

Fluoxetine Treatment and Testosterone Levels

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Background. Two published case studies have reported SRI/SNRI-associated low testosterone levels. Apathy and low testosterone, observed during venlafaxine treatment in one report, both resolved upon venlafaxine discontinuation. No studies have investigated the effect of chronic SRI treatment on human testosterone levels.

As decreased testosterone has several negative health effects, we conducted a pilot study investigating the effect of fluoxetine treatment on testosterone levels.

Methods. Fourteen depressive disorder patients in good health ($BDI \geq 15$) were studied. In addition, 4 non-depressed patients were studied. Testosterone levels were drawn, and an apathy questionnaire (under development, not yet validated) was administered at intake.

Fluoxetine was provided (10 mg/day for 7 days then 20 mg/day). To measure outcome, a follow-up testosterone level was drawn after 1 month's treatment.

Results. Eleven depressed, and 3 non-depressed, patients completed the study. While there were large differences — both increases and decreases — in some individuals' testosterone levels after fluoxetine treatment, for the study population as a whole, there was no relationship (depressed patients, $p = 0.4$; non-depressed patients, $p \approx 0.3$) between fluoxetine treatment and testosterone levels.

In patients with $BDI \geq 20$, testosterone levels at intake were highly associated with intake apathy levels ($p = 0.0033$).

Conclusions. Further, larger, studies correlating changes in testosterone levels during SRI treatment with treatment response, apathy levels and possibly sexual dysfunction seem indicated.

Keywords Testosterone, Fluoxetine, Serotonin reuptake inhibitors, Apathy, Antidepressive agents

INTRODUCTION

In a previously published case study, Bell (1) reported the case of a 26-year-old patient who experienced severe apathy, decreased libido and emotional blunting, as well as control of paraphilic urges during treatment with venlafaxine XR. The

patient's testosterone level was drawn and found to be below normal (153 ng/dl: reference 270–970 ng/dl). The medication was discontinued at the patient's insistence. Apathy/emotional blunting resolved and libido increased, and the testosterone level two weeks after drug discontinuation increased to 371 ng/dl, a 142% increase.

Another case report (2) found a significant decrease in testosterone levels after chronic high dose — 60 mg/day — fluoxetine treatment. Both cases involved patients with paraphilia.

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Although it would seem prudent to know if SRI medications affect testosterone levels — or if their effect on sexual function is testosterone mediated — this area has not been well studied.

Patients commonly ask physicians, “Is it safe for me to take this medication long term?” Because low testosterone levels are associated with negative health effects, including bone loss (3,4), we undertook a pilot study to investigate if chronic SRI treatment is associated with decreased testosterone levels. We also compared intake testosterone levels to intake apathy/emotional blunting levels as measured by a self-administered, five-question rating scale currently under development by the authors.

Although the effect of testosterone on mood symptoms has been studied, and although there is known interaction between testosterone and serotonin, there has been little research to determine if chronic SSRI/SNRI treatment affects testosterone levels. In an animal study, fluoxetine was not found to affect testosterone levels in rats (5). One study (6), which has not been replicated, reported the treatment of neonatal rats with clomipramine for a 13-day period. Four months later the treated rats, as compared to non-treated controls, were found to have decreased spontaneous sexual activity and a decreased testosterone response upon exposure to an estrogenized stimulus female.

In human studies, a study utilizing a single dose of 80 mg fluoxetine in non-depressed controls found no effect on testosterone levels (7). The serotonin depleting agent fenfluramine increased testosterone levels in hypogonadotropic hypogonadal males (8). In another study, (+) – oxaprotiline (a noradrenalin uptake inhibitor) was not found to affect the secretion of testosterone (9).

Patients in another study who received three months of treatment with clomipramine were reported to have testosterone levels within the normal range. Pre-treatment levels were not obtained (10). Trimipramine and imipramine, which have mild effects on serotonin, were not found to affect significant changes in testosterone levels in one four-week study (11).

METHODS

The participants were recruited from the outpatient practice of one of the authors (DSB). The study was approved by the Human Subjects Committee of The Los Angeles County Department of Mental Health, and informed consent was obtained from all subjects. Individuals with concurrent medical illness or who were taking any prescribed medications, psychiatric or nonpsychiatric, were excluded, as were individuals who had received psychiatric medication during the 30 days prior to study intake. Also excluded were patients who reported taking dehydroepiandrosterone (DHEA), over-the-counter herbal preparations, St. John’s Wort, or S-adenosylmethionine (SAM-E) in the 30 days prior to study intake. Exclusion criteria also included assessed risk of suicide; substance abuse in the 30 days prior to study intake; substance dependence in the six months prior to study intake; or the presence of schizophrenia, schizoaffective disorder or bipolar disorder.

Fourteen depressive disorder subjects (Beck Depression Inventory ≥ 15) were studied. In addition, four non-depressed (anxiety disorder) subjects were also studied. Testosterone levels were drawn and an apathy/emotional blunting questionnaire (under development, see Table 1) was administered at intake. Brand-name fluoxetine was provided at a dosage of 10 mg/day for seven days, followed by 20 mg/day for the remainder of the study. After one month of fluoxetine treatment, a follow-up testosterone level was drawn and the BDI was repeated. Because testosterone levels show diurnal variation, each participant’s testosterone level was drawn within one hour — in most cases within 15 minutes — of the time of day of the intake blood draw. Total testosterone levels were measured by radioimmunoassay (12).

Pre- and post-treatment groups were compared used paired sample t-test. For apathy levels versus testosterone, we fit a linear regression model (straight line).

RESULTS

The changes in testosterone levels in individual patients involved increases of up to 109% in some patients, and decreases of up to 39% in others (see Table 2). For the study population taken as a whole, there was no change in pre- versus post-treatment testosterone levels (depressed participants $p = 0.4$; non-depressed participants $p \approx 0.3$).

Testosterone levels at intake were highly inversely associated ($p = 0.0033$) with apathy/emotional blunting levels, as measured by the questionnaire, in moderately to severely depressed indi-

Table 1

After reading each statement carefully, please circle the number corresponding to the answer which best describes your experience during the past week, including today. Please be sure to consider each statement carefully before making your choice.

1. I feel “middle of the road” on everything...nothing gets me very upset:

0	1	2	3	4	5
strongly disagree					strongly agree
2. Lately, I don’t feel the same urgency/ “push” towards achieving my goals – my goals don’t mean as much to me as they used to:

0	1	2	3	4	5
strongly disagree					strongly agree
3. I feel “disconnected” from my feelings – if things happen to me that I used to feel sad or happy about, I don’t feel sad or happy about them now:

0	1	2	3	4	5
strongly disagree					strongly agree
4. Lately, I feel that I can do things that violate my moral code without it bothering me as much as it usually would:

0	1	2	3	4	5
strongly disagree					strongly agree
5. Lately, I notice that things that I used to be enthusiastic about – things that used to get me excited or stimulated – no longer cause me to feel enthusiastic, excited, or stimulated:

0	1	2	3	4	5
strongly disagree					strongly agree

Scale © 2003 D. Stewart Bell, M. D.

Table 2 Data for Testosterone/Fluoxetine/Apathy Study

Patient	Age (yrs.)	Ethn.	First Visit Testos. Level	1 mo. Visit Testos. Level	Change/% Change	Intake BDI	1 mo. BDI	Intake Apathy
(1)	20	Cau.	10/16/00 @ 10:43 am 346 ng/dL	11/20/00 @ 11:17 am 713 ng/dL	↑ 376 ng/dL ↑ 109%	7	6	11
(2)	21	Cau.	8/17/00 @ 10:09 am 413 ng/dL	9/14/00 @ 11:05 am 476 ng/dL	↑ 63 ng/dL ↑ 15%	15	4	10
(3)	38	Hispanic	4/28/00 @ 3:00 pm 240 ng/dL	5/26/00 @ 3:05 pm 256 ng/dL	↑ 16 ng/dL ↑ 7%	13	9	
(4)	26	Cau.	1/29/01 @ 12:28 pm 587 ng/dL	2/26/01 @ 12:46 pm 655 ng/dL	↑ 68 ng/dL ↑ 12%	17	2	9
(5)	21	Cau.	2/6/01 @ 2:15 pm 534 ng/dL	3/6/01 @ 1:49 pm 651 ng/dL	↑ 117 ng/dL ↑ 22%	24	10	14
(6)	20	Cau.	3/20/01 @ 4:48 pm 494 ng/dL	4/19/01 @ 4:18 pm 440 ng/dL	↓ 54 ng/dL ↓ 11%	26	17	15
(7)	27	Cau.	3/23/01 @ 4:23 pm 528 ng/dL	(withdrew from study)		8		7
(8)	20	Cau.	4/13/01 @ 5:13 pm 448 ng/dL	(withdrew from study)		33		16
(9)	20	Cau.	4/26/01 @ 4:00 pm 478 ng/dL	5/24/01 @ 3:30 pm 292 ng/dL	↓ 186 ng/dL ↓ 39%	15	16	10
(10)	19	Cau.	4/30/01 @ 10:02 am 400 ng/dL	5/24/01 @ 10:52 am 490 ng/dL	↑ 90 ng/dL ↑ 23%	9	6	5
(11)	20	Cau.	6/25/01 @ 3:37 pm 398 ng/dL	7/23/01 @ 3:39 pm 413 ng/dL	↑ 15 ng/dL ↑ 4%	37	29	18
(12)	20	Cau.	7/3/01 @ 1:42 pm 398 ng/dL	7/31/01 @ 1:55 pm 570 ng/dL	↑ 172 ng/dL ↑ 43%	19	not done	10
(13)	21	Cau.	7/17/01 @ 3:55 pm 498 ng/dL	8/14/01 @ 3:41 pm 518 ng/dL	↑ 20 ng/dL ↑ 4%	18	10	not done
(14)	20	Cau.	7/26/01 @ 1:55 pm 405 ng/dL	(withdrew from study)		25		17
(15)	19	Cau.	8/10/01 @ 3:42 pm 364 ng/dL	9/6/01 @ 3:53 pm 437 ng/dL	↑ 73 ng/dL ↑ 20%	19	15	13
(16)	20	Cau.	9/10/01 @ 4:01 pm 457 ng/dL	10/8/01 @ 4:11 pm 404 ng/dL	↓ 53 ng/dL ↓ 12%	17	8	11
(17)	29	Hispanic	5/15/02 @ 10:43 am 244 ng/dL	(withdrew from study)		34		not done
(18)	20	Cau.	10/17/02 @ 2:40 pm 470 ng/dL	11/19/02 @ 2:28 pm 376 ng/dL	↓ 94 ng/dL ↓ 20%	21	6	not done

viduals ($BDI \geq 20$) (Figure 1), but not in individuals with less serious depression (Figure 2). For study completers, the mean BDI at baseline was 18.5 and the mean BDI after one month of treatment was 10.6. Using a paired sample T-test, $p = 0.000097$.

CONCLUSIONS

This study provided some indication that pre-treatment levels of apathy/emotional blunting, in moderately to severely depressed individuals, correlate with testosterone levels.

The study did not find an overall change in testosterone levels after four weeks of fluoxetine treatment in the 14 patient group taken as a whole. There were, however, large differences — both increases and decreases — in individual patients, but these changes for the group as a whole canceled each other out, resulting in no overall change.

It is possible that these individual increases or decreases in testosterone levels were random events, as testosterone release is pulsatile. It is also possible that they represent biological changes with medication, and that increases in testosterone correlate with recovery from depression during SRI treatment; whereas decreases in testosterone correlate with the development of apathy or sexual side effects during SRI treatment. Due to limited sample size, this could not be analyzed in our study, but could be evaluated with a larger study of several months duration that could evaluate testosterone levels pre- and post-SRI treatment and investigate any possible correlation between testosterone levels and treatment response or the development of side effects.

This was a pilot study with several limitations. The treatment period was for one month, not the several months' duration necessary for fluoxetine to reach steady state and its full effects to be seen. Only total — not free — testosterone levels were checked. Total testosterone consists of free (unbound) testosterone plus testosterone bound to testosterone binding globulin or

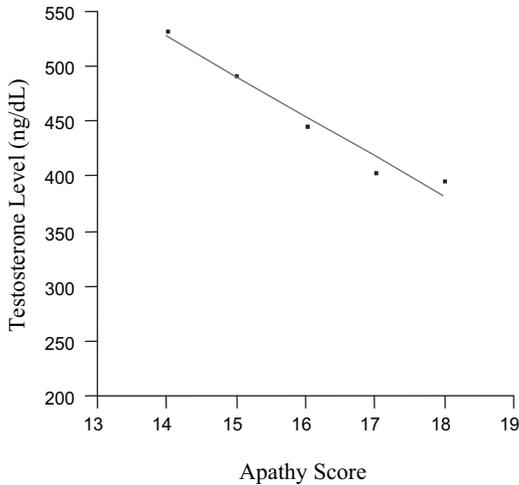


Figure 1 Intake Serum Testosterone Levels by Intake Apathy Score in Depressed Patients with Beck Depression Inventory (BDI) ≥ 20 .

Apathy score as measured by questionnaire; higher score represents higher level of apathy / emotional blunting. Apathy and testosterone levels strongly correlated ($p = 0.0033$).

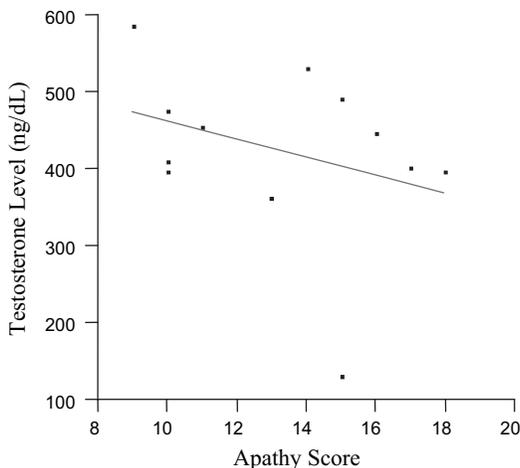


Figure 2 Intake Serum Testosterone Levels by Intake Apathy Score in Depressed Patients with Beck Depression Inventory (BDI) ≥ 15 .

Apathy score as measured by questionnaire; higher score represents higher level of apathy / emotional blunting. No significant correlation ($p = 0.3$) between testosterone levels and apathy.

to albumin or other proteins. Total testosterone levels are generally more reflective of the actual hormonal status in younger individuals such as in our study population, and less accurate in older individuals in which the increased levels of testosterone binding globulin that accompany aging give a falsely elevated indication of testosterone levels. Another reason that total testosterone levels were studied was because of their reliability and availability; free testosterone levels done by analogue assay are unreliable and the preferred dialysate method is not routinely available in commercial laboratories.

This study was of a very young (mean age 20.9 years) patient population. We do not know if our findings are applicable to an

older population. To find out would require a separate study, which would be more complex due to the confounding variables that exist in an older age group, that is, more organic illness and more use of prescribed medications which can affect testosterone levels.

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