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Antipsychotic-Induced Hyperprolactinaemia
Mechanisms, Clinical Features and Management

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Abstract

Hyperprolactinaemia is an important but neglected adverse effect of antipsychotic medication. It occurs frequently with conventional antipsychotics and some atypical antipsychotics (risperidone and amisulpride) but is rare with other atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone). For this reason the terms 'prolactin-sparing' and 'prolactin-raising' are more useful than 'atypical' and 'conventional' when considering the effect of antipsychotic drugs on serum prolactin.

During antipsychotic treatment prolactin levels can rise 10-fold or more above pretreatment values. In a recent study approximately 60% of women and 40% of men treated with a prolactin-raising antipsychotic had a prolactin level above the upper limit of the normal range. The distinction between asymptomatic and symptomatic hyperprolactinaemia is important but is often not made in the literature. Some symptoms of hyperprolactinaemia result from a direct effect of prolactin on target tissues but others result from hypogonadism caused by prolactin disrupting the normal functioning of the hypothalamic-pituitary-gonadal axis.

Symptoms of hyperprolactinaemia include gynaecomastia, galactorrhoea, sexual dysfunction, infertility, oligomenorrhoea and amenorrhoea. These symptoms are little researched in psychiatric patients. Existing data suggest that they are common but that clinicians underestimate their prevalence. For example, well conducted studies of women treated with conventional antipsychotics have reported prevalence rates of approximately 45% for oligomenorrhoea/amenorrhoea and 19% for galactorrhoea. An illness-related under-function of the hypothalamic-pituitary-gonadal axis in female patients with schizophrenia may also contribute to menstrual irregularities. Long-term consequences of antipsychotic-related hypogonadism require further research but are likely and include premature bone loss in men and women. There are conflicting data on whether hyperprolactinaemia is associated with an increased risk of breast cancer in women.

In patients prescribed antipsychotics who have biochemically confirmed hyperprolactinaemia it is important to exclude other causes of prolactin elevation, in particular tumours in the hypothalamic-pituitary area. If a patient has been amenorrhoeic for 1 year or more, investigations should include bone mineral density measurements. Management should be tailored to the individual patient. Options include reducing the dose of the antipsychotic, switching to a prolactin-sparing agent, prescribing a dopamine receptor agonist and prescribing estrogen replacement in hypoestrogenic female patients. The efficacy and risks of the last two treatment options have not been systematically examined.

Antipsychotic-induced hyperprolactinaemia should become a focus of interest in the drug treatment of psychiatric patients, particularly given the recent introduction of prolactin-sparing antipsychotics. Appropriate investigations and effective management should reduce the burden of adverse effects and prevent long-term consequences.

It has been recognised for more than 25 years that antipsychotic drugs can elevate serum prolactin and that this can cause various clinical manifestations.[1] Despite this the syndrome of antipsychotic-induced hyperprolactinaemia has been relatively neglected. A recent survey indicated that both psychiatrists and psychiatric nurses tended to underestimate the prevalence of key symptoms associated with hyperpro-

lactinaemia.[2] Certainly the extrapyramidal effects of antipsychotics have attracted far more research and clinical interest. For example, our search of the Medline database (1966–2004) in July 2004, using the terms 'antipsychotics and extrapyramidal symptoms' revealed 1717 journal articles, whereas a search on 'antipsychotics and hyperprolactinaemia' revealed only 375 articles.

In this review we discuss the physiology of prolactin secretion, the effect of conventional and atypical antipsychotic drugs on serum prolactin levels and the clinical manifestations of hyperprolactinaemia in men and women. Since antipsychotic treatment is often initiated when patients are in their late teens or 20s and continued for years or decades, we also consider the possible consequences of prolonged endocrine dysfunction, particularly with respect to bone mineral density (BMD). The investigations and differential diagnosis of the patient treated with an antipsychotic drug who has biochemically confirmed hyperprolactinaemia are discussed, as is the subsequent management.

1. Prolactin Physiology

1.1 Normal Serum Prolactin Levels and Physiological Functions

Prolactin is a 199-amino acid polypeptide hormone that is secreted by the lactotroph cells in the anterior pituitary. It is released in a pulsatile manner with 13–14 peaks per day and an interpulse interval of about 95 minutes. The mean pulse amplitude represents a 58% increase above the preceding nadir.[3] Prolactin levels show a marked circadian variation. The maximum level is reached about 4 hours after the onset of sleep and is approximately 160% of the 24-hour mean. The minimum level is reached about 6 hours after waking and is approximately 40% of the 24-hour mean.[4] As a result, prolactin levels can vary up to 4-fold depending on the time of day or night. Transient and mild increases of prolactin levels occur in response to meals, stress and sexual activity.[5] In women prolactin levels are higher during mid cycle and the second half of the menstrual cycle.

Despite significant variation in serum prolactin values, both within- and between-individuals, there is a reasonable consensus regarding the upper limit of the normal range. Bevan[6] cites this as being 500 mU/L in both men and women, that is approximately 15 μg/L (15 ng/mL). However, some authorities suggest an upper limit of 25 μg/L (approximately 800 mU/L).[7,8] Serum prolactin levels are sometimes given as nanomoles per litre. The conversion factor between the units differs somewhat depending on the radioimmunoassays used but 1 μg/L is approximately equivalent to 30 mU/L or 0.043 nmol/L.[6]

In women serum prolactin levels increase during pregnancy to reach levels 10–20 times the non-pregnant value. Although there is marked individual variation, prolactin levels can reach 200 μg/L (approximately 6500 mU/L) at term and 300 μg/L (approximately 9000 mU/L) during nursing.[9] In the absence of breast-feeding, serum prolactin levels fall to normal within approximately 3 weeks after child birth. Levels normalise after several months in breast-feeding women.

The main physiological function of prolactin is to cause breast enlargement during pregnancy and milk production during lactation. The reductions in libido and fertility that are associated with nursing may have evolutionary advantages. Prolactin is known to have an important function in promoting maternal behaviour in animals but its role in humans is not known in this respect.

1.2 Inhibitory Factors

The secretion of prolactin is under the complex control of peptide and steroid hormones and neurotransmitters, which act as both inhibitory and stimulatory factors.[10] Dopamine is the predominant prolactin-inhibiting factor in animals and humans. It is produced by the tuberoinfundibular neurons in the hypothalamus, released from their nerve endings in the median eminence and transported by the portal hypophyseal circulation to the pituitary, where it binds to the dopamine D_2 receptors on the membrane of lactotroph cells.[11] D_2 receptor stimulation has effects on prolactin gene transcription, synthesis

and release and these are mediated in a complex fashion, involving several signal transduction systems.[5,10] Gonadotropin-associated protein and acetylcholine have been identified as prolactin-inhibiting factors in animals but their physiological significance in humans is uncertain.[5,10]

1.3 Stimulatory Factors

Animal and human studies demonstrate that serotonin stimulates prolactin secretion and is involved in the mediation of nocturnal surges and suckling-induced rises.[12] The serotonergic neurons involved project from the dorsal raphe nucleus to the medial basal hypothalamus and exert their effects via serotonin 5-HT_{1A} and 5-HT_2 receptor mechanisms.

Estrogens have an important regulatory function in prolactin secretion. They bind to specific intracellular receptors in lactotrophs and can enhance prolactin gene transcription and synthesis as well as DNA synthesis and mitotic activity.[5] In animal studies estrogens have also been shown to counteract the effect of dopamine by inhibiting dopamine synthesis in the tuberoinfundibular neurons in some species[13] and reducing D_2 receptor levels on lactotrophs.[14]

Several peptide neurotransmitters, including thyrotropin-releasing hormone and cholecystokinin, have prolactin-releasing properties in animals.[10] GABA has both stimulatory and inhibitory effects on prolactin secretion.[15] The physiological role of these substances in humans is uncertain.

1.4 Hyperprolactinaemia and the Hypothalamic-Pituitary-Gonadal Axis

High prolactin levels inhibit the hypothalamic-pituitary-gonadal axis at several levels. Under normal physiological conditions, in both men and women, gonadotropin-releasing hormone (GnRH) is secreted in a pulsatile manner from the hypothalamus and stimulates the release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. Prolactin inhibits the release of GnRH by the hypothalamus and also inhibits its action at the pituitary. In women prolactin also blocks the positive feedback effect of estradiol on LH secretion. The end result is that high circulating prolactin levels can cause reduced gonadal hormone levels (i.e. reduced estrogen levels in women and reduced testosterone levels in men) and this can present with a variety of symptoms. There appears to be marked individual variation in the prolactin level at which gonadal under-function occurs. According to Marken et al.,[7] amenorrhoea usually develops at a serum prolactin level above 60–100 μg/L (approximately 2000–3000 mU/L), although in our experience amenorrhoea can be caused by much lower prolactin values.

2. Effects of Antipsychotic and Other Psychotropic Drugs on Prolactin Secretion

Virtually all antipsychotic drugs have the capacity to block D_2 receptors, and indeed D_2 receptor blockade in the mesolimbic and mesocortical areas appears integral to antipsychotic efficacy. However, in other brain areas D_2 receptor blockade can cause adverse effects. Parkinsonism results from D_2 receptor blockade in the striatum, while blockade of D_2 receptors on lactotroph cells causes hyperprolactinaemia, as it removes the main inhibitory influence on prolactin secretion. When considering antipsychotic-induced hyperprolactinaemia it is important to differentiate between asymptomatic and symptomatic hyperprolactinaemia. Many research papers reporting clinical trials of antipsychotics are limited to reporting the prevalence of hyperprolactinaemia (i.e. the proportion of patients with a serum prolactin above the upper limit of normal) without determining whether this causes symptoms.

2.1 Research in Unmedicated Patients with Psychiatric Illness

Several studies have compared mean serum prolactin levels in unmedicated patients with schizophrenia and healthy controls.[16-20] A consistent finding is that prolactin levels are not elevated in unmedicated schizophrenic patients. Indeed, there is some evidence[16] that, compared with healthy women, female drug-free schizophrenic patients have a lower daily mean prolactin level and lower

amplitude of the circadian variation of serum prolactin, findings that are consistent with schizophrenia being associated with increased dopaminergic activity. A study of men with endogenous depression and age-matched healthy men showed no difference in 24-hour mean prolactin levels.[21]

Unmedicated patients with schizophrenia show a phase advance of circadian serum prolactin levels compared with healthy controls, with the peak prolactin level being reached 1.5 hours earlier.[16,17] This phase shift is not corrected by antipsychotic treatment. A prolactin phase advance of a similar magnitude has been demonstrated in patients with unipolar depression.[21] The significance of these findings is unknown, although a phase advance of the circadian rhythm of other hormones is recognised in several psychiatric disorders, including serum cortisol and melatonin in depression[22,23] and melatonin in schizophrenia.[17]

In summary, in unmedicated patients with acute and chronic major psychiatric disorders, daytime prolactin secretion does not appear to be enhanced. It is therefore reasonable to attribute elevated serum prolactin levels in medicated psychiatric patients to drug effects rather than to the illness itself. Confirmation is provided by longitudinal studies in which prolactin concentration is measured during antipsychotic treatment with baseline measurements before the initiation of treatment and/or measurements after the antipsychotic drug has been withdrawn or switched.

2.2 Conventional Antipsychotics

Some data suggest that patients with schizophrenia show a smaller and slower prolactin response to a single dose of intravenous haloperidol than healthy controls.[19] This implies that schizophrenia involves some abnormality in the relationship between dopamine and prolactin. Irrespective of this, both healthy individuals[19] and patients with schizophrenia[19,24] show prolactin elevation within minutes to hours of starting treatment with conventional antipsychotics. Prospective studies with an open-label or double-blind design indicate that medium-term treatment (3–9 weeks) with therapeutic doses of antipsychotics increases mean baseline prolactin levels up to 10-fold.[25-29]

Low daily dosage regimens (e.g. chlorpromazine 200mg) can cause significant prolactin elevations[24] and levels have been reported to increase in a dose-dependent manner up to about chlorpromazine 600mg equivalents.[30,31] A significant correlation between the dose of conventional antipsychotic drug and the serum prolactin level was seen in a recent UK study of 67 outpatients with schizophrenia.[32] In one study from the 1970s there was a tendency for thioridazine to produce higher prolactin levels than therapeutically equivalent doses of trifluoperazine or chlorpromazine.[24]

Whether patients develop a partial tolerance to the pituitary effect of antipsychotics after several months of treatment is unclear.[33,34] If tolerance does occur it is likely to be partial, since patients treated for several years still have significantly higher prolactin levels than untreated healthy controls.[35,36]

Two recent cross-sectional studies from US and UK estimated the prevalence of hyperprolactinaemia in clinically representative samples of patients receiving antipsychotics.[37,38] The cross-sectional study from the US assessed 402 inpatients and outpatients with schizophrenia, schizophreniform disorder or schizoaffective disorder who had been prescribed a conventional antipsychotic or risperidone for at least 3 months.[37] Patients taking concomitant medications known to raise prolactin were excluded. The prevalence of hyperprolactinaemia in men (>18.77 μg/L) was 42.4% and in women (>24.20 μg/L) was 59.2%. The cross-sectional study from the UK assessed 101 patients prescribed conventional antipsychotics and found similar results.[38] The prevalence of hyperprolactinaemia (>480 IU/L) in men was 34% and in women it was 75%.

When oral antipsychotics are discontinued prolactin levels usually fall to normal within 48–96 hours.[39] However, prolactin levels may take up to 3 weeks to return to the normal range, depending on the half-life of the drug and its metabolites as well as storage in fatty tissues.[40] In the case of oil-based

depot antipsychotics it may take as long as 6 months after stoppage of the depot preparation for serum prolactin levels to normalise.[41]

2.3 Atypical Antipsychotics

Atypical antipsychotics are generally defined as agents that cause minimal extrapyramidal symptoms (EPS) at therapeutic doses. Eight commercially available drugs are generally regarded as atypicals: amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone and zotepine. A number of other agents are in development.

The term 'atypical' should not obscure the fact that the agents within this class show major differences in:

- chemical structure
- pharmacodynamics
- pharmacokinetics
- adverse effect profiles
- efficacy (clozapine is associated with significantly greater efficacy in treatment-resistant schizophrenia than the other atypical antipsychotics).

The different propensity of the atypical antipsychotics to cause hyperprolactinaemia is an excellent example of their differing adverse-effect profiles, and this may be due to more than one mechanism (section 2.4).

Clozapine[42] and quetiapine[28,43] do not elevate plasma prolactin levels across their full dose range. Olanzapine has little effect on prolactin levels and is generally regarded as prolactin sparing, although at higher doses hyperprolactinaemia can occur.[29,44] In contrast, risperidone[45] and amisulpride[46] cause a marked and sustained increase in serum prolactin levels in a sizeable proportion of patients. Although the division of atypical antipsychotics into 'prolactin-sparing' and 'prolactin-raising' is useful, such a categorical division is a simplification; in reality one has a series of drugs whose likelihood of raising prolactin in any individual patient varies on a dimension. This is analogous to the likelihood of these drugs causing other adverse effects such as EPS or weight gain.

A randomised, double-blind, parallel-group study[46] compared the effect of amisulpride (1000 mg/day) and oral flupentixol (25 mg/day) on serum prolactin levels in a mixed-sex sample (n = 32). All participants had schizophrenia and had been free of oral antipsychotics for at least 4 weeks and depot antipsychotics for at least 3 months before entry into the study. After 4 weeks of treatment, mean serum prolactin levels were significantly elevated in both groups, in the amisulpride group by a factor of 10 and in the flupentixol group by a factor of 5. In female patients the difference in serum prolactin levels between amisulpride and flupentixol treatment was statistically significant ($p < 0.05$).

Kleinberg et al.[47] pooled the data of two large randomised, double-blind, controlled clinical trials comparing 8 weeks of treatment with fixed daily doses of risperidone (1, 2, 4, 6, 8, 10, 12 and 16mg), haloperidol (10 and 20mg) and placebo. Both risperidone and haloperidol produced dose-related increases in plasma prolactin levels in men and women. The mean increase at endpoint in women treated with risperidone was significantly higher than in women treated with 10mg, but not 20mg, haloperidol. In a naturalistic cross-sectional study of patients with schizophrenia the prevalence of hyperprolactinaemia in women (>24.20 μg/L) was higher among those prescribed risperidone (88%) than among those prescribed a conventional antipsychotic (47.6%).[37]

Breier et al.[48] compared the effects of risperidone and clozapine in 29 patients (male and female) using a 6-week double-blind, parallel-group design. Patients underwent a 2-week period of baseline fluphenazine treatment (20 mg/day) and were then switched to receive either clozapine (mean dose 404 mg/day) or risperidone (mean dose 6 mg/day). At the end of the baseline fluphenazine treatment phase plasma prolactin levels were increased about 2-fold above the normal reference range in each group. After switching, levels decreased significantly into the normal reference range in the clozapine group, whereas they did not change significantly in the risperidone group.

David et al.[49] reported a double-blind, randomised clinical trial which compared olanzapine 5–20 mg/day, risperidone 4–10 mg/day and halo-

peridol 5–20 mg/day in schizophrenia. There were 21–23 patients in each arm and the study lasted for 54 weeks. Patients treated with risperidone had significantly higher plasma prolactin levels than those treated with either olanzapine or haloperidol.

Further evidence of the different propensity of olanzapine and risperidone to raise prolactin level comes from a study by Kim et al.[50] They prospectively examined the effect of switching from risperidone to olanzapine in 20 female patients with schizophrenia who had symptoms suggestive of raised prolactin (menstrual disturbances, galactorrhoea and/or sexual dysfunction). Patients were switched from risperidone to olanzapine over a 2-week period and then continued on olanzapine for a further 8 weeks. Serum prolactin was measured every 2 weeks. Sexual and menstrual functions were assessed at baseline and at the endpoint of 10 weeks. During the study serum prolactin decreased significantly ($p < 0.01$) and this was accompanied by improvements in menstrual functioning and a decrease in sexual adverse effects that the women attributed to antipsychotic medication. Scores on the Positive and Negative Syndrome Scale significantly decreased ($p < 0.01$) during the 10 weeks, indicating that, in this sample at least, the switch in antipsychotic treatment did not cause any worsening of the patients' psychiatric condition.

Preliminary evidence indicates that zotepine can cause prolactin elevation in humans after acute and long-term treatment.[51-53] Ziprasidone is not currently licensed in the UK but is licensed in several countries including the US. A randomised clinical trial compared ziprasidone at four fixed dosages with haloperidol 15 mg/day over 4 weeks.[54] Haloperidol was associated with sustained hyperprolactinaemia, whereas ziprasidone was associated only with transient elevations in prolactin that returned to normal within the dosage interval. Similar effects on prolactin have been reported in studies of ziprasidone in healthy volunteers.[55]

Aripiprazole is the first of a new class of atypical antipsychotic characterised by partial agonist activity at D_2 and 5-HT_{1A} receptors.[56] It is also an antagonist at 5-HT_{2A} receptors.[56] In clinical trials aripiprazole did not increase prolactin compared with placebo, whereas prolactin was significantly elevated with risperidone and haloperidol.[57,58]

2.4 Reasons for Differential Effect of Antipsychotics on Prolactin Secretion

Various hypotheses have been put forward to explain the pharmacological basis of 'atypical' action of atypical antipsychotics, that is, antipsychotic efficacy combined with low propensity to cause EPS. These include a relative limbic versus striatal selectivity for these agents, interactions with neurotransmitter receptors other than D_2, and the interaction at the D_2 receptor itself. The last mechanism appears to be particularly relevant to the issue of hyperprolactinaemia.

The occupancy of anterior pituitary D_2 receptors cannot be directly measured in positron emission tomography (PET) studies. However, striatal D_2 receptors have been used as a substitute taking advantage of the finding that their affinity is, at least in *in vitro* and *in vivo* studies in rats, similar to that of pituitary D_2 receptors.[59] Two studies in patients treated with conventional antipsychotics found that a 50% striatal D_2 receptor occupancy was associated with a significant increase of hyperprolactinaemia.[60,61] Another study, in patients with first-episode schizophrenia treated with low-dose haloperidol, reported a threshold occupancy of 72% for the development of hyperprolactinaemia.[62] In PET studies most typical antipsychotics produce a 70–90% D_2 receptor occupancy in the basal ganglia at therapeutic doses, suggesting that the threshold for hyperprolactinaemia is lower than or similar to the threshold for a therapeutic response.[63]

Therapeutic doses of clozapine consistently produce a lower striatal D_2 receptor occupancy than conventional antipsychotics with values ranging between 16% and 67%.[63,64] Similar values have been reported with quetiapine.[65] Risperidone has been associated with higher D_2 receptor occupancy than clozapine,[66] whereas results for olanzapine have been inconsistent with reports of values equal to that of risperidone[66] and lower than that of typical antipsychotics and risperidone.[67] These striatal neuro-

imaging data are broadly consistent with the relative effects of typical and atypical antipsychotics on prolactin secretion.

Bringing together results from animal and clinical studies, Kapur and Seeman[68] suggested that the mechanism underlying antipsychotic differences in D_2 receptor occupancy and adverse-effect profiles is largely determined by their receptor-binding characteristics and half-lives. According to this model, all antipsychotics attach themselves with a similar rate constant to the D_2 receptor but they differ in how fast they dissociate from it. A drug with a short half-life and fast dissociation from the D_2 receptor would, at therapeutic doses, achieve a reduction in dopaminergic activity sufficient for an antipsychotic effect while at the same time allowing some physiological activity to take place. In the case of prolactin-sparing atypical antipsychotics it is postulated that this residual activity is sufficient to avoid EPS and symptomatic hyperprolactinaemia.

Most available atypical antipsychotics possess antagonist action at both 5-HT_2 and D_2 receptors. Given that 5-HT_2 receptor stimulation can cause prolactin release, it has been suggested that the 5-HT_2 receptor antagonism of atypical antipsychotics may counteract the prolactin-elevating tendency incurred as a result of their D_2 receptor antagonism. However, it is unlikely that this mechanism is relevant. First, persistent prolactin elevation may occur only at pharmacological levels of 5-HT_2 receptor stimulation;[69] that is, it may not be a physiologically relevant control mechanism for sustained prolactin release. Second, some atypical antipsychotics, such as risperidone, cause hyperprolactinaemia despite being 5-HT_2 receptor antagonists.

The ability of antipsychotics to pass the blood-brain barrier may also contribute to their different propensity to cause hyperprolactinaemia. The pituitary gland lies outside the blood-brain barrier, and one would expect that drugs with poor brain penetrability and higher serum concentrations, such as sulpiride,[70] would have a greater effect on pituitary prolactin secretion. However, this has, to our knowledge, not been systematically investigated.

2.5 Other Psychotropic Drugs

Antidepressants with serotonergic activity, including selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors and some tricyclic antidepressants, can cause modest elevations of prolactin levels.[34,71] When they are given as monotherapy, symptoms of hyperprolactinaemia have been reported but are rare.[71] In patients whose prolactin secretion is already stimulated by antipsychotic drugs, serotonergic antidepressants have the potential to elevate prolactin levels above the threshold required to cause symptoms.

3. High-Risk Groups

Although any patient prescribed a prolactin-raising antipsychotic is at risk of developing hyperprolactinaemia, research suggests that certain patient groups are at higher risk. These include women, particularly during the postnatal period, children and adolescents.

3.1 Women

It has consistently been shown that women have significantly greater prolactin elevations than men during long-term treatment with the same antipsychotic dose.[20,72]

3.2 The Postnatal Period

During pregnancy serum prolactin levels rise several-fold.[73] If women do not breast-feed, prolactin levels usually fall to pre-pregnancy levels within 3 weeks of childbirth but in breast-feeding women prolactin levels remain elevated for several months. Some data suggest that postnatal mothers are particularly sensitive to the prolactin-elevating effect of antipsychotics. Goode et al.[74] compared prolactin levels in six nonlactating psychiatric patients within 6 months of childbirth and 11 female psychiatric patients who had never been pregnant. Prolactin levels were measured before and after treatment with the same antipsychotic medication administered for at least 1 week. The antipsychotic-induced increase in prolactin levels was greater in the postnatal women than the nonpuerperal group.

3.3 Children and Adolescents

Preliminary data suggest that children and adolescents may be particularly sensitive to the prolactin-raising effect of antipsychotics. Wudarsky et al.[75] reported on 35 children and adolescents with early-onset psychosis (mean age 14 years, range 9–19 years) who were recruited for several antipsychotic drug trials involving clozapine, haloperidol or olanzapine. Serum prolactin levels were measured at baseline after a 3-week washout period and after 6 weeks of treatment. Mean prolactin levels were elevated on all three drugs. Prolactin was raised above the upper limit of normal in all ten patients prescribed haloperidol (100%), in seven of the ten olanzapine-treated patients (70%) and in none of the 15 patients prescribed clozapine (0%). These results are limited by the small samples but suggest that paediatric patients may show greater prolactin elevations in response to both haloperidol and olanzapine than adult patients. In contrast, in an 8-week study in 15 adolescents with psychotic disorders quetiapine (final average dose 467 mg/day) did not cause any elevation of prolactin.[76]

3.4 Other High-Risk Groups

Women of reproductive age may be more susceptible to developing antipsychotic-induced hyperprolactinaemia than postmenopausal women. In a cross-sectional study of 147 women prescribed conventional antipsychotics or risperidone, the prevalence of hyperprolactinaemia among the 90 premenopausal women was 65.6% (mean serum prolactin 69.0 μg/L), whereas among the 51 postmenopausal women it was 45.1% (mean serum prolactin 49.0 μg/L).[37] However, this difference may reflect factors other than menopausal status, for example antipsychotic drug and dosage. This study[37] also found that non-Caucasian women had a higher prevalence of hyperprolactinaemia than Caucasian women, but again this may reflect differences between the two groups in terms of antipsychotic drug and dosage.

4. Symptoms of Hyperprolactinaemia

Hyperprolactinaemia can cause a wide range of clinical symptoms:

- gynaecomastia
- galactorrhoea
- infertility
- menstrual irregularities: oligomenorrhoea, amenorrhoea
- sexual dysfunction: decreased libido, impaired arousal, impaired orgasm, and
- acne and hirsutism in women (due to relative androgen excess compared with low estrogen levels).

There is great individual variation in the plasma prolactin level at which symptoms appear. Some symptoms, for example galactorrhoea, reflect raised prolactin acting on target tissues while other symptoms, for example amenorrhoea, are due to secondary hypogonadism. Chronic gonadal under-function may also have long-term health effects which are initially asymptomatic. Of particular note is decreased BMD, which may lead to an increased risk of osteoporosis, and a possible increased risk of breast cancer. These issues are discussed in sections 5 and 6.

A crucial question is how often antipsychotic-induced hyperprolactinaemia causes hypogonadism in men and women. In women it appears common. For example, in a recent cross-sectional survey, 31.6% of premenopausal women with antipsychotic-induced hyperprolactinaemia had estradiol levels typical of those seen in postmenopausal women.[37] In another cross-sectional study of women prescribed conventional antipsychotics, prolactin levels were significantly negatively associated with sex hormone levels ($p < 0.05$) and more than 50% of the women were hypogonadal.[32] There are fewer data on the prevalence of hypogonadism in men prescribed antipsychotics. In a recent study the mean testosterone level in male patients prescribed conventional antipsychotics was within the normal range.[32] However, this may reflect the fact that the mean prolactin level in these men was also within the normal range, which in turn may reflect the relatively low mean dose of antipsychotic med-

ication that was prescribed. In another study of 56 male schizophrenic patients receiving antipsychotic drugs the mean serum prolactin level was elevated but the mean serum testosterone level remained within normal limits.[77] In the largest cross-sectional study to date of 255 men treated with conventional antipsychotics or risperidone, hyperprolactinaemia was associated with significantly lower testosterone levels.[37] In summary, hypogonadism appears common in female patients receiving antipsychotics, though this may be partly due to illness-related factors rather than antipsychotic-induced hyperprolactinaemia alone (section 4.5). The prevalence, and hence clinical relevance, of antipsychotic-induced hypogonadism in men has been less often investigated.

Long-term elevation of prolactin levels may have a number of as yet unknown physical effects. Binding sites for prolactin are widely distributed in the body, and several hundred different actions have been described, at least in vertebrate animals.[78] For example, prolactin is a known immunomodulator and has been linked to tumour growth. However, the clinical significance of these actions has not yet been firmly established.

Several studies have reported an association of hyperprolactinaemia with hostility, anxiety and depression, although the severity of these symptoms appears to be mild.[79,80]

Determining the prevalence of symptomatic hyperprolactinaemia raises various methodological problems. It depends on which symptoms are chosen and how these are defined. Furthermore, a cross-sectional study can show only an association between symptoms and raised prolactin. Proving a causal relationship is more complex. Causality may be implied from a close temporal association between starting an antipsychotic drug and the occurrence of prolactin elevation accompanied by characteristic symptoms. However, ideally it requires a follow-up study to determine whether reversal of hyperprolactinaemia is accompanied by symptom resolution. Few studies have taken account of these issues.

Research suggests that health professionals often fail to detect antipsychotic-induced hyperprolactinaemic symptoms.[2] There are several reasons for this, including the nature of the symptoms and the attitudes of both patients and health professionals. Some patients and professionals may be embarassed to discuss endocrine and sexual symptoms. Patients who do not associate these symptoms with antipsychotic treatment are unlikely to volunteer their presence to psychiatric staff. If health professionals are unaware of the symptoms of hyperprolactinaemia they will be unable to screen for their presence or recognise their relevance if patients complain of them. Finally, unlike some antipsychotic adverse effects (e.g. extrapyramidal symptoms and weight gain), symptoms of hyperprolactinaemia are not visibly stigmatising and this reduces the likelihood of their detection.

4.1 Gynaecomastia and Galactorrhoea

Hyperprolactinaemia can cause gynaecomastia in men and galactorrhoea in both sexes. Galactorrhoea is much more common in women than men.[81,82] Gynaecomastia is uncommon and can be unilateral or bilateral.[81,83,84] Estimates of the prevalence of galactorrhoea in women treated with conventional antipsychotics vary widely from 10% to more than 50%.[82] These differences partly reflect differences in methodology including how galactorrhoea is defined. In most women who have given birth, small amounts of serous fluid can be expressed from one or both breasts despite normal prolactin levels, but significant milk production usually occurs when prolactin levels are above the normal reference range.[85]

A well conducted study found that 21 of 150 women (14%) developed galactorrhoea within 75 days of commencing typical antipsychotic treatment.[82] Another seven women developed galactorrhoea during antipsychotic treatment in the run-up to entering the study, giving a prevalence rate of 19% (28 of 150). Only 8 of the 28 women reported the symptom on their own initiative to their researcher or doctor, partly because of its being perceived as a personal experience or as embarrassing.[86] This il-

lustrates that symptomatic hyperprolactinaemia is often unrecognised. Out of 28 women with galactorrhoea 24 women had a serum prolactin estimation.[82] The median value was 37.5 μg/L (range 10.0–246.0 μg/L), and 20 of the 24 women had values ≥16 μg/L. The incidence of galactorrhoea in this study in parous women was approximately twice that in nonparous women, suggesting that hormonal priming of the mammary gland in the form of pregnancy increases the risk of galactorrhoea.

In a pooled analysis of two clinical trials comparing haloperidol and risperidone the prevalence of galactorrhoea was 2.4% and 2.2%, respectively.[47] However, both values are likely to be an underestimate, as the study population included postmenopausal women, who may be less likely to develop drug-induced hyperprolactinaemia. Furthermore, it is not clear whether the data refer to the prevalence of these symptoms during the trial or an increase in severity compared with the pretrial antipsychotic medication. Mammary adverse effects of the other two prolactin-raising antipsychotics, amisulpride and zotepine, have not been systematically studied.

4.2 Sexual Dysfunction

Sexual dysfunction in patients with psychosis is poorly researched but existing data suggest that it is common and distressing. In a sample of 55 outpatients with schizophrenia treated with antipsychotics, Ghadirian et al.[87] reported sexual dysfunction in 54% of males and 30% of females during treatment. Finn et al.[88] reported that patients rated drug-induced sexual dysfunction as more 'bothersome' than most psychiatric symptoms of their illness. In another study of more than 800 patients with schizophrenia sexual dysfunction was perceived as a common adverse effect of medication (39% of respondents) and was rated second only to weight gain in how much it bothered patients.[89] In this study sexual dysfunction was associated with reduced adherence to antipsychotic treatment.[89] This association held after confounding variables, including use of other psychotropic medications and demographic variables, were considered.

Investigating the effect of sexual functioning in patients with schizophrenia is methodologically complex. Sexual functioning has various facets including desire/libido, ability to achieve arousal (lubrication in women, erection in men) and ability to achieve orgasm. Each facet can be affected in various ways by the illness itself or the drugs used to treat it, that is, antipsychotic-induced hyperprolactinaemia is only one of several mechanisms that may contribute to sexual problems (table I). The existence of these different mechanisms means that in some patients antipsychotic medication may improve sexual functioning compared with that when they were psychiatrically ill but untreated, but in other patients medication may cause a worsening of sexual functioning, even if the medication is effective in treating their illness.[90]

Evidence from both medical and psychiatric populations supports an association between hyperprolactinaemia and sexual dysfunction, but it is unclear to what extent this is due to a direct effect of raised prolactin and/or is caused by hypogonadism. Lundberg and Hulter[91] reported that 62.4% of 109 women with hypothalamic-pituitary disorders experienced decreased libido. In the subgroup of women with hyperprolactinaemia the incidence was 84%, but in those with normal prolactin levels the incidence was 32.6% ($p < 0.001$).

Table I. Cause of sexual dysfunction in patients with schizophrenia

Social impact of illness
Psychiatric symptoms
positive
negative
affective
cognitive
Peripheral and central drug effects
sedation
antidopaminergic activity
anticholinergic activity
antiadrenergic activity
hyperprolactinaemia
Factors unrelated to schizophrenia and its treatment
medical illness
alcohol (ethanol) misuse

Turning to psychiatric populations, Ghadirian et al.[87] reported that elevated prolactin correlated with increasing sexual dysfunction scores in men but not women treated with antipsychotics. Two subsequent studies of male patients with schizophrenia also reported higher serum prolactin levels in those with greater sexual dysfunction, although both studies had small samples.[92,93] One of the most recent studies in this area was conducted by Smith et al.[38] and involved 101 patients prescribed conventional antipsychotics. In male patients there was no correlation between prolactin levels and any measure of sexual response. However, when analysis was confined to men with hyperprolactinaemia (34% of the men in the study), prolactin was negatively correlated with erectile dysfunction ($r = -0.562$; $p = 0.023$) and quality of orgasm ($r = -0.56$; $p = 0.023$), whereas age, depression and autonomic adverse effects were not related. Thus, raised prolactin level appeared to be the main cause of sexual dysfunction in hyperprolactinaemic men. In female patients prolactin level correlated negatively with libido ($r = -0.46$; $p = 0.03$) and physical arousal problems such as poor vaginal response ($r = 0.52$; $p = 0.02$). After controlling for the effect of dose of medication and depression, the association between prolactin level and libido became nonsignificant, whereas the association between prolactin level and poor vaginal response/arousal was strengthened.

There is a paucity of published data on sexual dysfunction with atypical antipsychotics. Two studies have reported lower rates of sexual dysfunction with clozapine than with other antipsychotics.[94,95] In a group of 60 men with schizophrenia, Aizenberg et al.[94] reported improved sexual functioning in several domains (including desire, ability to achieve orgasm and sexual satisfaction) in those prescribed clozapine versus those prescribed conventional antipsychotics. Wirshing et al.[95] prospectively compared male patients in three treatment groups: clozapine, risperidone and a combined fluphenazine/haloperidol group. All three groups showed a decrease in sexual dysfunction but the group treated with clozapine developed significantly less impairment of sexual interest than the other two groups and significantly less impairment of erections and orgasmic function than the risperidone group. However, the lack of prolactin assays in both studies makes it impossible to comment on whether prolactin accounted for the differences between the drug groups. Case reports have noted improvements in sexual functioning when patients with antipsychotic-induced hyperprolactinaemia are switched to prolactin-sparing agents and their prolactin level normalises.[50,84,96]

4.3 Menstrual Abnormalities

Five cross-sectional studies have investigated menstrual irregularities in women with severe psychiatric illnesses receiving long-term treatment with various conventional antipsychotics at therapeutic doses and found point prevalences of 26%,[97] 40%,[87] 45%,[98] 55%[99] and 78%.[32] However, these figures need to be interpreted with caution because of small sample sizes (11–40 subjects) and in some studies the absence of a clear definition of what constitutes oligomenorrhoea or amenorrhoea.

The pooled analysis by Kleinberg et al.[47] of data from two randomised controlled trials of risperidone versus haloperidol has already been referred to in section 4.1. In this analysis the prevalence of amenorrhoea in women treated with risperidone was 8%, which was similar to that seen in the haloperidol and placebo groups. However, the data are likely to be an underestimate, as 20% of the sample were taking oral contraceptive medication, and postmenopausal women were included in the study. Furthermore, it is not clear whether the data refer to the total prevalence of amenorrhoea or to the onset of amenorrhoea since stopping the pre-trial antipsychotic medication.

In a cross-sectional study of 42 women prescribed risperidone, 48% of those of reproductive age experienced abnormal menstrual cycles (secondary amenorrhoea, oligomenorrhoea or polymenorrhoea).[37] Nonacs[100] studied 30 premenopausal psychotic women who were treated over 4 months with various antipsychotic drugs; 33% developed menstrual irregularities during treatment with risperidone and 17% during treatment with conven-

tional antipsychotics. No woman treated with olanzapine developed endocrine symptoms.

Amisulpride and zotepine are, like risperidone, prolactin-raising antipsychotics. However, we are unaware of any published studies of sufficient duration that systematically investigated the prevalence of menstrual irregularities with these agents.

4.4 Infertility

If a woman has amenorrhoea or oligomenorrhoea, she is clearly either infertile or subfertile. However, some hyperprolactinaemic women who menstruate with normal frequency may have an increased number of anovulatory cycles, which may also render them subfertile. Some amenorrhoeic women treated with antipsychotics may assume they are infertile and consequently stop using contraception. If such women are switched to a prolactin-sparing antipsychotic they are likely to regain their fertility. If this is not explained to them an unwanted pregnancy may arise. The effect of antipsychotics and hyperprolactinaemia on male fertility has not been investigated systematically.

4.5 Disease-Related Dysfunction of the Hypothalamic-Pituitary-Gonadal Axis

Recent studies have challenged the view that menstrual irregularities in schizophrenic women are due to drug-induced prolactin elevation alone.[101] Prentice and Deakin[98] investigated 40 schizophrenic patients of premenopausal age attending a depot antipsychotic clinic; 18 (45%) women had irregular menses or amenorrhoea. Both the current dose of antipsychotic and illness factors, including age of onset and cognitive impairment, were independently related to menstrual dysfunction. Although prolactin levels were higher in the women with menstrual disturbances than in the normally menstruating patients, the difference did not reach significance.

A role for illness-related factors is also supported by prevalence figures of menstrual irregularities in schizophrenic women studied in the pre-neuroleptic era. For example, a retrospective study published in 1957 reported that over a 5-year period hospital staff recorded at least one missing menstrual period in 73% of women with a diagnosis of schizophrenia compared with 12–59% of women with other psychiatric diagnoses.[102] However, it is not clear whether this difference was due to longer hospital admissions in schizophrenic patients.

In medicated women with an established schizophrenic illness, Bergemann[103] found a high incidence of anovulatory cycles as judged by estradiol and progesterone measurements in three serum samples taken over 3 weeks. Prolactin levels were higher in women treated with conventional antipsychotics but sex steroid levels were also low in those treated with prolactin-sparing atypical antipsychotics.

These findings could indicate either that in some women an organic impairment leads to both the schizophrenic illness and a disturbance in the neuroendocrine regulation of ovarian activity, or that their reproductive function might be affected by other mechanisms, such as stress resulting from the illness, or indeed an as yet unknown action of antipsychotics on hypothalamic-pituitary function. Irrespective of the mechanism, the data suggest that the hypothalamic-pituitary system in schizophrenic women is particularly sensitive to further disturbances such as hyperprolactinaemia.

In order to assess the respective contributions of a pre- or coexisting hypothalamo-pituitary-ovarian dysfunction, hyperprolactinaemia and other drug effects to hypoestrogenism in schizophrenic women it would be important to prospectively follow-up patients whose medication is being discontinued or switched to a prolactin-sparing agent. Such studies should include women of premenopausal age, use instruments that are designed to elicit these adverse effects, take into account past ovarian activity and carryover effects of recent antipsychotic usage, and observe women for several months. There are no such systematic studies but there are case reports of amenorrhoeic schizophrenic women who resumed menstruation after their antipsychotic medication was discontinued or switched to a prolactin-sparing agent.[1,50,84,104]

5. Effects on Bone Mineral Density (BMD)

5.1 Measurement of BMD

Peak bone mass is normally distributed with the variance being due to differences in genotype and its interaction with environmental influences during growth, including weight, gonadal hormone activity, calcium intake, vitamin D levels, nutrition and physical activity. Radiologically measured BMD is an index of bone mass and is calculated by dividing mineral content by the area or volume of bone scanned. Techniques commonly used are single- or dual-energy x-ray absorptiometry (DEXA) or CT scanning. BMD measurements are usually expressed in units of standard deviations above or below the mean value of young, healthy populations (the T score) or an age-adjusted mean value (the Z score). The WHO has proposed two diagnostic thresholds.[105] 'Osteoporosis' denotes a value for BMD that is ≥2.5 standard deviation below the adult peak mean and 'osteopenia' is a T score that lies between −1 and −2.49. It has been estimated that, at the most vulnerable sites, the risk of fracture approximately doubles with each standard deviation of decrease in age-adjusted mean BMD.[106]

5.2 Effect of Hypogonadism Unrelated to Antipsychotics on BMD

In women there is abundant evidence that hypoestrogenic states can lead to decreased BMD. The prevalence of osteoporosis increases dramatically after the menopause and estrogen is effective in stabilising BMD in postmenopausal osteoporosis.[107] The hypoestrogenic state that is associated with breast-feeding is associated with a reduction in BMD that reverses once breast-feeding stops and 'normal' endocrine status is re-established.[108] Women who have a premature menopause after ovariectomy show decreased BMD, which is prevented by estrogen treatment. Other hypoestrogenic states associated with decreased BMD include anorexia nervosa[109] and deficiency of GnRH.[110]

Of particular relevance to this article is research on women with hyperprolactinaemia unrelated to medication; many of these women have prolactin-secreting tumours. The consensus established by studies in this population is that reduced BMD (compared with age-matched controls) occurs in women with elevated prolactin and amenorrhoea but not in women with elevated prolactin and normal menstrual function.[110,111] In other studies of women with hyperprolactinaemic amenorrhoea the reduction in BMD has been shown to correlate with estradiol but not prolactin levels[112] and with the duration of amenorrhoea.[113] Changes are most marked in the spinal trabecular bone, where BMD has been reported to be 20–25% lower than in age-matched controls, whereas the BMD in the forearm, which has mostly cortical bone, was decreased by only 5% in the same studies.[113,114] In patients in whom prolactin levels and menstrual cycles normalise with treatment, spinal and forearm BMD values increase but remain significantly lower than that of age-matched normal women.[114,115]

In summary, there is convincing evidence that hyperprolactinaemia can cause a reduction in BMD in women and that this is mediated via reduced estrogen levels. Hyperprolactinaemia may reduce BMD in women through other mechanisms, including alteration of androgen levels[110,111] and a direct effect of prolactin on bone, but the supporting evidence is less than that implicating hypoestrogenism.

In comparison to women, there has been less research in men regarding the role of gonadal steroids in maintaining skeletal integrity. Nevertheless, there is evidence that testosterone deficiency can lead to decreased BMD. Men with congenital hypogonadism have significant bone loss and an increased risk of fractures[116] but this could result from a deficiency of peak bone mass attained during adolescence. Greenspan et al.[117] investigated 18 men with testosterone deficiency acquired in adulthood (secondary to prolactin-secreting tumours) and demonstrated a significant loss of both vertebral and radial bone density which correlated with the duration of the disease. A prospective follow-up of 20 men with hyperprolactinaemic hypogonadism

showed that reversal of hypogonadism, independent of the prolactin level, was associated with an increase in bone mass.[118]

To summarise, in both men and women hyperprolactinaemic hypogonadism (unrelated to antipsychotics) can lead to decreased BMD that can be halted, or partially reversed, by correcting the hypogonadism. Extrapolating from these data, one would expect that antipsychotic-induced hyperprolactinaemia, sufficient to cause hypogonadism, could also result in decreased BMD. This is of concern for two reasons. First, many psychiatric patients commence antipsychotic medication in their late teens or early 20s and if they developed hyperprolactinaemic hypogonadism at this age it may result in a reduced peak bone mass. Secondly, many patients continue antipsychotic treatment for years or even decades and chronic hypogonadism may lead to premature acceleration of bone loss.

5.3 Non-Endocrine Risk Factors for Osteoporosis in Psychiatric Patients

In addition to drug-induced gonadal dysfunction there are other factors that can place psychiatric patients at increased risk of osteoporosis. Patients with severe mental illness are two to three times more likely to smoke cigarettes than the general population.[119] It has been estimated that smoking 20 cigarettes a day for several years is associated with a perimenopausal reduction in BMD of 5–10%.[120] Patients with severe mental illness also have a high prevalence of excessive alcohol intake,[121] which can lead to bone loss.[122] This may reflect a direct toxic effect of alcohol on bone tissue or the secondary consequences of alcohol abuse. Inadequate dietary calcium and protein intake is known to reduce BMD and may be more common in chronically ill psychiatric patients. Polydipsia, a now less common behaviour among patients with schizophrenia, can also cause osteopenia due to excessive renal calcium loss.[123]

Although it is known that weight loss is associated with bone loss, it is not clear whether obesity counteracts bone loss caused by hypogonadism. It may be that antipsychotic-induced weight gain may have a small protective effect on BMD.

5.4 Studies of BMD in Psychiatric Patients

In patients exposed to antipsychotic medication the relationship between BMD and prolactin has been assessed in four studies.[124-127] All four studies assessed BMD at the spine and femoral neck and compared the results with age- and sex-related normative data. The first two studies[124,125] used dual photon absorptiometry, while Meaney et al.[127] used DEXA, a more accurate technique that has now superseded photon absorptiometry. Akande et al.[126] used CT scanning and DEXA.

Ataya et al.[124] studied ten female psychiatric patients (mean age 31 years) who were hyperprolactinaemic and had been treated with antipsychotic drugs for an average of 10 years. Three patients had long-standing drug-induced amenorrhoea and seven patients had oligomenorrhoea. BMD was reduced at three sites of the femoral head by 12% but not in the spine. BMD correlated positively with a histological measure of vaginal maturation used as an index of the biological effects of estrogens.

Halbreich et al.[125] assessed 68 male and female patients who were treated with antipsychotic, antidepressant and mood-stabilising medication, either alone or in combination. In the 33 female patients BMD values were highly significantly lower in the lumbar spine but not in the femoral neck. Estradiol levels were not significantly correlated with BMD measurements in women at any site. However, this could reflect the fact that the study sample included pre- and postmenopausal patients, thereby obscuring an effect due to antipsychotics. Within the 33 male patients BMD was significantly reduced in both the lumbar region and femoral neck. There was a significant correlation for men between BMD and both free and total testosterone in the lumbar region and between BMD and free testosterone at the femoral neck. For men, but not women, BMD was negatively correlated with prolactin in the lumbar spine.

Meaney et al.[127] assessed 55 patients who had received prolactin-raising antipsychotics for over 10 years; 57% of male and 32% of female patients had

age-relevant reduced BMD measures. Multivariate regression analysis showed that bone loss for the whole group was correlated with medication dose and for the male group was inversely correlated with testosterone levels. As the female group was postmenopausal, the investigators could not investigate whether there was a relationship between gonadal status and BMD.

Akande et al.[126] investigated nine premenopausal women with schizophrenia who had antipsychotic-induced hyperprolactinaemia and amenorrhoea. CT scanning was used to assess BMD in the radius and has the advantage of allowing independent assessment of the BMD of the cortical and trabecular bone. In contrast, DEXA provides a single overall measurement. There was a significant reduction in the density of the trabecular bone, but not the cortical bone, of the radius. There was no reduction of BMD in the lumbar spine or the femoral neck and this may be due to the use of DEXA to assess these sites and/or the relatively short duration of amenorrhoea in this study (mean duration 2.5 years).

Reduced BMD has been reported in patients with major depression and it is thought that this is due to raised plasma cortisol levels and changes in cytokine activity.[128] Although depression is common in schizophrenia, it is unlikely to contribute to bone loss, since it is not associated with alterations in hypothalamic-pituitary-adrenal function in these patients.[129,130]

The findings of reduced BMD in patients treated with antipsychotics[124-127] are preliminary and suffer from small sample sizes and methodological shortcomings. However, they are of concern and need to be followed up in future studies of subjects who have homogeneous diagnoses and psychotropic treatments and clear histories of prolonged hyperprolactinaemia and gonadal deficiency confirmed by hormone measurements. Cross-sectional studies can show only an association between BMD and endocrine abnormalities. Confirmation of causality requires intervention studies, for example switching patients with demonstrated reduced BMD and hyperprolactinaemia to prolactin-sparing antipsychotics and then reassessing endocrine status and BMD at a later date.

6. Possible Relationship with Breast Cancer

Prolactin is known to increase the incidence of spontaneously occurring mammary tumours in mice[131] and to increase the growth of established carcinogen-induced mammary tumours in rats.[132] These studies cannot automatically be extrapolated to humans, as rodent and human tumours differ in various aspects, including hormone responsiveness. Several epidemiological studies have investigated whether female psychiatric patients receiving treatment with antipsychotic drugs have a higher incidence of breast cancer but the results have been conflicting.[133-135] However, the most recent study, and the strongest methodologically, found that antipsychotic dopamine receptor antagonists conferred a small but significant risk of breast cancer.[136] This study had a retrospective cohort design and compared women who were exposed to prolactin-raising antipsychotics with age-matched women who were not. There were more than 50 000 women in each group and the total follow-up period was more than 200 000 person-years. Incident cases of breast cancer were identified through a cancer registry, and definitive breast cancer surgeries, and adjusted hazard ratios of breast cancer were calculated using multivariate analysis. Use of antipsychotic dopamine receptor antagonists was associated with a 16% increase in breast cancer (adjusted hazard ratio 1.16; 95% CI 1.07, 1.26) with a dose-response relationship between larger cumulative dosages and greater risk. The possibility of a causal link between raised prolactin and breast cancer received further support, as the researchers also found an increase of breast cancer in women who used prolactin-raising antiemetic dopamine receptor antagonists despite these women having a different breast cancer risk profile from that of antipsychotic users. The increased risk of breast cancer could not be explained by increased surveillance. The investigators concluded that antipsychotic dopamine receptor antago-

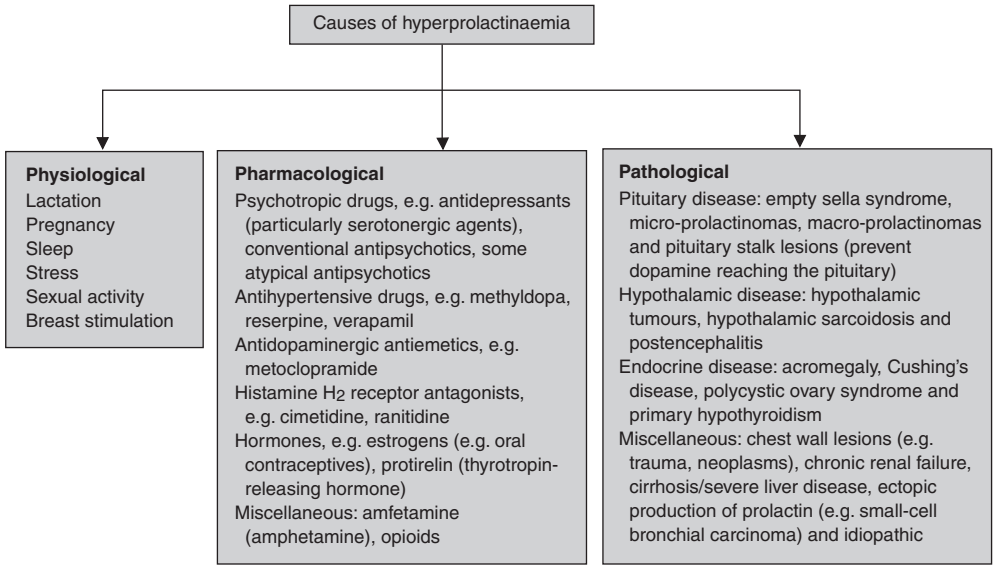

Fig. 1. Causes of hyperprolactinaemia.

nists may confer a small but significant risk of breast cancer. The findings require replication.

In theory it is possible that hyperprolactinaemia could be associated with an increased risk of endometrial carcinoma. Some premenopausal women with drug-induced hyperprolactinaemia are anovulatory but produce sufficient estradiol to stimulate the endometrium. This action remains unopposed by progesterone normally present in the luteal phase of the menstrual cycle. In polycystic ovary syndrome this constellation has been reported to lead to endometrial hyperplasia, which can be a precursor to endometrial carcinoma in one-third of cases.[137] Whether this is of clinical significance in drug-induced hyperprolactinaemia is not clear, since no corresponding studies have been carried out in this type of patient.

A minority of human breast cancers is prolactin sensitive. Consequently, it seems prudent to avoid prescribing prolactin-raising antipsychotics in patients with a past history of breast cancer.

7. Investigations and Differential Diagnosis

If a patient prescribed an antipsychotic drug presents with symptoms suggestive of hyperprolactinaemia, a serum prolactin level should be obtained. Mild-to-moderate elevations should be checked with a second sample to exclude physiological surges above the laboratory's upper reference value. If hyperprolactinaemia is confirmed, this merely demonstrates an association between the antipsychotic drug and hyperprolactinaemia; it does not prove that the antipsychotic drug is the cause, though the likelihood of this is high. Nevertheless, it is important for the clinician to consider other possible causes of raised prolactin (figure 1). A patient history, physical examination, pregnancy test, thyroid function test, blood urea and creatinine level can help determine if other aetiologies are responsible. The presence of headache and visual field defects is suggestive of a sellar space-occupying lesion, but the absence of these features does not exclude such pathology.

A close temporal relationship between the onset of hyperprolactinaemic symptoms and the date when the antipsychotic drug was either started or increased in dose suggests that the drug is responsible. For example, in a study of female patients the median time to onset of galactorrhoea was 20 days (range 7–75 days) after commencement of antipsychotic medication.[82] However, symptoms can

begin after a long period of treatment with a stable dose of an antipsychotic.[84] To help clarify the temporal link we recommend that, whenever possible, a history of menstrual cycling (duration, amount, and intervals of menstruation) as well as of lactation and sexual functioning should be taken before antipsychotic medication is initiated. Furthermore, when prolactin-raising antipsychotics are used it is helpful to obtain a pretreatment prolactin level, which one can compare with subsequent samples if the patient develops symptoms associated with relatively modest hyperprolactinaemia.

The degree of prolactin elevation can provide some guide to aetiology. In the absence of pregnancy and breastfeeding, a serum prolactin level of >4500 mU/L is highly suggestive of a prolactinoma[138] and concentrations >2500 mU/L suggest a micro-prolactinoma or a non-functioning (i.e. non-prolactin-secreting) adenoma.[139] Antipsychotics usually produce moderate prolactin elevation of up to six times the upper limit of the reference range (i.e. up to approximately 3000 mU/L).[34] However, it must be stressed that these are approximate guides. Non-prolactin-secreting tumours in the hypothalamic-pituitary region may present with relatively modest prolactin elevations within the range usually associated with antipsychotic drugs. Furthermore, antipsychotics can sometimes elevate serum prolactin to values well above 3000 mU/L. For example, Pollock and McLaren[140] reported on eight patients (collected over an 18-month period) who were treated with antipsychotic drugs and had serum prolactin levels within the range 3600–7300 mU/L. Particularly high prolactin levels may occur when antipsychotic drugs are administered to post-natal women or when patients receive concomitant treatment with more than one prolactin-elevating drug.

In summary, the following features suggest, but do not prove, that an antipsychotic is the cause of hyperprolactinaemia:

- use of an antipsychotic that is well documented to cause hyperprolactinaemia, that is, any conventional agent, amisulpride, risperidone or zotepine;
- onset of hyperprolactinaemic symptoms shortly after starting an antipsychotic or increasing the dose;
- absence of signs and symptoms suggestive of a sellar space-occupying lesion;
- a prolactin level <2000 mU/L;
- other laboratory tests are normal.

The only way to be sure that hyperprolactinaemia is drug induced is to stop the drug and for this to be followed by the prolactin level falling to the normal range. In some patients hyperprolactinaemic symptoms will have led to a decision to stop antipsychotic treatment or to switch to a prolactin-sparing agent. In these cases the management itself serves to confirm the diagnosis. However, when stopping or switching the antipsychotic is not feasible, clarification of the cause of hyperprolactinaemia is still needed. In patients treated with oral antipsychotics one can consider a diagnostic short-term cessation of medication (72 hours usually suffices) to determine if the prolactin level falls to near normal levels. This is not feasible in patients treated with intramuscular oil-based depot antipsychotics, as prolactin levels can remain elevated for up to 6 months after stopping a depot antipsychotic.[41] An alternative approach is magnetic resonance imaging (MRI) of the brain to exclude a space-occupying lesion. The sensitivity of MRI for surgically proved microadenoma approaches 100%, compared with 50% with CT.[141] If there is doubt about the cause of the hyperprolactinaemia, the patient should be referred to an endocrinologist.

8. Management

8.1 Is Intervention Warranted?

Whether a patient with antipsychotic-induced hyperprolactinaemia requires intervention depends on several factors, which include:

- how distressing the patient finds the hyperprolactinaemic symptoms;
- the duration of secondary amenorrhoea in a premenopausal woman; the risk of a decrease in BMD increases with the duration of amenorrhoea;

- how long treatment with the antipsychotic drug is expected to continue; if treatment is envisaged to be short term, the patient may be agreeable to tolerating the symptoms;
- the degree of benefit that the patient has gained from the antipsychotic drug;
- the risk of a relapse should the antipsychotic be substantially reduced in dose or switched and how serious the repercussions of a relapse are likely to be; the duration of antipsychotic treatment and the patient's past history will help in estimating these risks.

Given preliminary evidence linking antipsychotic-induced hyperprolactinaemia to decreased BMD,[124-127] we recommend that any woman with hyperprolactinaemia and 12 months' amenorrhoea should have BMD measurements. This is in keeping with guidelines from the Royal College of Physicians in England,[106] although these guidelines do not mention antipsychotics as a possible cause of secondary amenorrhoea. BMD measurements should be taken at several sites (e.g. lumbar spine, femoral neck and forearm), as an estimation at one site can produce misleading results. The results should be incorporated into the assessment of risks and benefits of continuing the current antipsychotic. We recommend that patients with either osteopenia or osteoporosis on one or more sites be referred for specialist advice on further management.

Assessing the risk of osteoporosis in male patients is hindered by the fact that men do not have an objective indicator of gonadal function in the way that menstrual function acts in women. At present there is insufficient evidence to conclusively state that antipsychotic-induced hypogonadism in men is a cause of decreased BMD. If these data do emerge in future there would be a case for routinely monitoring serum prolactin and testosterone in men prescribed prolactin-raising antipsychotics.

In summary, the risk-benefit ratio for treatment of antipsychotic-induced hyperprolactinaemia needs to be assessed on an individual patient basis. As a general rule, the patient should be fully involved in the assessment and discussion about management options. However, as with many other clinical issues, the degree to which this is done must be tailored to the individual patient, taking account of their mental state, educational level, and how much information and involvement they want.

8.2 Treatment Options

Table II summarises the treatment options available for hyperprolactinaemia, the symptoms that each treatment option is, in theory, effective against and the main advantages and disadvantages of each.

A reduction in dose of the offending antipsychotic is the simplest treatment strategy but its effectiveness is unpredictable and it carries the risk of precipitating an exacerbation or relapse of psychotic symptoms. Switching the patient to a prolactin-sparing antipsychotic (i.e. aripiprazole, olanzapine, quetiapine or clozapine) usually proves effective, though there is also a risk of relapse.[50,84]

Table II. Treatment options for symptomatic antipsychotic-induced hyperprolactinaemia

Treatment	Symptoms, against which treatment, in theory, is effective	Advantages	Disadvantages
Decrease dose of existing antipsychotic	All symptoms of hyperprolactinaemia	Simple	Risk of relapse Unpredictable effectiveness
Switch to a prolactin-sparing antipsychotic	All symptoms of hyperprolactinaemia	Only method that allows confirmation that hyperprolactinaemia was caused by antipsychotic	Risk of relapse Inappropriate if compliance is of concern and patient is maintained on a long-acting depot injection[a]
Dopamine receptor agonist	All symptoms of hyperprolactinaemia	Allows continued treatment with existing antipsychotic	Risk of relapse Dopamine receptor agonist-induced adverse effects
Combined oral contraceptive (females only)	Symptoms of estrogen deficiency	Allows continued treatment with existing antipsychotic	Thromboembolism Breast cancer

a Prolactin-sparing antipsychotics are not currently available as depots.

There are sometimes good reasons to continue treatment with a prolactin-elevating antipsychotic. For example, a long-acting intramuscular depot may be the only way to ensure adequate adherence with antipsychotic treatment, and the risks of relapse may be felt to be too high to justify stopping the depot antipsychotic (at present prolactin-sparing atypical antipsychotics are not available as depot injections). In such cases a D_2 receptor agonist, such as bromocriptine or cabergoline, can be considered. Most experience relates to using bromocriptine to treat symptomatic hyperprolactinaemia caused by pituitary tumours rather than antipsychotic medication and the outcome seems less effective in the latter group. Amenorrhoea responds better than galactorrhoea.[142-145] Dopamine receptor agonists can cause psychotic relapse, although the risk is fairly small in stable patients taking maintenance antipsychotic medication.[145-148] Other adverse effects depend on the agent used; for example, bromocriptine can cause postural hypotension, gastrointestinal symptoms and vasospasm of the fingers and toes, especially in those with Raynaud's syndrome.

If there are good clinical reasons for a premenopausal female patient to remain on a prolactin-raising antipsychotic but this is causing amenorrhoea (i.e. a clinical marker of estrogen deficiency), the use of combined oral contraceptives should be considered. This will prevent symptoms associated with estrogen deficiency, including possible loss of BMD, although symptoms directly due to hyperprolactinaemia (e.g. galactorrhoea) will be unaffected. The oral contraceptive is associated with an increased risk of thromboembolism and breast cancer,[149] and these risks should be carefully assessed and discussed with the patient before commencing estrogen replacement. In patients with antipsychotic-induced hyperprolactinaemia, it has been recommended that prolactin levels are monitored every 2–3 months for the first 6 months of hormone replacement therapy, followed by annual measurements.[150]

9. Conclusions and Future Research

In men and women treated with conventional and certain atypical antipsychotics hyperprolactinaemia is common and can lead to a range of symptoms with important clinical consequences. In spite of this the phenomenon has attracted much less interest than extrapyramidal adverse effects. Hyperprolactinaemia should become a focus of interest, particularly given the introduction of prolactin-sparing antipsychotics and increasing knowledge about its possible long-term adverse effects.

Several key problems are apparent in the existing literature. First, there is a paucity of data reflecting the low priority given to this phenomenon. Second, when effects on prolactin secretion are reported in drug trials this is usually in the form of the number of patients with hyperprolactinaemia, with little or no attempt to relate it to its clinical manifestations. Third, the short duration of most randomised controlled trials (several weeks) means that it is impossible to identify amenorrhoea or oligomenorrhoea, as these are usually defined as occurring over a period of at least 3 months. Fourth, the existing cross-sectional studies of patients on long-term medication can identify only an association between raised prolactin levels and symptoms. Proving a causal relationship requires a follow-up study to determine whether reversal of hyperprolactinaemia is accompanied by symptom resolution. Further research is badly needed in this area

The extent to which a latent dysfunction of the hypothalamic-pituitary-ovarian axis in women with schizophrenia, and pharmacological effects unrelated to prolactin, contribute to endocrine and sexual symptoms needs to be clarified. Future research should also address the degree of distress that hyperprolactinaemic symptoms cause and how this may affect medication compliance in the long term. Finally, the long-term adverse effects of raised prolactin and secondary hypoestrogenism are unclear, especially the potential effects on BMD.

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chotics and funding for a small investigator-initiated study from Astra-Zeneca, the manufacturers of quetiapine.

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