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Prolactin and Schizophrenia, an Evolving Relationship

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1. Introduction

Prolactin is a polypeptide hormone originally discovered from the crop glands of pigeons in 1933 (Riddle et al, 1933; Bushe and Pendlebury, 2010), however there was some scepticism that prolactin even existed in humans until the 1970s as human prolactin was considered identical to growth hormone (GH). During the 1970s, the development of radioimmunoassay techniques allowed the isolation of prolactin and its subsequent measurement (Kohen and Wildgust, 2008). Since that time, awareness of the consequences of hyperprolactinaemia in psychiatry has been less than rapid despite clear evidence that many psychotropic agents, in particular antipsychotics, elevate prolactin levels to some degree in many patients. As a result, prolactin monitoring is not commonplace and many clinicians remain unsure of its utility. In part, this may relate to lack of knowledge regarding pathological endpoints caused by hyperprolactinaemia.

In the last decade, however, awareness has begun to emerge of the potential consequences of untreated hyperprolactinaemia including short-term adverse events of sexual dysfunction, amenorrhoea and infertility and longer term consequences that may include bone fractures and breast cancer. This has been due in part to a number of reviews focussing on the potential consequences of hyperprolactinaemia and the relatively high prevalence of this adverse event (Haddad and Wieck, 2004; Bostwick et al, 2009; Bushe and Pendlebury, 2010),). In 2008 the first set of prolactin monitoring guidelines was published and more recent data have begun to evaluate the use of specific polypharmacy to reduce prolactin levels (Peveler et al, 2008). There remain, however, many unanswered questions; most relate to the need to establish the true incidence of longer term sequelae of hyperprolactinaemia and to the simple question- what level of prolactin actually carries consequences and when? When one considers that prolactin has at least 300 biological actions it may be that this diversity of function will lead to research that further defines the precise role of and subsequent pathology induced by hyperprolactinaemia (Fitzgerald and Dinan, 2008).

2. Prolactin – What do we know about the hormone?

2.1 Structure and release

Prolactin, a polypeptide hormone that binds to prolactin receptors, is considered part of the Class 1 cytokine receptor family present in various organs including pancreas, liver, uterus

and prostate and consequently may have some immunological activity. It is predominantly synthesised and secreted from the lactotroph cells of the anterior pituitary (Fitzgerald and Dinan, 2008). Lactotrophs form around 20-50% of the cellular population of the pituitary with those in the more inner zones being more responsive to dopamine. Structurally, prolactin is a single chain of 199 amino-acids containing six cysteine residues and three disulfide bonds with 40% homology between the genes encoding prolactin and GH (Fitzgerald and Dinan, 2008).

Prolactin is released from the anterior pituitary in a pulsatile manner and has a half life of around 50 minutes (Citrome, 2008). It peaks around 10 times per day in young adults (Holt, 2008) with a marked circadian rhythm highest during sleep and reaching a nadir during waking hours. Time of measurement is thus important to standardise and is best undertaken before drug dosing in a fasting state in the morning, although this is not always pragmatic in schizophrenia due to the nature of the illness. Measurement of levels during the day needs to be relatively precise as stress factors, exercise and eating can alter levels. In addition, there appears to be an annual circadian variation though with little clinical relevance. Garde et al (2000) reported that prolactin was highest in healthy female subjects in March-May (153 mIU/L) and lowest in September-November (98 mIU/L) (Garde et al, 2000).

Increasingly other confounding factors are being recognised that potentially also affect prolactin levels and any clinical interpretation of abnormality. For example, fluctuating prolactin levels have been found to be greater over the 24-hour period after dosing with perospirone than with either risperidone or olanzapine, despite the magnitude of hyperprolactinaemia being greater with risperidone (Yasui-Furukori et al, 2010). Recent data are supportive of current smokers taking antipsychotics having both a lower mean prolactin level (odds ratio [OR] 2.3, 95% confidence interval [CI] 1.2-4.7, $p=0.002$) and a lower prevalence of hyperprolactinaemia (Mackin et al, 2010) and other data are supportive at a minimum that is true in females (Ohta et al, 2011). This may be a critical confounder in schizophrenia where almost all patients smoke and indeed smoke more cigarettes than smokers in the general population. Other confounders are much better recognised with a study of 154 schizophrenia patients taking 6mg risperidone reporting that prolactin levels correlate with gender (higher in females), age (lower in older patients) and smoking status ($p<0.01$) based on a multiple regression analysis (Ohta et al, 2011).

Control of prolactin secretion from the anterior pituitary is predominantly under the control of dopamine released via hypothalamic dopaminergic neurons, the tuberoinfundibular and tuberohypophyseal dopaminergic neurones (Holt, 2008). Dopamine is transported from the hypothalamus to the anterior pituitary via the long hypophyseal portal vessels and inhibits the high basal secretory tone of the lactotroph. This high basal secretory activity is unique amongst endocrine cells. The released prolactin regulates the dopamine synthesis from the hypothalamus via a feedback loop.

The mechanism whereby prolactin is elevated by D2 blockade remains undetermined. However, the most likely explanations relate to speed of D2 dissociation and the ability of the antipsychotic to cross the blood brain barrier (Bushe et al, 2010), with drugs dissociating slowly being associated with greater prolactin elevation. In contrast, quetiapine, an example of an antipsychotic with fast dissociation, has low rates of prolactin elevation being associated with central D2 occupancy that falls from initial blockade of 60-70% at 2 hours post-dosing to around 30% at 24 hours.

3. Measurement of prolactin and definition of hyperprolactinaemia

Units of measurement have the potential to cause some confusion as US and EU data are often presented in ng/ml whereas most UK data are in mIU/L. Conversion rates from ng/ml to mIU/L are not standardised and vary between 21.2 and 36 dependent on the assay employed (Bushe et al, 2008). Furthermore, clinical reports do not always report either the normal range utilised or sometimes the units of measurement (McEvoy et al, 2007).

Definitions of hyperprolactinaemia vary depending upon the upper limit of normal (ULN) for the local assay. Normal ranges for females tend often to be around 30% higher than males, with some laboratories also reporting separate ranges for premenopausal and postmenopausal females. In the psychiatric literature, some of the highest ULNs for females are around 700 mIU/L and, for males, 500 mIU/L (Bushe and Shaw 2007), with lowest ULN at 300 mIU/L for females (Meaney et al, 2004). The Maudsley guidelines 10th edition (Taylor et al, 2009) gives fairly specific advice on blood sampling (1 hour after waking or eating) and cites normal ranges in both ng/ml and mIU/L. In their view, the ULN for females is <530 mIU/L and for males is <424 mIU/L; re-testing is advised if the prolactin level is between 530-2120 mIU/L.

There is currently also no specific definition for an elevated prolactin level that may be regarded as clinically non-significant and when we published our original data set there was no specific guidance to either diagnose or grade level of severity of hyperprolactinaemia (Bushe/Shaw 2007). Thus, we created three specific grades of hyperprolactinaemia: slightly elevated (<1000 mIU/L), significant elevation (1001-2000 mIU/L) and severe elevation (>2000mIU/L). This was based on empirical judgement and not with relation to specifically defined outcomes. In general terms, prolactin levels <2000 mIU/L may be due to a medication effect but other causes can include microprolactinoma, pituitary stalk compression, renal failure or hypothyroidism (Holt, 2008). The literature currently reports that macroprolactinomas are the most common cause of prolactin levels >2120 mIU/L in the general population (Bushe et al, 2010) although other authors propose higher levels (3180 mIU/L) at which hyperprolactinaemia can be assumed to be caused by a macroprolactinoma (Holt, 2008).

When evaluating hyperprolactinaemia it is also critical to understand the incidence or prevalence of hyperprolactinaemia from the patient perspective as opposed to a mean level from a cohort. Recent data are now tending to more commonly include both variables (Mackin et al, 2011) whereas in our 2008 review of this topic we reported that though 60% of studies reporting prolactin data included some degree of categorical analysis, this was seen mainly in the naturalistic studies (88%) rather than the randomised controlled trials (42%) (Bushe et al, 2008).

4. Consequences of hyperprolactinaemia

Many of the longer term definitive outcomes associated with elevated prolactin remain unknown. Recent findings of prolactin receptors in atherosclerotic plaques in coronary arteries of healthy subjects indicate a possible role of prolactin even in coronary artery disease (Reuwer et al, 2009). There are, however, three areas of pathology that would seem to be closely linked to elevated prolactin, sexual function, bone loss and cancer and these can be considered as short- and longer term potential adverse events.

4.1 Short term consequences of hyperprolactinaemia

4.1.1 Sexual function

Sex hormone dysregulation may be the underlying cause of both acute and longer term adverse events associated with hyperprolactinaemia as prolactin has a significant effect on sex hormone regulation and prolactin levels in patients treated with antipsychotics are inversely related to steroid sex hormone concentrations (Smith, 2002). However, the absolute link between prolactin and sexual dysfunction is complex. The relative short-term consequences of hyperprolactinaemia are well described and, in addition, to sexual dysfunction include menstrual disturbances, acne, infertility, galactorrhea and gynaecomastia although prevalence rates were until recently not well reported. In 2011, the European First Episode Schizophrenia Trial (EUFEST) study of first episode schizophrenia patients reported that sexual dysfunction was very common at baseline (Malik et al, 2011) and although often attributed to antipsychotics this is not the complete picture as smoking, physical illness, depressive and negative symptoms may also be relevant (Malik et al, 2011). Over the 1-year study, changes in prevalence of sexual dysfunction were small and varied little between antipsychotics despite hyperprolactinaemia being very common and moderately severe (Kahn et al, 2008). The authors concluded that their data emphasized that schizophrenia the illness was a key influence on sexual dysfunction although hyperprolactinemia undoubtedly plays an additional role (Malik et al, 2011). There is also an important investigational aspect to consider. In most antipsychotic studies previous medication prior to study entry is either inadequately or incompletely described, which makes interpretation of variables such as prolactin and sexual dysfunction complex. It is possible that changes measured during the trial may relate to the removal of a previous antipsychotic. As such the only data that can give a true baseline are data in treatment-naïve subjects from studies such as EUFEST. Not all data, however, are consistent with this view that prolactin may play a smaller role in sexual dysfunction than expected (Knegtering et al, 2008). For example, in a 6-week, open label study including 264 patients treated with antipsychotics, prolactin-raising antipsychotics were linked with significantly more sexual-related adverse events than patients treated with prolactin-sparing antipsychotics. The authors concluded that around 40% of emerging sexual adverse events in schizophrenia are attributable to prolactin (Knegtering et al, 2008). The importance of seeking overt symptomatology however is that it offers the opportunity to measure prolactin as many guidelines have previously not suggested prolactin measurements until the presence of relevant symptoms. The literature is fairly conclusive that sexual dysfunction is not always regarded as an important aspect to discuss with patients in routine clinical practice.

4.2 Longer term consequences of hyperprolactinaemia

4.2.1 Bone

Data on hyperprolactinaemia and bone loss have appeared during the last decade predominantly due to the work of Veronica O'Keane. Her group systematically followed the link between hyperprolactinaemia and sex hormones (males and females) and then between hyperprolactinaemia and bone loss. Some studies suggest that even relatively short periods of hyperprolactinaemia can have significant adverse effects on bone density (Meaney and O'Keane, 2007; O'Keane, 2008). Young women may be particularly susceptible to hyperprolactinaemia, and osteoporosis and osteopenia may develop in the first 8 years of antipsychotic treatment (Meaney and O'Keane, 2007; O'Keane, 2008). Of more concern is

the finding that deterioration can be measured over a single year and essentially cannot be prevented (Meaney and O'Keane, 2007; O'Keane, 2008). A second set of key epidemiological studies evaluating fractures in large UK cohorts was published suggesting that hip and other bone fractures are a sequelae of mental illness and its treatment. Howard reported that hyperprolactinaemia and prolactin-elevating antipsychotics have been associated with a doubling of the risk of hip fracture in schizophrenia patients in a large UK study (OR 2.6, CI 2.43-2.78) (Howard et al, 2007). A second study also using the UK General Practice Research Database (GPRD) reported that in women the highest relative risk of fracture in a mentally ill population were in the youngest cohorts, whereas in males the greatest risks were seen in older age (Abel et al, 2008). The results showed that the relative risk (RR) of any fracture was increased more than double in females with psychotic disorders (RR 2.5: CI 1.5-4.3) but that even greater risk was measured in the cohort aged 45-74 years with psychotic disorders, with a relative risk in women of RR 5.1 (CI 2.7-9.6) and in males RR 6.4 (CI 2.6-16.1) when looking specifically at hip fractures (Abel et al, 2008). This risk may be seen to an even greater extent in males than females (Howard et al, 2007) and is present after adjusting for the other risk factors for osteoporosis highly prevalent in a cohort of patients with severe mental illness (poor diet, low exercise rates, increased alcohol consumption and decreased sunlight exposure). Other data however are needed for other fracture sites (radius and vertebrae) together with some indication as to whether it is the cumulative length of hyperprolactinaemia that is crucial (a sort of area under the curve measurement) or the effect of a critical peak level of prolactin. Recent data in non-schizophrenic males with prolactinoma reported that using DEXA scanning of the lumbar spine vertebral fractures were diagnosed in 37.5% of patients compared with 7.8% of controls ($p < 0.001$) (Mazziotti et al, 2011) and that these developed independently of hypogonadism.

4.2.2 Possible association with cancer

A recent systematic review concluded that breast cancer is significantly increased in females with schizophrenia but the data have simply not been published to establish the degree of the putative role of prolactin in this increased risk (Bushe et al, 2009). A number of epidemiological studies have reported data over the last 25 years but it is only in the last few years that clarity has emerged. The importance of systematic review in addressing a clinical question is clear. In this case, when studies with adequate powering and follow up undertaken in an age group where cancer developed (>50 yrs for breast cancer predominantly) are considered, the results were clear. The specific relevance of breast cancer is that it is the most common cancer in women in the UK, it accounts for 23% of all female cancer cases worldwide, there is a lifetime risk of 1 in 9 in the general population and this risk is increasing (Bushe et al, 2010). A recent meta-analysis that included fewer studies than our systematic review (Catts et al, 2008) reported a 12% increased risk (Standardised Incidence Ratio [SIR] 1.12, 95% CI 1.02-1.23) with a more recent UK study reporting an increased risk of 52% in schizophrenia adjusting for recognised confounders such as poverty (Hippisley-Cox et al, 2007). One can only speculate over the role of prolactin and mammary carcinogenesis, however in animal toxicity and molecular studies, it has been recognised over many years (Harvey 2008) that there is a very strong association. The US Nurses' Health Study evaluated prolactin samples from 32,826 patients with normal prolactin levels during the period 1989 to 1990 and these subjects have been extensively followed over 20 years, providing conclusive evidence linking prolactin and breast cancer in the general

population. Many of their study reports suggest prolactin levels to be linked to the risk of breast cancer development both in pre- and postmenopausal women (Tworoger and Hankinson, 2006; Tworoger et al, 2007). An example of these data found prolactin levels in the upper quartile of normal to be associated with an increased risk compared to the lower quartile of normal (OR 1.34, 95% CI 1.02-1.76) (Tworoger et al, 2007). Any definitive link, however, has yet to be established in schizophrenia and bipolar disorder.

A large retrospective cohort study of 52,819 females receiving antipsychotics and 55,289 control women reported a 16% increased risk of breast cancer (Wang et al, 2002) with a dose response relationship suggesting a greater risk of breast cancer with increased doses of antipsychotic. Regardless of relationship with prolactin, identical breast cancer screening should be encouraged in all schizophrenia subjects as in the general population. Screening rates for schizophrenia patients are very low compared with the general population for an illness that is very common (lifetime prevalence 1 in 9 and rising) and often curable (Bushe et al, 2010).

Hyperprolactinaemia has also been linked to pituitary adenomas and adenocarcinomas and putatively to prostate cancer (Harvey et al, 2008). The US Food and Drug Administration Adverse Event Reporting System pharmacovigilance database study strongly linked risperidone (adjusted reporting ratio 18.7) with the highest frequency of pituitary adenomas compared with haloperidol (5.6), ziprasidone (3.0) and olanzapine (2.3) (Szarfman et al, 2006). A recent case series is suggestive that amisulpride may also be associated with the development of prolactinomas mediated via hyperprolactinaemia (Akkaya et al, 2009).

The multiple actions of prolactin and relative lack of research into hyperprolactinaemia suggest that additional potential long-term effects may be discovered potentially in glands such as the thyroid. Recent data suggest there may be an association with autoimmune thyroiditis and in 75 schizophrenia patients, the prevalence of hyperprolactinaemia was higher in patients with thyroid autoantibodies ($p=0.045$) (Poyraz et al, 2008).

5. Relationship between serum prolactin concentration and adverse events

This is a complex question that remains totally unanswered for the potential longer term sequelae but can be partially addressed for short-term adverse events. There would seem to be two potential associations. Firstly, a chronic prolactin elevation that reaches a cumulative threshold over a longer term and secondly, a peak prolactin level that requires a trigger threshold to initiate pathology. Levels <1000 mIU/L are associated with decreased libido and infertility, 1000-1600 mIU/L with oligomenorrhoea, and >2000 mIU/L with amenorrhoea and hypogonadism (Peveler et al, 2008). Hypogonadism is the main driver for bone mineral density loss and fractures although the possibility exists that prolactin may have a direct osteoclastic effect. Data on longer term prolactin levels tend not to report the associated changes in sex hormones making interpretation complex. The topic has, however, been reviewed (Bushe et al, 2008) and in cross-sectional prevalence studies that report bone mineral density loss in association with typicals or risperidone over 8-21 years, the mean cohort values ranged 908-3024 mIU/L (Bushe et al, 2010). These levels are common and are reached quickly in patients treated with risperidone and amisulpride (Bushe and Shaw 2007; Bushe et al, 2008). A small case series of patients receiving paliperidone reported hyperprolactinaemia within 3 weeks with levels ranging from 1500-3996 mIU/L (Skopek et al, 2010). Prolactin levels related to breast cancer in schizophrenia and bipolar disorder are unknown, however data are supportive of levels

as low as 500 mIU/L being associated with an increased risk of breast cancer in the general population over the medium term (Tworoger and Hankinson 2006, Tworoger et al, 2007). However, it is critical to understand that whereas there is a strong link between prolactin and breast cancer in the general population, there are no data to address this topic in schizophrenia and bipolar disorder. In addition, breast cancer has very many aetiological factors that include social demographics, education, obesity and family history and the role of prolactin is simply not known.

6. How common is hyperprolactinaemia in an antipsychotic-treated cohort?

6.1 Overview

There are few cohorts where prolactin levels have been obtained in a complete cohort and rates of hyperprolactinaemia will be dependent on many factors including medication choice, gender, age and length of follow up. Data derived from epidemiological databases is also confounded by selection bias. Without knowing how many subjects were tested there is little way to put perspective around these data (Montgomery et al, 2004). A true perspective requires a complete cohort to be tested. Many other confounders will remain, however, including gender, smoking status, adherence to treatment, age and time on treatment.

Olanzapine, for example, may give a transient elevation of prolactin that reduces over the first months in some patients but during chronic administration prolactin elevation may remain (Bushe et al, 2008). Naturalistic data may thus be informative as prolactin monitoring is not routine and prevalence rates in complete populations screened will reflect previous under-diagnosis. Two recent naturalistic analyses in which asymptomatic schizophrenia populations have been screened for prolactin report similar prevalence of hyperprolactinaemia: 38% and 39% in UK (n=194) and Norway (n=106), respectively (Bushe and Shaw 2007; Johnsen et al, 2008). The UK study measured prolactin in the total population of a catchment area in Halifax receiving antipsychotics for schizophrenia or bipolar disorder. The population was clinically asymptomatic prior to the study. Hyperprolactinaemia was more common in females than males (52 vs. 26%), consistent with most other data (Bushe et al, 2008), and significantly elevated levels (>1000 mIU/L) were measured in 21% of subjects. For 13% of females and 19% of males, prolactin levels were above the normal limit but below 1001 mIU/L. Categorical rates of hyperprolactinaemia in trials range from 33 to 69% and confirm that no antipsychotic is prolactin neutral (Bushe et al, 2008). Most studies report both a higher prevalence and severity of hyperprolactinaemia in females as was the case in the Halifax study which found 13% of females had levels >2000 mIU/L compared with 2% of males (Bushe and Shaw, 2007).

6.2 Rates of hyperprolactinaemia with individual antipsychotics

The ideal studies to evaluate prolactin would be a long-term, first episode study where the confounding factor of previous antipsychotic usage would not need addressing and which included multiple treatment arms and a longer term randomised study in chronic schizophrenia. There are few such studies with the exception of EUFEST (Kahn et al, 2008) and CATIE (Lieberman et al, 2005). EUFEST was a 1-year, first episode study and CATIE, an 18-month study with multiple treatment arms. Both these studies concluded that hyperprolactinaemia was common though EUFEST failed to find a direct link between prolactin and sexual dysfunction.

The totality of the data is convincing that there is no such entity as a “prolactin-sparing” antipsychotic, however, data are sometimes complex to interpret. There are numerous confounding factors but broadly psychotropic polypharmacy, the choice and the dose of medication are relevant factors as are often the lack of reported data on previous antipsychotic treatment. Adherence is also important as many typicals are now administered by long-acting depot formulations whereas rates of non-adherence to all forms of antipsychotic are high. When these factors are compounded with other confounders (gender, age and smoking), definitive statements regarding prolactin become less precise though some conclusions can be made with reasonable certainty.

Much of the reported data tend to come from relatively short-term clinical trials, often done for drug registration purposes, or cross-sectional prevalence data. Neither data set has properly established the long-term trajectory of hyperprolactinaemia and there are no data to support the concept of regression back to baseline.

There are, however, a number of disparate data on comparable rates of hyperprolactinaemia amongst antipsychotics and the largest data sets reporting prolactin include a 6-week paliperidone study in 628 schizophrenia patients (Kane et al, 2007) and a 1-year risperidone and haloperidol in first episode psychosis study in 555 patients (Schooler et al, 2005). Cohort sizes range from <50 to 2725 (Bushe et al, 2010). There is also surprisingly little dissonance amongst the data sets despite many of the confounders already discussed. .

In summary, for individual antipsychotics the prevalence of hyperprolactinaemia is highest in risperidone, paliperidone and amisulpride-treated patients and approaches 100% in female patients (72-100%) being significantly higher than in patients treated with conventional antipsychotics (33% in a UK cohort on depot antipsychotics) (Bushe et al, 2008; Bushe and Shaw 2007). The recently licensed paliperidone, which is 9-hydroxyl-risperidone, the active metabolite of risperidone, has similar prolactin elevation to risperidone (Berwaerts et al, 2010).

Clinicians have been aware for many years that risperidone is associated with hyperprolactinaemia, however there has been less clarity regarding whether hyperprolactinaemia with risperidone is more prevalent than with conventional antipsychotics. A key study was a long-term, randomised clinical trial (RCT) in first-episode psychosis with subjects randomised to risperidone or haloperidol and a median treatment-length of 206 days (Schooler et al, 2005). This study reported significantly higher rates of hyperprolactinaemia (74% vs. 50%) and mean prolactin levels in the risperidone cohort than the haloperidol cohort. CATIE also reported significantly greater prolactin elevation with risperidone than perphenazine (Lieberman et al, 2005) though only mean changes in individual drug cohorts were reported, not categorical numbers of patients with hyperprolactinaemia.

Although conventional antipsychotics were for a long time regarded as almost uniformly being associated with hyperprolactinaemia, the data are not supportive of this conclusion and recent data on conventional antipsychotics suggest significantly lower prevalence rates of 33-35% in a depot-treated population (Bushe and Shaw, 2007). In part, this may relate to dosing issues. For example, Asian populations using higher doses of haloperidol (15-16mg) than typically used in Europe, have prevalence rates of hyperprolactinaemia (60-66%) approaching those of risperidone and amisulpride (Bushe et al, 2010). Supportive of this dosing issue is the excellent study from Kleinberg in approximately 2000 patients which

concluded that although risperidone was associated with higher rates of hyperprolactinaemia compared with 10 mg haloperidol, no comparative differences emerged with 20mg haloperidol (Kleinberg et al, 1999). Doses of haloperidol currently used are more reflective of studies such as EUFEST, in which the maximum permitted dose was 4 mg.

Our own naturalistic series concluded that hyperprolactinaemia with oral risperidone was indeed almost 100% in females and between 63-100% in males (Bushe et al, 2008). Similar levels of hyperprolactinaemia are measured with amisulpride though data in large cohorts is lacking other than from EUFEST (Bushe et al, 2008). Depot formulations of risperidone may have a lower prevalence of hyperprolactinaemia relating to dose (53-67%) (Bushe et al, 2008; Bushe and Shaw, 2007). Paliperidone is the major metabolite of risperidone (9-hydroxyl-risperidone) and prolactin values are either similar or greater than those of risperidone (Berwaerts et al, 2010).

Aripiprazole is associated with the lowest rates of hyperprolactinaemia with prevalence rates of 3-5% in RCTs that increase to incidence rates of 17% in naturalistic studies (Bushe et al, 2010). Recent data have evaluated aripiprazole as a prolactin-lowering agent when combined with haloperidol or risperidone with some success. Although studies report rapid reductions in prolactin levels after commencing aripiprazole (Shim et al, 2007), this may partially relate to removal of a previously used prolactin-elevating drug. Aripiprazole, however, in a placebo controlled trial when added to high-dose haloperidol (20-25 mg/day) in a cohort of schizophrenia patients resulted in normalisation of prolactin in 85% of subjects by 8 weeks contrasting with 3.6% of the placebo group ($p < 0.001$) (Shim et al, 2007). Further research is indicated into the dosage of aripiprazole that may give maximal benefit.

For the remaining antipsychotics, hyperprolactinaemia is sometimes reported though significantly less often than for risperidone and amisulpride. Our review of the data found that for quetiapine reported rates range from 0-29% and for olanzapine from 6-40% (Bushe et al, 2008) although most studies report rates at the lower end of the spectrum. In a recent 6-month study of schizophrenia, patients randomised to quetiapine or olanzapine, 33% had hyperprolactinaemia at baseline which normalised in almost all patients as early as 14 days (Bushe et al, 2009). There were no significant differences between the drugs in changes in prolactin.

The depot formulation of olanzapine has recently been trialled in a complex, non-inferiority study compared with oral olanzapine. The quality of the data and trial design has meant that aspects such as dose response with variables such as prolactin have been investigated (Hill et al, 2011). Significant dose-related changes in prolactin were measured over the 24-week study, however it should be noted that a small mean increase in prolactin was measured only in the cohort receiving 600 mg/month (oral equivalent estimated as 20 mg/day). In this 600 mg/month cohort, 7/21 of female subjects (33%) moved from a normal into a high range level (Table 1). This emphasises the importance of analysing prolactin data not only as mean changes in a cohort but also the categorical changes to provide data that are meaningful in terms of patient outcomes (Bushe et al, 2008). This concept is also well demonstrated in the 555 schizophrenia patient study, Schizophrenia Trial of Aripiprazole (STAR), in which subjects were randomised to either aripiprazole or standard of care treatment (Hanssens et al, 2008; Kerwin et al, 2007). There was a mean decrease of 34.2 mg/dl in the aripiprazole-treated cohort, however using a categorical analysis, hyperprolactinaemia was reported in 16.8% of subjects.

	300 mg/month (N=140)	405 mg/month (N=318)	600 mg/month (N=141)
Mean change (micrograms/l) (SD)	-5.61 (12.49)	-2.76 (19.02)	3.58 (33.78)

Table 1. Prolactin changes over 24 weeks with depot olanzapine at various dosages in a randomised controlled trial (Hill et al, 2011)

7. What are the current views of EU guidelines on all aspects of prolactin?

Only one set of guidelines, published in 2008, is devoted to prolactin and it provides both advice and the data and rationale behind the consensus group’s conclusions (Peveler et al, 2008). Prior to this many guidelines did not give specific recommendations (Citrome et al, 2008). In general terms, other guidelines and relevant Summaries of Product Characteristics do not provide a specific monitoring schedule and tend to advocate prolactin monitoring only when symptoms are detected.

In 2006, guidelines on bipolar disorder from the National Institute of Clinical Excellence recommended limited pre-treatment monitoring of prolactin levels for risperidone with further monitoring should symptoms develop. The only other guideline to recommend pre-treatment monitoring are the Maudsley guidelines (Taylor et al, 2009). These guidelines recommend baseline prolactin monitoring, followed up at 6 and 12 months. Furthermore, the guidelines advise switching medications if hyperprolactinaemia is symptomatic or, alternatively, adding aripiprazole. The guidelines also concur broadly that hyperprolactinaemia is associated with both short- and longer term adverse events that include bone mineral density loss and a possible increase in the risk of breast cancer. The 2005 recommendations from the World Federation Society of Biological Psychiatry (WFSBP) curiously conclude that whereas prolactin elevation was frequent with amisulpride and typicals (>10%), it was measured only “sometimes” (<10%) with risperidone (Falkai et al, 2006). Current data now seems to have clarified these frequencies rather differently (Bushe et al, 2010; Bushe et al, 2008). The 2008 UK prolactin guidelines recommend prolactin monitoring in all patients pre-treatment regardless of medication and after 3 months of treatment with a stable dose, in addition to further monitoring when there are relevant clinical symptoms (Peveler et al, 2008). With a normal prolactin level there is no further need for monitoring in the absence of clinical symptoms. Significant dose change should also lead to consideration of further monitoring. These UK guidelines give a clear strategy for investigating the aetiology of hyperprolactinaemia in patients receiving antipsychotics and warn against concluding too easily that antipsychotics are responsible. A differential diagnosis must be considered but must always include a pregnancy test in females and thyroid function tests. Prolactin levels can be elevated to levels in excess of >2000 mIU/L in patients taking antipsychotics, however in any patient with prolactin elevation greater than 3000 mIU/L, a prolactinoma should be considered and referral to an endocrinologist is warranted. In the Halifax cohort we measured prolactin levels >2000 mIU/L in 13% of all antipsychotic-treated females and 2% of males. Antipsychotic cessation even for short

periods has not been clinically recommended due to risk of worsening of the mental state although in theory this could be considered a diagnostic tool for patients taking oral preparations (Peveler et al, 2008).

8. The management of treatment-emergent hyperprolactinaemia

The management of treatment-emergent hyperprolactinaemia is complex and many of the issues have been considered by the 2008 prolactin guidelines who referenced previous recommendations (Serri et al, 2003). However, newer data have since emerged allowing novel potential management strategies to be considered (Peveler et al, 2008). Levels <1000 mIU/L can simply be monitored but in the presence of symptoms that suggest sex hormone deficiency, it is suggested that such levels should not be allowed to continue long-term due to the potential risk of bone mineral density loss (Peveler et al, 2008). Persistent levels >1000 mIU/L need consideration for medication change or dose reduction, if appropriate. The consensus group concluded that the use of dopamine agonists should be considered only in exceptional circumstances due to the risk of worsening the psychosis (Peveler et al, 2008). This view however is challenged by the Maudsley guidelines (Taylor et al, 2009) which advocate use of dopamine agonists if patients need to remain on the specific prolactin-elevating antipsychotic. They make an interesting observation that although the three agents cited (amantadine, cabergoline and bromocriptine) have the potential to worsen psychosis, that this has not been shown in clinical trials. Although there are many reviews relating to prolactin in the context of severe mental illness, there are currently few, if any, systematic reviews and meta-analyses. A recent systematic review that incorporated a meta-analysis compared the effects of bromocriptine and cabergoline in treating hyperprolactinaemia due to idiopathic causes and prolactinomas (Dos Santos Nunes et al, 2011). They concluded that cabergoline was significantly superior to bromocriptine in normalising both prolactin levels and resuming normal ovulatory cycles. Thus, cabergoline may potentially be the dopamine agonist of choice should this be mandated.

What is currently emerging in an early research phase is the use of specific polypharmacy designed to reduce prolactin levels whilst maintaining treatment on the original antipsychotic. There is little doubt that aripiprazole may have the lowest potential for prolactin elevation, although as we have already stated, in the STAR study 17% of patients did have hyperprolactinaemia (Kerwin et al, 2007 ;Hanssens et al, 2008) although in RCTs, the prevalence rates of 3% seem consistent (Bushe et al, 2008). The combination of adding aripiprazole to risperidone results in significant reductions in plasma concentrations of prolactin of between 35-63%, with maximal benefit measured with aripiprazole doses around 6 mg (Yasui-Furukori, 2010) and possibly doses as low as 3 mg. In 2009, the Maudsley guidelines stated their view that in the presence of symptomatic hyperprolactinaemia options included changing antipsychotics or adding aripiprazole to the existing treatment. As a strategy it is clear that there may be benefit to some patients, however aripiprazole as a partial dopamine agonist has been shown to be associated with worsening of psychosis in some patients. The complete risk-benefit equation for use of aripiprazole in this manner will require further clinical trials. Other salient issues to consider include the reality that schizophrenia the illness, and its associated symptomatology, is the cause of some of the more overt sexual dysfunction (Malik et al, 2011). Reducing prolactin may not always lead to clinical improvement. The correlation between prolactin and sexual dysfunction however is thus complex. In a case series

although all subjects had reduction in prolactin levels, only around half reported improved sexual function (Chen 2011). The reality of the situation is that individual patients will require individual solutions. A physician considering changing an antipsychotic in a stable patient must carefully balance the risks and benefits of continued treatment.

There will be patients who are clearly at high risk of prolactin-related adverse events for whom usage of potentially prolactin-elevating antipsychotics needs to be carefully considered, eg, patients with a history of breast cancer or osteoporosis. The other angle to management is to ensure high screening rates for patients at high risk of treatment-emergent osteoporosis and provision of relevant treatment to potentially reduce fracture incidence (Graham et al, 2011).

9. Hyperprolactinaemia in children and adolescents

There would seem to be an increasing usage of antipsychotic drugs in the treatment of many childhood psychiatric illnesses including attention deficit hyperactivity disorder, bipolar disorder and childhood schizophrenia. In general, it would seem that prolactin levels are elevated in children by the same antipsychotics that induce hyperprolactinaemia in adults (Rosenbloom, 2010). For example, in a recent review, 100% of a cohort of 34 children aged 5-14 years treated with risperidone had prolactin elevation (Rosenbloom, 2010). Prolactin levels were also assessed in a naturalistic study of children and adolescents receiving antipsychotics and in some cases concurrent stimulants (Penzner et al, 2009). This analysis revealed a number of interesting findings, however, the addition of a stimulant did not affect prolactin levels compared to no usage. It had been hypothesised that stimulant treatment may reduce any hyperprolactinaemia induced. Adolescents treated with olanzapine when compared to adults treated in clinical trials are also likely to have greater increases in prolactin levels.

The data on prolactin elevation and longer term outcomes in childhood is clearly complex to obtain. Data however do exist and broadly seem to mirror the findings in adults where hyperprolactinaemia is associated with decreased bone mineral density (O'Keane, 2008). A cross-sectional study of 83 boys aged 7-17 years treated for 3 years with the combination of selective serotonin reuptake inhibitors (SSRIs) and risperidone reported that after adjustments, a negative association was found between bone mineral density at the distal radius and serum prolactin level (Rosenbloom, 2010). The data furthermore was suggestive that this bone mineral density reduction may relate to a direct effect of prolactin on bone turnover as there was no relationship between testosterone levels and prolactin. The risk associated with longer term hyperprolactinaemia can be postulated to be a deleterious effect on peak bone mass attainment (Rosenbloom, 2010).

When considering their prolactin guidelines in 2008, the consensus group concluded that there were two groups in whom prolactin elevation should be avoided where possible. Firstly, in those when peak bone mass has not yet been attained, such as in children and young adults up to the age of 25 years (Peveler et al, 2008) with females being more vulnerable to the adverse effect of prolactin elevation than males. Risperidone is certainly being used in a variety of childhood psychiatric illnesses at young ages. A recent report in a small cohort of patients with conduct disorder (mean age 42 months) treated with risperidone at a mean dosage of 0.78mg/day and a maximum of 1.5mg/day (Ercan et al, 2011) found substantial increase in prolactin from a baseline mean of 5.3 ng/ml to 70 ng/ml at 8 weeks. Six of the eight children who completed the study had hyperprolactinaemia

without clinical symptoms, as stated by the authors. Studies suggest that children are more sensitive to the prolactin elevating adverse effects of antipsychotics and care is needed to keep these to a minimum (Correll, 2011). The second high risk group would include those with a relevant strong family history of breast cancer or osteoporosis.

10. Further research. What are the unanswered questions?

1. **What are the longer term trajectories of prolactin levels for patients with elevated prolactin?** Research has firmly established that hyperprolactinaemia emerges within days as a consequence of treatment and, as we have shown in a large RCT, equally rapidly reverts to normal with removal of the prolactin-elevating antipsychotic (Bushe et al, 2009). What is less well established is the trajectory of prolactin levels over a longer term period. Do they remain at the same level? Short-term RCTs are unlikely to address this issue and current data that follow patients for 1 year have only reported baseline and endpoint data, not the trajectory of the prolactin response (Schooler et al, 2005). In the absence of a proven mechanism for how and why antipsychotics elevate prolactin differentially (Bushe et al, 2010), one can only speculate.
2. **What are the longer term outcomes for patients with elevated prolactin?** Over the last 10 years patients receiving biologics to treat rheumatoid arthritis have been entered into voluntary, long-term databases that have addressed, albeit in a naturalistic manner, incidence of potentially associated adverse events (cancers, reactivation of tuberculosis (TB), serious infections). There is a need to formally determine the longer term harm of untreated hyperprolactinaemia in psychiatry. The last decade has better defined potential longer term sequelae of hyperprolactinaemia and these clearly cannot be measured within formal RCTs. In 2011, the clear options involve using either large epidemiological databases, prospectively and retrospectively or creating prospective collections of clinical data such as through usage of registers. The challenge exists in creating appropriate databases that allow long-term follow up of both prolactin levels and clinical outcomes. Certainly the data on bone fractures (Howard et al, 2007; Abel et al, 2008) has shown us the potential. The World Health Organization (WHO) initiated a number of databases to measure cancer rates in schizophrenia in the 1970s (Bushe and Hodgson, 2010) and have the knowledge and ability to conduct similar projects worldwide relating to outcomes of hyperprolactinaemia.
3. **What is and how can we measure the true risk-benefit of switching antipsychotic treatments?** There is absolute agreement that usage of drugs such as dopamine agonists have significant potential to worsen schizophrenia illness (Peveler et al, 2008). This creates a dichotomy where the clinician can reduce the dose or change the antipsychotic, or do nothing. There is no single pragmatic endpoint that captures this risk. A relatively short-term RCT (1 year or less) looking at formal changes in rating scales, remission levels or relapse rates may be helpful. At a minimum, it may tell us the psychiatric outcome of switching patients from prolactin-elevating antipsychotics compared to maintaining the status quo. It is difficult to see any individual institution or pharmaceutical company undertaking such a complex and expensive study, and the only viable option would be for larger bodies, such as the European Medicines Agency, National Institute of Mental Health or potentially WHO to undertake this work.

4. **Can genetics help us predict individual responses to potentially prolactin-elevating antipsychotics?** Data allow us to predict which antipsychotics are more likely to elevate prolactin but not with any precision. Potentially any patient given any antipsychotic may have prolactin elevation ranging from small to large. In the future, one can imagine that genetics will better help us understand which patients are more at risk of adverse events associated with individual antipsychotics and also their likelihood of a clinical response. Genetic variation is likely to contribute substantially. Certainly this work is ongoing in the area of weight change with antipsychotic treatment and we can expect that pharmacogenetics may play a critical role (Reynolds, 2007).
5. **Can antipsychotic polypharmacy be a potential treatment option?** Aripiprazole is already cited as a potential treatment option as an additive treatment in the influential Maudsley guidelines (Taylor et al, 2009). With the increasing availability of generic antipsychotic options over the next decade one can envisage a greater degree of polypharmacy similarly designed to reduce or prevent specific adverse events. Prolactin is one area where at least five established antipsychotics are cited as not usually associated with hyperprolactinaemia (Taylor et al, 2009). Such experimental combinations have not been well researched to date and will require a solid trial base before definitive conclusions can be drawn.
6. **How important is the prolactin receptor in terms of cancer?** The prolactin signalling cascade may be important in the pathology of breast and prostate cancers. The antagonism of the prolactin receptor and its pathways may also be important. As we learn the molecular and genetic perspectives of the role of prolactin and its signalling pathways, we may learn more about any potential role of antipsychotic treatments and their relevance in these pathways (Jacobson et al, 2011).

11. Conclusion

Long-term antipsychotic treatment currently represents a usual outcome for patients with schizophrenia and bipolar disorder. Hyperprolactinaemia can be measured in between 33-69% of patients in antipsychotic studies and many antipsychotics significantly elevate prolactin with no suggestion of any longer term decline in prolactin levels. Hyperprolactinaemia can no longer be regarded in any sense as a benign abnormality and it may have significant potential short- and potential longer term consequences. Whereas the short-term adverse events are more easily detectable, the potential longer term consequences may remain hidden and undetectable until a bone fracture or cancer emerges. Over the last 10 years, patients receiving biologics to treat rheumatoid arthritis have been entered into voluntary, long-term databases that have addressed, albeit in a naturalistic manner, incidence of potentially associated adverse events (cancers, reactivation of TB, serious infections). There is a need to formally determine the longer term harm of untreated hyperprolactinaemia in psychiatry. In addition, future research needs to focus on the risk-benefit for the usage of prolactin-elevating antipsychotics.

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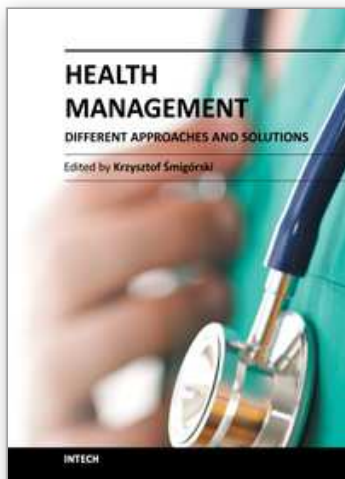
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The development in our understanding of health management ensures unprecedented possibilities in terms of explaining the causes of diseases and effective treatment. However, increased capabilities create new issues. Both, researchers and clinicians, as well as managers of healthcare units face new challenges: increasing validity and reliability of clinical trials, effectively distributing medical products, managing hospitals and clinics flexibly, and managing treatment processes efficiently. The aim of this book is to present issues relating to health management in a way that would be satisfying for academicians and practitioners. It is designed to be a forum for the experts in the thematic area to exchange viewpoints, and to present health management's state-of-art as a scientific and professional domain.

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