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ORIGINAL ARTICLE

Prolactin, flupenthixol decanoate and first episode schizophrenia – clinical and laboratory correlates

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Abstract

First-episode psychosis (FEP) patients are more sensitive to neuroleptic side-effects such as hyperprolactinemia. We examined the prolactin levels of previously minimally treated patients with first episode schizophrenia over their first year of treatment with flupenthixol decanoate and the relationship between prolactin levels, gender and clinical features of schizophrenia. Prolactin levels were assessed at three monthly intervals in 126 patients with first-episode schizophrenia in a single-site study conducted over 12 months during treatment with flupenthixol decanoate according to a fixed protocol. The mean prolactin level for the total sample was 11.91 ng/ml (standard deviation [SD]15.52) at baseline. Women had higher levels of prolactin than men at month 3, 6 and 12, reaching statistical significance at month 12 ($p = 0.02$). At 12 months more women than men had hyperprolactinemia (defined as more than 20 ng/ml for males, and as more than 25 ng/ml for females ($p = 0.007$). Using a mixed effect model, there was a significant association between prolactin change scores over 12 months and gender ($p = 0.025$) as well as Positive and Negative Syndrome Scale (PANSS) total scores ($p = 0.001$). In addition female gender ($p = 0.04$) and age ($p = 0.02$) correlated with the risk of hyperprolactinemia as categorical variable. In this study treatment with flupenthixol decanoate was associated with relatively low levels of hyperprolactinemia, likely owing to flupenthixol's relatively atypical mode of action, as well as to the low doses used in our study. We found an inverse correlation between total PANSS scores and prolactin levels, which could support the suggested theory of prolactin having antipsychotic properties. Our study confirms the importance of gender on the prolactin raising effects of antipsychotic treatment.

Keywords Hyperprolactinemia · Long acting injectable · Antipsychotic · Gender

Introduction

Schizophrenia is a serious mental illness associated with significant morbidity and mortality (Zhang et al. 2013). Patients experiencing their first psychotic episode represent a unique subset of cases that often require lower antipsychotic doses than their more chronically ill relapsing counterparts (Zhang et al. 2013). Long acting injectable (LAI) antipsychotic agents such as flupenthixol decanoate have been used to ensure continuous drug delivery and decrease non-adherence to medication (Nasrallah 2007). Several research groups have argued that LAIs have a key role to play in first-episode schizophrenia (FES), as these patients have most to lose through relapsing (Chiliza et al. 2008). The relationship between FES and prolactin appears to be a complex one. Studies describe normal to lower prolactin levels pre-antipsychotic treatment in FES, and lower prolactin levels has been postulated underlie psychopathology (Albayrak et al. 2014). D_2 receptor occupancy by prolactin has also been well shown to predict efficacy of antipsychotics (Matei et al. 2019; Taneja et al. 2017) while FES patients are often more sensitive to neuroleptic side-effects such as hyperprolactinemia (Robinson et al. 2005).

Prolactin is a polypeptide hormone produced by the anterior pituitary lactotrophic cells (Haddad and Wieck 2004; Marrag et al. 2015). Its diverse functions include lactation, regulation of sex steroid and reproductive function, regulation of parental behaviour, osmoregulation, immune system

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homeostasis as well as angiogenesis (Meaney and O'Keane 2002). Dopamine is the main hypothalamic factor regulating prolactin secretion by means of tonic inhibition, with prolactin releasing peptide also playing a role (Inder and Castle 2011; Haddad and Wieck 2004). Antipsychotics may increase prolactin secretion by blocking the action of dopamine on the D2 receptors, which can result in menstrual abnormalities, fertility problems, hypogonadism, oestrogen deficiency in females and testosterone deficiency in males, osteoporosis, sexual dysfunction and galactorrhoea (Meaney and O'Keane 2002). Hyperprolactinemia and its resultant clinical sequelae may be among the most commonly found side effects of antipsychotic treatment (Bushe et al. 2008). However the risk benefit of increased prolactin warrants consideration, given that these effects may only emerge as pathologically significant with prolonged prolactin increase, and that increased prolactin has been associated with decreased psychopathology (Albayrak et al. 2014).

An increase in prolactin levels has been found in patients with schizophrenia within minutes to hours of commencing treatment with a typical antipsychotic (Haddad and Wieck 2004). Medium term treatment (3–9 weeks) with antipsychotics at therapeutic doses has been associated with dose-dependent increases of prolactin by up to 10-fold (Haddad and Wieck 2004). Prolactin levels may fall to normal within 48–96 h of discontinuation of antipsychotics, although this return to normal can take up to 3 weeks depending on the half-life of the drug (Haddad and Wieck 2004). Females are at higher risk of hyperprolactinemia and this gender difference is an important consideration (Haddad and Wieck 2004; Bushe and Shaw 2007).

The effect of different antipsychotics on prolactin levels varies considerably (Haddad and Wieck 2004). Clozapine, quetiapine, olanzapine, aripiprazole and ziprasidone are all described as relatively 'prolactin sparing' (Haddad and Wieck 2004; Crespo-Facorro et al. 2017). Lower dopamine D2 receptor occupancy, faster dissociation from the receptor and varying blood brain barrier crossing are all proposed theories explaining these prolactin sparing effects (Sykes et al. 2017). In contrast, the 'prolactin raising' drugs risperidone and amisulpiride have a propensity to increase prolactin levels significantly (Bushe et al. 2008). Hyperprolactinemia has been reported in up to 100% of patients taking amisulpiride, and between 72 and 100% of patients on risperidone (Bushe et al. 2008). The type of antipsychotic used and dose are the strongest predictors of elevation of prolactin (Inder and Castle 2011) rather than method of administration i.e. LAI versus oral formulation. However, risperidone LAI has been associated with lower rates of prolactin elevation than oral risperidone, related to the overall lower dosage used (Bushe et al. 2008). Higher rates of hyperprolactinemia have also been described in patients on both forms of risperidone than those on typical LAIs (Bushe and Shaw, 2007).

Flupenthixol decanoate is widely available internationally, and is an effective and well-tolerated treatment for schizophrenia. Evidence regarding its effect on prolactin although limited is relatively favourable. Crockett et al. describe hyperprolactinemia in 25.9% of patients with schizophrenia treated at a LAI clinic, of which 63% were treated with flupenthixol decanoate (Crockett and Goldstein 2008). When comparing amisulpiride to oral flupenthixol over a four week study, prolactin elevation in the amisulpiride group was double that of the flupenthixol group (Bushe and Shaw 2007). Here, we examine prolactin levels of 126 people with FES (93 males, 33 females) over their first year of antipsychotic treatment with flupenthixol decanoate. We aim to describe the relationship between prolactin levels, gender and clinical features of schizophrenia. We hypothesise that flupenthixol decanoate will be relatively prolactin sparing and female participants will be more susceptible to increases in prolactin and hyperprolactinemia.

Methods and materials

Study design

This was a single-site study conducted over 12 months of standardised treatment in a sample of patients with first episode schizophrenia. It consisted of a secondary data analysis from the original open label trial which assessed the feasibility and effectiveness of flupenthixol decanoate combined with an assertive monitoring program in first-episode schizophrenia (Chiliza et al. 2016).

Participants

Patients were recruited from in- and outpatient facilities at Stikland and Tygerberg Hospitals and surrounding community clinics, in Cape Town, South Africa. They were carefully screened and those who met inclusion criteria were invited to participate in the study. Written, informed consent was obtained from participants. In the case of minors, written assent was obtained as well as parental consent. Inclusion criteria for patients were male or female subjects age 16 to 45; diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder and a negative history of current substance abuse (as confirmed by a urine drug screen) or a serious medical condition. Patients were excluded if they had, during their lifetime, been exposed to more than 4 weeks of antipsychotic medication or had been treated with a LAI antipsychotic or had intellectual disability (IQ < 70). Further, patients were excluded from the prolactin substudy if they were pregnant or breastfeeding at any point in the twelve-month follow-up. Patient diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder was based on the Structured

Clinical Interview for DSM-IV (SCID) – Patient Edition (First et al. 2002). This study was approved by the Stellenbosch University Institutional Review Board and conducted in accordance with the International Conference on Harmonization guidelines on good clinical practice (GCP) (ICH GCP 2001).

Assessments

Investigators were physicians who were trained in the use of the key assessment instruments, and inter-rater reliability testing was conducted periodically (intraclass correlation 0.7 or greater). Symptoms of schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1988) and motor side-effects were assessed by the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese 2005). Serum prolactin levels and clinical assessments were performed at baseline, and months 3, 6, 9 and 12. Normal adult serum prolactin level was defined as 10-25 ng/ml (210-530mIU/L) in women and 10-20 ng/ml (210-420mIU/L) in men (Citrome 2008). Hyperprolactinemia was defined as more than 20 ng/ml for males, and more than 25 ng/ml for females.

Treatment

All patients were treated with a standard regimen of flupenthixol decanoate intramuscular injection (IMI) medication. There was a washout phase of up to seven days during which all psychotropic medications were discontinued. All participants were treated for 1 week prior to the first flupenthixol decanoate dose with flupenthixol oral to test for hypersensitivity. We started participants on 1 mg oral flupenthixol daily (including adolescents), which was increased to a maximum of 2 mg oral flupenthixol daily if clinically indicated. The starting dose of flupenthixol decanoate was 10 mg every two weeks IMI, with six weekly increments of 10 mg IMI permitted, to a maximum of 30 mg every two weeks IMI. The starting dose could be reduced to 5 mg IMI every two weeks in patients younger than 18 years. The efficacy and tolerability of using relatively low dose of flupenthixol decanoate in this study has been described elsewhere (Chiliza et al. 2015). A treatment response (≥50% PANSS total score improvement) to medication was achieved in 82% of participants. Other permitted concomitant medications included orphenadrine, trihexyphenidyl or biperiden for parkinsonism or dystonia; propranolol for akathisia; and antidepressants and medication for medical conditions at the investigators' discretion. Other antipsychotics, mood stabilizers and psychostimulants were not permitted. At study enrolment, concomitant medication included medication for diabetes, asthma and iron deficiency anaemia. None of the concomitant medication are known to have a significant effect on prolactin levels. No patients were on antidepressant medication.

Data analysis

Analyses were conducted using Stata 13 software. We used descriptive statistics, reporting means (SD) and percentages. To compare demographic characteristics between males and females, we used two sample t-tests for continuous variables and chi-square test for categorical variables. We performed mixed effect regression models to examine the relationship between key demographic and clinical variables and prolactin levels over 12 months. We employed a mixed effect logistic regression models to identify variables predicting hyperprolactinemia and a mixed effect linear regression models for repeated measures to identify variables predicting change in prolactin levels. We entered the following variables in both models: gender, age, total PANSS score, ESRS, medication dose, and metabolic parameters [high density lipoprotein (HDL), low density lipoprotein (LDL), cholesterol, body mass index (BMI), and glucose].

Prolactin values were skewed, therefore parametric statistics involving prolactin level calculations are based on log-transformed data, antilogged in the tables.

Ethical considerations

Ethical approval was obtained from the Health Research Ethics Committee of Stellenbosch University (ref #: N06/08/148). Participation was voluntary and all participants provided written, informed consent. All data were anonymised to ensure privacy and confidentiality of participants' personal information.

Results

Baseline demographic and clinical characteristics

Our study included 126 patients, of which 93 (74%) were male and 33 (26%) females (Table 1). The mean age was 24.07 years, with no difference between males and females ($p = 0.06$). In addition, there were no differences between males and females with regard to PANSS, Body Mass Index, ESRS or duration of untreated psychosis (DUP). At study entry, 54% of male participants and 57% of females were neuroleptic naïve. There was no difference in baseline prolactin levels between antipsychotic naïve participants and those that had prior antipsychotic exposure ($p = 0.72$).

Prolactin levels, hyperprolactinemia and gender

Figure 1 (and table 1 in Supplementary Information) shows the change in prolactin levels over time in males and females. Figure 2 (and table 1 in Supplementary Information) shows categorical data on hyperprolactinemia.

Table 1 Clinical characteristics of the patients at study entry (Baseline)

Variable	Male ($n = 93$, 74%)	Female ($n = 33$, 26%)	Total ($n = 126$)	P value
Mean age (SD), years	23.41 (5.95)	33 (5.93)	24.07 (6.60)	0.06
Neuroleptic naïve, n (%)	51 (55%)	19 (58%)	70 (56%)	0.79
Mean PANSS (SD)	94.20(17.38)	96.39(13.72)	94.78(16.48)	0.51
Mean BMI (SD)	21.48(3.38)	21.91 (4.97)	21.59(3.85)	0.59
Median ESRS (range)	0(0–26)	0(0–24)	0(0–26)	0.80
Median DUP (range), days	160[8–2207]	101[21–598]	140[8–2207]	0.08
Median duration of prior treatment (range), days	3[0–28]	4.5[0–25]	3[0–28]	0.90

PANSS Positive and Negative Syndrome Scale, *BMI* body mass index, *ESRS* Extrapyramidal Symptom Rating Scale, *LDL* low-density lipoprotein, *DUP* duration of untreated psychosis

The mean prolactin level of all the subjects at study entry was 11.91 ng/ml. There was no significant difference in prolactin levels between males (11.36, ±16.94) and females (13.46, ±10.60) ($p = 0.11$) at baseline. A total of 7 patients (5.56%) had hyperprolactinemia at baseline. In both genders, there was an increase in prolactin levels from baseline to Month 3. The prevalence of hyperprolactinemia at 3, 6 and 12 months was 18%, 11% and 12% respectively. Females had a higher prevalence of hyperprolactinemia at all measurement points, with values ranging between 11% at baseline to 28% at month 12. This gender differentiation was significant at month 12 ($p = 0.007$).

Predictors of a change in prolactin levels

We entered gender, age, PANSS scores, ESRS scores, metabolic parameters (BMI, glucose, LDL, HDL, cholesterol levels and flupenthixol decanoate dose into a linear mixed effect repeated measures model to assess for predictors of prolactin change scores over 12 months (Table 2). There was

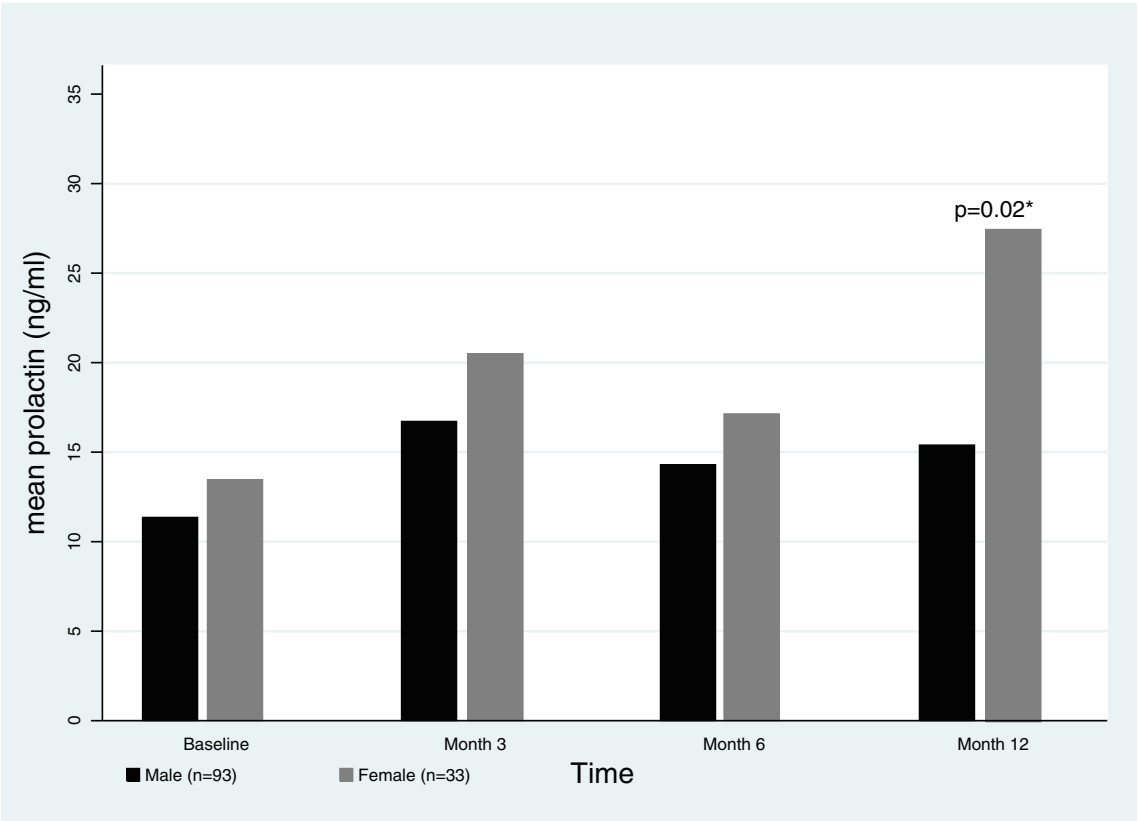

Fig. 1 Prolactin levels at different time points

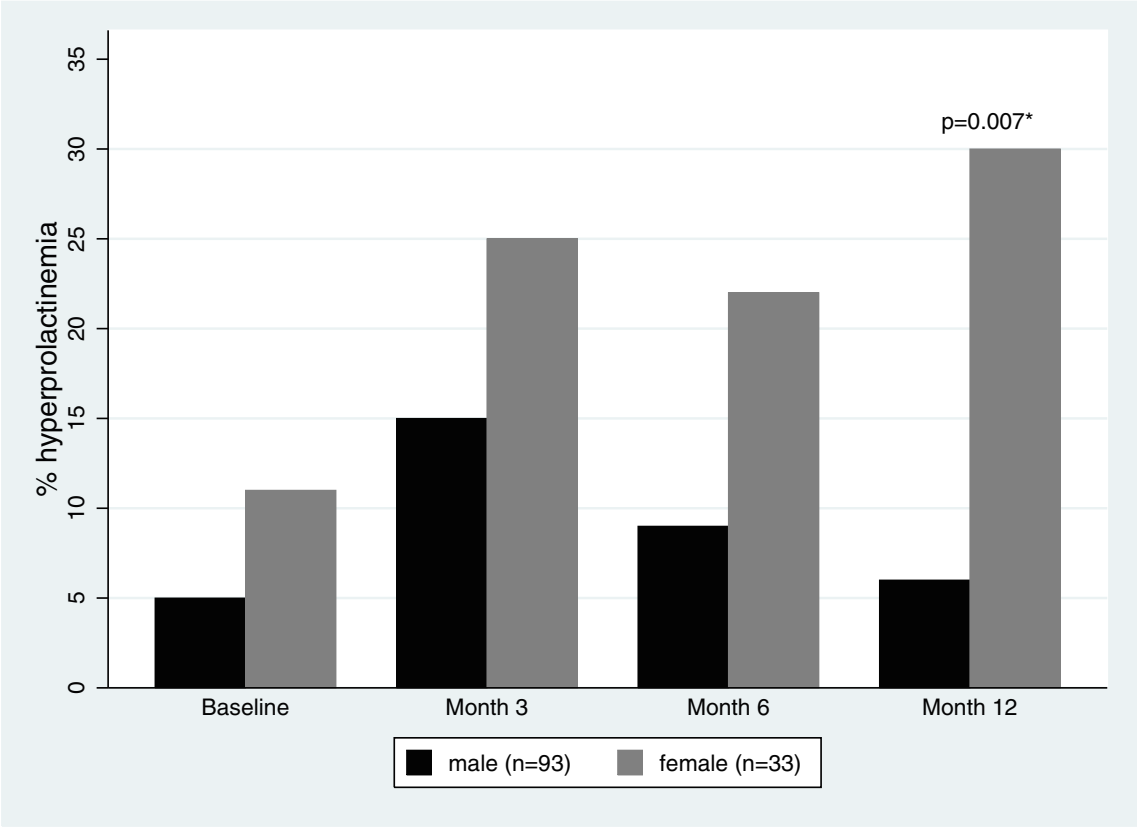

Fig. 2 Hyperprolactinemia at different time points

a significant association between prolactin change scores and gender, with females having higher levels of prolactin over time (β = −0.258, 95% CI -0.48 to −0.03, $p = 0.025$). We also found a significant inverse association with total PANSS scores, in that prolactin levels increased as total PANSS scores decreased (β = −0.893, 95% CI -1.29 to −0.49, $p = 0.001$).

Predictors of hyperprolactinemia

We investigated risk factors for the development of hyperprolactinemia. We examined age, gender, PANSS and ESRS scores and also included metabolic parameters (BMI, Glucose, LDL, HDL, cholesterol levels). The results showed

Table 2 Linear mixed effect repeated measures model describing the relationship between prolactin change scores and covariates

Clinical characteristic	Coeff	std error	z	p value	95% CI
Gender					
Male	REFERENCE				
Female	−0.258	0.115	−2.24	0.025	−0.48 to −0.03
Age	−0.016	0.008	−1.91	0.056	−0.03 to 0.00
PANSS	−0.893	0.205	−4.35	0.001	−1.29 to −0.49
Metabolic parameters					
BMI	0.022	0.011	1.94	0.052	−0.00 to 0.04
Glucose	0.013	0.034	0.39	0.700	−0.05 to 0.08
LDL	−0.114	0.090	−1.27	0.204	−0.30 to 0.06
HDL	0.060	0.088	0.69	0.490	−0.11 to 0.23
Cholesterol	0.141	0.078	1.82	0.070	−0.01 to 0.30
Dose	0.015	0.057	0.26	0.800	−0.10 to 0.13
ESRS	0.008	0.008	1.04	0.300	−0.01 to 0.02

PANSS Positive and Negative Syndrome Scale, *BMI* body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ESRS* Extrapyramidal Symptom Rating Scale

Table 3 Logistic mixed effects model on the risk of hyperprolactinemia

Clinical characteristic	Coeff	Std error	z	p value	95% CI
Gender					
Male gender	REFERENCE				
Female gender	−1.27	0.63	−2.03	0.04	−2.50 to −0.04
Age	−0.14	0.06	−2.34	0.02	−0.26 to −0.02
PANSS	−0.01	0.01	−1.18	0.24	−0.03 to 0.01
Metabolic parameters					
BMI	0.04	0.06	0.56	0.58	−0.09 to 0.16
Glucose	0.24	0.21	1.15	0.25	−0.17 to 0.64
LDL	0.17	0.67	0.25	0.80	−1.14 to 1.48
HDL	0.48	0.66	0.74	0.46	−0.80 to 1.77
Cholesterol	0.24	0.62	0.38	0.70	−0.98 to 1.45
Dose	0.86	0.40	2.16	0.03	0.01 to 1.34
ESRS	0.07	0.06	1.27	0.20	−0.04 to 0.18

PANSS Positive and Negative Syndrome Scale, *BMI* body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ESRS* Extrapyramidal Symptom Rating Scale

that female gender (β = −1.27, 95% CI -2.50 to −0.04, p = 0.04), younger age (β = −0.14, 95% CI -0.26 to −0.02, p = 0.02), and higher antipsychotic dose (β = 0.86, 95% CI 0.01 to 1.34,p = 0.03) predict absolute hyperprolactinemia (Table 3). Metabolic parameters, PANSS and ESRS scores did not predict hyperprolactinemia independently of other variables.

Discussion

Here, we investigated the prolactin levels over time in a cohort of first-episode schizophrenia patients treated with flupenthixol decanoate. The key finding of our study is that the number of patients with elevated prolactin was relatively low. To our knowledge this is one of the longest longitudinal studies examining prolactin levels in patients treated with a typical LAI.

Our results showed rates of hyperprolactinemia ranging between 11%–29% in females and 5%–16% in males. This compares favourably to previously reported prevalence rates of 33%–35% in patients receiving LAI formulations (Bushe and Shaw 2007). In a 2008 review Bushe et al. (2008) reported a summary of studies reporting the prevalence of hyperprolactinemia. Four of the studies included first-generation antipsychotics and reported rates of 64%–93% in females, and 34–60% in males (Bushe et al. 2008). In one of the few studies looking at patients on first generation LAI antipsychotics, Crockett et al. found hyperprolactinemia in 25.9% of patients treated at a LAI clinic, 63% of which were treated with flupenthixol decanoate (Crockett and Goldstein 2008). This was however a once-off cross-sectional measurement and findings were not reported for males and females separately. Marrag et al. (2015) conducted a study in Tunisia and found low rates similar to ours: 10.9% for all first generation antipsychotics and 5.4% for Haloperidol. This was again a cross-sectional study, with no gender distinction and on average a much older population, which could influence reported prolactin levels.

Looking at other first onset psychosis populations, the CAFÉ cohort compared the mean change in prolactin levels over 52 weeks in patients treated with Olanzapine, Risperidone and Quetiapine (McEvoy et al. 2007). They found change from baseline values of −15.9, −18.7 and + 12.1 in olanzapine, quetiapine and risperidone groups respectively (McEvoy et al. 2007). A direct comparison with our results is challenging, as none of the CAFÉ patients were treatment naïve, versus 55% of our patients. A change score in the CAFÉ study might therefore be due to switching from one antipsychotic to another, rather than the actual prolactin raising or sparing effect of the drug.

The levels of hyperprolactinemia from our sample were also lower than those reported by the EUFEST first episode psychosis study. EUFEST examined prolactin changes on oral antipsychotic treatment, and found mean changes from baseline to 52 weeks of +23.6 ng/ml for Amisulpiride, −18.87 ng/ml for Haloperidol, −9.43 ng/ml for both Olanzapine and Quetiapine and − 56.6 ng/ml for Ziprazidone (Kahn et al. 2008). The categorical measures of hyperprolactinaemia were 89% (amisulpiride), 44% (haloperidol), 50% (olanzapine), 41% (quetiapine) and 46% (Ziprazidone) (Kahn et al. 2008). Our results compare favourably even to olanzapine and quetiapine – drugs typically described as prolactin sparing (Haddad and Wieck 2004).

The low levels of hyperprolactinemia found in our study might be explained by the pharmacodynamics of a LAI

formulation, the low dose strategy that we employed (average of 11 mg 2 weekly) and the relatively atypical method of action of flupenthixol decanoate LAI. Flupenthixol decanoate antagonizes dopamine binding at D1, D2, D3 and D4 receptors. In addition it affects serotonin binding at the 5-HT2A and 5-HT2C receptors as well as noradrenalin binding at the ά1-adrenergic receptors (Wiesbeck et al. 2001). In this regard its mechanism of action is not unlike that of several of the second generation antipsychotics (Chiliza et al. 2015). A higher ratio of serotonin 5HT2/dopamine D2 receptor binding affinity and greater D1 antagonism are possible mechanisms for mitigating the effects of D2 receptor blockade (Bargiota et al. 2013; Li et al. 2016). Faster dissociation of an antipsychotic-drug from D2 receptors and the ability of antipsychotic-drugs to cross the blood-brain barrier are also associated with olanzapine and quetiapine which are generally regarded as prolactin sparing medication (Haddad and Wieck 2004). The pharmacodynamic properties of a LAI formulation itself may be advantageous, e.g. lower rates of hyperprolactinemia have been described with the LAI versus oral formulation of risperidone (Bushe et al. 2008). One possible reason for this is that LAIs take longer to attain steady state, and due to their slow release there is a more predictable and stable serum drug concentration, with less peak plasma levels (Nasrallah 2007).

We found females to have higher levels of prolactin as well as absolute hyperprolactinemia when compared to males. This has consistently been found in studies examining prolactin changes and antipsychotic use (Haddad and Wieck 2004; Marrag I, Hajji K, Braham MY, Dhifallah M, Nasr M (2015)). Estrogens increase the number of lactotrophic cells of the anterior pituitary and act on the hypothalamus to decrease dopamine content (Peuskens et al. 2014). These hormones therefore have the ability to elevate serum prolactin levels and enhance responsiveness to prolactin-releasing stimuli in women of reproductive age (Haddad and Wieck 2004). Some studies have described later menarche and menstrual cycle abnormalities in females with schizophrenia as well as an association between illness onset and age of puberty (Leung and Chue 2000). In fact, women of reproductive age experience raised prolactin secondary to antipsychotic medication more frequently than postmenopausal women (Peuskens et al. 2014). We therefore emphasize the importance of reporting gender findings separately with regard to prolactin. This gender distinction is frequently omitted from studies and can lead to potential bias. Reporting prolactin data as only total mean values could skew the findings depending on the proportion of males in the study.

We found that higher prolactin levels (but not hyperprolactinemia) was associated with a lower PANSS score in keeping with other studies that have also found a relationship between plasma prolactin and treatment response. Some authors have also suggested that the milder course of psychotic disease in females could be explained by higher prolactin levels. In fact, they generally requiring lower antipsychotic dose (Eberhard et al. 2007). Prolactin release is inhibited by dopamine and regulated by the female reproductive cycle, including pregnancy and the post-partum period. Greater prolactin elevation in women may suggest a higher sensitivity to dopamine receptor blockade by antipsychotics (Abel, Drake, & Goldstein, 2010), possibly due to the antidopaminergic effect of estrogen (da Silva and Ravindran 2015). In females, estrogen levels have also been found to be inversely related to fluctuations in symptomatology that occur with the menstrual cycle, pregnancy post-partum and menopause. This includes onset of symptoms and symptom relapse (Leung and Chue, 2000).

Our finding of higher prolactin levels associated with lower psychopathology scores is independent of gender. This is consistent with results from Zhang et al. 2002 who explored the effect of raised prolactin levels and psychopathology in male inpatients. They found a positive and significant relationship between the change in prolactin and reduction rate of the PANSS positive subscores. Their baseline prolactin levels could in fact predict treatment responses. Collectively these findings suggest that prolactin may have an antipsychotic effect (Eberhard et al. 2007). While some studies have also found an inverse correlation between prolactin and psychopathology, other studies have not possibly due to methodological inconsistencies. This inverse relationship between total PANSS scores and prolactin levels could putatively also have been caused by flupenthixol decanoate crossing the blood-brain barrier more effectively in some patients. Furthermore, the relationship between prolactin increase and PANSS decrease could also be explained by the intensity of D2 receptor antagonism, with some patients more sensitive to dopamine blockade.

Strengths of our study include the carefully selected sample, minimal previous exposure to antipsychotic treatment, long-term follow up with multiple measurement points and a standardized treatment protocol that ensured medication adherence. Limitations are the lack of a control group, as well as a lack of accompanying data on clinical manifestations of hyperprolactinemia, such as clinical rating scales. A further limitation is the wash out period of seven days prior to starting flupenthixol decanoate. This might be too short to rule out previous psychotropic's actions on prolactin. We also did not formally assess whether adolescent participants had achieved puberty.

Conclusion

This study indicates that flupenthixol decanoate is associated with relatively low levels of hyperprolactinemia despite being historically described as a first generation antipsychotic. Our study supports the fact that antipsychotics represent a

heterogeneous group of drugs, and that judicious use of a first generation LAI such as flupenthixol decanoate can limit side effects such as hyperprolactinemia. Clinicians should therefore consider the propensity for individual drugs to increase prolactin when choosing a treatment for their patients, keeping in mind that female gender, younger age and higher antipsychotic dose is associated with the development of hyperprolactinemia. We also found that higher prolactin levels, but not hyperprolactinemia, was associated with improved symptomatology suggesting that potential beneficial effects of prolactin warrant further investigation. Future studies should ideally investigate the association between prolactin and specific antipsychotics longitudinally, and as a primary aim, with robust sample sizes and taking into account gender. Continuous and categorical measures of prolactin should be considered as well as careful documentation of emergent side-effects.

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