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# A naturalistic, 9-month follow-up, comparing olanzapine and conventional antipsychotics on sexual function and hormonal profile for males with schizophrenia

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## Abstract

Second generation antipsychotics have less influence on prolactin levels than conventional antipsychotics (CA), which are commonly associated with sexual dysfunction and hyperprolactinaemia. However, only a few studies have been conducted assessing these newer antipsychotics and sexual function/dysfunction. The aim of this study is to evaluate the sexual function and hormonal profile of male schizophrenic patients taking olanzapine or CA. Sixty-three inpatients with acute episodes of schizophrenia were randomly assigned to take either olanzapine, or go on conventional antipsychotic treatment. The Dickson–Glazer sexual functioning questionnaire was used to assess sexual functioning where serum prolactin, luteinizing hormone, follicle-stimulating hormone, total testosterone, free testosterone, and sex hormone-binding globulin concentrations were measured. All measurements were taken on discharge from the inpatient unit (baseline), and again at 3 and 9

months after discharge. Prolactin levels in the olanzapine group decreased more rapidly and were significantly lower than in the CA group after 3 months ( $12.1 \pm 6.3 \mu\text{g/L}$ ,  $p=0.01$ ;  $18.1 \pm 11.2 \mu\text{g/L}$ ,  $p=0.564$ , respectively). After nine months, there was a tendency toward normal levels in both groups, and the frequency of sexual complaints did not differ between the groups. This study showed no difference between olanzapine and conventional antipsychotics regarding sexual complaints in the treatment of schizophrenia, but did show a difference in the hormone level normalization rate.

## Keywords

schizophrenia, sexual dysfunction, hormones, prolactin, olanzapine, antipsychotics

## Introduction

The incidence of sexual dysfunction induced by antipsychotic treatment in patients with schizophrenia ranges from 10% to 60% (Bobes *et al.*, 2003; Sullivan and Lukoff, 1990; Montejo, 2000). It is possible that antipsychotics may induce sexual desire dysfunction, but may also improve sexual performance, due to the reduction of positive and negative symptoms (Aizenberg *et al.*, 1995).

The highest incidence of sexual dysfunction has been shown

with both conventional treatments and also with atypical antipsychotic risperidone (Kotin *et al.*, 1976; Shiwach and Carmody, 1998; David *et al.*, 2000). The impact of second generation antipsychotics on the sexual functioning of patients with schizophrenia has not yet been studied in any depth. In a recent cross-sectional study conducted in Spain (Bobes *et al.*, 2003), the Outcomes Research Study into Schizophrenia (EIRE study), 61 psychiatrists recruited 669 patients from outpatient clinics. These patients were treated for at least 4 weeks with a single antipsy-

chotic (risperidone, olanzapine, quetiapine or haloperidol). The authors found that 38.1% of the patients experienced some kind of sexual dysfunction. Moreover, they found that quetiapine presented the lowest frequency of sexual dysfunction (18.2%), differing significantly from both haloperidol (38.1%) and risperidone (43.2%). The most common sexual complaints in men were erectile dysfunction (30.8%) and decreased sexual desire (30.8%). Surprisingly, second generation antipsychotics, with the exception of quetiapine, did not differ from each other or from haloperidol, with regard to frequency of sexual dysfunction. Montejo (2000), in a prospective 8-week naturalistic study, found a sexual dysfunction rate ranging from 10% to 33% for olanzapine, depending on the dosage used.

Regarding prolactin, it appears that, with the exception of risperidone, atypical antipsychotics do not present a significant increase in prolactin (Goodnick *et al.*, 2002). Olanzapine may have modest effects on prolactin when compared to conventional antipsychotics and risperidone (Beasley *et al.*, 1996; Tran *et al.*, 1997). Quetiapine, ziprasidone and aripiprazole have also been found to have little effect on prolactin levels (Arvanitis and Miller, 1997; Keck *et al.*, 2001). David *et al.* (2000) analysed acute and long-term data from three double-blind randomized clinical trials, assessing prolactin increases with olanzapine, risperidone and haloperidol use. For these three antipsychotics, the prolactin level was only moderately elevated by olanzapine. Crawford *et al.* (1997) also analysed prolactin levels for olanzapine and haloperidol in a randomized 6-week study, with an extension period of 46 weeks. Prolactin elevation rates induced by olanzapine were approximately one-half to one-third of those observed with haloperidol, and were significantly more transient. Montgomery *et al.* (2004) analysed three electronic databases in a more recent paper, and found hyperprolactinaemia in 68% of patients treated with conventional antipsychotics, 11% with clozapine, 91% with risperidone, 40% with olanzapine and 22% with quetiapine.

From a large database of data from 6-week studies, Knegeting *et al.* (2003a), Knegeting *et al.* (2003b), and Knegeting *et al.* (2004) analysed the sexual side effects attributed to the use of the following antipsychotics: conventional, clozapine, olanzapine, quetiapine and risperidone. Comparing the different antipsychotics, risperidone induced significantly more sexual dysfunction. Moreover, conventional antipsychotics induced sexual dysfunction more frequently than clozapine, olanzapine or quetiapine. High frequencies of erectile and ejaculatory dysfunction were reported in male patients treated with risperidone and conventional antipsychotics.

Most of the studies on antipsychotic-induced sexual dysfunctions have been based on cross-sectional designs or short-term clinical trials. The aim of this study is to evaluate the sexual functioning and the hormonal profile of male patients with schizophrenia. Sexual dysfunction in olanzapine and conventional antipsychotic users will be compared over a follow-up period of 9 months after hospital discharge.

## Methods

The study was conducted at Pax Clínica Psiquiátrica (Goiânia), and at Santa Mônica Hospital (Salvador), both being Brazilian public psychiatric inpatient units that provide care for severely-ill patients.

Male inpatients over 18 and under 55 years old, who had been diagnosed with any psychotic disorder according to DSM-IV, having a score higher than 24 in the BPRS<sup>1</sup> (Kay *et al.*, 1986), (score extracted from PANSS<sup>2</sup>) were eligible for this trial.

Subjects who presented a severe physical disorder or a history of convulsion, or those who had been using any antipsychotic drug within 6 months prior to hospitalization, were excluded. The use of benzodiazepines was allowed. Since sexual functioning is generally easier and more objectively assessed in males, the study was restricted to male subjects.

Subjects were randomized into two groups: one group received conventional antipsychotics (conventional group) whilst the other received olanzapine (olanzapine group). Randomization was performed by allotment. The follow-up was naturalistic (patients and doctors were not blind to the treatment). The psychiatrists performed their routine clinical procedures where doses were titrated up and down according to clinical indications. Prophylactic use of anticholinergics was discouraged but not prohibited, and benzodiazepines could also be prescribed if necessary.

The baseline was time of discharge from the inpatient unit. Blood samples were taken and an assessment with the Dickson Glazer Scale for the Assessment of Sexual Functioning Inventory was performed, at discharge, and again 3 months after (midpoint assessment) and 9 months after discharge (end point assessment). The period from the start of study medications and baseline (discharge) spanned 53 days (mean for both groups).

Data collected in this study comprised a sub-analysis of a parent study, which examined the efficacy of olanzapine versus conventional antipsychotics (Mari *et al.*, 2003).

The time points for follow up (3 and 9 months) were chosen so as to analyse both short- and long-term influences of antipsychotics, since hormonal changes may present in the short term, whilst sexual dysfunctions, over the longer term.

Blood samples were taken to determine prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (TT), free testosterone (FT) and sex hormone-binding globulin (SHBG) levels.

The biochemical analysis of LH, FSH, TT, PRL, and SHBG were performed using commercially available radioimmunoassay kits employing an automatic measuring system (Fluorometer, Wallac-Delfia 1234/1296). To measure free testosterone, radioisotope analysis using an auto-gamma counter (Packard-Cobra II counter) was carried out.

The Dickson Glazer Scale for the Assessment of Sexual Functioning Inventory (DGSFi) is a computerized self-report questionnaire of sexual functioning for antipsychotic-treated patients

- 1 Brief Psychiatric Rating Scale (BPRS) is a multi-item inventory of general psychopathology designed to assess patients with major psychiatric disorders, particularly schizophrenia.
- 2 Positive and Negative Syndrome State.

diagnosed with schizophrenia spectrum disorders (Dickson and Glazer, 2000).

The male version is composed of 32 items and as DGSFi is a categorical, qualitative scale back-translation was performed. This is the first use of this instrument in the Portuguese language. Since the patients' general level of education was low, the questionnaire was administered by interviewers. Interviews were performed by psychiatrists and psychologists who were blind to the treatment.

For men, the questionnaire evaluates sexual desire (thoughts about sex), sexual arousal (erection, masturbation), sexual activity (frequency of sexual intercourse and masturbation), orgasmic function (number and frequency of orgasms), sexual satisfaction (pleasure and fulfillment in sexual relations) and sexually-related problems (failure to achieve erection, lack of sexual interest, premature or delayed ejaculation, priapism). Questions on perceptions of sexual side effects included ratings of how the patients were bothered by sexual side effects on a five-point scale, ranging from 'not bothered at all' to 'extremely bothered'.

The study was conducted in compliance with the Declaration of Helsinki and its amendments, and it was approved by the institutional ethics committees. Eligible patients, or their responsible caregivers, provided written informed consent.

Gauss curves were developed by Fleury Laboratory to show the normal distribution of the patients' hormonal levels, as compared to those of normal healthy individuals from the general population not taking antipsychotics. A two-sided Kolmogorov–Smirnov test (KS-test) (Conover, 1999) was used to determine if the groups differed. The Mann-Whitney test (Conover, 1999), a non-parametric test, was used to compare the two groups, measuring the correlation coefficient between hormones levels and sexual functioning. The Spearman correlation coefficient was calculated, since it provides a good indication of non-linear relationships between variables.

## Results

A total of 68 patients were eligible for the study, five of whom were excluded according to the inclusion/exclusion criteria. There-

fore, the study population comprised 63 patients (30 on olanzapine and 33 on conventional antipsychotics). Four refused to answer the questionnaire and/or to perform blood tests, and three were unable to answer the questions at the 3-month evaluation due to disorganized thinking. At study end point, two patients were unable to answer the questions (confounded thinking), whilst one patient refused, and another was lost at follow-up. A total of 52 patients completed the study, representing an overall completion rate of 86%.

Table 1 shows distribution of patients' social, demographic and clinical features. No significant differences were found between the two treatment groups. A total of 26% of patients in the olanzapine group, and 36% in the conventional group, had not received any medication for 6 months prior to embarking on the trial. The remaining patients had previously been on treatment, most taking haloperidol (84.2%).

Since this was a naturalistic study, the physician was free to treat patients using monotherapy or a combination of antipsychotics. Among the group taking conventional antipsychotics, 48.5% of the patients were treated with haloperidol alone, 42.4% with combined haloperidol and chlorpromazine, and 9.1% with chlorpromazine alone. In the olanzapine group, 91.5% of the patients were taking only olanzapine, and 8.5% took olanzapine in combination with conventional antipsychotics. The dose ranges for haloperidol, chlorpromazine, and olanzapine were 5–20 mg/day, 100–500 mg/day, and 10–20 mg/day, respectively. Mean doses for haloperidol, chlorpromazine, and olanzapine were  $10.5 \pm 5$ ;  $300 \pm 141$ ; and  $17.5 \pm 7.1$  mg/day, respectively. No patient changed their allocated group.

Normal levels for FSH, LH, PRL, TT, FT, and SHBG are presented in Table 2. At baseline, patients in both groups began the study having higher prolactin levels than the general population. Table 2 also shows the hormone levels at baseline and end point, for the olanzapine and conventional treatment groups. Paired sample comparisons of hormone levels were performed and overall, hormone levels did not differ between the two groups at baseline.

In the conventional treatment group however, patients showed an increase in SHBG concentrations. PRL levels were significantly reduced for both the olanzapine and conventional treatment

**Table 1** Distribution of socio-demographic and clinical variables for olanzapine and conventional groups

	Olanzapine	Conventional	P
Sample size – N(%)	30 (79%)	33 (89%)	0.552
Age (mean $\pm$ SD, years)	32.9 $\pm$ 9.2	33.5 $\pm$ 9.6	0.787
History of disease (mean $\pm$ SD, years)	11.2 $\pm$ 10.0	11.4 $\pm$ 7.3	0.897
Marital status (single, separated, or divorced) – N (%)	26 (86%)	28 (85%)	1.00
Sexual drive (heterosexual) – N (%)	24 (80%)	28 (85%)	0.613
Involved with sexual partner – N (%)	7 (23%)	5 (15%)	0.409
Ever had sexual intercourse – N (%)	24 (83%)	24 (73%)	0.346
PANSS, positive symptoms (mean $\pm$ SD)	24 $\pm$ 5.9	22.6 $\pm$ 5.8	0.292
PANSS, negative symptoms (mean $\pm$ SD)	26.2 $\pm$ 7	25.5 $\pm$ 5.4	0.665
PANSS, total score (mean $\pm$ SD)	92.9 $\pm$ 21.8	89.7 $\pm$ 19.8	0.554
Mean length of admission (mean $\pm$ SD, days)	53.50 $\pm$ 18.2	52.91 $\pm$ 20.0	0.907

**Table 2** Comparison of hormone levels at baseline and end point for olanzapine and conventional groups, following discharge

	Mean		t-Student	df	p
	Baseline±SD	End point±SD			
Conventional group					
FSH (IU/l)	3.7±2.3	3.2±2.1	1.374	23	0.119
LH (IU/l)	4.7±2.5	4.1±2.2	0.914	23	0.37
PRL (µg/l)	19.8±14.0	15.4±12.5	2.193	23	0.039
TT (nmol/l)	18.6±6.2	19.4±7.9	-0.431	23	0.67
SHBG (nmol/l)	30.9±13.5	44.4±23.1	-2.886	22	0.009
FT (nmol/l)	0.06±0.03	0.07±0.03	-0.27	23	0.79
Olanzapine group					
FSH (IU/l)	4.5±4.2	4.2±3.7	1.306	21	0.206
LH (IU/l)	5.4±3.1	4.6±3.2	0.921	22	0.367
PRL (µg/l)	20.4±14.0	9.0±5.1	3.797	23	0.001
TT (nmol/l)	18.2±7.6	18.9±5.5	-0.512	24	0.613
SHBG (nmol/l)	37.4±27.0	39.7±29.1	-1.466	21	0.158
FT (nmol/l)	0.06±0.03	0.07±0.02	-0.493	20	0.627

Normal values – FSH: 1.0–10.5 IU/L; LH: 1.0–8.4 IU/L; PRL: 2;3–11;5 µg/l; TT: 8.67–32.96 nmol/L; SHBG: 14.9–103.0 nmol/L; FT: 0.02–0.09 nmol/L

groups. However, the PRL levels in the olanzapine group decreased more rapidly, and were significantly lower than in the conventional treatment group after 3 months (values 12.1±6.3 µg/l;  $p=0.01$ ; 18.1±11.2 µg/l;  $p=0.564$ , respectively). Regarding the conventional antipsychotic group, there was no significant change in prolactin levels from baseline to midpoint. However, from midpoint to end point prolactin levels had decreased.

There was no statistical difference between the two groups regarding sexual complaints at baseline. A total of 87% of individuals in the olanzapine group, and 85% in the conventional group, were single/divorced. Of the olanzapine group, 80% and 85% in the conventional group, were heterosexuals. Eighty-three percent of patients in the olanzapine group, and 73% in the conventional group, had had sexual intercourse at the endpoint, although only 17% stated they had done so over the previous 2 weeks.

The distribution of sexual complaints, as reported in the DGSFi, was similar for both groups (Table 3). There was a greater frequency of sexual thoughts, a stronger desire for sex and a reduced length of time comfortable with abstinence, in the olanzapine treated group, although this did not reach significance.

The Mann-Whitney test was performed to find any correlation between changes in hormone levels and sexual functioning. For both groups, significant positive correlation coefficients were found between time without sexual activity and PRL use (Spearman coefficient=0.384;  $p=0.023$ ), and time without sexual activity and LH levels (Spearman coefficient=0.399;  $p=0.021$ ). The longer the time without sexual activity, the higher the prolactin and LH levels. For both groups, a negative correlation coefficient was found between SHBG levels (Spearman coefficient=-0.361;  $p=0.048$ ) and time comfortable with abstinence.

## Discussion

The main findings of this study are related to hormonal serum concentrations. In the olanzapine treated group, patients presented a significant decrease in their prolactin levels 3 months after hospital discharge. After 9 months, prolactin levels had decreased in both groups. The distribution of sexual complaints did not differ significantly. As this was a naturalistic study, a combination of drugs routinely used in clinical practice was allowed, the results therefore can be considered a closer reflection of everyday practice.

Dickson and Glazer (2000) assessed 119 patients with the DGSFi in a stable phase of treatment with antipsychotics. Of these, 83 of the men studied reported having had sex with a partner, but only 9% had done so within the previous 2 weeks; 40% believed they had had a decrease in sexual thoughts, 30% believed that their medication affected arousal and 36% had had ejaculatory problems. Moreover, a third of the sample was not satisfied with the treatment results. Our study found lower rates of such dysfunctions, when compared to Dickson and Glazer's reports. The DGSFi in this study was applied by clinical staff where this might have been a barrier preventing patients from revealing their actual situation. The sample size in this study was relatively small, and may not be large enough to detect small differences, which could explain the similar effects on sexual functioning in both groups. Our results are similar to those reported in the study by Bobes *et al.* (2003), which compared haloperidol and second generation antipsychotics.

In the baseline assessment, patients had higher PRL levels than healthy individuals. However, there was no difference between patients who had been taking medication in the 6 months prior to

**Table 3** Sexual complaints reported with DGFSi for olanzapine and conventional antipsychotics

	Olanzapine		Conventional antipsychotics	
	Baseline N (%)	End point N (%)	Baseline N (%)	End point N (%)
Frequency of sexual thoughts in the past 2 weeks (less than twice)	12/28 (40.0%)	4/28 (14.3%)	16/33 (49.0%)	13/30 (43.3%)
Strength of desire for sex (never)	5/30 (17%)	1/28 (3.6%)	1/33 (3.0%)	5/30 (16.7%)
Time comfortably without sex (always)	3/25 (12.0%)	2/28 (7.1%)	2/32 (6.0%)	7/30 (23.3%)
Frequency of masturbation, past 2 weeks (none)	20/29 (69.0%)	10/28 (35.7%)	18/33 (55.0%)	10/30 (33.3%)
Sexual intercourse in the last 2 weeks	4/23 (17.0%)	4/25 (16%)	4/25 (16%)	5/23 (21.7%)

the assessment, and patients who had not (Costa *et al.*, 2005). The other hormones showed a distribution closer to normal, although the distribution curves presented minor shifts, compared to healthy individuals.

During regular treatment, and 3 months after discharge, the group taking olanzapine showed a significant decrease in PRL levels. In contrast, PRL levels of patients on conventional antipsychotics remained unchanged during the first 3 months of treatment after discharge, although these levels subsequently decreased significantly towards end point. There was a trend in the olanzapine group, although not reaching significance, toward having a greater frequency of sexual thoughts, a stronger desire for sex, and a reduced time comfortable with abstinence than in the conventional group. This may be explained by the lower PRL levels in the olanzapine group, since a positive correlation was found between PRL levels and length of abstinence. Even though the Spearman correlation coefficients were not close to one, the difference was significant.

In the conventional antipsychotic group, mean SHBG levels increased significantly, but there was greater dispersion. The circulating SHBG concentration has an impact on the bio-available testosterone level, because it combines with a large proportion of the free available testosterone in circulation. Therefore, changes in SHBG concentrations result in large shifts in FT and albumin-bound testosterone fractions. Although the exact mechanism is unknown, hyperprolactinaemia can induce lower levels of testosterone (Tolis, 1980). In normal adult males, there is a wide inter-individual variability in circulating testosterone levels, which do not seem to be linked in a meaningful way with inter-individual differences in levels of sexual drive or behaviour (Schiavi and White, 1976). However, in a study carried out by Alexander *et al.* (1997), which assessed mood and response to auditory sexual stimuli in hypogonadal men undergoing testosterone replacement therapy, testosterone increased sexual arousal and enjoyment, yet had a positive effect on mood only among men with abnormally low levels of testosterone.

Beumont *et al.* (1974) followed up male patients for several

months (not specified) who were taking conventional antipsychotics, and reported that testosterone levels during chronic treatment were below or within the normal range. Prolonged administration of neuroleptics produced subclinical endocrine effects leading to significant changes in plasma hormone levels, although these often fell within the normal range of absolute values. Consequently, the authors believed that the finding of a hormone level within the normal range during neuroleptic treatment, does not exclude the possibility of a drug-induced change in hormone output in that individual. The finding that changes in testosterone, LH, PRL, and GH levels were not correlated suggested that the mechanisms regulating the secretion of these hormones are not equally susceptible to changes by any particular neuroleptic treatment. The authors concluded that increased PRL and suppressed testosterone, without accompanying changes in LH, suggested the possibility of selective effects of neuroleptic drugs on the hypothalamus (prolactin), and on the peripheral gland (testosterone).

Clinical staff should always actively query patients for side effects, especially for sexual dysfunctions. Approximately 40% of patients undergoing treatment for schizophrenia stop taking their conventional antipsychotic medication within 1 year and this, in turn, can be linked to relapse of psychotic symptoms. According to Perkins (2002), the main reasons for non-adherence were found to be extrapyramidal side effects, neuroleptic dysphoria, akathisia, sexual dysfunction and weight gain. However, it remains questionable whether sexual dysfunction is mainly induced by medication, or is a symptom of the disease itself.

This study showed no difference between olanzapine and conventional antipsychotics regarding sexual complaints in the treatment of schizophrenia. However, in terms of hormone levels, the difference between olanzapine and the conventional antipsychotics appears to lie in their hormone-level normalization rates. Despite having a small sample size and difficulties in gathering information on the sexual domain, and considering the symptoms of the underlying disease might have clouded the findings, our study may prove of assistance to researchers seeking to understand

better these sexual problems afflicting schizophrenic patients, an important factor in their non-compliance with antipsychotic treatment and consequent relapse rates.

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### Declaration of interest

This study was sponsored by an educational grant from Eli Lilly Brazil. Dr Jair de Jesus Mari and Dr Mauricio Silva de Lima are researchers from the Brazilian Research Council (CNPq). Dr Mauricio Silva de Lima and Marité Faria work for Eli Lilly Brazil. Dr Anna Maria Costa is currently an employee of Bristol-Myers-Squibb (BMS) Brazil. This study was performed prior to her joining BMS.

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