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Hyperprolactinaemia in first episode psychosis - A longitudinal assessment

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ABSTRACT

Little is known about hyperprolactinaemia (HPL) in first episode psychosis (FEP) patients. We investigated longitudinal changes in serum prolactin in FEP, and the relationship between HPL, and antipsychotic medication and stress.

Serum prolactin was recorded in FEP patients at recruitment and again, 3 and 12 months later. HPL was defined as a serum prolactin level >410 mIU/L (~19.3 ng/ml) for males, and a serum prolactin level >510 mIU/L (~24.1 ng/ml) for females.

From a total of 174 people with serum prolactin measurements at study recruitment, 43% ($n = 74$) had HPL, whilst 27% ($n = 21/78$) and 27% ($n = 26/95$) had HPL at 3 and 12 months respectively. We observed higher serum prolactin levels in females versus males ($p < 0.001$), and in antipsychotic treated ($n = 68$) versus antipsychotic naïve patients ($p < 0.0001$). Prolactin levels were consistently raised in FEP patients taking risperidone, amisulpride and FGAs compared to other antipsychotics. No significant relationship was observed between perceived stress scores ($\beta = 7.13$, $t = 0.21$, $df = 11$, $p = 0.084$ 95% CI – 72.91–87.16), or objective life stressors ($\beta = -21.74$, $t = -0.31$, $df = 8$, $p = 0.77$ 95% CI – 218.57–175.09) and serum prolactin.

Our study found elevated rates of HPL over the course of the first 12 months of illness. We found no evidence to support the notion that stress is related to elevated serum prolactin at the onset of psychosis.

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1. Introduction

Hyperprolactinaemia (HPL) is a relatively common, but often unacknowledged side effect of antipsychotic medications. In general, all antipsychotic medication can be associated with HPL, with the propensity for an antipsychotic to cause HPL mainly associated with its degree of D-2 receptor antagonism (Bushe et al., 2008a), and a higher ratio of pituitary to striatal D-2 receptor occupancy (Kapur et al., 2002). The highest prevalence of HPL is seen with amisulpride, risperidone, and paliperidone, even at relatively low doses, followed by the first generation antipsychotics (FGAs) (Bushe et al., 2008b). A recent meta-analysis identified that standardised mean differences compared with placebo for prolactin increase varied from 0.22 for aripiprazole (best drug) to −1.30 for paliperidone (Leucht et al., 2013). Hyperprolactinaemia is important to patients as it has been linked with sexual dysfunction, hypogonadism, (Howes et al., 2007) cancer and osteoporosis (De Hert et al., 2015; Howes et al., 2005; Meaney et al., 2004; Peuskens et al., 2014).

There is a paucity of information on the prevalence of hyperprolactinaemia in early psychosis, particularly among those who are antipsychotic naïve. The largest study in early psychosis identified that 74% of patients treated with risperidone had HPL at some point over a two year period (Schooler et al., 2005), while HPL rates of 71% were identified in the European First Episode Schizophrenia (EUFEST) study, half of those being antipsychotic naïve (Kahn et al., 2008). In two cross sectional studies of antipsychotic naïve FEP patients, 29–39% were identified as having HPL (Aston et al., 2010; Riecher-Rössler et al., 2013). A recent meta-analysis of prolactin in antipsychotic-naïve patients, found significantly elevated prolactin levels in both males and females, though the findings were limited by the small number of identified studies (Gonzalez-Blanco et al., 2016).

The heightened prevalence of HPL, even in antipsychotic naïve FEP patients, does not appear to be attributable to important confounding variables such as sex, smoking status, body mass index (BMI), thyroid stimulating hormone or ghrelin (Garcia-Rizo et al., 2012). This has led some to hypothesise that stress may be causative of HPL, which may in turn be a contributing factor to the emergence of the psychotic episode (Howes and Kapur, 2009; Riecher-Rössler et al., 2013). A postulated mechanism suggests that increased dopamine in psychosis may in part be due to its role as a prolactin-inhibiting factor (PIF), and as part of a regulatory mechanism to down regulate excess prolactin which has been caused by stress (Riecher-Rössler et al., 2013). However, this hypothesis regarding the relationship between stress and HPL has not yet been tested in a FEP group of patients.

1.1. Aims of the study

Given the paucity of longitudinal research investigating HPL in people with early psychosis (Pérez-Iglesias et al., 2012), we set out to investigate the prevalence of HPL during the first year of treatment for psychosis. Specifically, we set out to examine a) the relationship between HPL and antipsychotic medication use, gender, ethnicity, age, smoking and psychopathology at the time of the study recruitment; b) to evaluate any differences in serum prolactin levels and HPL among antipsychotic naïve and antipsychotic treated patients. For the first time, we aimed to elucidate any associations of perceived stress and stressful life events with serum prolactin in antipsychotic naïve patients.

2. Methods

Subjects were recruited in the context of the Physical Health and Substance Use Measures in First Onset Psychosis (PUMP) study, part of the NIHR funded IMPaCT programme. PUMP is a naturalistic longitudinal study assessing the relationship between lifestyle habits and the emergence of cardiometabolic risk over the first year of psychosis. The study was approved by the Joint South London and Maudsley and The

Institute of Psychiatry NHS Research Ethics Committee (REC reference number:08/H0807/53).

2.1. Eligibility criteria

Study participants were required to meet the ICD-10 criteria for FEP (codes F20-29 and F30-33) (World Health Organization, 1992) and were aged between 18 and 65. The baseline diagnoses were made from face-to-face interviews and mental health records according to ICD-10 criteria (WHO, 1992) utilising the Operational Criteria Checklists (OPCRIT) (McGuffin et al., 1991). Individuals with comorbid substance use disorders were not excluded. We excluded individuals who met the criteria for organic psychosis (F09) or moderate or severe learning disabilities (as defined by ICD-10, World Health Organization, 1992) (World Health Organization, 1992), who presented with evidence of transient psychotic symptoms resulting from acute intoxication as defined by ICD-10, and who were pregnant.

2.2. Recruitment

Patients were recruited as soon after first presentation as possible and were followed up prospectively over a twelve month period during which they remained under the care of mental health teams. Antipsychotic medication changes were made by the treating psychiatrists as part of routine clinical care over the course of the follow up period.

2.3. Serum prolactin measurement and hyperprolactinaemia definition

There are a variety of reported units of measurement for serum prolactin levels. Studies performed outside of the UK generally report data as ng/ml, whereas most UK data is in mIU/L (the accepted SI unit for prolactin measurement). We measured serum prolactin levels in mIU/L, but have also presented data in ng/ml, calculated on the basis of 1 ng/ml equaling 21.2 mIU/L (Bushe et al., 2008a). All serum prolactin measurements were performed by the same laboratory and a fasting sample was taken in the morning by direct venepuncture without regard to timing of medication in those who were already treated with antipsychotics.

Quantitative determination of prolactin serum levels were evaluated by a direct chemiluminometric method using The ADVIA Centaur® Prolactin assay, which is a two-site sandwich immunoassay. A direct relationship exists between the amount of prolactin present in the patient sample and the amount of relative light units detected by the system. Intraassay and interassay coefficients of variation for serum prolactin are 2.75% and 3.60% (Bayer Diagnostics).

Hyperprolactinaemia was defined in accordance with the hospital laboratory reference range as a serum prolactin level >410 mIU/L (~19.3 ng/ml) for males, and a serum prolactin level >510 mIU/L (~24.1 ng/ml) females. In order to highlight the severity of HPL, we further categorised HPL into those with a serum prolactin above 1000 mIU/L (~47.4 ng/ml) and a serum prolactin level greater than 2000 mIU/L (~94.8 ng/ml). Although arbitrary, this categorisation has been implemented previously in a population with multi-episode schizophrenia (Bushe et al., 2008b), and mirrors previously defined serum prolactin cut offs linked to clinical symptoms, and those commonly used in endocrine practice.

2.4. Antipsychotic medication use

Subjects were interviewed in detail about antipsychotics they were taking at the time of blood sampling. Also, medical records were taken into account to obtain the date when antipsychotic medication was initiated.

Antipsychotic medication doses were standardised as defined daily doses (DDD) based on the dose prescribed at the time of the prolactin measures (WHO Collaborating Centre for Drug Statistics Methodology,

2015). Additionally, the duration of antipsychotic medication use in days prior to study recruitment and from study recruitment to the end of the follow up period was recorded.

2.5. Demographic data and clinical outcome measures

Baseline data included demographics, diagnoses, antipsychotic status, treatment setting, and smoking status. The severity of psychopathology was rated on the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1989) and by the Global Assessment of Functioning (GAF) scale at first presentation for psychosis.

The perceived stress scale (Cohen et al., 1983) was used to measure the participants appraisal of how stressful events in their lives were at study recruitment. The brief life event (BLE) questionnaire (also known as the list of threatening experiences (LTE) questionnaire) was used to measure objective recent life stressors (Brugha and Cragg, 1990).

2.6. Data analysis

Between groups comparisons were made using χ^2 test for categorical variables; independent student's *t*-test for continuous variables, or the Mann-Whitney *U* test if variables were not normally distributed.

Linear regression was used to test the hypothesis that stress was related to prolactin levels, by examining the association between serum prolactin levels and the Perceived Stress Scale and the BLE total score, controlling for potential confounding factors of gender, age and ethnicity. Statistical significance was defined as $p < 0.05$. All analyses were conducted in STATA release 12 (STATACorp LP, USA).

3. Results

3.1. Sample characteristics

174 FEP patients had a serum prolactin measure at baseline and were included in this study. Clinical and demographic characteristics of the study population are shown in Table 1. Sixty four percent ($n = 112$) of this population was male. The mean age (SD) of the participants was 29.8 years (SD = 10.2) (range 17–61 years). Seventeen percent ($n = 28$ out of 167 with antipsychotic medication data) were antipsychotic naïve at study recruitment. The mean duration of antipsychotic treatment at study recruitment in the 139 others was 50.0 days (SD = 43.6, range = 1–193 days pre blood measure), 22 (16%) of whom received exclusively low risk of HPL antipsychotics (i.e. aripiprazole), with 40 (29%) receiving antipsychotics associated with a high risk of HPL (i.e. amisulpride, risperidone, FGAs) and 77 (55%) who had been prescribed antipsychotics with an intermediate or medium risk of HPL (i.e. olanzapine, quetiapine). All were treated with antipsychotic monotherapy at study recruitment. The DDDs for antipsychotic medication at study recruitment and at follow up are shown in supplementary Table 1.

3.2. Hyperprolactinaemia (HPL) prevalence rates

At study recruitment, HPL was found among 43% (95% CI = 35–49.9%) ($n = 74$) of patients at recruitment; in 27% (95%CI = 16.6–36.5) ($n = 21$) at 3 months and in 27% (18.2–36.5) ($n = 26$) at 12 months.

Prevalence rates of HPL according to antipsychotic status and sociodemographic and clinical characteristics are shown in Table 2.

Prolactin levels above 1000 mIU/L (~47.4 ng/ml) were found in 16% ($n = 27$) of patients at study recruitment, with 5% ($n = 8$) at study recruitment having a prolactin of greater than 2000 mIU/L (~94.8 ng/ml) (exclusively female). Seven of those with HPL > 2000 mIU/L (~94.8 ng/ml) had been treated with antipsychotic medication at study recruitment (amisulpride = 2; olanzapine = 1; aripiprazole = 2; risperidone = 2) for a mean of 50.1 days (SD = 46.6; range 11–

146 days), while the remaining patient was antipsychotic naïve. At follow up two non-antipsychotic treated females had a prolactin level > 2000 mIU/L (~94.8 ng/ml) (both with previous antipsychotic medication discontinued for >100 days).

At study recruitment, females had significantly higher serum prolactin levels (mean = 706.6 mIU/L (SD = 807.6) (~33.5 ng/ml (SD = 38.3)) compared to males (mean prolactin of 238.5 mIU/L (146.9) (~11.3 ng/ml (SD = 6.9)) (Mann-Whitney *U* test = -3.91 , $p < 0.0001$). Females were not more likely to be prescribed antipsychotics with a high risk of causing HPL at study recruitment (T1-F:M 25% vs 31%; $p = 0.45$). However, the prevalence of HPL at all three time points did not differ by gender (T1-M:F-40% vs 47% $p = 0.25$; T2-M:F- 31% vs 20%, $p = 0.22$; T3-M:F- 31% vs 21%, $p = 0.19$).

3.3. Antipsychotic effects

Patients were treated with up to eight different antipsychotic medications over the course of the year. Fifty seven percent ($n = 95$) of those treated with an antipsychotic medication at recruitment remained on the same antipsychotic over the year.

Figs. 1 and 2 shows mean serum prolactin levels and the prevalence of HPL in antipsychotic treated patients at all three timepoints.

Forty nine percent ($n = 68$) of antipsychotic treated patients had HPL at study recruitment, which was significantly higher than 11% ($n = 3$) of the antipsychotic naïve patients with HPL (OR = 7.9 (95% CI 2.29–27.49) $p < 0.001$).

There was no significant association between the mean DDDs of antipsychotic medication in those with HPL at study recruitment compared to those with no HPL (T1 HPL-DDD = 0.95 (SD = 0.64); T1 No HPL-DDD = 0.96 (0.67) ($t = 0.130$, $df = 137$, $p = 0.897$). Similarly at follow up (T3), the mean DDD was not significantly different in those with HPL (mean DD = 1.05 (SD = 0.60)) compared with those with no HPL (mean DDD = 1.08 (SD = 0.54)) ($t = 0.181$, $df = 57$, $p = 0.857$).

Those with HPL at study recruitment had similar durations of antipsychotic treatment (mean = 46.6 days (SD41.8)) compared to those without HPL (mean = 53.3 days (SD 45.3) ($t = 0.896$, $df = 133$, $p = 0.37$). Neither was duration of antipsychotic use associated with HPL at follow up (T3) (T3 HPL: mean duration of antipsychotic use = 391.6 days (SD = 153.2); T3 with no HPL: mean duration of antipsychotic use = 421.3 days (SD = 177.3) ($t = 0.726$, $df = 81$, $p = 0.47$).

Fig. 3 shows mean serum prolactin levels for those who remained on the same antipsychotic medications over the study period. Those continuously treated with risperidone ($n = 14$) over the year had diminishing serum prolactin levels over the study period (with a rate of HPL of 70% at study recruitment and 40% at 12 months). There was a similar effect in those who remained on olanzapine over the year, with HPL rates of 42% at study recruitment, 24% at 3 months and 16% at 12 months. Prolactin levels were higher in those treated with risperidone, amisulpride or FGAs compared to those treated with olanzapine, quetiapine or aripiprazole at all time-points (T1: F(6, 84) = 11.9 $p < 0.001$ T2: F(5, 33) = 20.0 $p < 0.001$; T3: F(5, 45) = 1.30 $p = 0.28$).

3.4. Influence of perceived stress and psychopathology

Patients with HPL had more severe clinical symptoms, as identified by a significantly lower GAF symptom score (52.9 (18.0) at presentation, compared to those with no HPL (59.4 (16.7)) ($t = 2.15$, $df = 131$, $p = 0.03$). This was not accounted for by increased mean DDDs of antipsychotic medication in those with HPL (see above).

Serum prolactin levels in the antipsychotic naïve group at study recruitment were not associated with perceived stress scores ($\beta = 7.13$, $t = 0.21$, $df = 11$, $p = 0.084$ 95% CI -72.91 – 87.16), or BLE scores ($\beta = -21.74$, $t = -0.31$, $df = 8$, $p = 0.77$ 95% CI -218.57 – 175.09). Similarly serum prolactin levels in the antipsychotic treated group were not associated with perceived stress scores ($\beta = 11.7$, $t = 0.81$, $df = 75$, $p =$

Table 1
Demographic, diagnostic and prolactin level data for the overall sample ($n = 174$); the subgroup receiving antipsychotic medications ($n = 139$); and antipsychotic naïve subgroup ($n = 28$).

Demographic, diagnostic and prolactin level		Overall sample ($n = 174$)	Antipsychotic naïve ($n = 28$; 16.8%)	Antipsychotic subgroup ($n = 139$; 83.2%)	Comparisons between antipsychotic vs antipsychotic naïve subgroups		
					Test-statistic	df	p-Value
Age years							
Mean years (SD)		29.3 (10.0)	31.2 (11.4)	29.0 (9.7)	0.65 ^a		0.51
Range years		17–61	18–56	17–61			
Men		28.2 (9.4)	29.4 (9.6)	28.0 (9.4)	0.61 ^a		0.53
Women		31.0 (10.6)	34.1 (14.0)	30.5 (10.0)	0.43 ^a		0.67
Gender $n(\%)$					0.28 ^b	1	0.38
Male		112(64.4%)	19 (67.9%)	87 (62.6%)			
Female		62 (35.6%)	9 (32.1%)	52 (37.4%)			
Ethnicity $n(\%)$					0.45 ^b	2	0.83
White		80 (46.2%)	13 (46.4%)	62 (44.9%)			
Black		62 (35.8%)	11 (39.3%)	49 (35.5%)			
Other		31 (17.9%)	4 (14.3%)	27 (19.6%)			
Prolactin level					– 3.28 ^a		0.001
Mean mIU/L (SD)		457.9 (646.7)	352.7 (571.3)	694.7 (801.6)			
Mean ng/ml (SD)		21.2 (30.5)	16.6 (26.9)	32.8 (37.8)			
Range mIU/L		71–4047	108–3117	71–4047			
Range ng/ml		(3.3–190.9)	(5.1–147.0)	(3.3–190.9)			
Patients with prolactin elevation $n(\%)$							
All		74 (42.5%)	3 (10.7%)	68 (48.9%)	13.92 ^b	1	<0.001
Men		45 (40.2%)	2 (10.5%)	41 (47.1%)	8.66 ^b	1	0.002
Women		29 (46.8%)	1 (11.1%)	27 (51.9%)	5.15 ^b	1	0.02
Diagnoses $n(\%)$					0.59 ^b	1	0.32
Affective psychosis		32 (45.1)	7 (53.8)	24 (42.1)			
Non-affective		39 (54.9)	6 (46.2)	33 (57.9)			
Antipsychotic medication $n(\%)$							
None		28 (16.8%)	28 (100%)				
Olanzapine		64 (38.3%)		64 (46.0%)			
Quetiapine		13 (7.8%)		13 (9.4%)			
Risperidone		32 (19.2%)		32 (23.0%)			
Aripiprazole		22 (13.2%)		22 (15.8%)			
FGA		4 (2.4%)		4 (2.9%)			
Amisulpride		4 (2.4%)		4 (2.9%)			
PANSS							
Total	Mean (SD)	58.7 (13.2)	55.5 (9.7)	59.2 (13.7)	– 1.08 ^c	122	0.28
Positive symptoms	Mean (SD)	14.4 (5.6)	14.1 (3.8)	14.5 (5.8)	0.23 ^a		0.82
Negative symptoms	Mean (SD)	14.6 (5.7)	12.7 (4.2)	15.0 (5.9)	– 1.32 ^a		0.19
Perceived stress scale	Mean (SD)	13.6 (7.2)	17.6 (9.4)	13.0 (6.6)	1.61 ^a		0.11
Life events scale	Mean (SD)	5.0 (4.7)	7.1 (6.0)	4.8 (4.5)	1.19 ^a		0.23
GAF scores							
GAF disability	Mean (SD)	29.4 (13.1)	28.4 (14.0)	31.8 (16.6)	– 1.07 ^a		0.28
GAF symptoms	Mean (SD)	57.0918.0)	70.4 (20.0)	55.1 (17.0)	2.68 ^a		0.007

df, degrees of freedom; SD, standard deviation.

^a Mann-Whitney U test for non-parametric continuous variables.

^b χ^2 test for categorical variables.

^c Independent student's t -test for parametric continuous variables.

0.418 95% CI – 16.97–40.39) or BLE scores ($\beta = 17.7$, $t = 0.83$, $df = 78$, $p = 0.41$ 95% CI – 25.03–60.52).

There was no elevation in perceived stress levels between those patients with FEP who were hospitalised at study recruitment compared to those who were treated in the community.

4. Discussion

The current study is to our knowledge the first naturalistic study in FEP to investigate the prevalence of HPL in categorical terms using a longitudinal design. In this study we demonstrate elevated rates of HPL in both antipsychotic treated and untreated patients with FEP, with 43% meeting criteria for HPL at study recruitment. The current study is also the first to investigate stress and its relationship with prolactin in FEP; we did not determine any effect.

We chose to present our findings in categorical terms (along with mean values), in order to optimise the clinical utility of the data. In relation to this we categorised HPL by rates of severity (HPL > 1000 mIU/L (~47.4 ng/ml) and > 2000 > mIU/L (~94.8 ng/ml)), with 16% demonstrating HPL > 1000 mIU/L (~47.4 ng/ml) at baseline and 11% at 12 months. These rates are similar to those identified in patients

receiving maintenance antipsychotic treatment for schizophrenia (Bushe and Shaw, 2007; Bushe et al., 2008b).

The prevalence of HPL for those patients who were antipsychotic naïve was 11%, a lower rate than found in other samples of antipsychotic naïve FEP patients (Aston et al., 2010; Riecher-Rössler et al., 2013), though substantially higher than rates of 0.4% in the general population (Biller et al., 1999). However, the finding that 11% of those who were antipsychotic naïve had evidence of HPL at baseline reinforces the need for prolactin measures to be measured before any antipsychotic treatment is started to ensure that HPL is not a pre-existing state (Peuskens et al., 2014). Our finding of higher mean serum prolactin levels in females is consistent with previous literature in established psychosis (Bushe et al., 2008a), and is expected given that females are primed to respond to prolactin during physiological states such as pregnancy and breast feeding.

4.1. Antipsychotics and HPL

In relation to antipsychotic treatment, we identified large amounts of treatment switching during the course of the first twelve months of

Table 2

Prevalence of hyperprolactinaemia in first episode patients by risk factors at baseline.

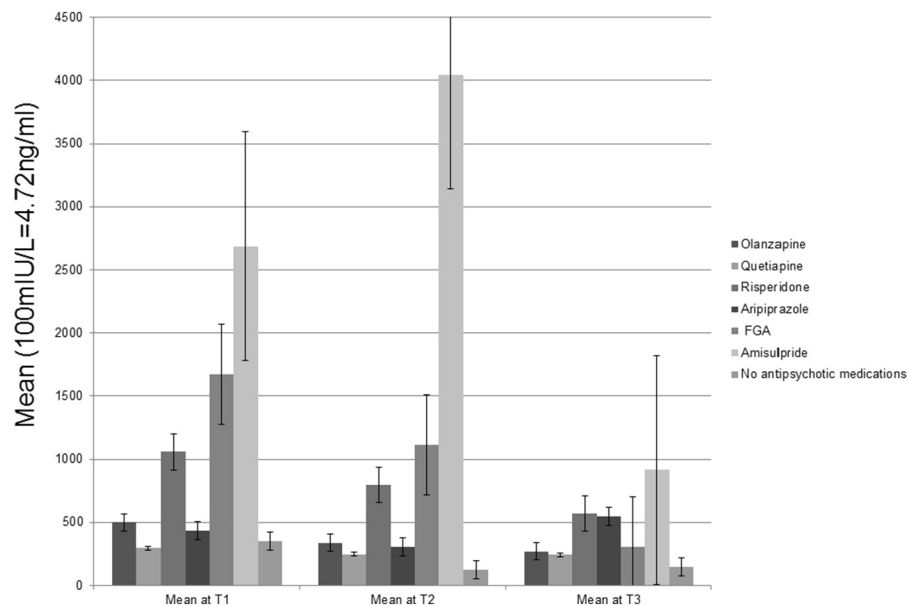
Demographic, diagnostic and antipsychotics	No Abnormal hyperprolactinaemia at baseline (n = 100, 57.5%)	Abnormal hyperprolactinaemia at baseline (n = 74, 42.5%)	Test-statistic	df	p-Value
	Mean (SD)/n(%)	Mean (SD)/n(%)			
Ethnicity					
White British	53 (66.3%)	27 (33.7%)	5.04 ^a	2	0.08
Black (all categories)	30 (48.4%)	32 (51.6%)			
Other	16 (51.6%)	15 (48.4%)			
Gender					
Male	67 (59.8%)	45 (40.2%)	0.71 ^a	1	0.25
Female	33 (53.2%)	29 (46.8%)			
Age years	30.10 (10.74)	28.88 (9.71)	0.57 ^b		0.57
Smoking status					
No	11 (50.0%)	11 (50.0%)	0.56 ^a	1	0.30
Yes	57 (58.8%)	40 (41.2%)			
PANSS					
Total	57.5 (12.8)	60.8 (14.5)	−1.40 ^c	127	0.16
Positive symptoms	13.95 (5.83)	15.23 (5.31)	−1.77 ^b		0.08
Negative symptoms	14.13 (5.18)	15.48 (6.35)	−1.01 ^b		0.31
Perceived stress scale	13.86 (7.31)	13.40 (7.08)	0.34 ^b		0.73
Life events scale	4.84 (4.39)	4.73 (4.59)	0.28 ^b		0.78
GAF scores					
GAF disability	30.66 (16.99)	30.78 (14.99)	−0.05 ^c	166	0.96
GAF symptoms	59.43 (16.72)	52.85 (17.99)	2.15 ^c	131	0.03
Diagnosis					
Affective psychosis	27 (69.3%)	12 (30.7%)	3.25	1	0.05
Non-affective	36 (51.4%)	34 (49.6%)			
Antipsychotic medications			17.9 ^a	5	0.001
Olanzapine	33 (51.6%)	31 (48.4%)			
Quetiapine	3 (23.1%)	10 (76.9%)			
Risperidone	9 (28.1%)	23 (71.9%)			
Aripiprazole	18 (81.8%)	4 (18.2%)			
FGA	1 (25%)	3 (4.2%)			
Amisulpride	–	4 (100.0%)			

^a chi squared test^b z scores^c t test

illness, with just over half of the patients maintained on the same treatment over the 12 month period ($n = 95$; 57%).

We confirmed that risperidone, along with amisulpride and FGAs (though these findings are limited by the small numbers) are more potentially associated with increased prolactin levels in FEP than other antipsychotics. However, all antipsychotics, including aripiprazole, were associated with HPL at some point over the 12 month period. However, due to frequent changes in antipsychotics, attributing and isolating the

corresponding HPL to any given medication is challenging. Nevertheless, we identified that the highest prevalence rate for HPL associated with risperidone was seen at study recruitment (70% with HPL), followed by a decline in rates of HPL over the study period (40% of those patients treated continuously from baseline with risperidone had HPL at the end of the study period). Forty two percent of olanzapine treated patients had HPL at study recruitment, one quarter had HPL at 3 months, and only 16% had HPL at the end of the study period. This declining

**Fig. 1.** Mean prolactin levels (mIU/L) for individual antipsychotic medication use at each time point.

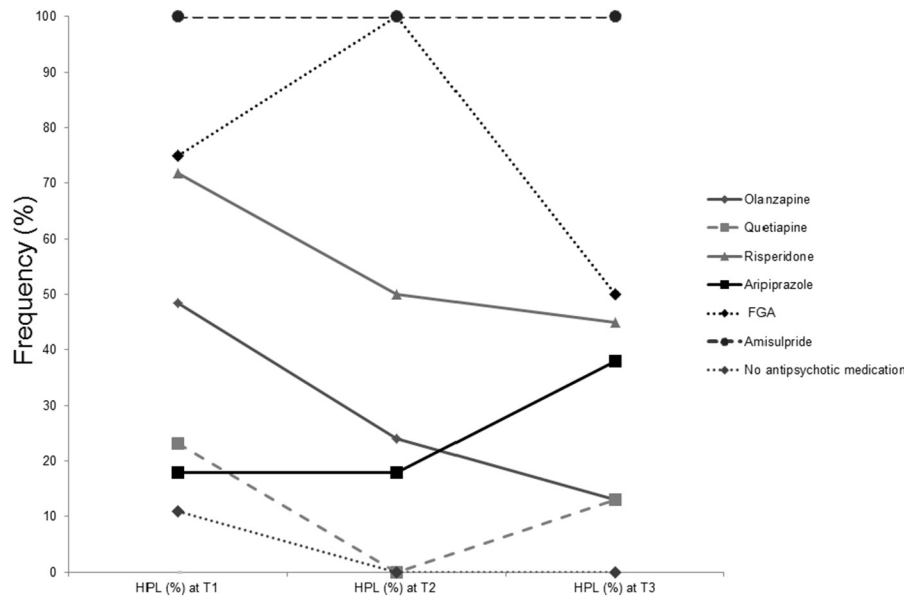


Fig. 2. Prevalence of hyperprolactinaemia for individual antipsychotic medication at each time point.

prevalence of HPL in continuously used antipsychotics has previously been demonstrated in FEP with the use of olanzapine, haloperidol and risperidone (Pérez-Iglesias et al., 2012). It has been previously suggested that prolactin can induce a negative feedback on its own secretion, a possible explanation for the declining HPL prevalence (Grattan et al., 2001). Further, medication non adherence during follow up may have been a contributing factor to the declining rates of HPL. Despite long antipsychotic exposure, there was no significant effect of antipsychotic treatment duration on rates of HPL at follow up (nor at study recruitment). Further, we did not identify a dose effect of antipsychotics with HPL, with higher DDDs not associated with increased rates of HPL at study recruitment or at follow up. These findings indicate that neither the cumulative effect of antipsychotic exposure nor the dose of antipsychotic used is associated with the emergence (or persistence) of HPL.

Our finding that amisulpride was associated with HPL in all patients across the study period, is consistent with previous studies identifying

substantial increases in serum prolactin and rates of HPL in FEP with amisulpride use (Kahn et al., 2008; Peuskens et al., 2014). We identified a HPL rate of 25% for aripiprazole monotherapy (continuous use over the study period) at the end of the follow period. The elevations in prolactin seen in aripiprazole treated patients are somewhat surprising, though previous studies have found HPL rates of 10% in FEP patients treated with aripiprazole (Kwon et al., 2009). Even though aripiprazole has perhaps the most benign impact of all antipsychotic medication on prolactin measures (Leucht et al., 2013), our findings indicate that in some patients HPL can still occur.

The course and persistence of HPL in relation to antipsychotic use overtime remains a complex question, and one with which the literature is limited by a lack of prospective studies (Eberhard et al., 2007; Pérez-Iglesias et al., 2012). However, our naturalistic study provides further evidence that rates of HPL do decline over the first year of illness, but that HPL persists with all antipsychotics used, with higher rates of sustained HPL seen with amisulpride, risperidone and FGAs.

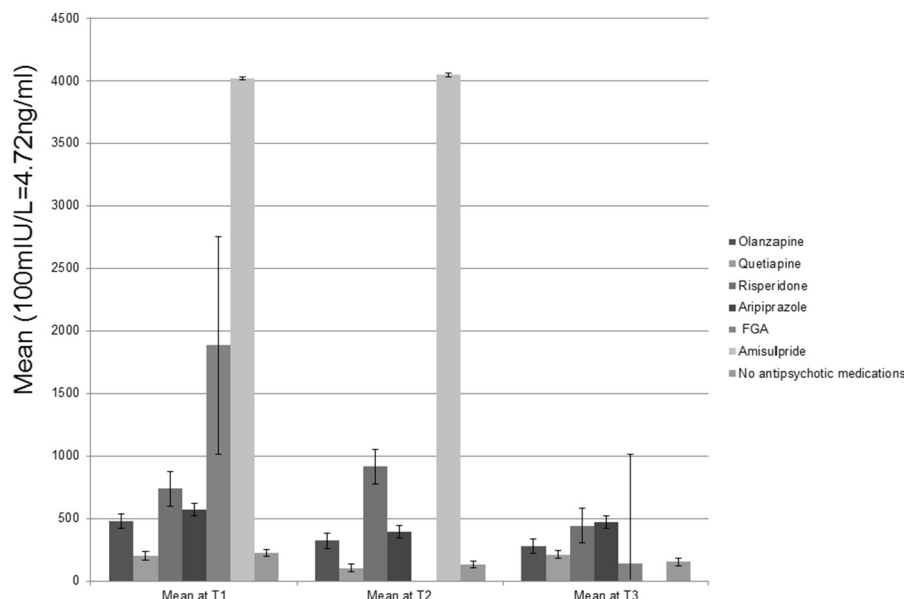


Fig. 3. Mean prolactin levels (UI/L) for those with continuous use of antipsychotic medications.

4.2. Stress, symptoms and HPL

We did not find evidence supporting the hypothesis that stress induced HPL may play a role in the emergence of FEP. There was no evidence of an association between perceived stress or objective life stressors and HPL, either in the antipsychotic treated or in the antipsychotic naïve groups. We were able to measure the patients' perceived stress at the time of study recruitment, and also relate this to stressful life events experienced over the preceding weeks or months—meaning that we were able to comprehensively assess serum prolactin levels in the context of patient's stressors and their experience of them after the onset of the psychotic episode. However, our null finding in this regard may possibly be due to limitations in the data, including the sample size.

Our lack of association between psychotic symptoms and HPL is consistent with earlier findings in FEP, though this remains a poorly researched area (Riecher-Rössler et al., 2013). For the first time we have identified an association between HPL in the early stages of FEP and a reduced level of functioning as measured by GAF, compared to those FEP patients with no HPL. Further, we did not find an association between higher antipsychotic DDDs and HPL rates, thus reducing the chance that this finding of an association between HPL and lower GAF scores was a case of confounding by indication (i.e. those with a more severe illness presentation might have received higher doses of antipsychotics, thereby increasing their risk of HPL).

4.3. Strengths

This is the largest naturalistic study in FEP to report on the prevalence of HPL over the first year of illness. The use of categorised HPL data ensures that our findings have clinical applicability. Serum prolactin levels were measured in the same laboratory for all patients, thus enhancing the standardisation of the prolactin results.

4.4. Limitations

We acknowledge that our findings in this group are limited by the lack of homogeneity inherent to a FEP population of patients. A limitation of our study is the relatively high number of participants who did not have a prolactin measure at study follow up (45% ($n = 79$) at follow up with no prolactin measure). There was no association identified between serum prolactin and stress in antipsychotic naïve patients, though caution is required in the interpretation of this finding due to the small numbers of cases. We did not measure medication adherence over the study period, raising the possibility that non adherence may have contributed to our finding of a lack of dose effect between antipsychotic use and HPL, and which may have distorted the associations between antipsychotics and HPL.

We did not record the timing of antipsychotic administration in relation to prolactin measurement. We attempted to sample all patients in the fasting state, but this was not always feasible, and we had to sample some patients later in the day according to their availability. As this situation mirrors the realities of managing patients with psychosis, we believe that our data on HPL remain applicable to clinical practice. We did not measure thyroid status in patients, a potential confounding factor for a minority of those with HPL. Nor did we record symptoms which may be related to raised serum prolactin, such as sexual dysfunction or menstrual abnormalities, data which may have further increased the clinical relevance of our findings.

4.5. Implications for practice

In recent years, the occurrence of cardiometabolic risk factors has been more prominently recognised in psychotic disorders (Mitchell et al., 2013). However, the routine monitoring of serum prolactin levels is not included in the most recent UK guidelines as part of ongoing

monitoring of physical health side effects of antipsychotic treatment (NICE., 2014).

The high rates of HPL identified in this study indicate that serum prolactin measures should be routinely incorporated into baseline assessments before the start of any antipsychotic treatment, including before a switch to a new antipsychotic. Monitoring for prolactin levels should be incorporated into established fasting blood sampling at all stages of antipsychotic treatment. If prolactin is already raised at baseline, then prolactin sparing antipsychotics are preferentially used (e.g. aripiprazole and asenapine).

Further, in recent years, it has become more widely recognised that sustained hyperprolactinaemia can have longer term adverse effect potential, primarily mediated by inhibition of the hypothalamopituitary-gonadal axis. These effects are particularly marked on bone integrity, increasing the risk for low bone mineral density (Crews and Howes, 2012), osteoporosis (O'Keane, 2008), and osteoporotic fractures (Stubbs et al., 2015). These effects could be additive to those of low vitamin D, commonly seen in psychosis (Crews et al., 2013; Lally et al., 2016). Our findings of high rates of HPL in this young population of antipsychotic treated patients, is important given the putative detrimental effect on bone mineral density (Crews and Howes, 2012), and the fact that exposure to antipsychotic medication and hyperprolactinaemia is likely to be present over a prolonged period of time. However, given the multifactorial aetiology for many of these adverse effects, uncertainty relating to the specific physical effects of hyperprolactinaemia persists, and probably contributes to the low level of monitoring which occurs in clinical practice.

4.6. Management during antipsychotic treatment

While in the majority of cases, HPL in FEP is likely to be related to physiological and medication-related causes, consideration should also be given to the possibility of a primary endocrinology cause, with a prevalence of HPL in the general population of 0.4% (Billir et al., 1999).

Consideration should be given to any past history of symptoms that might suggest pituitary disease prior to the onset of psychosis and antipsychotic medication use, particularly a history of menstrual disturbance in women or erectile dysfunction in men, but also less common symptoms including headache and visual disturbance.

It is helpful to establish the temporal relationship of the change in the prolactin level to the initiation of the antipsychotic. If there has been a clear change in prolactin following the introduction of the antipsychotic, and no prior symptoms of pituitary disease, then further investigation is not required. Provided the patient is asymptomatic, consideration for continuation of the antipsychotic can be made.

Initial investigations in female patients with HPL should include a pregnancy test. Other relevant investigations include renal, liver and thyroid function tests and measurement of oestradiol or testosterone in those with symptoms suggestive of hypogonadism. A serum prolactin level of >2000 mIU/L (~ 94.8 ng/ml) can occur with antipsychotic medication, but a level of >2500 mIU/L (~ 117.9 ng/ml), in the absence of pregnancy or breast-feeding, should prompt an endocrinology referral for further investigation to exclude a micro or macro pituitary adenoma (Haddad and Wieck, 2004).

All patients should be questioned about their sexual functioning in the context of an abnormal prolactin, and the finding of an abnormal prolactin level provides an opportunity, or prompt, to do so. This is important, as sexual dysfunction has been associated with increased dissatisfaction, and reduced compliance with medication (Lambert et al., 2004), and acknowledging and managing this is an important adherence maintenance intervention.

If a patient is asymptomatic, and not reporting disrupted menstruation (for women) or sexual dysfunction, then simple reassurance may be the most appropriate response, as many HPLs in FEP will improve with time, as identified in our and other studies (Brown and Laughren, 1981; Pérez-Iglesias et al., 2012). However, if sexual dysfunction is

present then consideration for a dose reduction or a switch to an antipsychotic with a lower risk of causing HPL should be made. If a switch of antipsychotic is deemed to carry too great a risk of psychotic relapse, then the introduction of low dose aripiprazole to the current antipsychotic could be considered, as it is associated with reduction in serum prolactin levels (Shim et al., 2007). For those with HPL and confirmed secondary hypogonadism, oestrogen and testosterone replacement may improve symptoms and may counter against the risk of longer term skeletal effects of HPL (Melmed et al., 2011).

4.7. Conclusions

We found no relationship between HPL and perceived stress, thus failing to provide support for the prolactin/stress model of early psychosis. However, HPL is often present at the time of FEP and is associated with the use of all antipsychotics, and is more prominent with the use of amisulpride, FGAs and risperidone, with rates plateauing at 12 months but remaining high. This has been a consistent finding in studies of maintenance treatment in schizophrenia, and while emerging evidence indicates that it occurs in FEP populations as well, this study confirms these findings.

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Role of the funding source

The funder of the study had no role in study design, data analysis, data interpretation, and preparation, writing, review, and approval of the study report, and the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethics

Ethical approval for this study was obtained from The Joint South London and Maudsley and The Institute of Psychiatry NHS Research Ethics.

The REC reference number for the study is 08/H0807/53.

Contributors

We affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

All authors made substantial contributions to the conception and design of the work. JL, OA, BS, HRW, MC, EC, SF, PGS and FG were involved in the acquisition and analysis of the data; and JL, OA, VM, OH, DMT, SS, DH, RMM and FG in the interpretation of data for the work;

JL and FG created the first draft of the work and all authors (JL, OA, BS, HRW, MC, EC, SF, PGS, KG, ZA, VM, KI, OA, VM, OH, DMT, SS, DH, RMM and FG) were involved in the revision and completion of the work;

All authors (JL, OA, BS, HRW, MC, EC, SF, PGS, KG, ZA, VM, KI, OA, VM, OH, DMT, SS, DH, RMM and FG) gave final approval of the version to be submitted and published and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interests

This is a National Institute of Health Research (NIHR) funded study (grant number:: RP-PG-0606-1049).

DT has the following declaration of interest. Advisory Board member for: Lundbeck, Servier, Sunovion; lectures for Janssen, Lundbeck, Otsuka, Servier: research funding from: BMS, Janssen, Lundbeck. OH has received investigator-led grants and/or served as a speaker/consultant for Eli Lilly, Roche, Leyden-Delta, Lundbeck, Servier and Janssen-

Cilag (J&J). RMM has received payment for lectures, including service on speakers' bureaus for BMS, Janssen, AZ. FG has received support or honoraria for CME, advisory work and lectures from Bristol-Myers Squibb, Janssen, Lundbeck, Otsuka, Roche, and Sunovion, has research funded by an NHS Innovations/Janssen-Cilag award and has a family member with professional links to Lilly and GSK, including shares.

The other authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; there are no other relationships or activities that could appear to have influenced the submitted work.

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