A review of hyperprolactinaemia and severe mental illness: Are there implications for clinical biochemistry?

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Abstract
Hyperprolactinaemia is a common adverse event reported in association with treatments used in schizophrenia and bipolar disorder. Recent data are suggestive that hyperprolactinaemia may have a range of significant short-and long-term clinical consequences. The objective of this review is to examine the causes, frequency and clinical consequences of hyperprolactinaemia in the severely mentally ill (SMI) with a focus on patients taking antipsychotic medications. A Medline search was carried out to identify relevant publications. Reference lists from previous review articles were also examined to search for additional data. Hyperprolactinaemia may be one of the most common adverse events associated with some antipsychotic medications. Precise rates with individual drugs had however until recently been poorly categorized. The relationship between hyperprolactinaemia and adverse outcomes in the SMI population appears similar to that in the general population. Adverse outcomes (such as sexual dysfunction) can occur acutely and in the longer term (bone fractures and possibly breast cancer), but the precise link between degree and length of hyperprolactinaemia and adverse outcome remains to be established. In conclusion, hyperprolactinaemia is a common treatment-emergent adverse event of some antipsychotic medications and may have clinical consequences. Physicians must balance the benefits and risks of treatment when determining appropriate therapy for individual patients.


Introduction
Hyperprolactinaemia is often one of the most common adverse events reported in a schizophrenia clinical trial involving antipsychotics, but it is only recently that the potential longer term effects of chronic hyperprolactinaemia have been given more attention.¹–⁵ This is all more confusing as prolactin has more physiological functions than the other entire pituitary hormones combined, totalling over 300 different biological effects.⁶ Measurement of prolactin has been feasible since the 1970s but it is only in 2008 that the first set of specific guidelines was published detailing advice for clinicians’ regarding prolactin monitoring,⁷ in contrast to cardiovascular disease and schizophrenia where numerous guidelines have been published.⁸

Dopamine plays a pivotal role in the regulation of prolactin secretion and many treatments utilized in psychiatry have some effect on dopamine. Indeed currently available antipsychotics, which are the mainstay of both acute and maintenance treatment of schizophrenia and play an increasing role in the management of bipolar disorder, all function by blocking D2 receptors and thus can be expected to exert some influence over prolactin concentrations in psychiatric patients.

The focus of this review is to examine the causes, rates and clinical consequences of hyperprolactinaemia in the severely mentally ill (SMI) with a focus on patients taking antipsychotic medications.

Structure, release and regulation of prolactin
Prolactin, discovered from the crop glands of pigeons in 1933,⁹ is a polypeptide hormone that is predominantly synthesized and secreted from the lactotroph cells of the anterior pituitary although there are other peripheral sites of synthesis.¹⁰ Until the 1970s scientists were sceptical that prolactin existed in humans, as human prolactin was considered identical to growth hormone.¹¹ Lactotrophs form around 20–50% of the cellular population of the pituitary with those in the more inner zones being more responsive to dopamine and those in the outer zone responsive to thyrotrophin releasing hormone (TRH).¹² Structurally prolactin belongs to the same family of hormones as growth
hormone (GH) and placental lactogen and is a single chain of 199 amino acids containing six cysteine residues and three disulphide bonds with 40% homology between the genes encoding prolactin and GH. Prolactin binds to prolactin receptors that are 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.

Prolactin is released from the anterior pituitary in a pulsatile manner with around 10 peaks per day in young adults with a marked circadian rhythm highest during sleep and reaching a nadir during waking hours. Concentrations during rapid eye movement sleep may peak around 640 mIU/L. Prolactin half-life is 50 min and concentrations increase at numerous times in the day dependent on activity such as exercise, meals and stress. In addition there appears to be an annual circadian variation though with little clinical relevance. Garde et al. reported in healthy female subjects a mean prolactin concentration after multiple sampling of 136 mIU/L with cyclical seasonal variation. Prolactin was highest in March–May (153 mIU/L) and lowest in September–November (98 mIU/L).

Control of prolactin secretion from the lactotrophs of the anterior pituitary is predominantly under the control of dopamine released via hypothalamic dopaminergic neurons, the tuberoinfundibular and tuberohypophyseal dopaminergic neurons. 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 among endocrine cells. The released prolactin binds to prolactin receptor family present in various organs including pancreas, liver, uterus and prostate and consequently may have some immunological activity.

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Definition of hyperprolactinaemia and prevalence in general population

Serum prolactin concentrations can vary both within and between individuals and hyperprolactinaemia is often regarded by psychiatrists as a prolactin concentration greater than the upper reference limit (URL) of the local laboratory, which varies depending on the type of assay used. Reference intervals for women often tend to be around 30% higher than those for men, with some laboratories also reporting separate intervals for premenopausal and postmenopausal women. In the psychiatric literature some of the highest URL for women are around 700 mIU/L and for men 500 mIU/L, with the lowest being 300 mIU/L. Large differences between men and women URL are also reported. In one study, the URL for men is reported as 360 mIU/L compared with 975 mIU/L for fertile women and 530 mIU/L for postmenopausal women.

Units of measurement also cause some confusion as US data are often presented in ng/mL whereas most UK and EU data are in mIU/L. Conversion rates are not standardized from ng/mL to mIU/L and vary between 21.2 and 36 dependent on the assay employed and clinical reports do not always report the reference interval or the units of measurement employed.

The prevalence of hyperprolactinaemia in a general population is dependent upon the precise population studied. In a general UK population aged over 38 y, the prevalence of 0.7% in men and 2.5% in women is significantly lower than in anovulatory women 15% and in men with erectile dysfunction 16%. Although hyperprolactinaemia is detected more commonly in women, it cannot be clearly stated that a gender difference exists as hyperprolactinaemic symptoms in men are often less easily diagnosed.

Causes of hyperprolactinaemia

There are numerous putative causes of an elevated prolactin that include physiological, pharmacological and pathological aetiologies and these have been well reviewed. Classes of drugs known to cause hyperprolactinaemia include antipsychotics, antidepressants, H2 antagonists, opioids and oestrogens. An initial challenge is to confirm that clinical hyperprolactinaemia is indeed present, as it has been suggested that stress and poor venepuncture technique can lead to a transient elevation of serum prolactin leading to a false-positive test result. If there is any doubt then the sample collection should be repeated, although the literature is controversial. Dynamic tests of prolactin secretion are rarely helpful.

In general terms prolactin concentrations are often due to a medication effect, but other causes can include microprolactinoma, pituitary stalk compression, renal failure or hypothyroidism. The literature currently reports that macroprolactinomas are the most common cause of prolactin concentrations >2120 mIU/L in the general population although other authors propose higher concentrations (3180 mIU/L) at which hyperprolactinaemia can be assumed to be caused by a macroprolactinoma. Concentrations can rise to >20,000 mIU/L as prolactin concentration correlates with tumour size. Many factors in a general population influence prolactin concentrations and blood sampling should be undertaken 1 h after waking before medication in a fasting state; however, the reality is this is often not feasible in outpatients.

Hyperprolactinaemia in antipsychotic-treated subjects

Antipsychotics have been utilized in the treatment of schizophrenia and other psychotic illnesses since 1950s. The
original antipsychotics (chlorpromazine, haloperidol) are termed first generation or conventional antipsychotics and the more recent antipsychotics, second-generation antipsychotics or atypicals. All currently licensed antipsychotics function predominantly by blocking D2/D3 receptors.

Whereas antipsychotics have been the mainstay of treatment for schizophrenia, some are also licensed for the treatment of bipolar disorder and in some countries almost all bipolar patients receive an antipsychotic as part of their treatment.29 Schizophrenia and bipolar disorder are chronic conditions that require long-term and maybe lifelong treatment with antipsychotics and mood stabilizers to both treat and prevent recurrence of the illness. Antipsychotics are also often utilized outside of their licensed indications (dementia, psychotic depression) and it is likely that prevalence of antipsychotic usage at any time exceeds the prevalence of SMI of around 2–3%.30

There is no suggestion that any of the illnesses for which antipsychotics are utilized are associated with prolactin elevation as part of their pathology and usually prolactin elevation will be an adverse event of the antipsychotic.1,7

Antipsychotics and hyperprolactinaemia – potential mechanisms

All antipsychotics are blockers of D2 receptors and to some extent all antipsychotics are associated with a degree of prolactin elevation. Direct blockade of D2 receptors on the anterior pituitary gland by antipsychotics blocks the inhibitory effect of dopamine on the high basal secretory tone of the lactotroph thereby increasing prolactin release.6 Conventional antipsychotics were initially reported to be associated with prolactin release in 197431 and during the 1980s atypical antipsychotics were developed including clozapine and amisulpride and later risperidone, olanzapine, quetiapine and aripiprazole. Early research showed that not all atypical antipsychotics were associated with a high incidence of prolactin elevation and putative explanations included the 5-hydroxytryptamine (5HT-2)/D2 receptor affinity that varied between atypicals. Risperidone however was found to have a higher 5HT-2/D2 ratio than some of the other atypical antipsychotics but was associated with significant prolactin elevation,32 thus making this hypothesis untenable.

Current theories relate to two different pharmacological attributes:

1. Fast dissociation from the D2 receptor.33 Antipsychotics associated with lesser degrees of prolactin elevation have fast D2 dissociation. All antipsychotics are associated with small transient increases in prolactin,34 but those that dissociate slowly from the D2 receptor, such as risperidone, result in more prolonged blockade and therefore greater prolactin release.33 Quetiapine, as an example of an antipsychotic with fast dissociation, is associated with central D2 occupancy that falls from initial blockade of 60–70% at 2 h postdosing to around 30% at 24 h.35 Typical antipsychotics in contrast are all associated with high affinity for the D2 receptor and slow dissociation;

2. As the anterior pituitary is outside the blood–brain barrier, the relative penetration of antipsychotics into the brain may be relevant. Atypical antipsychotics associated with prolactin elevation (risperidone and amisulpride) have a higher pituitary versus central (striatal) D2 occupancy than quetiapine and olanzapine in rats.36 This concept is supported by the observation that domperidone, a D2 blocker that does not cross the blood–brain barrier, is associated with significant prolactin elevation.36 Further support is provided by the observation that paliperidone (which is 9-hydroxy risperidone) is associated with a greater elevation in serum prolactin concentration than risperidone2 and is less lipophilic than risperidone. It is therefore less able to cross the blood–brain barrier than risperidone and the prolactin-elevating potential for risperidone relates predominantly to 9-hydroxy risperidone, its primary metabolite.37

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.38 There are however three areas of pathology that would seem to be closely linked to elevated prolactin, sexual function, bone loss and cancer.

Sexual function

Prolactin has a significant effect on sex hormone regulation with hyperprolactinaemia causing suppression of gonadotrophin-releasing hormone leading to hypogonadism and menstrual disturbances.39 Prolactin concentrations in patients treated with antipsychotics are inversely related to sex steroid hormone concentrations including oestrogen, progesterone and testosterone.40 In a study of 103 schizophrenia subjects 92% of premenopausal women and 28% of men showed biochemical hypogonadism although this exceeded the numbers with hyperprolactinaemia indicating other contributory factors.41 In another cross-sectional study the majority (81%) of premenopausal women taking prolactin raising antipsychotics were found to be hypogonadal (oestradiol concentration <300 mIU/L) compared with 33% taking a relatively prolactin-sparing antipsychotic olanzapine (P < 0.001).42 Sex hormone dysregulation may be the underlying cause of both acute and longer terms adverse effects associated with hyperprolactinaemia; however, low concentrations of oestrogen and testosterone have been reported in schizophrenia patients regardless of antipsychotic medication. Testosterone concentrations in acutely ill first episode schizophrenia patients were lower than in controls.43 Low concentrations of oestrogen were found in patients treated with both prolactin raising and relatively prolactin-sparing antipsychotics.44

The relative short-term consequences of hyperprolactinaemia are well described and in addition to sexual dysfunction
include menstrual disturbances, acne, infertility, galactorhea and gynaecomastia. Prevalence rates however are not well described as systematic questioning is not routinely carried out by all clinicians. A recent review was of the opinion that if mildly elevated prolactin was accompanied by amenorrhea for three months bone mineral density may be compromised, hence converting a short-term into a longer-term problem. There are conflicting reports regarding a direct correlation between prolactin elevation and sexual adverse effects. One cross-sectional survey of 106 patients taking antipsychotics, of which 39% had hyperprolactinaemia, found no association between prolactin concentration and sexual adverse events. In another open study including 264 subjects treated with antipsychotics for six weeks, the investigators found that patients treated with prolactin-raising antipsychotics reported 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 the prolactin-raising properties of antipsychotic. In addition, some reports do correlate reduction in prolactin with clinical improvements in sexual function. That there is no clear picture regarding prolactin and sexual functioning is not surprising as there are multiple causes for sexual dysfunction in schizophrenia and prolactin elevation should be considered as one potential mechanism only.

**Longer term consequences of hyperprolactinaemia**

**Bone**

Longer term consequences have only recently been well described and relate to predictable effects of elevated prolactin. Some studies suggest that even relatively short periods of hyperprolactinaemia can have significant adverse effects on bone density. Young women may be particularly susceptible to hyperprolactinaemia and osteoporosis and osteopenia may develop in the first eight years of treatment. Of more concern is that deterioration can be measured over a single year. Hip fractures and other bone fractures are the sequelae and prolactin-elevating antipsychotics have been associated with a doubling of the risk of hip fracture worldwide and there is a lifetime risk of one in nine in the general population. A recent meta-analysis reported a 12% increased risk (standardized incidence ratio [SIR] 1.12 [1.02–1.23]) with a more recent UK study reporting an increased risk of 52% in schizophrenia. Although data interpretation is complex, a recent systematic review on this topic concludes that larger studies that are better powered and include subjects of appropriate ages do report a consistently elevated risk of breast cancer. The aetiology for this increased risk is currently unproven but may be related to hyperprolactinaemia. The role of prolactin and mammary carcinogenesis in animal toxicity and molecular studies has been recognized over many years. The US nurses’ study established in 1976 provided prolactin samples on 32,826 general subjects in 1989–1990 and who have been extensively followed over 20 y, providing conclusive evidence linking prolactin and breast cancer. Many of their study reports suggest prolactin concentrations to be linked to risk of breast cancer development both in pre- and postmenopausal women. A report in 1994 on 851 cases found prolactin concentrations in the upper quartile of normal to be associated with an increased risk compared with the lower quartile of normal OR 1.34 (1.02–1.76). In reference to the high underlying risk any further increase is important. This definitive link however has yet to be established in SMI. A large retrospective cohort study of 52,819 women receiving antipsychotics and 55,289 control women reported a 16% increased risk of breast cancer (1.16; CI 1.07–1.26) 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 SMI subjects to the general population. Screening rates 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. Further evidence that prolactin may be associated with breast cancer derives from a prospective European cohort study of over 500,000 subjects followed over 10 y that found for many cancers, and particularly in women, there was a linear link between an increase in blood glucose and increased incidence and mortality of various cancers. Breast cancer however was not one of the cancers linked to glucose and is consistent thus with other factors including prolactin being relevant.

Hyperprolactinaemia has also been linked to pituitary adenomas and adenocarcinomas and putatively to prostate cancer. The report from the USA FDA (Food and Drug Administration) AERS (Adverse Event Reporting System) database pharmacovigilance 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). A recent case series is suggestive that amisulpride may also be associated with the development of prolactinomas mediated via hyperprolactinaemia. Neither clinical studies nor epidemiologic studies conducted to date have shown a definitive association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

**Possible association with cancer**

Breast cancer is also significantly increased in women with schizophrenia. There have been a number of epidemiological studies reporting data over the last 25 y, but it is only in the last few years that clarity has emerged. Breast cancer specifically is the most common cancer in women in the UK and accounts for 23% of all female cancer cases
Hyperprolactinaemia is among the most common adverse events reported in a clinical trial, but is rarely recognized as such due to incomplete presentation of the data. This is exemplified by data reported from an open label 6–12 week phase utilizing olanzapine in bipolar 1 (n = 304) patients in which hyperprolactinaemia was present in 25.6% and weight gain >7% in 29.5%. This contrasted with reported treatment emergent adverse events ranging from 20.4% dry mouth to 3.9% for insomnia. There remains however a tendency to report only mean change data in some randomized controlled trials (RCTs), whereas categorical data (such as prevalence or incidence of measured hyperprolactinaemia) may be more informative to clinicians. In a review on this topic although 60% of clinical studies reported some element of categorical reporting of the prevalence of hyperprolactinaemia, this derived predominantly from the observational and retrospective epidemiological studies (88%) rather than the RCTs (42%). More recent data however are now tending to report at least the prevalence of hyperprolactinaemia, if not the severity.

How common is hyperprolactinaemia in an antipsychotic-treated cohort?

The clinical relevance of this question is that prolactin monitoring is not widely undertaken and for many clinicians it may represent the first time prolactin concentrations have been measured in their patients. Absolute rates of hyperprolactinaemia will be dependent on many factors that include medication choice, gender, age and length of follow-up. Timing in relation to medication may also be relevant as all D2 blocking drugs will at least temporarily elevate prolactin for a few hours. This may be a relevant confounder for some data-sets. However, there is not enough data to be prescriptive regarding any clinical relevance. Some medications, such as olanzapine, may give a transient elevation of prolactin that reduces over the first months but still may be present in significant numbers in the early part of treatment. Naturalistic data may 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, both report a similar prevalence of hyperprolactinaemia of 38% and 39% in UK (n = 194) and Norway (n = 106), respectively. 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 women than in men (52% versus 26%), consistent with most other data, and significantly elevated concentrations >1000 mlU/L were measured in 21% of subjects. For 13% of women and 19% of men prolactin concentrations were above the normal limit but below 1000 mlU/L. This may be an important cohort to re-test as the ULN was >500 men and >700 women, as this degree of hyperprolactinaemia in the absence of symptoms might be considered mild. A similar naturalistic study in a preliminary analysis

Prolactin monitoring and data reporting

With an increased awareness of potential long-term adverse sequelae of hyperprolactinaemia (bone mineral density loss, fractures, and breast cancer and pituitary tumours), more prolactin monitoring has been undertaken in patients treated with antipsychotic drugs in the last few years. There has been a tendency to report prolactin as mean cohort values that do not easily allow interpretation of the precise number of patients developing either hyperprolactinaemia or severity.
reported that repeat testing in subjects with normal or borderline concentrations receiving risperidone found increased concentrations in some subjects reflecting variable adherence to medications. The clinical relevance being the rapidity of development of hyperprolactinaemia with adherence to risperidone.

Categorical rates of hyperprolactinaemia in trials range from 33% to 69% and confirm that no antipsychotic is prolactin neutral. The data can be generalized in that most studies report a higher prevalence and severity of hyperprolactinaemia in women as was the case in the Halifax study which found 13% of women had concentrations >2000 mIU/L compared with 2% of men.

**Rates of hyperprolactinaemia with individual antipsychotics**

The clinical realization that there is no such entity as a ‘prolactin-sparing’ antipsychotic has developed in parallel with the knowledge as to how and why hyperprolactinaemia develops. Numerous factors can confound the data but broadly the choice and the dose of medication are relevant factors. Adherence also may be important as many typicals are now administered by long-acting depot formulations whereas rates of non-adherence to all forms of antipsychotics are high.

There are data on comparable rates of hyperprolactinaemia among antipsychotics and the largest data-sets reporting prolactin include a six-week Paliperidone study in 628 schizophrenia subjects and one-year risperidone and haloperidol in first episode psychosis study in 555 subjects. Cohort sizes range from 33% to 69% and confirm that no antipsychotic is prolactin neutral. The data can be generalized in that most antipsychotics are high.

Rates of hyperprolactinaemia with conventional antipsychotics suggest significantly lower prevalence rates of 33–35% in a depot-treated population. But studies in Asian populations using higher doses (15–16 mg) than that are often used in European populations report a higher prevalence of 66%. Similar data derived from a trial in which 72% of subjects receiving 15 mg haloperidol had hyperprolactinaemia at two weeks and around 60% at six weeks. A large analysis from Kleinberg in 1999 from over 2000 patients concluded that although risperidone was associated with higher rates of hyperprolactinaemia compared with doses of 10 mg haloperidol, no comparative differences emerged with doses of 20 mg haloperidol.

A recent data review concluded that hyperprolactinaemia with risperidone oral was almost 100% in women and between 63% and 100% in men. Similar hyperprolactinaemia is measured with amisulpride. Depot formulations of risperidone may have a lower prevalence of hyperprolactinaemia relating to dose (53–67%). The dosage comparison in the Halifax study equated to 2 mg risperidone long-acting intramuscular injection (LAIM) and 4.89 mg oral. The comparative data from oral risperidone and risperidone LAIM are also consistent with this interpretation. Paliperidone (9-hydroxy-risperidone) is the major metabolite of risperidone, and prolactin concentrations in patients receiving paliperidone are double than those of patients receiving risperidone and 9-hydroxy-risperidone itself is probably responsible for the prolactin elevation.

Aripiprazole is associated with a low rate of hyperprolactinaemia with the prevalence rates of 3–5% in RCTs that increase to incidence rates of 17% in naturalistic studies and in a six-week RCT evaluating aripiprazole and perphenazine hyperprolactinaemia was reported in 4.4% of the aripiprazole cohort and 57.7% of the perphenazine cohort.

In some patients aripiprazole may also have a lactin-lowering effect; however, this does not occur in every patient. Although many studies report rapid reductions in prolactin concentrations after commencing aripiprazole, this may primarily 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/d in a cohort of schizophrenia patients resulted in normalization within eight-weeks of prolactin in 85% of subjects contrasting with 3.6% of the placebo group (P<0.0001) although there are many significant caveats to such antipsychotic polypharmacy.

For the remaining antipsychotics, hyperprolactinaemia is sometimes reported though significantly less often than risperidone and amisulpride. For quetiapine reported rates range 0–29% and for olanzapine 6–40% although most studies report rates at the lower end of the spectrum. The hyperprolactinaemia with olanzapine is often mild and transient with early elevations reported to have reverted to placebo concentrations by week 6 in a dose-ranging study; however, a modest elevation of prolactin may persist during chronic administration of olanzapine. In a recent six-month RCT prolactin was elevated at baseline in 33% of schizophrenia patients randomized to olanzapine or quetiapine, by 14 days prolactin had normalized in almost all subjects.

**What do guidelines advise regarding prolactin?**

In 2008 the first specific guideline on prolactin was published giving advice on monitoring practices and rationales for medication changes. Prior to this many guidelines did not give specific recommendations. In general terms existing guidelines did not provide a monitoring schedule and
tended to advocate prolactin monitoring only when symptoms were detected. This may have been somewhat problematic as routine enquiry for relevant symptoms is not often undertaken and there is evidence not only that patients do not volunteer important symptoms but that they may not also recognize them as adverse treatment events. NICE bipolar guidelines in 2006 recommended limited pretreatment monitoring for risperidone with further monitoring should symptoms of hyperprolactinaemia develop. The only other guideline to recommend pretreatment monitoring is the Maudsley guidelines 9th edition. The recommendations from the World Federation Society of Biological Psychiatry in 2005 curiously concluding that whereas prolactin elevation was frequent with amisulpride and typicals (>10%), it was measured only ‘sometimes’ (<10%) with risperidone. Current data now seem to have clarified these frequencies rather differently. For major US guidelines from the American Psychiatric Association and the Mount Sinai group, the recommendations essentially are to only measure prolactin when symptoms have been ascertained. They do advise however pretreatment screening for relevant symptoms.

The 2008 UK prolactin guidelines recommend prolactin monitoring in all patients pretreatment regardless of medication and after three months of treatment with a stable dose, in addition to further monitoring when there is development of relevant clinical symptoms. With a normal prolactin concentration there is no further need for monitoring in the absence of clinical symptoms. Significant dose change should also lead to consideration of further monitoring.

The UK guidelines give a clear strategy for investigating the aetiology of hyperprolactinaemia in patients receiving antipsychotics. A differential diagnosis must be considered but must always include a pregnancy test in women and thyroid function tests. Prolactin concentrations may be exceptionally high in patients taking antipsychotics; however, in any subject with prolactin elevation greater than 3000 mIU/L a prolactinoma should be considered and referral to an endocrinologist is warranted. In the Halifax cohort prolactin concentrations >2000 mIU/L were measured in 13% of all antipsychotic-treated women and 2% of men. It is well recognized that prolactin may be greatly elevated in patients taking antipsychotics, and these authors suggest a threshold of >2500 mIU/L for exclusion of prolactinoma. Concentrations of up to 7300 mIU/L have been reported. 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. Ideally though antipsychotic medication should be stopped for 72 h before repeating prolactin measurement.

**Management of treatment-emergent hyperprolactinaemia**

This is complex and will form part of a considered risk-balance evaluation. The plethora of issues has been considered by the authors of the 2008 prolactin guidelines. Concentrations <1000 mIU/L can simply be monitored but in the presence of symptoms that suggest sex hormone deficiency it has been suggested that such concentrations should not be allowed to continue long term due to the potential risk of bone mineral density loss. Concentrations >1000 mIU/L that are persistent will need consideration for medication change or dose reduction if appropriate. The use of dopamine agonists should be considered only in exceptional circumstances due to the risk of worsening the psychosis.

Some patients may also require bone mineral density monitoring using dual energy X-ray absorptiometry and such subjects would include those with prolonged hyperprolactinaemia.

**Conclusion**

Prolactin is a highly biologically active molecule that we are only now beginning to understand. As long ago as 1968 there was call to change its name to better reflect the enormous variety of its actions (to versatilin or omnipotin). Recent clinical data support an argument that hyperprolactinaemia may often be one of the most common adverse events reported in a clinical trial of antipsychotic agents and yet there is little evidence of routine monitoring. The longer term effects of hyperprolactinaemia are becoming more recognized and it should be of concern that not only is the risk of fractures doubled by the usage of prolactin-elevating antipsychotics but also that significant bone mineral density loss may be measured in young female populations after as little as eight years of treatment. The current trend in treating psychotic illness is to encourage long-term treatment with antipsychotics, many of whom have potential to rapidly and significantly elevate prolactin, starting at a young age. Prolactin concentrations correlate with risk of breast cancer in the general population and may have a role in the aetiology of the increased risk of breast cancer in the schizophrenia population. Clinicians should be recommended to take note of advice in the product licences of medication regarding changes in prolactin concentrations.

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