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Sexual Dysfunction in First-Episode Schizophrenia Patients: Results from EUFEST

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ABSTRACT

Sexual dysfunctions (SD) occur frequently in schizophrenia patients and have a huge impact on quality of life and compliance. They are often associated with antipsychotic medication. Nicotine consumption, negative or depressive symptoms and physical illness are also discussed as contributing factors. Data on SD in first-episode schizophrenia patients are scarce.

As part of the European First Episode Schizophrenia Trial (EUFEST), first-episode schizophrenia patients were randomly assigned to five medication groups. We assessed SD by analyzing selected items from the Udvalg for Kliniske Undersugelser (UKU) at baseline and five following visits.

Differences between antipsychotics were small for all SDs and fairly little change in the prevalence of SDs was seen over the course of the study. A significantly larger increase of amenorrhea and galactorrhea was seen with amisulpride than with the other medications. In men, higher age, more pronounced Positive and Negative Symptom Scale (PANSS) general psychopathology symptoms and higher plasma prolactin levels predicted higher rates of erectile and ejaculatory dysfunctions. PANSS negative symptoms and higher age were predictors for decreased libido.

In women, higher prolactin plasma levels were identified as a predictor of amenorrhea. PANSS negative symptoms predicted decreased libido.

All evidence taken together underscores the influence of the disease schizophrenia itself on sexual functioning. In addition, there is a strong correlation between the prolactin-increasing properties of amisulpride and menstrual irregularities.

INTRODUCTION:

Sexual dysfunctions (SD) are frequent in both male and female schizophrenia patients (1-3). As patients rarely report this problem spontaneously, it is difficult to explore. Both quality of life (QOL) and compliance are affected by SD (4). In a study by Olfson and colleagues (5), patients with SD reported poorer QOL and lower levels of enjoyment in life, were less likely to have a romantic partner and less satisfied with the quality of their romantic relationships. 36% of the patients attributed changes in their sexual functions to antipsychotic medication. Antipsychotic treatment has frequently been associated with SD (6-9). Several mechanisms are discussed in this context: next to sedation due to antihistaminergic and antiadrenergic effects of antipsychotics or serotonergic blockade (10), low gonadal hormone levels and elevated prolactin may be contributing factors. Elevation of prolactin is caused by the antidopaminergic effect of antipsychotics in the hypothalamus (9) and has been suggested to impair sexual functioning via altering sex hormone release in the hypothalamic-pituitary-gonadal axis (11). Conventional antipsychotics induce hyperprolactinemia more often than second generation antipsychotics, except for amisulpride, risperidone (12) and paliperidone (13). In addition, peripheral effects of antipsychotics on the sexual target organs need to be taken into account (2, 14). Clinically, a large range of SDs have been described in schizophrenia patients, including disturbances of sexual functioning such as erectile or ejaculatory dysfunction as well as disturbances of sexual experience like arousal or orgasmic dysfunction.

Montejo et al. (15), in a recent study, also confirmed SD to be common in antipsychotic-treated patients. According to this report, SD also play an important role in adherence to medication.

Whether there is a causal relationship between SD and prolactin levels in schizophrenia patients, remains an open question. Studies addressing this issue so far have yielded divergent

results. Canuso et al. (16) have studied women taking antipsychotics and found high rates of SD in normoprolactinemic and hyperprolactinemic patients. Howes et al. (3) have investigated patients with schizophrenia and schizoaffective disorders and reported high rates of SD and hypogonadism but no association between prolactin levels and sexual functioning. Smith et al. (17), when examining conventional antipsychotics, also failed to find a correlation between prolactin and SD in male patients. Only in a subgroup (hyperprolactinemic men), prolactin levels were negatively correlated with erectile dysfunction. In women, prolactin correlated negatively with libido and physical arousal problems.

On the other hand, a number of groups have described an association between plasma prolactin and SDs. Knegtering et al. (18), when comparing sexual side effects of quetiapine and risperidone, indicated a higher rate of increased prolactin levels and sexual disturbances in patients on risperidone. They also reported significant correlations between prolactin elevation and SD in men. In another study by the same group (19), only 40% of emerging SD in schizophrenic patients were attributable to the prolactin-raising properties of antipsychotics. Rettenbacher et al. (20), in a drug monitoring program, found a correlation between diminished sexual desire and prolactin levels in male and female schizophrenia patients.

Besides antipsychotics, other factors also play a role in the etiology of SD in schizophrenia, as it can also be observed in untreated schizophrenia patients, the main complaint being diminished libido (21). Contributing factors include excessive nicotine consumption, negative or depressive symptoms (2) and a high comorbidity with physical illness (22).

So far, the focus of research has been on SD in chronic schizophrenia patients. Little is known concerning SD in first-episode patients. We have therefore explored this question by analyzing safety data from the European First Episode Schizophrenia Trial (EUFEST) (23, 24).

METHODS

Results were obtained as a part of EUFEST, the methodology of which has been described in more detail in previous publications (23, 24). A total of 50 centres participated. Eligible patients were aged 18-40 years and met criteria of the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) for schizophrenia, schizophreniform disorder, or schizoaffective disorder. Onset of positive symptoms had to have occurred no more than two years before study entry, no more than 6 weeks lifetime exposure to antipsychotics was allowed.

498 patients were randomly assigned to receive haloperidol (1-4 mg/d, n=103), amisulpride (200-800 mg/d, n=104), olanzapine (5-20 mg/d, n=105), quetiapine (200-750 mg/d, n=104), or ziprasidone (40-160 mg/d, n=82). All study drugs were given orally, within the above dose ranges, at the treating psychiatrist's discretion. Baseline data were collected for demographics, diagnoses, treatment setting, psychopathology (Positive and Negative Syndrome Scale [PANSS]) (25), as well as other outcome parameters described in the original papers. Drug safety/tolerability was assessed through direct questioning by the researcher using the the Udvalg for Kliniske Undersugelser (UKU) (26) as well as the St Hans Rating Scale (SHRS) (27), for extrapyramidal adverse events. Furthermore, a physical examination was done in all patients; laboratory data (prolactin among other parameters) were recorded and an electrocardiogram (ECG) was obtained. The study lasted 52 weeks during which patients were seen at baseline, 2, 4, 6, 8 and 12 weeks later and in 3 monthly intervals from then on.

SDs were assessed by analyzing selected items from the UKU at baseline and after 1, 3, 6, 9 and 12 months of medication. The UKU Side Effect Rating Scale comprises a total of 48 symptoms. Out of these, the following items were used for this analysis: menorrhagia, amenorrhea, galactorrhea, gynaecomastia, increased sexual desire, diminished sexual desire,

erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, dry vagina. For each symptom, scores on the severity scale range from 0-3. Laboratory parameters were assessed at baseline and after 6 and 12 months.

Statistical methods

Two different methods were used to analyze the prevalence of the individual SDs (dichotomized into present vs. absent, UKU scores either 0 (SD absent) vs. >= 1 (SD present)) over the course of time:

1) A simple comparison of SDs at baseline and at the end of treatment (12 months) using the last-observation-carried-forward (LOCF) method for missing value replacement. This analysis involved the Chi-square test for a baseline comparison of the five antipsychotics with regard to the individual SDs, the McNemar test for an analysis of the SDs over the course of time (baseline vs. end of treatment) and ordinal logistic regression for comparing the individual antipsychotics with respect to changes of SDs from baseline to end of treatment. For comparison, the same analyses were also performed for observed cases (OC).

2) A comprehensive longitudinal data analysis of the individual SDs using generalized estimation equations (GEE) logistic regression assuming an autoregressive correlation structure in the course of time (28). Independent variables considered in this analysis were antipsychotic treatment (5-level factor: 5 antipsychotics), time (6-level factor: 0, 1, 3, 6, 9 and 12 months) and time-by-treatment interaction. In order to limit the degrees of freedom and to maintain an appropriate level of statistical power, the factor time was dichotomized into baseline and post-baseline for analyzing the time-by-treatment interaction. In order to identify differential treatment effects that may be overlooked when inspecting only the time-by-treatment interaction, the above analysis was performed a second time using post-baseline observations only, adjusting for baseline SD as a covariate. In this case, a significant main

effect of the factor "antipsychotic" indicates genuine treatment differences unaffected by potential baseline differences. Post-hoc treatment comparisons were carried out when the treatment effect or the time-by-treatment interaction was statistically significant; both the least significant difference (LSD) method and the Bonferroni method were used.

In order to explore the effect of factors other than antipsychotic medication on the prevalence of SDs, we additionally performed longitudinal GEE logistic regression analyses for the individual SDs considering the following variables as potential predictors: age, psychopathology (PANSS subscales for positive, negative and general symptomatology), prolactin level and the use of potentially prolactin-increasing comedications (yes/no). All of these variables except age were modeled as time-dependent covariates. The backward stepwise elimination method was used for variable selection. All statistical tests were performed at a 0.05 level of significance.

RESULTS

Prevalence rates of SDs in general

Prevalence rates of SDs in male and female subjects are shown in **Table 1**, both at baseline and at 12 months (end of treatment). As differences between the individual antipsychotics were small for all SDs (there were neither significant treatment main effects nor significant baseline differences between APs) prevalence rates for the individual APs were pooled. Significant interactions between antipsychotics and time were observed for two SDs and will be dealt with in more detail below.

Overall, fairly little change in the prevalence of SDs was seen over the course of the study. In men, the prevalence of increased libido was found to diminish with time. In women, the prevalence of galactorrhea showed a significant increase. However, the highly significant

interaction between time and antipsychotic (p=0.001) indicates that there was considerable heterogeneity among the individual drugs regarding the time course of galactorrhea. A similar heterogeneity was also observed for amenorrhea. In both cases a significantly stronger increase of SDs was seen with amisulpride than with the other medications (details in Table 1). A closer inspection of the time-by-treatment interaction for these two SDs is discussed in the following and detailed in table 2. No other SD in women showed a significant change over the course of time.

Modifications of the statistical analysis did not greatly affect these findings. When replacing the LOCF analysis by an analysis without imputation of missing values, the time-by-treatment interaction remained significant for galactorrhea ($\chi^2_4 = 14.2$, p=0.007) and almost significant for amenorrhea ($\chi^2_4 = 9.0$, p=0.060). When substituting the simple comparison of baseline and 12 months assessment by an analysis of the entire time course of the SD (using GEE logistic regression analysis), only one further SD was found to show a significant change over time, namely decreased libido in men (30.8% at baseline, 37.5% at 3 months, dropping to 27.4% at 12 months, $\chi^2_5 = 13.5$, p=0.015). However, this finding does not withstand a Bonferroni correction for multiple testing and thus the possibility of a chance finding cannot be ruled out.

Time course of amenorrhea and galactorrhea – comparison of the individual antipsychotics

Table 2 provides a detailed analysis of the time course of amenorrhea and galactorrhea, i.e. of the two SDs which had shown differential treatment effects. When considering the individual antipsychotics separately, significant changes over time of both amenorrhea and galactorrhea were seen in women receiving amisulpride, but not for any other drug. Significantly higher rates of amenorrhea, compared to baseline, were found after 3 and 6 months of treatment with amisulpride. Similarly, a significant increase in the prevalence of galactorrhea was observed after 3 months of treatment with amisulpride. Trend level significance (p<0.07) was also seen after 1, 6 and 12 months.

These findings were largely confirmed by GEE logistic regression analysis. For amenorrhea, the time-by-treatment interaction did not reach statistical significance. However, the main effect of the factor "antipsychotic" considering only post-baseline observations attained significance (p=0.037), confirming the presence of treatment differences regarding the prevalence of amenorrhea. Pairwise comparisons showed significantly higher rates of amenorrhea with amisulpride than with haloperidol, olanzapine or ziprasidone.
For galactorrhea, a significant time-by-treatment interaction was found, revealing a different time pattern of this SD for the individual antipsychotics. Post-hoc comparisons between drugs demonstrated higher rates of galactorrhea with amisulpride than with all other medications. No differences were observed between the other antipsychotics.

Effect of age, psychopathology and prolactin level on the prevalence of SDs

Demographic data and ranges of laboratory markers are described in detail in the original paper. Of relevance for the results reported here are the mean age of 26 years with an age range of 18.1-40.0 years, and prolactin levels ranging between 0.04-8.58 U/l with average levels of 0.70 U/l in men and 1.59 U/l in female patients. In order to explore the effect of factors other than antipsychotic medication on the prevalence of SDs, we performed GEE logistic regression analyses based on the data of all assessment times. Results are presented in Table 3. In men, higher age, more pronounced PANSS general psychopathology symptoms and higher plasma prolactin levels significantly predicted higher rates of both erectile and ejaculatory dysfunctions. Higher PANSS positive symptom scores were found to predict higher rates of increased libido, whereas more PANSS negative symptoms and higher age were identified as predictors of decreased libido. Higher age and more pronounced PANSS general symptoms predicted higher rates of orgastic dysfunction.
In women, PANSS positive symptoms were found to predict higher rates of menorrhagia. Higher prolactin plasma levels were identified as a predictor of amenorrhea, whereas none of

the variables tested was found to significantly predict galactorrhea. Like in men, more pronounced PANSS negative symptoms predicted decreased libido and, at a trend level, PANSS positive symptoms predicted increased libido. Unlike the situation in men, none of the variables tested significantly predicted orgastic dysfunction in women.

The use of co-medications with a potential impact on prolactin levels or sexual functioning was also considered as a potential predictor but did not attain statistical significance for any of the SDs.

As the incidence of diabetes in EUFEST was very low, statistical analyses concerning the possible influence of metabolic adverse events on SDs could not be performed.

DISCUSSION

The prevalence of SD in schizophrenia patients has been shown to be high in all well-designed previous reports (1-9). Unfortunately, the elucidation of causative factors remains challenging. With the exception of amenorrhea and galactorrhea, we did not find a significant difference in SDs between the different antipsychotics studied in EUFEST. Compared to most other studies, the rates of SDs were somewhat lower in our sample of first-episode patients. In support of this, van Bruggen et al. (29) have reported similar rates of SD at baseline in a sample of first episode patients, consisting mainly of males. We found little change from baseline over the observed time span. This is in contrast to findings of other groups, which have examined chronic schizophrenia patients. Montejo and colleagues (30), for example, have described quetiapine to improve SD in chronic schizophrenia patients over the course of 6 months in a naturalistic setting.

Other groups have also assessed the frequency of sexual disturbances, albeit with somewhat less rigorous methodology, as for instance relying on spontaneous reports of SDs, which is

likely to underestimate their true prevalence, given the reluctance of both patients and doctors to discuss sexuality. Hanssens and colleagues (31) found aripiprazole to reduce SDs to a larger extent than olanzapine, quetiapine or risperidone in a large open label switching study. This went hand in hand with a decrease of prolactin in aripiprazole-treated patients.

Rossi and colleagues (32) showed that switching schizophrenia patients from various antipsychotics to ziprasidone improved not only psychopathological symptoms, but also SD, a finding which was corroborated by a study carried out by Montejo et al. (33), who also reported that switching to ziprasidone is associated with a normalization of sexual function. A large multicenter study by Dossenbach and colleagues (34) suggested clinically relevant differences in the sexual side effect profiles of haloperidol, risperidone, olanzapine and quetiapine. Treatment with olanzapine and quetiapine led to less SD (measured by UKU) when compared to risperidone or haloperidol. Females on olanzapine or quetiapine reported a lower rate of menstrual irregularities than those on risperidone or haloperidol. The discrepancy to our results - we did not find a higher rate of menstrual irregularities in the haloperidol group - could be attributed to the fact that the haloperidol dose used in their study was considerably higher (on average 11.9 mg/d in contrast to 3 mg in EUFEST). Also, one needs to consider that theirs was an open observational study without random treatment assignment.

Using a more rigorous measurement, namely the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ- SALSEX) (35), Montejo and colleagues (36) found aripiprazole to improve SD in schizophrenic patients, both in patients taking it as their first antipsychotic as well as in those switched to it from another drug.

Given the small difference in SDs from baseline to endpoint in our study, one could assume a greater influence of the disease itself, as also underscored by the correlations between SDs and PANSS scores.

We found that the item “increased libido” decreased significantly over the course of time in men. As higher PANSS positive subscores predicted increased libido, this relationship is likely to reflect effective antipsychotic treatment. One could speculate that this is due to an amelioriation of specific symptoms such as for instance delusions of grandeur or an increase of drive.

In women, galactorrhea increased over the observation period. Our analysis shows, that this can be attributed to amisulpride, which led to a significantly higher likelihood of galactorrhea, when compared to the other antipsychotics. A differential risk could also be found with respect to amenorrhea in amisulpride-treated patients, in whom we found a stronger effect than in patients on haloperidol or olanzapine. The galactorrhea- and amenorrhea-inducing properties of amisulpride are well known (37, 38) and are attributed to hyperprolactinemia. A closer look at the time course (table 2) shows a marked increase after 3 and 6 months. In contrast to the rather stable rates of galactorrhea from month 3 until the end of the observation period, amenorrhea rates showed a certain decrease after the peak at month 6. However, as this decrease was not statistically significant, it may well be due to random fluctuation only and should therefore not be overrated.

The influence of prolactin levels on SD is still discussed controversially. In our study, higher prolactin levels predicted ejaculatory dysfunction and – at a trend level - erectile dysfunction. Hummer et al. (39) have compared haloperidol- and clozapine-treated patients and found little difference in the incidence of sexual disturbances in patients on these medications in the long term. Although prolactin was not measured in this study, it indirectly supports the notion that prolactin levels are not the major driving force behind antipsychotic-induced sexual problems as clozapine, in stark contrast to haloperidol, has no sustained influence on prolactin levels. Yet, there is also evidence for less sexual dysfunction on clozapine than on other antipsychotics (40, 41). Van Bruggen and colleagues (29) concluded that SDs in patients with first episode psychosis can occur despite normal prolactin levels. Konarzewska and

colleagues (42) described risperidone to elicit a higher prolactin elevation than olanzapine and associated this with lowered levels of testosteron and FSH. Patients receiving risperidone showed higher level of sexual dysfunction and treatment non-adherence than those treated with olanzapine.

When reviewing the research on the association between plasma prolactin and disturbances of sexual experience and function, one is struck by the inconsistency of findings. All evidence taken together one can conclude that it is highly unlikely that prolactin elevation is the sole cause of SD. Other neurobiological causative factors, including peripheral effects of antipsychotics on sexual target organs must also be appreciated. It is interesting that no SDs occur in women with idiopathic hyperprolactinemia, who are substituted with oestrogen, which suggests that hypogonadism, which has been found long before the introduction of antipsychotics (43), must also be considered. In contrast to the inconsistent effects on SDs, a close connection between the prolactin-increasing properties of amisulpride and menstrual irregularities is very likely, as substantiated in our study.

All patient groups showed a high prevalence of hyperprolactinemia at baseline. Whether or not patients were antipsychotic-naïve or had received any other medication prior to study entry had no influence (data not shown). Next to prolactin-producing tumors, which can be ruled out in our sample, various physiological factors may have contributed to hyperprolactinemia. Different types of stress and sleep disturbances can lead to an increase of prolactin levels (44). As patients in our study were acutely ill, psychotic stress and/or agitation may have led to prolactin increase. Extreme physical exercise, as sometimes performed by psychotic patients, has also been suggested as a possible cause (45).

Clearly, non-pharmacologic variables also have an impact on the sexuality of schizophrenia patients. In men, a high PANSS general psychopathology score was a predictor for a higher rate of erectile, ejaculatory and orgastic dysfunction. Age was a negative predictor for orgastic

dysfunction. As the latter finding is what one would intuitively expect, it can also be seen as an internal indicator for the validity of the SD assessment used in this study. Higher PANSS positive subscores predicted increased libido, which decreased over time in relation to symptom improvement. This indicates an association between psychopathological symptoms and sexual performance in men. In female patients (like in men), a high PANSS negative subscore predicted decreased libido. This is in contrast to Fan and colleagues (46), who found higher scores on the PANSS positive subscale to be significantly associated with more difficulty in both sexual arousal and orgasm in women but have not reported a connection between PANSS negative scores and decreased libido. This may well be explained by a considerably smaller sample studied by this group. Westheide and colleagues (47) found an association between SD and subjective well-being in risperidone-treated patients, emphasizing the clinical relevance of sexual functioning in schizophrenia and its potential influence on compliance behaviour, as also discussed by Montejo et al. (15).

In summary, our findings indicate that SD in first-episode schizophrenia patients is a common problem, as shown by its prevalence and chronicity. These adverse events were fairly evenly distributed between the five antipsychotics administered while patients on amisulpride presented with a clearly higher risk for amenorrhea and galactorrhea. Psychopathology and age also contributed to SD.

As sexual experiences are vulnerable to subjective interpretation, the open-label, although randomized, design of our study must be taken into account when evaluating the reported data. Furthermore, the UKU is a general adverse event scale which has not been specifically validated to assess SD in schizophrenia patients. Future studies should employ more specific rating scales like the aforementioned PRSexDQ- Salsex. Unfortunately, we also have no information about pretreatment sexual activity of our patient sample. We also have not collected information regarding the subjective relevance of SD. Lastly, the difficulties of

assessing sexual functioning in general and more specifically in schizophrenia patients need to be acknowledged.

Despite these potential limitations, this study is the first to report on a large, unselected sample of first-episode schizophrenia patients, about 30% being drug-naïve. All schizophrenia patients had a recent onset of the disorder, so that the debilitating effects of chronic schizophrenia could not yet have materialized. As first encounters with psychiatric institutions including the positive and negative effects of medication are known to shape future attitudes and the therapeutic alliance, this is a group of patients deserving special attention with respect to satisfaction with their sexual lives.

The EUFEST Steering Committee: RS Kahn, WW Fleischhacker, H Boter, IPM Keet, C Brugman, M Davidson, S Dollfus, W Gaebel, S Galderisi, M Gheorghe, I Gonen, DE Grobbee, LG Hranov, M Hummer, J Libiger, N Lindefors, JJ López-Ibor, K Nijssen, J Peuskens, D Prelipceanu, A Riecher-Rössler, JK Rybakowski, G Sedvall, M v Wilmsdorff.

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Table 1 Prevalence of sexual dysfunctions in male and female patients: baseline vs. 12 months (end of treatment)

	Prevalence of SD (UKU score ≥ 1) all APs pooled		Statistics[a]	
	Baseline	12 months (LOCF)	Time (baseline vs. 12 months)	Time (baseline vs. 12 m) x AP
Sexual dysfunctions in men				
Gynaecomastia	1.3 %	4.2 %	p=0.065	n.s.
Erectile Dysfunction	17.7 %	16.9 %	n.s.	n.s.
Ejaculatory Dysfunction	15.7 %	12.3 %	n.s.	n.s.
Increased Libido	7.1 %	2.1 %	p=0.017	n.s.
Decreased Libido	30.8 %	27.4 %	n.s.	n.s.
Orgastic Dysfunction	15.0 %	11.9 %	n.s.	n.s.
Sexual dysfunctions in women				
Menorrhagia	5.7 %	3.4 %	n.s.	n.s.
Amenorrhea	11.9 %	9.1 %	n.s.	χ^2_4=14.3, p=0.006 [b]
Galactorrhea	1.1 %	5.1 %	p=0.039	χ^2_4=18.6, p=0.001 [c]
Dry vagina	4.7 %	7.5 %	n.s.	n.s.
Increased Libido	8.2 %	5.2 %	n.s.	n.s.
Decreased Libido	27.5 %	25.3 %	n.s.	n.s.
Orgastic Dysfunction	11.3 %	17.9 %	n.s.	n.s.

[a] Analysis by Mc Nemar test (column “Time”) and by ordinal logistic regression on changes in sexual dysfunctions (column “Time x AP”)

[b] Analysis or treatment contrasts indicates significantly stronger increase of amenorrhea with Amisulpride than with Haloperidol or Olanzapine ($\chi^2 > 7.0$, $p<0.01$)

[c] Analysis or treatment contrasts indicates significantly stronger increase of galactorrhea with Amisulpride than with Olanzapin, Quetiapine or Ziprasidone ($\chi^2 > 6.0$, $p\leq0.014$)

SD=sexual dysfunction, AP=antipsychotic, LOCF=last observation carried forward, n.s. = not significant ($p > 0.1$)

Table 2: Prevalence of amenorrhea and galactorrhea over the course of time

	Randomized study medication (AP)					Statistics (Generalized estimating equations logistic regression)		
	Haloperidol	Olanzapine	Quetiapine	Amisulpride	Ziprasidone	Effect [a]	χ^2/d.f.	p-value
Amenorrhea								
Baseline	19.4%	15.8%	18.2%	6.5%	2.6%	Time	12.98/ 5	0.024
1 month	21.9%	21.1%	20.6%	17.4%	11.8%	AP	7.03/ 4	0.134
3 months	20.7%	13.5%	22.9%	28.2% ↑	6.1%	Time[b] x AP	6.31/ 4	0.177
6 months	4.0%	14.3%	22.6%	35.3% ↑	10.3%	AP without baseline[c]	10.19/ 4	0.037
9 months	9.1%	9.1%	17.9%	20.6%	10.3%	*Amisulpride vs. Haloperidol*	*6.35/ 1*	*0.012*
12 months	0.0%	5.9%	14.3%	18.2%	3.6%	*Amisulpride vs. Olanzapine*	*5.67/ 1*	*0.017*
						Amisulpride vs. Ziprasidone	*3.92/ 1*	*0.048*
Galactorrhea								
Baseline	2.8%	0.0%	0.0%	0.0%	5.3%	Time	6.87/ 5	0.230
1 month	6.3%	0.0%	0.0%	10.9% (↑)	5.9%	AP	19.21/ 4	0.001
3 months	3.4%	0.0%	5.9%	17.9% ↑	0.0%	Time[b] x AP	12.72/ 4	0.015
6 months	8.0%	2.9%	3.2%	14.7% (↑)	3.4%	*Amisulpride vs. Haloperidol*	*5.79/ 1*	*0.016*
9 months	4.5%	0.0%	3.6%	11.8%	3.4%	*Amisulpride vs. Olanzapine*	*7.71/ 1*	*0.005[d]*
12 months	7.7%	0.0%	0.0%	15.2% (↑)	0.0%	*Amisulpride vs. Quetiapine*	*5.81/ 1*	*0.016*
						Amisulpride vs. Ziprasidone	*9.42/ 1*	*0.002[d]*

[a] This column contains the main effects and interaction terms used in the GEE logistic regression analysis as well as the statistically significant time-by-treatment contrasts (galactorrhea) or post-baseline treatment contrasts (amenorrhea) evaluated by the least-significant-difference (LSD) method

[b] Time was dichotomized into baseline vs. post-baseline (see Statistical Methods section)

[c] Analysis of post-baseline observations only, with adjustment for baseline value (see Statistical Methods section)

[d] Statistical significance is maintained after Bonferroni correction for multiple comparisons

↑ Significantly higher than at baseline using McNemar's test, $p<0.05$ [(↑) $p < 0.07$]

AP=antipsychotic, GEE= Generalized estimating equations, d.f. = degrees of freedom

Table 3: Effect of age, psychopathology and prolactin level on sexual dysfunctions: Results of GEE logistic regression analysis

Gender	Sexual dysfunction	Predictor				
		Age	PANSS pos.	PANSS neg.	PANSS general	Prolactin level (ln)
Male	Gynaecomastia	n.s.	n.s.	n.s.	n.s.	n.s.
	Erectile Dysfunction	β = 0.080, χ^2 = 12.6 p<0.001	n.s.	n.s.	β=0.015, χ^2 = 5.5 p=0.019	β =.249, χ^2 = 3.7 p=0.053
	Ejaculatory Dysfunction	β = 0.060, χ^2 = 5.5, p=0.019	n.s.	n.s.	β = 0.015, χ^2 = 4.9 p=0.027	β = 0.296, χ^2 = 4.3 p=0.038
	Increased Libido	n.s.	β = 0.081, χ^2 = 18.2 p<0.001	n.s.	n.s.	n.s.
	Decreased Libido	β = 0.076, χ^2 = 16.1 p<0.001	n.s.	β = 0.047, χ^2 = 22.4 p<0.001	n.s.	n.s.
	Orgastic Dysfunction	β = 0.072, χ^2 = 8.4 p=0.004	n.s.	n.s.	β = 0.014, χ^2 = 3.8 p=0.050	n.s.
Female	Menorrhagia	n.s.	β = 0.057, χ^2 = 5.9 p=0.015	n.s.	n.s.	n.s.
	Amenorrhea	n.s.	n.s.	n.s.	n.s.	β = 0.49, χ^2 = 5.9 p=0.015
	Galactorrhea	n.s.	n.s.	n.s.	n.s.	n.s.
	Dry vagina	n.s.	n.s.	n.s.	n.s.	n.s.
	Increased Libido	n.s.	(β = 0.039, χ^2 =2.8, p=0.093)	n.s.	n.s.	n.s.
	Decreased Libido	n.s.	n.s.	β = 0.040, χ^2 = 9.6 p=0.002	n.s.	n.s.
	Orgastic Dysfunction	n.s.	n.s.	n.s.	n.s.	n.s.

GEE= Generalized estimating equations, PANSS = Positive and Negative Syndrom Scale, n.s. = not significant (p> 0.1)