluoxetine- cured carrying mice in a room and male light- exposed mice in another room, and let the female cured mice come to the cage of the male mice. Other female mice (healthy ones) were maintained in a separate room. The researchers found that the fluoxetine rapidly disrupt the pairing period so that 50% of the mice became sterile at the first 5 days. These findings show that the effects of fluoxetine on the sexual dysfunction of the females can be a result of the effects of the drugs and the disruptions in the axis of the hypothalamus and pituitaryendocrine glands of[6, 7, and 8].

Continuing the work of Jhimly Sarkra and his colleagues, Navin Maswood, et al, (2008) conducted a similar study on the healthy mice. This research intended to know if the treatment with fluoxetine affects the regular fertilization of normal mice (Sprague Dawley). In this regard, first they inject fluoxetine for a period of 24 days. After 11 to 14 daily treatment with fluoxetine, 40% of the mice showed a temporary disruption in their fertilization duration and their sexual arousal. Thus the effects of fluoxetine on the pairing period and sexual fertilization and the situation of the female Sprague Dawley mice were appeared and these findings confirms the probable relationship between the effects of the fluoxetine on the sexual activity and the disorders of the neurons [8].

Jhimly Sarkra, et al, (2009) studied the effects of the fluoxetine on the sexual conditions of the female mice. They conducted ovariectomy on the mice that were treated for regular 9 days with 10 mg/kl of fluoxetine. The understanding and acceptance sexual power was appeared for 30 minutes after the 10^{th} day injection of 10 or 20 mg/kl of fluoxetine with deionized distilled water. The fluoxetine (10 or 20 mg/ kl) significantly reduced the frequency of the curvature of the spine and at a lower level, it reduced the spent time for the male mice [6, 7, and 8].

John Curry, et al, (2010) studied 86 men and 110 women who were suffered from the depression since their adolescence. They studied these subjects for 12 weeks. These people were using 20 mg of fluoxetine in a daily term. The results of this research showed that in the subjects who have been cured, the sexual hormones (testosterone in men and estrogen and progesterone in women) had been reduced, and in 96% of the cases, these changes were accompanied with the return of the depression, while such a return has been higher in women [22].

Graham J. Emslie, et al, (2010) tested 334 participants who were at the aging range of 12 to 18 years old and who were depressed at a medium to severe level. They studied these subjects for 6 months and treated them with selective serotonin reuptake inhibitors (SSRIs) including fluoxetine. The group with mild depression was cured at the end of the 3^{rd} month, but the group with more severe depression showed improvement just after the end of the 6^{th} month. The studies on the testosterone level of the blood serum of these subjects at the time of their maturation showed that their level of testosterone production had been reduced at the time of fluoxetine usage [21].

3. METHODOLOGY OF THE TEST

Type of this study is application and will help many depressed patients. The testosterone hormone Measured by ELIZA[1] method. we had to select the samples whose duration of using fluoxetine can be studied. In referring to the Shiraz Psychiatric Hospital and the Hafez Mental Clinic of Shiraz, 42 men were identified at the age ranged from 22 to 48 years old who used fluoxetine. . Then 30 persons out of these patients who had used 20 mg of fluoxetine per day were selected as the samples. These patients were classified in two groups:

- First group: those patients whose use of the fluoxetine had been less than 6 months (15 patients)
- Second group: those patients whose use of the fluoxetine had been more than 6 months (15 patients)
- third group had been selected from the men who had no use of fluoxetine and their level of the blood fats and sexual hormones was normal. (Group Control ,15 patients)

After providing the test samples, we added 25 μl (equal to 0.25 ml) of control serum to each of the samples and then, the amount of 0.2 of the enzyme conjugate was added to each of the tubes as well/ then the contents of the tube were mixed for 10 seconds and were put in the room with the normal temperature for one hour without any cap. Note that the mixture process is very important and if you neglect this step, the results of the test will be negatively affected. After passing one hour, the washing step was done. In this step, each of the samples was washed three times with 40 X wash solution. After the washing, the tubes were carefully dried so that the result can be acceptable. Then 0.2 of the substrate solution was added to each of the samples and they were put in darkness for 15 minutes. And then, 0.1 of the stop solution was added to each of the samples and they were put in Human apparatus. After 10 minutes, the OD amount of each sample was read. OD amount shows the scale of absorbing the light and it is approximately 450±10 nanometer. The resulted values were compared to the special table and the scale of the hormone was extracted considering the scale of the light absorbance. The scale of the hormone in normal conditions was something between 2 to 6.9 for men and 0.26 to 1.22 for women.

4. ANALYSIS OF THE OBTAINED DATA

We took 2 to 5 ml of blood from each of the subjects, and after doing the centrifuge process, we separated the serum from the blood cells. Then the amount of testosterone hormone was measured. Besides, we tested the amount of testosterone of the blood serum of the third group who had no use of fluoxetine and their amount of the sexual hormones was normal.

Table 2. The mean of the testosterone concentration in three test groups (mg/ ml)

Duncan [a]			
		Subset for alpha = 0.05	
Studied groups	N	1	2
More than 6 months	15	4.44	
Less than 6 months	15	4.94	4.97
Control	15		5.26
Sig.		0.061	0.308

Means for groups in homogeneous subsets are displayed.
a. Uses Harmonic Mean Sample Size = 15.000.
* Explain 1 and 2 column: In the Tukey and Duncan tests, homogeneous subsets of means which do not differ are placed in one subgroup.

The obtained values were analyzed using SPSS[2] software and ANOVA statistical test. The latest diagram show that in the group who used fluoxetine for less than 6 months, there was no sensible change in the mean of testosterone concentration mean in comparison to the control group, and the observable changes are not statistically significant ($p>0.05$); but in the group who used fluoxetine for more than 6 months, more changes can be observed than the first group and the control group, these changes are statistically significant ($p<0.05$)

[1] - Shenzhen Lvshiyuan Biotechnology Co.
[2] - version of SPSS: 18

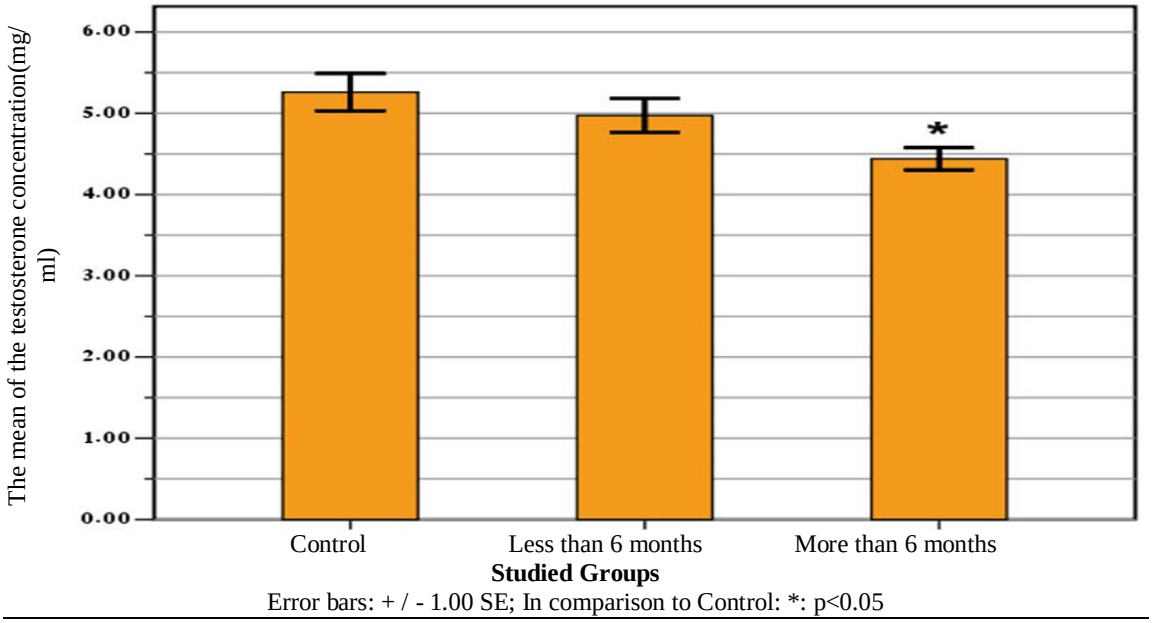

Figure 3. The comparison of the effect of usage duration of fluoxetine (20 mg per day) on the mean of the concentration of testosterone hormone

5. CONCLUSION

Regarding figure 3, the use of the fluoxetine did not lead to a sensible change of the testosterone concentration in the group who had used fluoxetine for less than 6 months in comparison to the control group, and the trivial changes were not statistically significant. But the use of fluoxetine for longer times (more than 6 months) leads to more sensible changes and shows that the use of fluoxetine and the longer duration of such a use will cause the reduction of the available testosterone level in the blood serum of the patients. According to the previous studies, the use of this drug affects the sexual behaviors of the animals (Narvin Maswood, et al, 2008; J. Sarkra, et al, 2009; and J. Danken, et al, 1997). The results of this research for the first group is compatible to the researches of Bell, et al, (2006) who had tested 14 depressed patients with health disorder, and showed that there is no significant relationship between the use of fluoxetine and the available testosterone level in the blood serum; although the results of the Bell, et al, is not consistent with the findings of this research for the second group. The reason of such inconsistency can be the duration of the drug use, because such duration was 1 month (4 weeks) in Bell's research but in the case of our second group, the mentioned duration was more than 6 months. Moreover, the results of this study are consistent with the tests conducted by John Curry, et al, (2010). They studied the sexual hormones of the depressed men and women and concluded that the use of fluoxetine reduces the sexual hormone (i.e. Testosterone in men and estrogen and progesterone in women). Additionally, the results of our research are consistent with the researches of Graham J. Emslie, et al, (2010). These researches had tested 334 participants who were at the aging range of 12 to 18 years old and who were depressed at a medium to severe level. They studied these subjects for 6 months and treated them with selective serotonin reuptake inhibitors (SSRIs) including fluoxetine. The group with mild depression was cured at the end of the 3rd month, but the group with more severe depression showed improvement just after the end of the 6th month. The studies on the testosterone level of the blood serum of these subjects at the time of their maturation showed that their level of testosterone production had been reduced at the time of fluoxetine usage. In sum, according to the results of our research, the time- dependent use of fluoxetine is effective on the sexual hormone, and more sensible changes will be observed on this factor with the extension of the time of using this medicine.

REFERENCES

1. Mozhdehi, Homayoun, Basic and Clinical Farmacology, Tehran, Arjmand Publications, 1998. [in Persian]
2. Motevallian, Asqar, Basic Farmocology, Tehran University Press, 2001. [in Persian]
3. Mokhtari, Mokhtar;Shariati, Mehrdad;&Tavakkoli, Farnaz, The Effects of the Fluoxamine on the Testosterone Hormones, LH, FSH, and the Changes of the Testis in Rats, Feiz Scientific Quarterly, Vol. 10, Winter 2006, pp. 31- 36. [in Persian]

4. Arjmand, Mohsen; Jahangiri, Bijan; and Fathollahi, Alireza, Basic and Clinical Farmacology, Arjmand Publications, 2001. [in Persian]
5. LorzadehmNahid; Kazemi, Sirous; MomenNasab, Marzieh; Lorzadeh, Mina; &Safa, Mitra, The Effects of Fluoxetine Daily Prescription in Treating the Premenstrual Syndrome, Medical Quarterly of Khorramabad University, No. 12, 2006. [in Persian]
6. JimlySarkar, Cindy Hiegel, NavinMaswood, and Lynda Uphouse, Daily Male Exposure Attenuates Estrous Cycle Disruption By Fluoxetine , Department of Biology, Texas Womanś University, Denton, Behav Brain Res. 2008,16;189: 83-91.
7. J. Sarkar, C. Hiegel, G. E. Ginis, E. Hilbun, and L. Uphouse, Subchronic Treatment With Fluoxetine Attenuates Effects of Acute Fluoxetine On Female Rat Sexual Behavior, Brain Res. 2008 January 23;1190:56-64.
8. NavinMaswood, JhimlySarkar, and Lynda Uphouse, Modest Effects Of Repeated Fluoxetine On EsrousCyclicity And Sexual Behavior In Sprague Dawley Female Rats, Brain Res. 2008 December 15;1245:52-60.
9. Maxine Norcross, MathurPoonam, Abigail J. Enoch, Rose-Marie Karlsson, Jonathan L. Brigman, Heather, A. Cameron, Judith Harvey-White, and Andrew Holmes, Effects of adolescent Fluoxetine treatment on fear, anxiety- or stress-related bebaviors in C57BL/6J or BALB/cJ mice, Psychopharmacology (Berl). 2008 October; 200(3): 413-424.
10. Wilson,K., Mottram,P., Sivanranthan,A. &Nightingale,A. (2001). Antidepressant versus placebo for depressed elderly. *Cochrane Database of Systematic Reviews* (2):CD000561.
11. Reed WL, Clark ME, Parker PG, Raouf SA, Arguedas N, Monk DS, Snajdr E, Nolan V, Ketterson ED (May 2006). "Physiological effects on demography: a long-term experimental study of testosterone's effects on fitness". Am. Nat. 167 (5): 667–83. ScienceDaily.
12. Bassil N, Alkaade S, Morley JE (June 2009). "The benefits and risks of testosterone replacement therapy: a review". TherClin Risk Manag 5 (3): 427–48.
13. Dabbs M, Dabbs JM (2000). *Heroes, rogues, and lovers*: testosterone and behavior. New York: McGraw-Hill.
14. Corbier P, Edwards DA, Roffi J (1992). "The neonatal testosterone surge: a comparative study". *Arch IntPhysiolBiochimBiophys*100 (2): 127–31.
15. Ajayi AA, Mathur R, Halushka PV (June 1995). "Testosterone increases human platelet thromboxane A2 receptor density and aggregation responses". *Circulation*91 (11): 2742–7.
16. Hirschfeld RM. Efficacy SSRIs and newer antidepressants in severe depression: comparison with TCAs. J Clin Psychiatry 60:326-335, 1999.
17. Wong DT, Bymaster FP and Engelman EA. Prozac (Fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: Twenty years since its first publication. Life Sci 57: 411-441, 1995.
18. Fava M, Judge R, Hoog SL, Nilsson ME, Koke SC. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. *J Clin Psychiatry*. 2000;61:863-867.
19. Raeder MB, Bjelland I, Emil Vollset S, Steen VM. Obesity, dyslipidemia, and diabetes with selective serotonin reuptake inhibitors: the Hordaland Health Study. *J Clin Psychiatry*. 2006 Dec;67:1974-1982.
20. Mohammadi M. R. ,Momeni F., Torkzaban R., Ghaely P., The Effects of Fluoxetine and Clomipramine on Blood Sugar, Cholesterol, and Weight of Obsessive-Compulsive Children and Adolescents. Iranian journal of psychaitry and clinical psychology, 2003; 8 (3) :12-19.
21. Graham J. Emslie, Taryn Mayes, Giovanna Porta, Benedetto Vitiello, Greg Clarke, Karen Dineen Wagner, Joan Rosenbaum Asarnow, Anthony Spirito, Boris Birmaher, Neal Ryan, Betsy Kennard, Lynn DeBar, James McCracken, Michael Strober, Matthew Onorato, Jamie Zelazny, Marty Keller, SatishIyengar, and David Brent. Treatment of Resistant Depression in Adolescents (TORDIA): Week 24 Outcomes. *American Journal of Psychiatry*, 2010.
22. John Curry; Susan Silva; Paul Rohde; Golda Ginsburg; Christopher Kratochvil; Anne Simons; Jerry Kirchner; Diane May; Betsy Kennard; Taryn Mayes; Norah Feeny; Anne Marie Albano; Sarah Lavanier; Mark Reinecke; Rachel Jacobs; Emily Becker-Weidman; Elizabeth Weller; Graham Emslie; John Walkup; Elizabeth Kastelic; Barbara Burns; Karen Wells; John March. Recovery and Recurrence Following Treatment for Adolescent Major Depression. Archives of General Psychiatry, 2010.

23. Hozumi Y, Kawano M, Miyata M: Severe hypertriglyceridemia caused by tamoxifen-treatment after breast cancer surgery. Endocr J 1997; 44:745-749.
24. Teitelbaum M: Severe and moderate hypertriglyceridemia secondary to citalopram and fluoxetine. Psychosomatics 2000; 41:448-449.
25. Killcross S, Robbins TW, Everitt BJ (1997). Different types of fear-conditioned behaviour mediated by separate nuclei within amygdala. Nature 388: 377–380.
26. Rabkin JG, Wagner GJ, McElhiney MC, Rabkin R, Lin SH.Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS: a placebo-controlled trial.J ClinPsychopharmacol. 2004 Aug; 24(4):379-385.
27. Bell S, Shipman M, Bystritsky A, Haifley T. Fluoxetine treatment and testosterone levels.Ann Clin Psychiatry. 2006 Jan-Mar;18(1):19-22.
28. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med.* 2005;142:532-546.
29. Jay W. Marks, MDMedicaland Pharmacy.2005.(22): 258-266.
30. Barbui,C., Hotopf,M. &Garattini,S. (2002). Fluoxetine dose and outcome in antidepressant drug trials. European Journal of Clinical Pharmacology 58(6):379-386.
31. Melander,H., hlqvist-Rastad,J., Meijer,G. &Beermann,B. (2003). Evidence b(i)ased medicine--selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *British Medical Journal*326(7400):1171-1173.