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RESEARCH

Serum prolactin level in patients taking olanzapine

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Abstract

Introduction: Olanzapine is a commonly used antipsychotic. Prolactin elevation is a common adverse effect of anstipsychotics, and serum prolactin elevation is seen in about 30% patients treated with olanzapine. There are confounding results about dose dependency of olanzapine and prolactin elevation, and also the duration of treatment.

Method: Fifty six patients, 36 male and 20 female, who were taking olanzapine for any condition for more than a month at a constant dose were enrolled in the study. Patients' age, weight, body mass index (BMI), serum prolactin levels, and some biochemical values were recorded. Patients were taken from the review outpatient department (OPD) after due consent.

Results: Five each in male and female groups showed elevation of serum prolactin (estimated to be high if >20 ng/dl for males, and >25 ng/dl for females.) In females, the elevation was found at lesser dose of olanzapine (13 mg/day, in males 18 mg/day) and early in the treatment (2.4 months vs. 9.7 months in males). Males tended to show raised prolactin with higher doses of olanzapine (mean 18 mg/day). Females (26.31%) also showed higher prevalence of prolactin elevation compared to males (13.51%). No other parameter was found to modify the prolactin levels.

Conclusion: Olanzapine causes elevation of serum prolactin, though lesser degree than some other antipsychotics. Females are more prone to have raised serum prolactin with olanzapine compared to males. However, the elevation seems to be transient. Higher doses of olanzapine tend to cause elevation of serum prolactin. Serum prolactin estimation in patients taking olanzapine may be undertaken to maintain quality life, particularly in females.

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Introduction

Olanzapine is a second generation antipsychotic drug, and one of the widely used in treatment of schizophrenia and other psychotic disorders.[1] The broad line efficacy of olanzapine in management of bipolar disorder and its antidepressant effect, besides use in psychotic disorders makes olanzapine one of the most frequently and long-term used medication in psychiatric patients. Metabolic effects of olanzapine like weight gain, diabetes mellitus, and hyperlipidaemia are well known.

Elevation of serum prolactin is another adverse effect associated with antipsychotics. The risk of hyperprolactinaemia is less with olanzapine than other second generation antipsychotics like risperidone or first generation

antipsychotics like haloperidol.[2-4] But, the risk is more compared to quetiapine and clozapine.[5-8]

Elevation of serum prolactin is seen in about 30% patients treated with olanzapine. Various studies have reported varied figures. Some even going up to 68%.[1,9-12] It is also found to be dose dependent and changing with the duration of treatment; rising quickly within first two weeks and then reducing,[13] while being persistently high in some patients. Dose-response relationship is not consistently confirmed as reported by other studies.[7,14,15] Female gender is more susceptible to hyperprolactinaemia with olanzapine and other antipsychotics, and it may give rise to problems of menstrual irregularities, infertility, and in long duration can give rise to loss of bone mineral density.[16,17]

Hyperprolactinaemia is often superficially asymptomatic and usually does not affect patient's quality of life. However, persistent elevation of prolactin may give rise to sexual dysfunction, reduction in bone mineral density, menstrual disturbances, breast growth and galactorrhoea, suppression of hypothalamo-pituitary-gonadal axis, and a possible increase in the risk of breast carcinoma.[6,18] Prolactin rise with antipsychotics are found to be acute. Hahn and colleagues[19] reported that rise of prolactin with olanzapine is evident on a single dose.

Serum prolactin levels are interpreted as follows based on reports by Holt[20] (table 1):

Table 1. Normal and elevated serum prolactin levels

Normal	Women: 0-25 ng/ml Men: 0-20 ng/ml	(~0-530 mIU/L) (~0-424 mIU/L)
Need for re-test	25-118 ng/ml	(~530-2120 mIU/L)
Need for referral to rule out prolactinoma	>118 ng/ml	(>380 mIU/L)

The present study's goal was to observe the elevation of prolactin in patients taking olanzapine for more than a period of one month, and the association with other factors.

Aim and Method

This study is aimed at finding out the serum prolactin in patients treated with olanzapine and its relation to other factors: sex, weight, body mass index (BMI), dose and duration of olanzapine, etc.

The study included 56 patients from the psychiatry outpatient department (OPD) of Fakhruddin Ali Ahmed Medical College Hospital (FAAMCH), Barpeta, Assam, India. The patients were enrolled serially from the OPD when they came for review, and met the eligibility criteria and gave informed consent.

Eligibility criteria

1. Subjects, both male and female, between 18 and 65 years.
2. Taking regular olanzapine from 2.5 to 25 mg/day for a period of minimum one month, and at a constant dose for at least one month.
3. Add-on drugs allowed were: sodium valproate, divalproex sodium, lorazepam, clonazepam, and fluoxetine.
4. Pregnant and breast-feeding mothers were excluded.
5. Associated co-morbid conditions and drugs that may influence the serum prolactin level were excluded from the study. The conditions for exclusion were including but not limited to known cases of diabetes mellitus, organic brain disorders, known hormone related conditions, use of drugs like thyroxin.

Patients were seen as regular follow-up patients in the OPD, and if found suitable for inclusion in study, were explained about the study. When patient or their legal guardian gave written consent, the blood sample was taken. Blood was drawn only if the patient is awake for at least one hour and the last meal was taken at least one hour back. If any of the periods was less than one hour, then the blood was collected after waiting one hour. The serum was estimated for prolactin, random blood sugar (RBS), creatinine, aspartate transaminase (AST), alanine transaminase (ALT), and thyroid stimulating hormone (TSH).

Estimation of the blood chemistry was done in the Central Laboratory of FAAMCH. Serum prolactin and TSH were analysed by using AVIDA Centure CP, which is a two side sandwich immunoassay using direct chemiluminometric technology that use constant amount of two antibodies. RBS, serum creatinine, AST, and ALT were assayed using principles of drychemistry with Vitros 350 Autoanalyzer from Johnson & Johnson.

Any difficulty or symptoms mentioned by the patient during clinical evaluation was noted in the data-collection sheet. Patients' height, weight, sex, olanzapine related parameters were also recorded in the data-collection sheet. Prolactin levels were considered high when the value ex-

ceeded 20 ng/ml (424 mIU/L) for males and 25 ng/ml (530 mIU/L) for females.[16]

Results

A total number of 56 patients were included in the study, of which 37 (66.1%) were male and 19 (33.9%) were female. The study population's mean age was 31.59 years (standard deviation [SD]=11.05). The mean duration for which the population was getting olanzapine was 9.41 months (SD=7.00). Minimum duration was one month, and maximum duration was found to be two years and three months. Average dose of olanzapine for the study group was 11.27 mg/day (SD=5.33 mg). Mean serum level of prolactin was found to be 13.5 ng/ml (SD=9.34).

The variation in the parameters between males and females were estimated using unpaired t-test. Male and female group differed significantly in height, weight, serum creatinine values, and dose of olanzapine. Males and females had difference in weight and height; the differences found were expected, and so was the variation in serum creatinine value. However, no significant difference was found in BMI of the sexes. Of significant mention was the difference in dose of olanzapine. While males got average dose of 12.43 mg/day (SD=5.49), females were on 9.07 mg/day average dose (SD=4.34). t-test for olanzapine dose between males and females showed significant difference at P-value 0.017 (table 2).

A total of ten patients out of 56 (17.85%) showed elevated levels of prolactin. As per the criteria, upper limit of normal serum level of prolactin was considered at 20.0 ng/ml for men, and at 25.0 ng/ml for women. Five each of male and female groups showed increased serum level of prolactin. The percentages were 13.51% and 26.31% for males and females, respectively. Females showed a higher percentage of elevated serum levels and so, the difference was tested as a two by two contingency table. The Fisher's exact test for the table showed a P-value of 0.2813, and so the difference was not statistically significant. The relative risk of female sex being a risk factor was 0.5135 (95% confidence interval [CI]=0.169 to 1.558) (figure 1).

The group of elevated serum prolactin (ESP) (n=ten) were tested for difference in study parameters against the normal serum prolactin (NSP) group (n=46). In the ESP group, prolactin level was found to be around six years younger than the NSP group (ESP mean age=26.4±7.58, NSP mean age=32.77±11.43). Unpaired t-test was performed and the difference was found significant at P-value 0.043 (table 3).

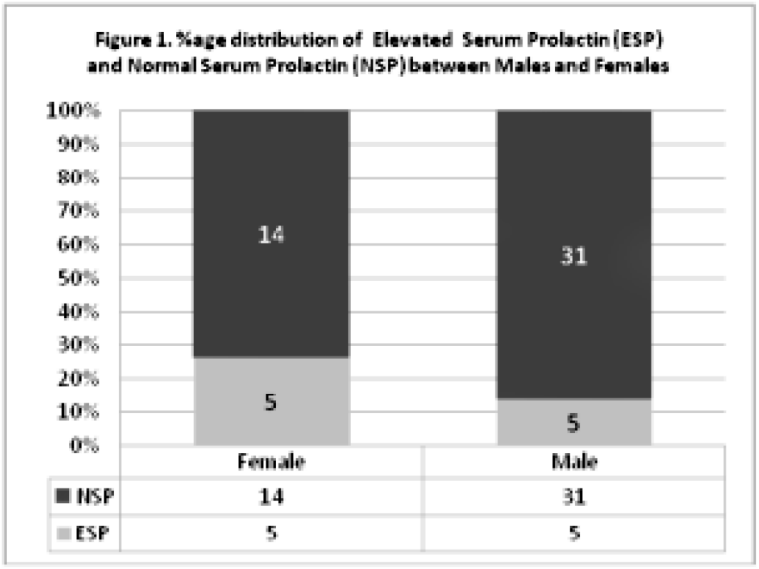
In the ESP group, the mean weight was found to be lower (52.9±9.07 kg) than the NSP group (63.15±11.93 kg) (P-value=0.007). Association with body weight was also reflected in BMIs of the group. ESP group had significantly lower BMI compared to NSP group (ESP group: 20.54±2.78, NSP group: 23.58±3.89; P-value: 0.009). There was no difference in the height of both the groups. Since height and weight were found significantly differing among males and females in the overall study population (table 2), so height, weight, and BMI

Table 2. Mean comparison between males and females across all study parameters

	Male (n=37) (Mean±SD)	Female (n=19) (Mean±SD)	Probability* (P-value)	Comment
Age (years)	33.05±11.59	28.89±9.69	0.167	No significant difference
Height (cm)	167.56±5.46	153.89±5.18	<0.0001	Significant difference, but expected
Weight (kg)	64.54±11.57	55.05±10.71	0.004	Significant difference, but expected
BMI	22.92±3.57	23.27±4.5	0.771	No significant difference
Olanzapine duration (months)	10.09±7.02	8.18±6.97	0.328	No significant difference
Olanzapine dose (mg/day)	12.43±5.49	9.07±4.34	0.017	Significant difference, males tend to get higher dosage of olanzapine
RBS (mg/dl)	121.97±63.41	114.55±27.93	0.554	No significant difference
Creatinine (mg/dl)	0.88±0.12	0.67±0.12	<0.001	Significant difference, expected.
TSH (µIU/ml)	2.45±1.24	3.2±1.94	0.141	No significant difference
AST (IU/L)	46.63±26.63	58.84±31.42	0.159	No significant difference
ALT (IU/L)	54.41±37.52	68.38±45.33	0.271	No significant difference
Prolactin (ng/ml)	12.35±5.55	17.45±12.69	0.067	No significant difference

**Unpaired t-test probability (two tailed, assuming SDs have equal variance)*

BMI=body mass index, RBS=random blood sugar, TSH=thyroid stimulating hormone, AST=aspartate aminotransferase, ALT=alanine aminotransferase, SD=standard deviation



were further tested within male and female groups (table 3).

Shown in table 4, when compared ESP male vs. NSP male, significant difference was seen in olanzapine dosage (ESP group: 18±4.47 mg/day, NSP group: 11.53±5.15 mg/day; P-value: 0.026). Comparison between ESP female and NSP female showed significant differences in the following parameters: BMI, duration of olanzapine intake, RBS, and serum creatinine level. The ESP female group had lower BMI (19.92±3.46) compared to NSP group BMI (24.46±4.30), lower RBS level (92.25±3.4 mg/dl) compared to NSP group's (120.92±28.65 mg/dl), and serum creatinine level (0.52±0.12) as compared to 0.71±0.08 in the NSP female group. These differences were probably explained by the finding that females with a shorter duration of olanzapine intake had higher serum prolactin levels. ESP female group had mean duration of 2.4 months (SD=3.13), while NSP female group's mean duration was 10.25 months (SD=6.76). This difference was significant at P-value of 0.003. Metabolic side effects of olanzapine like raised RBS level, weight gain etc. were increased with the increase in total duration of olanzapine intake. So, since the elevation of serum prolactin was found much earlier in females, it might be that during that short duration adverse events as glucose intolerance, weight gain, and increase in BMI was much less compared to the prolonged use of olanzapine. The fact that in male ESP group the elevation of serum proalctin was seen much later compared to the female ESP group probably explained lower BMI and RBS values in female ESP group. Mean duration of olanzapine use in male ESP group was 9.7±8.22 months, and in female ESP the same was 2.2±3.25 months. There was a difference of about seven months, but the difference was not statistically significant. ALT was another parameter which was significantly higher in NSP males (ESP group: 32.8±11.6 mg/dl, NSP group: 58.13±39.26 mg/dl; P-value: 0.009).

Tests were performed to see whether there was any significant difference among ESP male and female groups. Significant differences were noted in height and serum creatinine values (table 5). But, both these parameters were of

Table 3. Mean comparison between high and low prolactin groups

	ESP (n=10) (Mean±SD)	NSP (n=46) (Mean±SD)	Probability* (P-value)	Comment
Age (years)	26.4±7.58	32.77±11.43	0.043	Significant difference
Weight (kg)	52.9±9.07	63.15±11.93	0.007	Significant difference; low weight is found to associated with raised prolactin
BMI	20.54±2.78	23.58±3.89	0.009	Significant difference; low BMI is found to associated with raised prolactin
Olanzapine dose (mg/day)	15.5±4.97	10.33±4.98	0.01	Significant difference; high dose of olanzapine is found to associated with raised prolactin

** Unpaired t-test probability (two tailed, assuming SDs have unequal variance)*

*** Only statistically significant differences are shown*

ESP=elevated serumprolactin, NST=normal serum prolactin, SD=standard deviation, BMI=body mass index

Table 4. Mean comparison between ESP and NSP male & female groups

	Sex	ESP (m=5, f=5) (Mean±SD)	NSP (m=32, f=14) (Mean±SD)	Probability* (P-value)	Comment
BMI	M	21.16±2.11	23.19±3.69	0.113	Significant difference; low BMI is found to be associated with raised prolactin in females
	F	19.92±3.46	24.46±4.3	0.043	
Olanzapine duration (months)	M	9.7±8.22	10.15±6.96	0.91	Shorter duration was significantly associated with higher prolactin in females
	F	2.4±3.13	10.25±6.76	0.003	
Olanzapine dose (mg/day)	M	18±4.47	11.53±5.15	0.026	High dose of olanzapine is found to be associated with raised prolactin in males, but females did not show a significant difference
	F	13±4.47	7.67±3.46	0.053	
RBS (mg/dl)	M	108±21.38	124.22±67.76	0.306	Significant in females not in males
	F	92.25±3.4	120.92±28.65	0.002	
Creatinine (mg/dl)	M	0.9±0.12	0.87±0.12	0.717	Significant difference in females
	F	0.52±0.12	0.71±0.08	0.049	
ALT (IU/L)	M	32.8±11.6	58.13±39.26	0.009	Significant difference in males
	F	50.2±39.84	75.38±46.81	0.284	

** Unpaired t-test probability (two tailed, assuming SDs have unequal variance)*

ESP=elevated serum prolactin, NSP=normal serum prolactin, SD=standard deviation, BMI=body mass index, RBS=random blood sugar, ALT-alanine aminotransferase

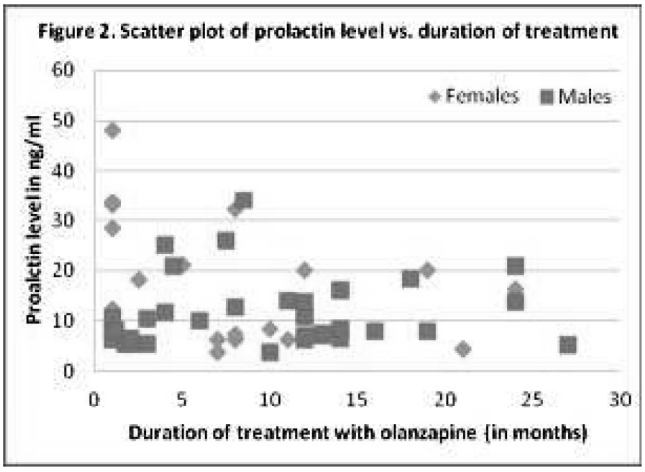
significant difference in the total study population also (table 2); hence, they were probably not modifying factors for difference in serum prolactin levels in male and female groups. Duration of olanzapine use was more in the ESP male group by seven months compared to the ESP female group (ESP male group: 9.7±8.22 months, ESP female group: 2.2±3.25 months; P-value: 0.113). The scatter plot in figure 2 shows the difference of treatment duration with olanzapine in relation to raised prolactin levels between males and females. NSP male and female groups were also subjected to mean comparison across various parameters, and significant changes were noted in height, weight, olanzapine dose, and serum creatinine level (table 5). All these differences were also present in the study population itself (table 1). So, these factors were general differences between male and female groups, and so were less likely to be modifying factors for difference of elevation serum prolactin in the sex groups.

Serum prolactin values were subjected to correlational statistics and none of the parameters were found to have significant correlation (table 6). All the parameters were also tested for correlation with duration of olanzapine treatment, and no correlation was found (table 6).

Discussion

The present study shows the overall percentage of elevated serum prolactin to be 17.85%. Earlier studies have shown raised prolactin up to 30%.[9,21-24] The less prevalence found in this study could be the result of taking patients coming voluntarily to the OPD for follow-up. Some patients who developed symptoms like amenorrhoea or galactorrhoea might opt to go to Gynaecology specialists or other specialists. It is noteworthy that during the study period none of the patients came with these mentioned symptoms.

A relation of higher dose of olanzapine to prolactin rise was noted in this study. In the overall group the mean olanzapine dose in ESP group was higher by 5 mg/day than in NSP group. In males again ESP groups showed a much higher olanzapine dose (18 mg/day) compared to the NSP male group (11.53 mg/day). Female ESP group also was getting higher doses; but, the difference was not statisti-



cally significant. Earlier studies are non-confirmatory about relation of olanzapine dose to prolactin rise. It was reported that due to the faster dissociation of clozapine and olanzapine, their prolactin raising is lesser compared to first generation drugs and risperidone.[25,26] But, at higher dosage the receptor occupancy is comparable and hence prolactin rise also becomes comparable.

Females are found to be at higher risk of rise of prolactin associated with olanzapine. Earlier studies have found the same.[7,23,25,27] The present study verifies the same as the percentage is much higher in females than males (m: 13.61% vs. f: 26.33%). However, this variation was not significant using Fisher's test. Still, the increased prevalence is more important when viewed with the finding that females were getting lower dosage of olanzapine than their counterparts (m: 12.43±5.49 mg/day, f: 9.07±4.34 mg/day).

Other studies have reported that with olanzapine, prolactin levels rise quickly in the initial two weeks and then comes down gradually.[6,10,15] In our study also, the early rise of prolactin was seen in females (mean duration was 2.2 months [SD=3.25]). Male and female combined together showed prolactin rise around 5.95 months, but males showed a much later period of raised prolactin levels (9.7±8.22 months). Thus, there appears to be different peaks of prolactin according to the duration of olanazapine prescription. However, it is important to note that ESP males showed a much higher dose of olanzapine compared to ESP females (m: 18±4.47 mg/day, f: 13±4.47 mg/day).

This dose difference may have an impact on the observed duration difference between males and females. It is important to remember that the duration was recorded for total period the olanzapine was started. Therefore, it might so happen that the dose escalation was done at a later date

Table 5. Mean comparison between ESP males and ESP females

	Male (n=5) (Mean±SD)	Female (n=5) (Mean±SD)	Probability* (P-value)	Comment
Age (years)	28.2±4.14	24.6±10.21	0.496	No significant difference
Height (cm)	165±7.07	155.4±2.88	0.035	Significant difference, explainable
Weight (kg)	57.8±8.34	48±7.44	0.086	No significant difference
BMI	21.16±2.11	19.92±3.46	0.516	No significant difference
Olanzapine duration (months)	9.7±8.22	2.2±3.25	0.113	No significant difference
Olanzapine dose (mg/day)	18±4.47	13±4.47	0.115	No significant difference
RBS (mg/dl)	108±21.38	92.25±3.4	0.176	No significant difference
Creatinine (mg/dl)	0.9±0.12	0.52±0.12	0.003	Significant difference, explainable
TSH (μIU/ml)	2.05±1.07	3.21±2.07	0.309	No significant difference
AST (IU/L)	39.8±2.58	56.2±37.56	0.384	No significant difference
ALT (IU/L)	32.8±11.6	50.2±39.84	0.394	No significant difference
Prolactin (ng/ml)	25.36±5.39	35.1±7.62	0.051	No significant difference

** Unpaired t-test probability (two tailed, assuming SDs have unequal variance)*

ESP=elevated serum prolactin, SD=standard deviation, BMI=body mass index, RBS=random blood sugar, TSH=thyroid stimulating hormone, AST=aspartate aminotransferase, ALT=alanine aminotransferase

and the rise represents the initial peak of prolactin as in females. So, period since dose escalation was individually noted for all the male patients in ESP group. It was found that out of four ESP male patients, three patients were taking olanzapine for five to seven months, and one patient was getting 20 mg olanzapine/day for one month. Thus, there is a possibility that duration of dose escalation may not be the explanation for late rise of prolactin in males taking olanzapine.

To see how duration of olanzapine treatment affects weight, BMI and RBS values, a correlation test was done for all the study parameter in relation to duration of olanzapine. No correlation was found for any of the study parameters.

We have seen in the study that prolactin rise is a common problem with olanzapine use. The risk is higher in females than males. However, the rise in females is seen in the first couple of months and in males, the change is seen later around 9th month. This study does imply that serum prolactin level should be monitored in patients taking olanzapine. The monitoring should be continued for a period of minimum one year; in males, the period may be extended to one and half years as the rise is found later. Also, it is important to note that raised serum prolactin in most patients is asymptomatic. So, an observant eye is required for symptoms of raised prolactin.

Table 6. Correlation of prolactin and duration of olanzapine treatment to study parameters

	Prolactin	Duration
Age	-0.27609	0.269035
Height	-0.30258	0.065181
Weight	-0.36923	0.183727
BMI	-0.25188	0.181339
Olanzapine duration	-0.1915	1
Olanzapine dose	0.229982	0.083586
RBS	-0.17476	0.084947
Creatinine	-0.38093	0.140176
TSH	0.0686	-0.15607
AST	-0.10851	-0.0706
ALT	-0.30722	0.099155
Prolactin	1	-0.1915

**Correlation co-efficient values are shown in the table*

BMI=body mass index, RBS=random blood sugar, TSH=thyroid stimulating hormone, AST=aspartate aminotransferase, ALT=alanine aminotransferase

Limitations and future directions

One of the limiting factors in this study was the small number of patients with raised prolactin levels. The small number leads to the problem of small statistical power of this study. Male patients outnumbered females by double. This brings some serious concern. Existing data states that males and females suffer equally from mental illnesses. Since the study was done on patients coming for review, the less number of patients probably meant that women are given less importance than men in the family when it comes to drug adherence and follow-ups. To overcome this limitation, future studies should try to include equal number of females.

One major limitation of the study is that dose adjustments of olanzapine were not recorded properly. When olanzapine is used for long-terms, dose adjustments are usually done by the physician. Many a times even patient themselves take lesser doses than prescribed. The present study did not take this factor into account. In view of the investigators, olanzapine dose combined with the actual duration could be a better parameter than considering these parameters separately. It was not possible to combine duration and dose as the dose adjustments done by the patient themselves and adjustments done by the prescriber was not recorded in details.

Though in this study lower weight and BMI in prolactin raised patients was explained as a consequence of the lower duration of olanzapine use, the authors feel that the relationship should be further investigated. To see how much the duration of treatment affects weight and BMI, and also prolactin. Study should be conducted with large number of patients and check the variation by dividing patients into different duration of olanzapine groups.

It is also important to note that in real-life situation, olanzapine is frequently co-prescribed. The role of other drugs in prolactin rise needs to be evaluated. This study did allow a few co-prescriptions, but the relation could be tested as each group had very few patients and thus making statistical inferences error-prone. A cohort design would be better for the study of relationship of changes in prolactin and olanzapine use.

Conclusion

The present study verifies earlier findings of prevalence of prolactin rise with olanzapine. The study corroborates to

the earlier findings that prolactin rise takes a peak in the early period of starting olanzapine. Earlier studies gave an unclear picture of dose-relation to prolactin rise. In this study, we found that with high doses of olanzapine rise of prolactin is more common. In male patients, the dose relationship is more profound. An interesting finding noted is the difference in duration at which prolactin rise was noted based upon gender. Females showed an earlier peak compared to males. Factors like age, weight, BMI, or studied biochemical measures do not seem to influence the change in the prolactin level.

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