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Sexual dysfunction and hyperprolactinemia in schizophrenia before and after six weeks of $D_{2/3}$ receptor blockade – An exploratory study

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ABSTRACT

Sexual side-effects along with antipsychotic treatment may be linked to hyperprolactinemia and dopamine D_2 receptor blockade. High prevalence of sexual dysfunction in un-medicated patients challenges the notion of sexual dysfunction as merely a side-effect of antipsychotic medication. Sexual dysfunction was assessed in fifty-six initially antipsychotic-naïve patients with schizophrenia using the UKU (Udvalget for Kliniske Undersøgelser) questionnaire. Serum-prolactin was obtained before and after six weeks of $D_{2/3}$ receptor blockade with amisulpride. At baseline 68% of patients reported one or more items of sexual dysfunction (males > females,), but the cumulative load of sexual dysfunction was similar in males and females. After 6 weeks treatment with amisulpride (mean dose 279 mg/day), 65% of patients reported one or more items of sexual dysfunctions (females > males). There was a significant sex*time interaction on mean sexual dysfunction load. All patients developed hyperprolactinaemia, and a significant effect of time and sex was found on s-prolactin (females > males). The results support that patients with schizophrenia report high levels of sexual dysfunction before antipsychotic exposure. After treatment, sexual side-effects were more frequent in females, coinciding with pronounced serum-prolactin increases. These findings suggest sex differences in sexual dysfunction before and after antipsychotic treatment.

1. Introduction

The majority of patients with schizophrenia suffer from life-long symptoms, which require either continuous or intermittent antipsychotic treatment. The symptoms typically develop during the late adolescence, and the diagnosis and prescription of antipsychotic treatment is often initiated in early adulthood (Pedersen et al., 2014). Since antipsychotics are often prescribed when the sexual identity is still evolving, sexual dysfunction may be associated with the recently initiated antipsychotic treatment as a potential side-effect, which may constitute an underestimated clinical problem. The prevalence of sexual dysfunction in patients treated with antipsychotic medication has been estimated to be from 30% to 80% in women and 45% to 80% in men (Just, 2015), with great variability depending on antipsychotic compounds (Serretti and Chiesa, 2011). Studies in un-medicated schizophrenia patients are scarce, but indicate a prevalence of sexual dysfunction in up to 30% of the patients (Aizenberg et al., 1995; Malik et al., 2011; Kahn et al., 2018). These high rates could suggest that schizophrenia itself may affect sexual function, although direct comparison with age and gender matched healthy volunteers is needed to draw this conclusion.

Sexual wellbeing is a complex state of intertwining aspects (Kelly and Conley, 2004), and multiple aspects like individual, relational, societal and cultural factors contribute to perceived sexual wellbeing or dysfunction (de Boer et al., 2015). Schizophrenia symptomatology contains numerous aspects that influence the patients' perception of others, the perception of sensorial inputs, and the understanding of the surrounding environments attitude towards the patient. These are all factors that may affect sexual wellbeing and recently different aspects of symptomatology has been associated with specific sexual complaints in first-episode schizophrenia (Malik et al., 2011). However, the higher prevalence observed in long-term, medicated patients could suggest that antipsychotic treatment may further impair sexual function, along with progression of the disease.

Multiple mechanisms may contribute to the development of sexual dysfunction during antipsychotic treatment: histaminergic blockade

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may lead to sedation; a direct effect on peripheral adrenergic receptors may negatively affect erectile function; and blocking of dopamine D_2 receptors may alter the reward system and thereby decrease sexual desire (Corona et al., 2015; Sansone et al., 2014; Zaazaa et al., 2013). During the course of illness, both antipsychotic treatment and life style factors may lead to development of hypertension, diabetes and/or obesity which further may compromise sexual function. Additionally, other life style factors like increased rates of tobacco use and substance abuse in schizophrenia patients may impact negatively on specific sexual functions and contribute to the development of e.g. erectile dysfunction. Collectively, these metabolic and lifestyle factors are influenced by factors such as age and gender, and the exact contributions on sexual dysfunction from each of the factors are difficult to disentangle.

Antipsychotic compounds have antagonistic properties on the dopamine D_2 receptor, and dopamine suppresses the release of prolactin from the anterior pituitary gland. Hyperprolactinemia is therefore a common side-effect of antipsychotic compounds and has been hypothesized to contribute to sexual dysfunction in schizophrenia. While the physiological link between dopaminergic blockade and hyperprolactinemia is well-described, the relation between antipsychotic induced serum-prolactin(s-prolactin) increase and development of sexual side-effects appears more elusive. In primary hyperprolactinemia, prolactin-induced hypogonadism may decrease sexual functioning (Galdiero et al., 2012). In patients treated with antipsychotics, higher prevalence of sexual dysfunction has been reported by patients receiving prolactinogenic compounds (Serretti and Chiesa, 2011; Rubio-Abadal et al., 2016), but direct associations between antipsychotic associated hyperprolactinemia and sexual dysfunction have not been consistently reported (Marques et al., 2012; Howes et al., 2007; Westheide et al., 2007). In this respect, physiological sex-differences may be of particular importance.

In females, s-prolactin is affected by the regulation of the menstrual cycle and breastfeeding (Marano and Ben-Jonathan, 2014). Accordingly, the physiological level of prolactin in females is higher (s-prolactin, $\leq$0.6 IU/L) and have more pronounced fluctuations than in men (s-prolactin $\leq$0.4 IU/L) (Beltran et al., 2008). Complaints in female patients treated with antipsychotics include menstrual disturbances, anorgasmia and lack of lubrication of the vagina, whereas males report erectile dysfunction and ejaculatory disturbances (Capozzi et al., 2015; Knegtering et al., 2008; Baggaley, 2008). Both sexes may report changes in sexual desire as well as gynecomastia and galactorrhea, but e.g. gynecomastia may have other sexually and social implications for males than for females. In addition to an effect on quality of life and social relations, sexual dysfunction may lead to discontinuation of antipsychotic treatment, which in turn may result in relapse of psychotic symptoms and a poorer long-term outcome (Carbon and Correll, 2014). Clarification of the complex relationships between antipsychotic exposure, s-prolactin levels and different aspects of sexual functioning are therefore of major clinical importance.

1.1. Aims of the study

The current data on sexual dysfunction and s-prolactin stem from a multimodal study on initially antipsychotic-naïve first-episode schizophrenia. Since the present outcome measures were not the primary focus of the larger study protocol (clinicaltrial.gov identifier NCT01154829), the analyses pertaining to the current study were motivated by their clinical relevance and should be considered explorative. Data were collected before and after six weeks of antipsychotic monotherapy with the selective dopamine $D_{2/3}$ receptor antagonist, amisulpride.

We expected amisulpride to increase s-prolactin levels, and we hypothesized that higher s-prolactin levels after treatment would be associated with increased reports of sexual side-effects at six weeks follow-up. Finally, we explored sex differences and relation to psychopathology.

2. Material and methods

2.1. Subjects

This project was approved by the research ethics committee (protocol HD-2008-008), and all participants signed informed consent (Clinicaltrials.gov, ID, NCT01154829). Antipsychotic-naïve patients with first-episode schizophrenia were recruited from mental health centers within the Capital Region of Copenhagen, Denmark. We included in- and outpatients fulfilling ICD-10 criteria for schizophrenia or schizoaffective disorder, as evaluated by a semi-structured interview (SCAN 2.1). Exclusion criteria were: mental disability, any other chronic diseases, use of antidepressive medicine during the last month, pregnancy, and subject to coercive treatment. Present recreational use of drugs was allowed, but substance dependency was not.

The main focus of the study was to examine the effect of a $D_{2/3}$ receptor antagonist on neurobiological measures and therefore the follow-up period was determined to six weeks to balance longest treatment duration to minimal risk of attrition. Data on functional magnetic resonance imaging (Nielsen et al., 2012a,b; Nielsen et al., 2016), structural MRI (Jessen et al., 2018a, b), electrophysiology (During et al., 2014, 2015), single-photon emission computed tomography (Wulff et al., 2015, 2019), diffusion tensor imaging (Ebdrup et al., 2016), cognition (Jensen et al., 2018), and across modalities (Bak et al., 2017; Ebdrup et al., 2018) from the current cohort have previously been published. Here we solely report on patient data related to sexual side-effects, s-prolactin, psychopathology and amisulpride dose.

2.2. Procedure

Self-reported sexual side-effects were measured using the UKU questionnaire (Udvalg for Kliniske Undersøgelser, Lingjaerde et al., 1987). This scale has been used both in clinical practice and in several larger studies (Malik et al., 2011; Kahn et al., 2018). Among other side-effects the scale contains items on both sex-specific and more general sexuality related side-effects, with the option of the patient refraining from answering.

S-prolactin was measured using Immunoassay Systems (ADVIA Centaur, Siemens, Deerfield, IL, USA) at the Department of Clinical Biochemistry, Herlev University Hospital, Denmark (Beltran et al., 2008). Because s-prolactin levels may be affected by diurnal variation and food intake (Coello et al., 2015), blood samples were acquired in the morning and in fasting state, after refraining from smoking for 30 min. Hyperprolactinemia was defined as $>$0.4 IU/L for males and $>$0.6 IU/L for females. Patients were treated with individual doses of amisulpride balancing optimal clinical effect to minimal side-effects. Psychopathology was measured using the positive and negative syndrome scale (PANSS) (Kay et al., 1987) and Calgary Depression Scale in Schizophrenia (CDSS) (Addington et al., 1993).

2.3. Statistical analysis

Demographic variables and clinical characteristics are provided in mean values with standard deviations and range for normally distributed, continuous variables. Differences between males and females were tested with independent *t*-tests. To enable comparison between our observed frequency of reported sexual dysfunction with previous reports (Malik et al., 2011), the UKU variables were dichotomized into 'no sexual dysfunction' (score = 0) or 'sexual dysfunction' (score > 0). Likewise, the change during treatment was dichotomized into "increased sexual dysfunction" (increase in UKU score on any item) or "stable/decreased sexual dysfunction" (no increase in UKU score on any items). Chi square test was used to test for potential sex differences in

the number of patients reporting any sexual dysfunction at baseline and any sexual side-effects at follow-up. Likewise, chi square test was used to evaluate sex differences in number of patients who increased score on any UKU item(s), and patients, who were stable or decreased on all UKU items. Additionally, the effect of time on each of the raw, non-dichotomized UKU score were analyzed using Wilcoxon signed rank test.

Because baseline s-prolactin values were not normally distributed according to Shapiro–Wilk test of normality, s-prolactin was logarithmic transformed to obtain a normal distribution. The effect of sex and time was tested using repeated measures ANOVA with and without PANSS and CDSS as covariates. In planned *post hoc* analyses sex-difference in s-prolactin at baseline and follow-up was tested with student's *t*-tests, and sex-specific effect of time was examined using paired *t*-test. Pearson correlation was used to test the possible associations between medication dose and s-prolactin change or s-prolactin after six weeks.

In order enable exploration of the relation between prolactin levels and sexuality related side-effects we estimated an overall 'load of sexual side-effects' as the sum of the raw UKU items for each patient. The sexual side-effect load was calculated both at baseline and after six weeks and potential effect of sex and time was tested using repeated measures ANOVA with and without PANSS and CDSS as covariates. The relation between sexual side-effect load and s-prolactin at baseline, at follow-up, and change was tested with Spearman's correlations. This was done for the complete sample and for each sex separately using a total of 3*3 Spearman's correlations. Finally, in exploratory analyses, the effect of age, medication dose, PANSS and CDSS scores on the sexual dysfunction load (at baseline, at follow-up, and change) were tested with Spearman's correlations.

All analyses were performed using SPSS (IBM SPSS statistics 22.0), and the level of significance set to $p < 0.05$ (two-sided). Analyses were repeated excluding patients with elevated prolactin at baseline, these results are reported in the supplement material.

3. Results

3.1. Demographics and psychopathology

Sixty-nine patients were included, but not all variables were available for all patients at all time points. Numbers and reasons for missing values are provided in Fig. 1 and demographics and clinical characteristics at baseline and follow-up are provided in Table 1. Patients were treated for six weeks with a mean dose of amisulpride of 279 (SD ± 149) mg/day. Males received a mean dose of amisulpride (289 mg/day, SD ± 132) comparable to that of females (266 mg/day, SD ± 170) ($p = 0.64$).

3.2. Sexual dysfunction and sexual side-effects

At baseline, UKU data were available for 59 patients (21 females), and after six weeks UKU data was available on 46 patients (18 females). Since not all UKU questionnaires were complete, the exact numbers of responders per UKU item are provided in Table 2.

At baseline, 68% of the patients reported scores >0 on one or more of UKU items. In the sex specific analyses, we found that at baseline significantly more males (77%) than females (52%) reported scores >0 on one or more of UKU items ($\chi^2 = 3.8, p < 0.05$). However, the mean sexual dysfunction load at baseline did not differ between sexes (mean sexual dysfunction load, males = 1.4 and females =1.4, $t = 0.8$, $p = 0.94$).

For the specific items, *decreased desire* was reported in 36% of all patients, and this was most pronounced in males (45% of males and 19% of females; $\chi^2 = 3.89, p < 0.05$). There were no sex-differences in the prevalence of *increased desire, galactorrhoe* and *gynaecomastia.*

After six weeks of antipsychotic treatment, UKU data were available for 46 patients. There were no differences in any psychopathology score or age between patients who dropped out and those who stayed in the study. At follow-up, 65% of the patients reported scores >0 on one or more of UKU items (46% of males and 94% of females, $\chi^2 = 11.1$, $p < 0.01$). Accordingly, the mean sexual dysfunction load after six weeks was significantly higher in females compared to males (mean sexual dysfunction load, males 0.8 and females=2.8, $t = 4.5$; $p < 0.01$). Repeated measure ANOVA showed no significant effect of time but a significant effect of sex ($F(1;40) = 10.4, p < 0.01$) and a sex*time interaction ($F(1;40) = 7.8, p < 0.01$). Adding PANSS and CDSS as covariates did not significantly alter these results. Post hoc paired *t*-test showed a significant decrease in sexual dysfunction load in males ($t = 2,1, p < 0.5$), and a trend towards increased load in females ($t = 1,8, p = 0.09$)

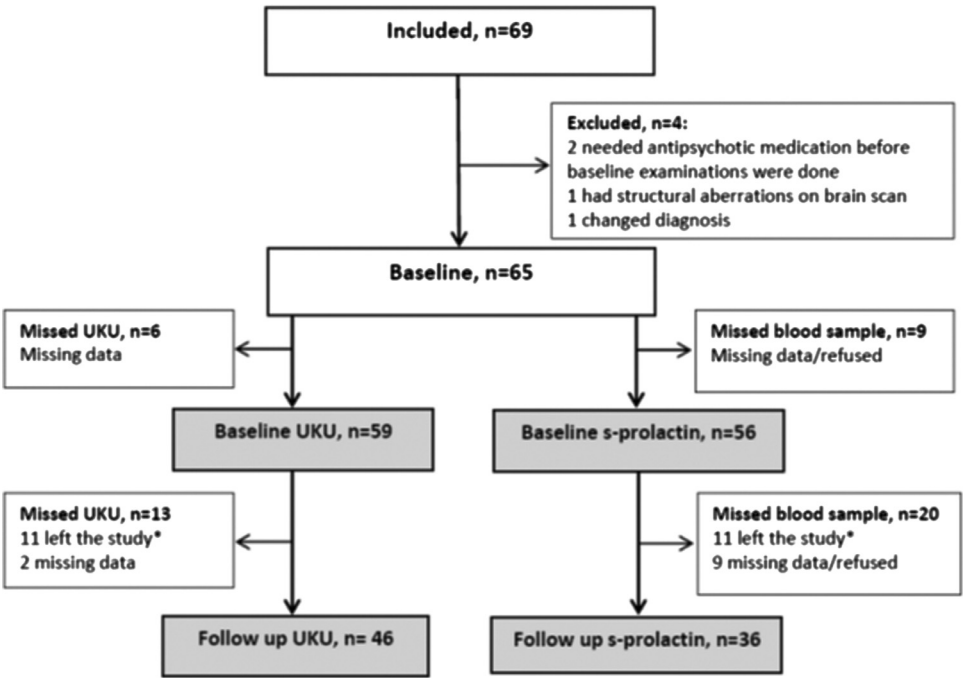

Fig. 1. Shows the flowchart of data collection. Grey boxes indicate the patients included in analyses, however not all questions of the UKU was answered by all individuals. Precise information on each item is available in Table 2. *11 patients left the study between baseline and 6 weeks follow-up examination; 7 patients refused, discontinued or changed medication, and 4 patients declined follow-up examination.

Table 1
Participants' distribution on age, sex, prolactin levels and psychopathology before and after six weeks of amisulpride monotherapy.

Baseline	All *N* = 56	Male *N* = 35	Female *N* = 21	Sex difference *p*-value
Age	24.7 (6.1)[18–42]	26.1 (6.5)[19–42]	22.6 (4.6)[18,34]	**<0.05**
PANSS, total	83 (16.1)[39–115]	84 (15.9)[41–115]	80 (16.5)[39–110]	0.85
positive	20 (4.3)[9–29]	20 (4.2)[9–28]	21 (4.6)[10–29]	0.73
negative	21 (7.3)[7–38]	22 (6.9)[9–38]	18 (7.4)[7–30]	**<0.05**
general	41 (8.4)[21–57]	41 (8.9)[21–57]	41 (7.7)[22–55]	0.93
CDSS (*N* = 48/32/16)	5.3 (3.7)[0–15]	4.1 (2.5)[0–9]	7.6 (4.7)[1–15]	**<0.05**
s-prolactin (IU/L)	0.28 (0.17)[0.08–1.0]	0.26 (0.17)[0.2–1.0]	0.33 (0.17)[0.08–0.7]	0.13
6 weeks	*N* = 36	*N* = 19	*N* = 17	*p*-value
Age	24.3 (6.4)[18–42]	25.4 (7.4)[19–42]	23.0 (5.0)[18–34]	0.26
PANSS, total	63 (11.7)[41–100]*	61 (12.9)[41–100]*	66 (10.0)[42–78]*	0.26
positive	14 (4.1)[7–21]*	14 (4.4)[7–19]*	15 (3.9)[9–21]*	0.38
negative	19 (5.4)[9–33]	18 (5.7)[10–33]	19 (5.2)[9–30]	0.43
general	30 (6.3)[20–48]*	29 (7.1)[20–48]*	31 (5.2)[20–39]*	0.30
CDSS (N = 30/17/13)	3.0 (2.9)[0–11]*	2.6 (3.2)[0–11]	3.5 (2.6)[0–9]*	**0.42**
s-prolactin (IU/L)	2.1 (0.9)[0.7–4.1]*	1.6 (0.8)[0.7–4.1]*	2.6 (0.7)[1.6–4.0]*	**<0.01**
s-prolactin increase**	1.8 (0.9)[0.6–3.7]	1.4 (0.8)[0.6–3.7]	2.3 (0.7)[1.4–3.6]	**<0.01**
Amisulpride (mg/day)	279 (149)[50–600]	289 (132)[100–600]	266 (170)[50–600]	0.64

Standard deviation () and range [] are provided. Differences between males and females were tested with independent *t*-test, p values are specified in the right column and significant sex differences are indicated in bold. Effect of time was tested with paired *t*-test for the PANSS scores, and with repeated measures ANOVA for logistically transformed s-prolactin (the shown s-prolactin values were not transformed).

* Indicate significant effects of time.

** s-prolactin increase was calculated as, s-prolactin (6 weeks) – s-prolactin (baseline).

Table 2
The reported prevalence of sexual dysfunction (UKU item) before and after six weeks of amisulpride monotherapy.

UKU item	All Baseline	 6 weeks	Male Baseline	 6 weeks	Female Baseline	 6 weeks
Increased desire	**20%** (12/59)	**13%** (6/46)	**18%** (7/38)	**14%** (4/28)	**24%** (5/21)	**11%** (2/18)
Decreased desire	**36%** (21/59)	**28%** (13/46)	**45%** (17/38)	**21%** (6/28)	**19%** (4/21)	**39%** (7/18)
Galactorrhoea	**7%** (4/58)	**30%** (13/44)	**5%** (2/38)	**4%** (1/26)	**10%** (2/20)	**67%** (12/18)*
Gynaecomastia	**14%** (8/56)	**27%** (12/44)	**14%** (5/37)	**4%** (1/26)	**16%** (3/19)	**61%** (11/18)*
Erectile dysfunction	n.a.	n.a.	**7%** (2/28)	**15%** (4/26)	n.a.	n.a.
Ejaculatory dysfunction	n.a.	n.a.	**15%** (4/27)	**15%** (4/26)	n.a.	n.a.
Orgasmic dysfunction	n.a.	n.a.	n.a.	n.a.	**26%** (4/15)	**17%** (3/18)
Menorrhagia	n.a.	n.a.	n.a.	n.a.	**6%** (1/17)	**6%** (1/18)
Amenorrhoea	n.a.	n.a.	n.a.	n.a.	**18%** (3/17)	**50%** (9/18)
Decreased lubrication	n.a.	n.a.	n.a.	n.a.	**14%** (2/14)	**17%** (3/18)

Not all questionnaires were complete. In brackets the total number of patients answering the question regarding the specific symptom is provided along with the number of patients who reported any sexual related dysfunction (a score of 1, 2 or 3 at the UKU).n.a. = not applicable (sex specific items).

* Indicates a significant effect of time ($p < 0.05$).

For the specific items, *galactorrhoea* was reported in 30% of all patients, and was significantly more pronounced in females (4% of males and 67% of females; $\chi^2 = 20.1, p < 0.01$). *Gynaecomastia* was reported in 27% of all patients and was significantly more pronounced in females (4% of males and 61% of females; $\chi^2 = 17.6, p < 0.01$). There were no sex-differences in the prevalence of *increased* and *decreased desire* (Table 2 for details).

After six weeks of amisulpride treatment 62% of all patients, and significantly more females (40% of males and 94% of females, $\chi^2 = 11.1, p < 0.01$), provided an increased report of symptoms on one or more UKU item. Wilcoxon signed rank test on separate UKU scores in the whole patient group, showed no significant overall change in UKU scores after six weeks ($N = 42$, *p*-values >0.1), except from *galactorrhea*, where a significant increase was observed ($N = 42$, $z = -3.01$, $p < 0.01$). In Wilcoxon analyses segregated on sex, females reported significant increases in *gynecomastia* ($N = 16$, $z = -2.31$, $p = 0.02$) and *galactorrhea* ($N = 17$, $z = -2.98$, $p < 0.01$). Apart from a trend level reduction in the number of males reporting *decreased desire* ($N = 25$, $z = 1.8$, $p = 0.06$), we found no significant effect of time on separate UKU items in males (Table 2).

In summary, at baseline, more males than females reported sexual dysfunction, especially regarding *decreased desire*. After six weeks of amisulpride treatment, more females reported sexual dysfunction, especially regarding *gynecomastia* and *galactorrhea*. Analyses were repeated excluding patients with increased prolactin at baseline, please see supplement material.

3.3. S-prolactin

At baseline, s-prolactin was available in 56 patients (Table 1). The median s-prolactin level in all patients was 0.27 IU/L [range 0.08–1.00] with no significant sex difference (males 0.20 IU/L [range 0.08–1.0]; females 0.34 IU/L [range 0.08–0.69]; $t = 1.6$, $p = 0.12$). Mean s-prolactin levels are provided in Table 1. At baseline, 11% (4/35) males and 10% (2/21) females had hyperprolactinemia (Fig. 2).

After six weeks of amisulpride treatment, s-prolactin was available for 37 patients (17 females), and both baseline and follow-up s-prolactin was available in 36 patients (17 females). After six weeks, all patients (100%) had hyperprolactinemia, with a median s-prolactin of 1.4 IU/L [range 0.67–4.06] in males and 2.5 IU/L [range 1.56–3.97] in females (Fig. 2). Repeated measures ANOVA showed significant effect of sex ($F(34,1) = 10.1, p < 0.01$) and time ($F(34,1) = 511, p < 0.01$),

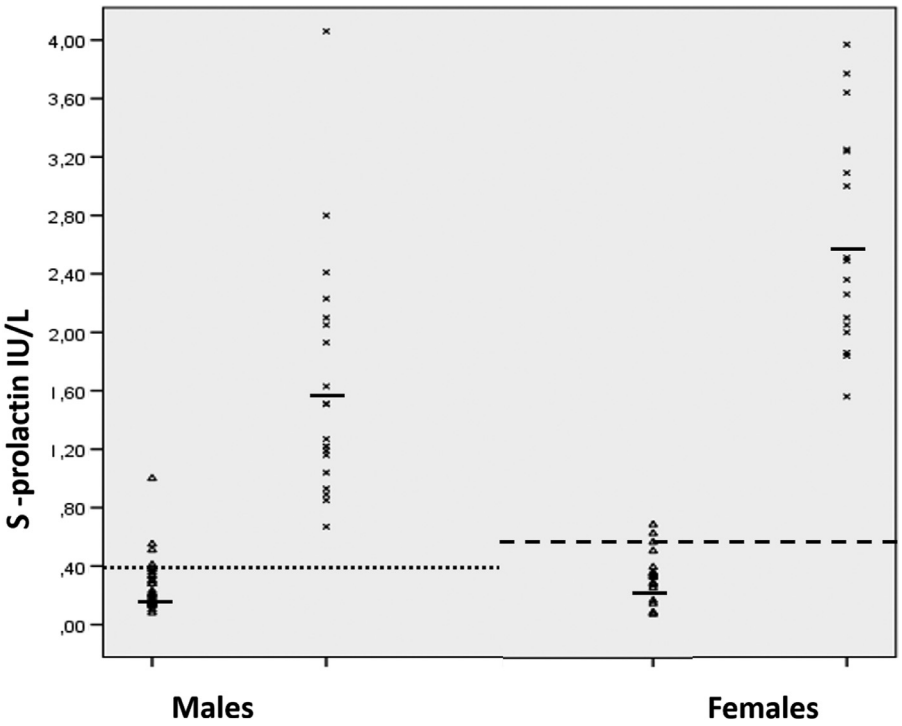

Fig. 2. shows serum prolactin before and after six weeks of amisulpride monotherapy. Baseline values are shown in triangles and values after 6 weeks in crosses. The calculated mean for each sex are marked with a line. Hyperprolactinemia is defined as S-prolactin > 0.40 IU/L for males and > 60 IU/L for females (indicated with dotted lines).

but no significant sex*time interaction ($F(34,1) = 1.4$, $p = 0.24$). Adding PANSS and CDSS as covariates did not significantly alter these results. Result of post hoc *t*-test are provided in Table 1. The mean dose of amisulpride was not correlated with change in s-prolactin or s-prolactin after six weeks (*p*-values >0.7).

3.4. Correlation between sexual dysfunctions and s-prolactin

At baseline, UKU data on sexual side-effects and s-prolactin were available for 50 patients (20 females). There was no correlation between sexual dysfunction load and s-prolactin in the whole group or in analyses segregated on sex. After six weeks, data on sexual side-effects and s-prolactin were available for 35 patients (16 females), but baseline and follow-up data for calculating change was only complete in 30 patients (15 females). There was a significant positive correlation between the increase in sexual dysfunction load and increase in s-prolactin for the whole group (rho = 0.37, $p < 0.05$), but this correlation was not significant when the analysis was separated on sex. Likewise, after six weeks there was a significant positive correlation between sexual dysfunction load and s-prolactin in the whole group (rho = 0.37, $p < 0.05$), but not in analyses segregated on sex (Fig. 3).

3.5. Explorative analyses on factors affecting sexual dysfunction

The planned explorative correlation analyses between sexual dysfunction load and age, medication dose and PANSS total scores, respectively, were not significant in the whole group or in females. In males, however, we found a correlation between higher age and increased sexual dysfunction load at follow-up ($p = 0.04$), and a correlation between increase in sexual dysfunction load and improvement in PANSS total score ($p < 0.01$).

There were no correlations with sexual dysfunction load and CDSS or any PANSS sub-scores at baseline or follow-up. For males, increase in sexual dysfunction load correlated with improvement in PANSS positive, PANSS general and CDSS score. In females, a correlation was found between increase in sexual dysfunction load and increase in CDSS and PANSS negative score. Thus, older males and males with most improvement in psychopathology, particularly positive, general and depressive symptoms reported more sexual dysfunction after amisulpride treatment. In females, sexual dysfunction was reported more frequently when there was an increase in depressive or negative symptoms (Supplementary Table S1 and S2).

4. Discussion

The overall aim of the presented analyses was to examine a possible relation between antipsychotic induced hyperprolactinaemia and sexual side-effects. Apart from gynecomastia and galactorrhea in females, our results did not support this association. One should however be careful to draw firm conclusions based on these negative findings, which call for replication in a larger sample. Despite the limited sample-size, several interesting observations appeared, which may inspire future hypotheses driven work and clinical practice.

4.1. Sexual dysfunction

In this cohort of antipsychotic naïve schizophrenia patients, there was a high report of sexual dysfunction at baseline, indicating that there may be an association between sexual dysfunction and the disease itself, even at earliest stage. In total 68% reported any kind of sexual dysfunction, highest in males, specifically regarding decreased desire. The report of any sexual dysfunction was at a similar level, 65%, after six weeks of medical treatment, but the reporting was significantly higher in females and mainly ascribed to gynecomastia and galactorrhea.

The prevalence of two thirds of patients reporting sexual dysfunction before treatment is higher than previous findings in first-episode patients, also using UKU in a dichotomized way (Malik et al., 2011). However, the baseline level of sexual dysfunction in our and other first episode studies was lower than most previous observations in long term, medicated patients (Montejo et al., 2010; Rubio-Abadal et al., 2016). Although differences in assessment methods can explain some of this variation (Serretti and Chiesa, 2011), there may be other important factors. Our results suggest that age could be an important factor in males, as we found a positive association between age and decreased desire after treatment, which may indicate that with increasing age,

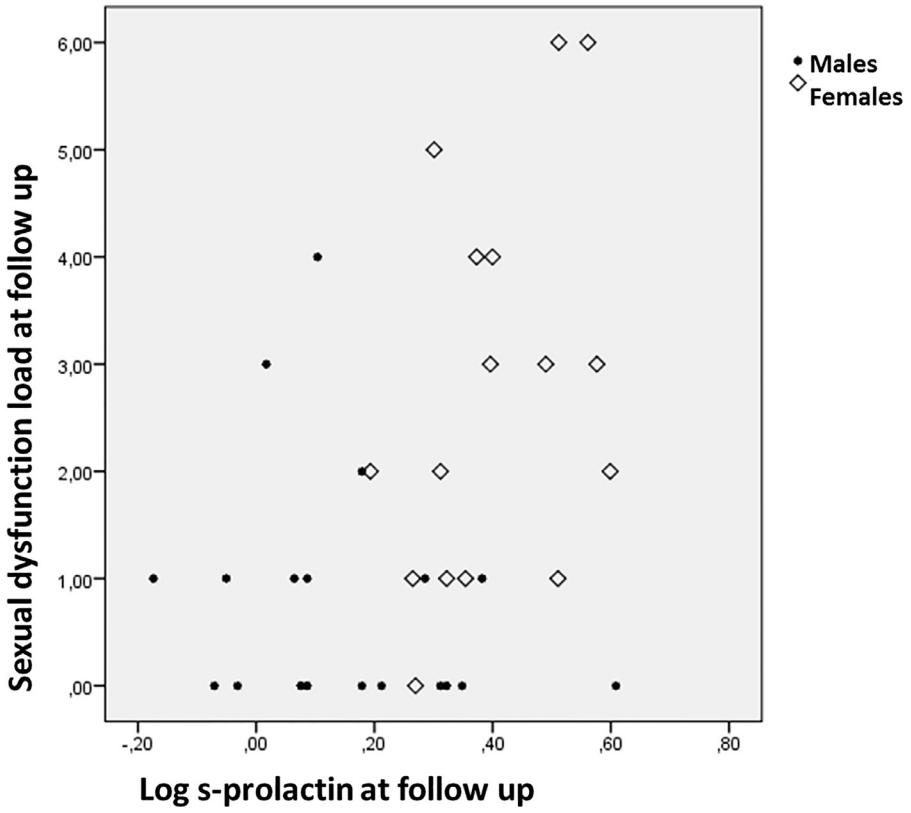

Fig. 3. shows the correlation between sexual dysfunction load and log serum prolactin after 6 weeks of amisulpride treatment for the 35 individuals where both baseline and follow-up data were complete ($r = 0.33$, $p < 0.05$).

males are more prone to sexual side-effects during antipsychotic treatment. The effect of increasing age in males is in line with previous studies (Malik et al., 2011; Martín et al., 2018) Sexual dysfunction in the general population also increases with age (Eisenberg and Meldrum, 2017) and some additional effects of antipsychotic treatment may add to the age effect, e.g. may secondary negative symptoms as anhedonia, and the increased age related erectile dysfunction leave the patient more sensitive to that particular side-effect.

Although we found a numerical increase in the number of females reporting menstrual problems, this increase did not reach significance. Previous studies have shown that up to 50% of women treated with antipsychotic medication have menstrual disturbances, such as amenorrhoea, oligomenorrhoea or dysmennorrhoea (Inder and Castle, 2011), but the follow-up periode in this case only covers one menstrual cycle and cannot fully describe the item.

4.2. Hyperprolactaenaemia

It has been proposed that schizophrenia itself may cause elevated s-prolactin levels and sexual dysfunction prior to treatment, perhaps through alterations in other hormones such as cortisol (Lennartsson and Jonsdottir, 2011). In the present study, 10% of the patients had hyperprolactinemia at baseline. This was markedly fewer than other studies on antipsychotic-naïve patients, where hyperprolactinemia was found in 24–50% of the patients (Riecher-Rossler et al., 2013; Aston et al., 2010). Apart from differences in the level of stress, the degree of affective or disorganized symptoms may play a role (Segal et al., 2004), but also the circumstances under which the blood samples were drawn are of importance. In the present study, s-prolactin was systematically measured during morning time, with patients fasting, as this factor can affect level of s-prolactin (Coello et al., 2015).

After six weeks of treatment with amisulpride, all patients had hyperprolactinemia, and there was no relation between medication dose and increase in s-prolactin. These observations are in line with a large body of evidence. In the recent review by Peuskens et al., amisulpride was claimed to be one of the most prolactin stimulating antipsychotics (Peuskens et al., 2014), and several studies have reported dose-independent prolactin increase, where significant increases can be observed even with doses as low as 50 mg (Kopecek et al., 2004). Therefore, the observation that 100% of our patients had post-treatment hyperprolactinaemia may not be surprising yet it is an important information to consider when treating first-episode patients with amisulpride. Interestingly, a resent study found that adjunctive treatment with aripiprazol decreased s-prolactin as well as sexual dysfunction (Fujioi et al., 2017). Although this was observed in a small, open-label study, this could point to a possible future treatment-strategy against hyperprolactinaemia.

4.3. Sex differences

Our main hypothesis was, that the increase in prolactin would be associated with an increase in sexual side-effects. Since the number of patients reporting sexual dysfunction did not change during treatment, this relation could not be confirmed. However, change in s-prolactin and s-prolactin at follow-up was positively correlated with the load of sexual dysfunction, whereas no relation between s-prolactin and sexual dysfunction was found at baseline. Our results suggest that there was a change in the pattern of reported sexual dysfunctions, which may to some extend be related to sex differences. As illustrated in Fig. 3, there seemed to be an effect of sex with females having a higher score on both variables, which was supported by the significant increase in gynecomastia/galactorrhea related complaints in females during treatment. The s-prolactin increase was significantly higher for females, and females reported a very high frequency of galactorrhea and gynecomastia after treatment.

Although there was also a significant increase in s-prolactin in

males, no significant increase in the report of any of the sexual dysfunctions was found in males. Conversely, males reported a decreased load of sexual dysfunction after treatment. Further, no direct association between prolactin increase and the report of any sexual dysfunction was observed in males. This observation suggests that primary medication induced increase in s-prolactin may not lead to an increased level of the sexual dysfunctions in males. A previous cross-sectional study and a meta analyses have found higher levels of sexual dysfunction in relation to prolactin raising antipsychotic compounds (Serretti and Chiesa 2011; Rubio-Abadal et al., 2016), especially in males (Montejo et al., 2010). Patients in these studies were older, which is interesting, since we found an association between increased report of sexual dysfunction after treatment and increased age and improvement in psychopathology. The increased report of sexual dysfunction in patients with the most improvement in psychopathology may indicate an increased awareness of sexual aspect of life when the psychiatric symptoms are reduced. Clinically, this finding is particularly important since a global assessment of sexual function before the patient commence on antipsychotic treatment, may prevent a later causal linkage between sexual dysfunction and antipsychotic treatment.

In females, there was a significant improvement in depressive symptoms at group level. The highest increase in reported sexual dysfunction was found in the females with the smallest reduction in depressive and negative symptoms, which may point to a possible relation between depressive and negative symptoms and reported sexual dysfunction in females. Decreased sexual desire is a common feature in patients with depressive symptoms; however, several other measures were included in the sexual dysfunction load. Additionally, there were no correlations between CDSS score and sexual dysfunction at baseline or at follow-up. Causal interpretation of these explorative findings should, however, be approached with caution due to limited sample size and multiple statistical testing.

4.4. Strengths

The sample is unique as all patients were initially antipsychotic-naïve, they had no known somatic comorbidity and did not receive any antidepressant medication before and during the study-period. As they all underwent monotherapy with a selective dopamine antagonist, our findings may reliably reflect effects of dopamine D_2/D_3 receptor blockade. Short-term follow-up can be regarded both a strength and weakness, since the sexual dysfunction observed cannot be attributed to increased age or progression of disease, on the other hand, only one menstrual cycle could be observed.

4.5. Limitations

Most importantly, the limited number of patients may explain why we do not detect any sex specific side-effects. UKU is designed for side-effect monitoring, and validated in general, and delivers only knowledge on sexual problems related to possible side-effects, and therefore UKU does not cover all aspects of sexual functioning. In sexology research, other instruments like the PLISSIT evaluation is used (Annon, 1976), but this instrument has not been validated in psychiatric illness. Several studies use PRSexDQ (Montejo et al., 2000), but this scale focus on sexual dysfunctions only and is not available in Danish. Since our study was a multimodal clinical study, the broader information about side-effects provided by UKU was preferred.

There was a considerable drop-out during treatment period. Although this was not higher than expected in comparable clinical studies, more males than females had missing data at follow-up. However, we cannot fully exclude that sexual side-effects could still have influenced the decision to leave the study. Further, the observation period was only six weeks, thus the results are most relevant for the short-term effect of antipsychotic treatment and sexual side-effects and are not representative for menstrual cycle problems. Additionally, there may be an effect of menstrual cycle to s-prolactin and sexual dysfunction which is therefore a potential confounder.

The multiple number of statistical tests in the current study increases the risk Type I errors, but we judged that the biological complexity of the interplay between antipsychotic induced hyperprolactinaemia and sexual side-effects was best addressed using an explorative design with subsequent cautious interpretation.

Overall, the study can be considered explorative as little is known on the subject and the results can be considered grounds for further research.

4.6. Conclusion

The results indicate that there are pronounced sex-differences in the pre-treatment level and the development of sexual dysfunction, in first episode schizophrenia patients receiving antipsychotic short-term treatment. Our results emphasize the importance of uncovering the level of sexual dysfunction before treatment start and monitor any development of sexual side-effects during antipsychotic treatment.

Contributors

MN, SD & BG designed the study. MN, BE & BG wrote the protocol. MN & SD collected the data. MN, SD & NB analyzed the data. MN, SD, NB & BE interpreted the data. SD & MN wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Conflicts of interest

Drs. SD, MN, NB and BG have no conflicts of interest in relation to the subject of this study. Dr. BE has received lecture fees and/or is part of Advisory Boards of Bristol-Myers Squibb, Eli Lilly and Company, Janssen-Cilag, Otsuka Pharma Scandinavia, Takeda Pharmaceutical Company and Lundbeck Pharma A/S.

Supplementary materials

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References

Addington, D., Addington, J., Maticka-Tyndale, E., 1993. Assessing depression in schizophrenia, the Calgary Depression Scale. Br. J. Psychiatry 3 (Suppl), 9–44.
Aizenberg, D., Zemishlany, Z., Dorfman-Etrog, P., Weizman, A., 1995. Sexual dysfunction in male schizophrenic patients. J. Clin. Psychiatry 56, 137–141.
Annon, J.S., 1976. The PLISSIT model, A proposed conceptual scheme for the behavioral treatment of sexual problems. J. Sex Educ. Therapy 2, 1–15.
Aston, J., Rechsteiner, E., Bull, N., Borgwardt, S., Gschwandtner, U., Riecher-Rossler, A., 2010. Hyperprolactinaemia in early psychosis not only due to antipsychotics. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 34, 1342–1344.
Baggaley, M., 2008. Sexual dysfunction in schizophrenia, focus on recent evidence. Hum. Psychopharmacol. 23, 201–209.
Bak, N., Ebdrup, B.H., Oranje, B., Fagerlund, B., Jensen, M.H., Düring, S.W., et al., 2017. Two subgroups of antipsychotic-naive, first-episode schizophrenia patients identified with a Gaussian mixture model on cognition and electrophysiology. Transl. Psychiatry 7, e1087.

Beltran, L., Fahie-Wilson, M.N., McKenna, T.J., Kavanagh, L., Smith, T.P., 2008. Serum total prolactin and monomeric prolactin reference intervals determined by precipitation with polyethylene glycol, evaluation and validation on common immunoassay platforms. Clin. Chem. 54, 1673–1681.
Capozzi, A., Scambia, G., Pontecorvi, A., Lello, S., 2015. Hyperprolactinemia, pathophysiology and therapeutic approach. Gynecol. Endocrinol. 31, 506–510.
Carbon, M., Correll, C.U., 2014. Clinical predictors of therapeutic response to antipsychotics in schizophrenia. Dialogues Clin. Neurosci. 16, 505–524.
Coello, K., Broberg, B.V., Bak, N., Madsen, A., Mortensen, H.B., Ebdrup, B.H., et al., 2015. Postprandial prolactin suppression appears absent in antipsychotic-treated male patients. Psychoneuroendocrinology 60, 1–6.
Corona, G., Vignozzi, L., Sforza, A., Mannucci, E., Maggi, M., 2015. Obesity and late-onset hypogonadism. Mol. Cell Endocrinol. 418 (Pt 2), 120–133.
de Boer, M.K., Castelein, S., Wiersma, D., Schoevers, R.A., Knegtering, H., 2015. The facts about sexual (dys) function in schizophrenia, an overview of clinically relevant findings. Schizophr. Bull. 41, 674–686.
During, S., Glenthoj, B.Y., Andersen, G.S., Oranje, B., 2014. Effects of dopamine D2/D3 blockade on human sensory and sensorimotor gating in initially antipsychotic-naive, first-episode schizophrenia patients. Neuropsychopharmacology 39, 3000–3008.
During, S., Glenthoj, B.Y., Oranje, B., 2015. Effects of blocking D2/D3 Receptors on mismatch negativity and P3a amplitude of initially antipsychotic naive, first episode schizophrenia patients. Int. J. Neuropsychopharmacol. 19, yv109.
Ebdrup, B.H., Raghava, J.M., Nielsen, M.O., Rostrup, E., Glenthoj, B., 2016. Frontal fasciculi and psychotic symptoms in antipsychotic-naive patients with schizophrenia before and after 6 weeks of selective dopamine D2/3 receptor blockade. J Psychiatry Neurosci. 41, 133–141.
Ebdrup, B.H., Axelsen, M.C., Bak, N., Fagerlund, B., Oranje, B., Raghava, J.M., et al., 2018. Accuracy of diagnostic classification algorithms using cognitive-, electrophysiological-, and neuroanatomical data in antipsychotic-naïve schizophrenia patients. Psychol. Med. 18, 1–10.
Eisenberg, M.L., Meldrum, D., 2017. Effects of age on fertility and sexual function. Fertil. Steril. 107, 301–304.
Fujioi, J., Iwamoto, K., Banno, M., Kikuchi, T., Aleksic, B., Ozaki, N., 2017. Effect of adjunctive aripiprazole on sexual dysfunction in schizophrenia: A preliminary open-label study. Pharmacopsychiatry 50, 74–78.
Galdiero, M., Pivonello, R., Grasso, L.F., Cozzolino, A., Colao, A., 2012. Growth hormone, prolactin, and sexuality. J. Endocrinol. Invest. 35, 782–794.
Howes, O.D., Wheeler, M.J., Pilowsky, L.S., Landau, S., Murray, R.M., Smith, S., 2007. Sexual function and gonadal hormones in patients taking antipsychotic treatment for schizophrenia or schizoaffective disorder. J. Clin. Psychiatry 68, 361–367.
Inder, W.J., Castle, D., 2011. Antipsychotic-induced hyperprolactinaemia. Aust. N. Z. J. Psychiatry 45, 830–837.
Jensen, M.H., Bak, N., Rostrup, E., Nielsen, M.Ø., Pantelis, C., Glenthøj, B.Y., et al., 2018. The impact of schizophrenia and intelligence on the relationship between age and brain volume. Schizophr. Res. Cogn. 5, 1–6.
Jessen, K., Rostrup, E., Mandl, R.C., Nielsen, M.Ø., Bak, N., Ebdrup, B., et al., 2018a. Cortical structures and their clinical correlates in antipsychotic-n + äive schizophrenia patients before and after 6 weeks of dopamine D 2/3 receptor antagonist treatment. Psychol. Med. 8, 1–10.
Jessen, K., Mandl, R.C.W., Fagerlund, B., Bojesen, K.B., Raghava, J.M., Obaid, H.G., et al., 2018b. Patterns of cortical structures and cognition in antipsychotic-naïve patients with first-episode schizophrenia: A partial least squares correlation analysis. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 25, 2451–9022.
Just, M.J., 2015. The influence of atypical antipsychotic drugs on sexual function. Neuropsychiatr. Dis. Treat. 11, 1655–1661.
Kahn, R.S., Winter van Rossom, I., Leucht, S., McGuire, P., Lewis, S.W., Sommer, I.E., et al., 2018. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE), a three-phase switching study. Lancet Psychiatry 5, 797–807.
Kay, S.R, Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.
Kelly, D.L., Conley, R.R., 2004. Sexuality and schizophrenia, a review. Schizophr. Bull. 30, 767–779.
Knegtering, H., van den Bosch, R., Castelein, S., Bruggeman, R., Sytema, S., van, O.J., 2008. Are sexual side effects of prolactin-raising antipsychotics reducible to serum prolactin? Psychoneuroendocrinology 33, 711–717.
Kopecek, M., Bares, M., Svarc, J., Dockery, C., Horacek, J., 2004. Hyperprolactinemia after low dose of amisulpride. Neuro Endocrinol. Lett. 25, 419–422.
Lennartsson, A.K., Jonsdottir, I.H., 2011. Prolactin in response to acute psychosocial stress in healthy men and women. Psychoneuroendocrinology 36, 1530–1539.
Lingjaerde, O., Ahlfors, U.G., Bech, P., Dencker, S.J., Elgen, K., 1987. The UKU side effect rating scale, a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic treated patients. Acta Psychiatri. Scand. 76, 1–100.
Malik, P., Kemmler, G., Hummer, M., Riecher-Roessler, A., Kahn, R.S., Fleischhacker, W.W., 2011. Sexual dysfunction in first-episode schizophrenia patients, results from European First Episode Schizophrenia Trial. J. Clin. Psychopharmacol. 31, 274–280.
Marano, R.J., Ben-Jonathan, N., 2014. Minireview, Extrapituitary prolactin, an update on the distribution, regulation, and functions. Mol. Endocrinol. 28, 622–633.
Marques, T.R., Smith, S., Bonaccorso, S., Gaughran, F., Kolliakou, A., Howes, O.D., et al., 2012. Sexual dysfunction in people with prodromal or first-episode psychosis. Br. J. Psychiatry 201, 131–136.
Martin, J.C., Acuña, M.J., Labrador, J., Blanco, M., Casas, C., 2018. Sexual dysfunction factors in patients with schizophrenia treated with second generation antipsychotics, not only prolactin. Actas espanolas de psiquiatria 46, 217–225.
Montejo, A.L., Garcia, M., Espada, M., Rico-Villademoros, F., Llorca, G., Izquierdo, J.A., 2000. Psychometric characteristics of the psychotropic-related sexual dysfunction questionnaire. Spanish work group for the study of psychotropic-related sexual dysfunctions. Actas espanolas de psiquiatria 28, 141–150.
Montejo, A.L., Majadas, S., Rico-Villademoros, F., Llorca, G., De La Gandara, J., Prieto, N., 2010. Frequency of sexual dysfunction in patients with a psychotic disorder receiving antipsychotics. J. Sex Med. 7, 3404–3413.
Nielsen, M.O., Rostrup, E., Wulff, S., Bak, N., Broberg, B.V., Glenthoj, B., et al., 2012a. Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. Arch. Gen. Psychiatry 69, 1195–1204.
Nielsen, M.O., Rostrup, E., Wulff, S., Bak, N., Kapur, S., Glenthoj, B., et al., 2012b. Alterations of the brain reward system in antipsychotic naive schizophrenia patients. Biol. Psychiatry 71, 898–905.
Nielsen, M.O., Rostrup, E., Wulff, S., Glenthoj, B., Ebdrup, B.H., 2016. Striatal reward activity and antipsychotic-associated weight change in patients with schizophrenia undergoing initial treatment. JAMA Psychiatry 73, 121–128.
Pedersen, C.B., Mors, O., Bertelsen, A., Waltoft, B.L., Agerbo, E., McGrath, J.J., Eaton, W.W., et al., 2014. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. JAMA Psychiatry 71, 573–581.
Peuskens, J., Pani, L., Detraux, J., De, H.M., 2014. The effects of novel and newly approved antipsychotics on serum prolactin levels, a comprehensive review. CNS Drugs 28, 421–453.
Riecher-Rossler, A., Rybakowski, J.K., Pflueger, M.O., Beyrau, R., Kahn, R.S., Fleischhacker, W.W., et al., 2013. Hyperprolactinemia in antipsychotic-naive patients with first-episode psychosis. Psychol. Med. 43, 2571–2582.
Rubio-Abadal, E., Del Cacho, N., Saenz-Navarrete, G., Arranz, B., Cambra, R.M., Barneda, V., et al., 2016. How hyperprolactinemia affects sexual function in patients under antipsychotic treatment. J. Clin. Psychopharmacol. 36, 422–428.
Sansone, A., Romanelli, F., Gianfrilli, D., Lenzi, A., 2014. Endocrine evaluation of erectile dysfunction. Endocrine 46, 423–430.
Segal, M., Avital, A., Rojas, M., Hausvater, N., Sandbank, S., Weizman, A., et al., 2004. Serum prolactin levels in unmedicated first-episode and recurrent schizophrenia patients, a possible marker for the disease's subtypes. Psychiatry Res. 127, 227–235.
Serretti, A., Chiesa, A., 2011. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. Int. Clin. Psychopharmacol. 26, 130–140.
Westheide, J., Cohen, S., Bender, S., Cooper-Mahkorn, D., Erfurth, A., Kuhn, K.U., et al., 2007. Sexual dysfunction in psychiatric inpatients the role of antipsychotic medication. Pharmacopsychiatry 40, 140–145.
Wulff, S., Pinborg, L.H., Svarer, C., Jensen, L.T., Nielsen, M.O., Glenthoj, B.Y., et al., 2015. Striatal D(2/3) Binding potential values in drug-naive first-episode schizophrenia patients correlate with treatment outcome. Schizophr. Bull. 41, 1143–1152.
Wulff, S., Nielsen, M.Ø., Rostrup, E., Svarer, C., Jensen, L.T., Pinborg, L., et al., 2019. The relation between dopamine D2 receptor blockade and the brain reward system: a longitudinal study of first-episode schizophrenia patients. Psychol. Med. 15, 1–9.
Zaazaa, A., Bella, A.J., Shamloul, R., 2013. Drug addiction and sexual dysfunction. Endocrinol. Metab. Clin. North Am. 42, 585–592.