Hyperprolactinaemia in the context of psychiatry

Karen Romain ⓘ, Sarah Fynes-Clinton, David Harmer & Manoj Kumar

Karen Romain is currently a core psychiatry trainee (CT3) doctor working in a forensic psychiatric unit with Coventry and Warwickshire Partnership Trust, UK. **Sarah Fynes-Clinton** is a specialty registrar trainee (ST4) doctor in older adult services with Coventry and Warwickshire Partnership Trust. **David Harmer** is a core psychiatry trainee (CT2) doctor currently working in older adult services with Coventry and Warwickshire Partnership Trust. **Manoj Kumar** is a general adult consultant psychiatrist who is currently Director at the Institute for Mind and Brain in Kerala, India. He is also an honorary senior lecturer at Keele University Medical School, Faculty of Psychiatry and an honorary consultant with Midlands Partnership NHS Foundation Trust, UK.
Correspondence Dr Karen Romain. Email: karen.romain@nhs.net

SUMMARY

Advocating for good physical healthcare for their patients is of the utmost importance to psychiatrists. This narrative review focuses on one part of this large goal, the topic of hyperprolactinaemia from the perspective of mental healthcare. For psychiatrists this often includes managing raised prolactin levels in the context of medication. However, they must consider the wider differentials of a raised prolactin level and the possible impact of treatments. For that reason, in this review we start with an overview of prolactin physiology before considering hyperprolactinaemia both in the context of antipsychotic therapy and its wider differentials, including prolactinoma. Investigation and management are considered and key practice points developed.

LEARNING OBJECTIVES

After reading this article you will be able to:
• demonstrate an understanding of problems caused by high prolactin levels
• discuss options for investigation
• demonstrate an understanding of available hyperprolactinaemia management strategies.

KEYWORDS

Prolactin; antipsychotics; physical health; drug interactions and side-effects; management.

There has been a drive to improve the physical healthcare of those within mental health services. This is of importance following the emergence of data suggesting that people with schizophrenia are 2–3 times more likely to die early from preventable causes (World Health Organization 2018).

An example of the overlap between psychiatry and endocrinology is hyperprolactinaemia, a common problem for those on antipsychotic medications (Cookson 2012). The National Institute for Health and Care Excellence (NICE) (2014) suggests that, before deciding on and commencing a specific antipsychotic, the patient should be given information on the benefits and side-effects, including the risk of hyperprolactinaemia. To best inform those due to commence antipsychotics, it is therefore important that clinicians keep up to date with this topic.

This review offers updated knowledge on prolactin and hyperprolactinaemia and considers investigative strategies. Management options are identified, with a focus on antipsychotic-induced hyperprolactinaemia and prolactinoma.

Prolactin

Prolactin is a polypeptide hormone produced primarily in the anterior pituitary gland. It has been further identified as having a role in the central nervous system (CNS) and immune system (Milano 2017). Secretion of prolactin is primarily controlled through a negative feedback loop, via hypothalamic dopamine. The dopamine receptors involved in this loop belong to the D_2 class and are located on the membranes of the lactotrophic (prolactin-producing) cells of the anterior pituitary gland. Three major forms of prolactin can be found, namely 'free prolactin', 'big prolactin' and 'big big prolactin' (or macroprolactin), with the last two forms being inactive (Saleem 2018).

The functions of prolactin are divided into five categories: lactation, reproduction, osmoregulation, metabolism and regulation of the immune system (Riecher-Rössler 2013; Milano 2017).

Hyperprolactinaemia

The prevalence of hyperprolactinaemia in the general adult population is approximately 0.4% (Majumdar 2013). Although definitions of hyperprolactinaemia and preferred units of measurement differ across literature and laboratories, for the purposes of this review, all levels have been reported in SI units (μg/L). A prolactin level can be considered to be raised if it is above 20 μg/L in men and above 25 μg/L in women (Milano 2017). Symptoms of hyperprolactinaemia may be present at even moderately raised levels, but levels above 70.5 μg/L, and especially levels over 141 μg/L, are likely to result in symptoms becoming evident. At levels of over 100 μg/L, the specialist involvement of an endocrinologist should be considered (Cookson 2012; Grigg 2017).

Hyperprolactinaemia subtypes

Hyperprolactinaemia can be divided into three subtypes, related to the underlying cause: functional or

Hyperprolactinaemia subtypes and common causes

Functional/physiological hyperprolactinaemia

- Pregnancy
- Lactation

Factitious/analytical hyperprolactinaemia

- Macroprolactin

Pathological hyperprolactinaemia

- Idiopathic effects
- Pituitary stalk damage
- Hypersecretion
- Systemic disorder
- Medication side-effect

(Majumdar 2013; Saleem 2018)

physiological; factitious or analytical; and pathological (Box 1).

Functional or physiological hyperprolactinaemia (with prolactin levels usually in the range of approximately 18.8–28.2 µg/L) primarily occurs as a result of prolactin's physiological functions related to pregnancy and lactation, hence prolactin may be above normal levels and not be a sign of any underlying pathology (Majumdar 2013; Saleem 2018).

Factitious or analytical causes of hyperprolactinaemia are secondary to macroprolactinaemia (Majumdar 2013; Saleem 2018). In macroprolactinaemia, high levels of biologically inactive macroprolactin molecules can be detected in immunoassay testing. These macromolecules are inactive owing to their inability to bind to receptors (Milano 2017).

Pathological causes of hyperprolactinaemia can further be divided into five subtypes: idiopathic; secondary to hypothalamic pituitary stalk damage; pituitary hypersecretion; as a by product of systemic disorders (such as chronic renal failure, hypothyroidism, liver cirrhosis, epilepsy); or drug/medication induced (Majumdar 2013; Saleem 2018). It can occur through various mechanisms. For example, in hypothyroidism hyperprolactinaemia is due to an increase in thyrotropin-releasing hormone (TRH), which increases both thyroid-stimulating hormone (TSH) and prolactin (Bahar 2011). Comparatively, in liver disease there is alteration in the type of amino acids entering the nervous system, inhibiting dopamine release (dopamine helps regulate prolactin) (Jha 2016).

Most importantly in the context of psychiatry, hyperprolactinaemia can be drug/medication induced. Hyperprolactinaemia has long been known as a possible side-effect related to the use of antipsychotics and this is one of the most commonly reported adverse effects in clinical trials (Bushe 2008; Milano 2017).

As prolactin release is mediated via hypothalamic dopamine, antagonism due to antipsychotics results in the interruption of negative feedback pathways, which leads to hyperprolactinaemia (Saleem 2018). Individuals with psychosis who are being treated with long-term antipsychotic medication are therefore at an increased risk of the long-term consequences of hyperprolactinaemia.

Prolactinoma

Another important cause of hyperprolactinaemia that must be considered are prolactin-secreting tumours called prolactinomas, which account for 40–66% of functional pituitary tumours and represent the most common organic cause of hyperprolactinaemia (Saleem 2018; Olarescu 2019). Majumdar & Mangal (2013) report that a prolactinoma is likely if the prolactin level is 250 µg/L and note that some medications, such as risperidone, can cause levels over 200 µg/L.

Prolactinomas can be broken down into adenomas and carcinomas. Adenomas can be subclassified by size as microadenomas (<10 mm), macroadenomas (≥10 mm) and giant prolactinomas (>40 mm). Carcinomas are defined by the presence and location of metastatic processes. Carcinomas are very rare among prolactinomas (approximately 0.2% of operated adenohypophyseal tumours). However, up to 15% of pituitary tumours may be defined as clinically aggressive because of rapid growth, invasive properties or continued growth despite treatment (Olarescu 2019).

In the case of a prolactinoma, symptoms may include features related to the compressive effect of the tumour. These could include headache, visual disturbances and hypopituitarism (most commonly with deficiencies in follicle-stimulating hormone (FSH) and luteinising hormones – with symptoms including fertility problems and deficiencies of oestrogen and testosterone) (Olarescu 2019). If the prolactinoma extends into surrounding cerebral structures there may be atypical symptoms such as reversible dementia, disorientation, olfactory hallucinations, temporal lobe epilepsy, hemiparesis and cranial nerve palsies (Shimon 2019).

Hyperprolactinaemia symptoms

Clinical symptoms are related to prolactin's physiological functions and are most commonly related to either hypogonadism or lactation. Women often present earlier, with abnormal menstruation (oligomenorrhoea or amenorrhoea), galactorrhoea, sexual dysfunction and infertility. Post-menopausal women may notice only a decreased frequency of hot

flushes and therefore may not report symptoms. Men may present with reduced sexual function and loss of libido, as well as infertility and gynaecomastia (Haddad 2004; Milano 2017; Saleem 2018). Early symptoms are summarised in Fig. 1.

Longer-term consequences of hyperprolactinaemia include altered bone mineral density and are summarised in Fig. 2. Importantly, an association has been identified between hip fracture and schizophrenia (OR = 1.73, 95% CI 1.32–2.28) as well as prolactin-raising antipsychotics (OR = 2.6, 95% CI 2.43–2.87). This study considered more than ten antipsychotics, including haloperidol, zuclopenthixol and sulpiride, and included both oral and depot preparations (Howard 2007).

Osteopenia resulting from hypoestrogenaemia occurs more frequently in women, and it can result in decreased spinal bone mineral density. Other potential long-term effects of hyperprolactinaemia in women include features of hyperandrogenism such as acne, increased facial and body hair growth and abnormal libido; these symptoms are due in part to increased endogenous steroid hormones, dehydroepiandrosterone and free testosterone (Majumdar 2013; González-Blanco 2016; Saleem 2018).

In men with chronic hyperprolactinaemia, long-term consequences again include osteopenia, alongside lower energy levels and reduced muscle mass. Osteopenia leads to an increased risk of pathological fractures due to altered bone structure. Furthermore, progressive atherosclerosis occurs in both genders, related to decreased oestrogen as a result of hypogonadism secondary to hyperprolactinaemia (Haddad 2004; Majumdar 2013; González-Blanco 2016; Saleem 2018).

Malignancy

Raised prolactin has been implicated in the pathogenesis of upper gastrointestinal and haematopoietic cancers (Sethi 2012). In addition to this, prolactin receptor pathways have been associated with the development of resistance to chemotherapy (Sethi 2012). In both cases there is insufficient evidence at this time to suggest causation.

The link with breast cancer has been more substantiated, with Johnston et al (2018) demonstrating in animal models that hyperprolactinaemia-inducing antipsychotics, in this case risperidone and pimozide, caused pre-existing premalignant cells to progress to breast cancer by supressing apoptosis. However, this was not supported by a cohort study and meta-analysis by Dekkers et al (2015), who concluded that there was no increased risk of breast cancer in people (men and women) with hyperprolactinaemia (RR = 1.04, 95% CI 0.75–1.43). A

subsequent meta-analysis by Wang et al (2016) that included seven case–control and cohort studies of the association between prolactin and breast cancer in women found a positive association (RR = 1.16, 95% CI 1.04–1.29).

Most recently, a meta-analysis by Ni et al (2019) attempted to quantify malignancy and mortality risks of site-specific cancer in people with schizophrenia. They found an increased risk of mortality in breast cancer (RR = 1.97, 95% CI 1.38–2.83), with lung and colon cancer also showing significantly increased risk (RR = 1.93, 95% CI 1.46–2.54 and RR = 1.69, 95% CI 1.60–1.80 respectively). They agreed that hyperprolactinaemia could be linked to increased breast cancer risk but felt that overall associations between cancer incidence and schizophrenia were unclear owing to many potential confounding factors, including gender, genetic background and antipsychotic medication use. They noted that further studies are necessary to identify a more robust association.

Investigations

What to monitor and when

Both the Maudsley Prescribing Guidelines (Taylor 2018) and the NICE Clinical Guideline (National Institute for Health and Care Excellence 2014) suggest that baseline prolactin levels should be measured routinely if a patient is due to commence antipsychotic therapy. However, other reviewers go further, suggesting that a sexual and menstrual history should be completed at the time of antipsychotic initiation to help clinicians identify symptom changes (Grigg 2017).

The Maudsley guidelines suggest that reassessment should then take place following 3 months of antipsychotic treatment, when a further prolactin level should be obtained if there are suggestive symptoms or the medication is known to be prolactin-elevating (Taylor 2018). If antipsychotic medication is altered with the goal of reducing prolactin, levels should be remeasured after 3 days to allow for response (Melmed 2011).

In their treatment algorithms, Grigg et al (2017) provide recommendations for later monitoring of prolactin levels. They advise that prolactin should be rechecked annually if the level is between 16.5 and 50 μg/L, every 6 months if over 50 μg/L and 3 months after any antipsychotic medication change.

Further indications for testing prolactin levels include clinical symptoms of hyperprolactinaemia such as galactorrhoea, amenorrhoea and sexual dysfunction (Cookson 2012). Discussing symptoms of high prolactin with individuals currently exhibiting symptoms of psychosis is challenging in itself. McCabe & Priebe (2008) considered the difficulties
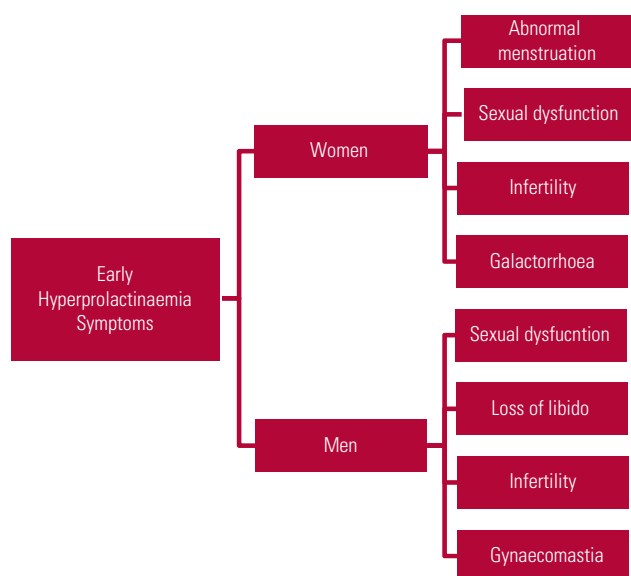
FIG 1 Early symptoms of hyperprolactinaemia (Haddad 2004; Milano 2017; Saleem 2018).

of communication and building an effective therapeutic relationship in these cases and reflected that this is a difficult area to research effectively, with little in the way of established guidance or training. More recently, McCabe & Healey (2018) compared two studies looking to use the conversation analysis 'repair' framework to reduce potential miscommunication with patients with psychosis. Although work such as this is in its early stages, with development needed to support its clinical utility, the key message is that clinicians should continue to work to understand the person's perspective and build effective therapeutic relationships.

Historically some evidence has supported checking prolactin levels following seizures to assist in differentiating epileptic activity from other seizure causes (Trimble 1978). This was reinforced more recently by Ahmad et al (2019) in a 2-year cross-

sectional study involving 90 participants, which found that prolactin levels were higher in those with tonic–clonic epileptic seizures than those with non-epileptic seizures. However, the evidence is not always consistent: in a 4-year retrospective study of 218 participants Abubakr & Wambacq (2016) reported that prolactin did not provide additional support when differentiating between epileptic and psychogenic non-epileptic seizures and concluded that it should not be routinely tested. A summary of when prolactin should be tested is contained in Box 2.

Checking prolactin

The Endocrine Society recommends that, if hyperprolactinaemia is suspected, a single blood test for serum prolactin is needed. If this is above the
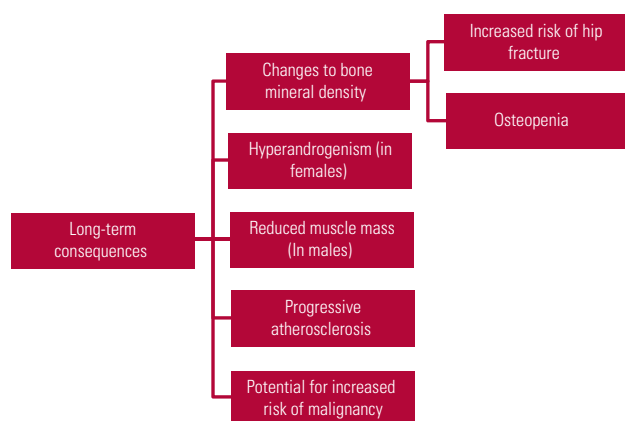

FIG 2 Long-term consequences of hyperprolactinaemia (Haddad 2004; Howard 2007; Majumdar 2013; González-Blanc 2016; Saleem 2018).

upper level of normal a diagnosis of hyperprolactinaemia can be made. These guidelines suggest that the sample should be obtained without significant venepuncture stress (Melmed 2011). However, it should be noted that other authors found no significant effect of stress on prolactin levels (Ferriani 1985), and others suggest testing serum levels twice before confirming the diagnosis (De Hert 2014). If the diagnosis is in doubt, a repeat test may therefore be appropriate.

For those with asymptomatic hyperprolactinaemia, Melmed et al (2011) suggest assessment of macroprolactin. Macroprolactin has a lower biological effect, so fewer investigation and management changes are needed as it is unlikely to cause symptoms. Hyperprolactinaemia caused by raised macroprolactin can be detected by polyethylene glycol (PEG) precipitation, which is the most common method for assessing for macroprolactin levels in clinical laboratories (Chen 2016). Some laboratories automatically test macroprolactin levels following a high prolactin result.

Other investigations

Further investigations are then dependent on the suspected cause. They involve close focus on the broader history and assessment for temporal links or disease-specific symptoms (De Hert 2014). This is likely to include blood tests for alternative causes, such as renal or thyroid dysfunction, and, in some cases, ordering magnetic resonance

imaging (MRI). The Endocrine Society advises a head MRI to assess for prolactinoma if it is not practicable to alter the antipsychotics or if the high prolactin level does not appear to be linked to the medication. The aim is to further investigate whether there is a pituitary or hypothalamic mass (Melmed 2011). Similarly, De Hert et al (2014) in their comprehensive review suggest an MRI of the pituitary when hyperprolactinaemia onset does not coincide with antipsychotic use.

Symptoms that may suggest that high prolactin is caused not by antipsychotics but by prolactinoma are those consistent with a space-occupying lesion, for example headache or visual field defects, the presence of which would warrant an MRI head scan (Miyamoto 2015).

Setting a prolactin level at which an MRI should be conducted is challenging. Grigg et al (2017) collated practice guidelines and concluded that computed tomography (CT) or MRI should be completed when prolactin levels reach 150 µg/L. However, Rand et al (1996), Kyritsi et al (2018) and Miyamoto et al (2015) suggest that lower levels – between 85.2 and 100 µg/L – require testing and provide evidence that the probability of adenoma increases as the prolactin level rises. Given that the 85.2 µg/L cut-off was suggested by work in a specific non-psychiatric population, we suggest that prolactin levels of over 100 µg/L warrant an MRI, particularly in the absence of other physiological explanations.

A summary of indications for MRI is contained in Box 3.

Management of antipsychotic-related hyperprolactinaemia

Link between antipsychotics and prolactin

Melmed et al (2011) explain that the most frequent cause of hyperprolactinaemia in the absence of a tumour is medication, further identifying antipsychotics as the most common culprit. Alongside this they report anticonvulsants, antihistamines and opiates among other causative agents.

The Maudsley Prescribing Guidelines suggest those at higher risk of significant adverse effects of hyperprolactinaemia to be people under 25 years of age (as this is before peak bone mass is achieved), those with osteoporosis and people with a history of hormone-dependent breast cancer (Taylor 2018). Serum prolactin levels associated with antipsychotics are typically 25–100 µg/L, although some can produce levels in excess of 200 µg/L (Grigg 2017).

Antipsychotics particularly associated with hyperprolactinaemia include amisulpride, risperidone, paliperidone, sulpiride, haloperidol and chlorpromazine (Bushe 2008; Melmed 2011; Cookson

TABLE 1 Comparative risk of hyperprolactinaemia for various antipsychotics

Hyperprolactinaemia risk		
High	**Moderate**	**Low**
Amisulpride	Olanzapine	Aripiprazole
Risperidone	Quetiapine	Clozapine
Sulpiride	Loxapine	
Chlorpromazine	Pimozide	
Haloperidol		

Source: Samperi et al, 2019.

2012; Taylor 2018; Samperi 2019). The comparative risk of hyperprolactinaemia for various antipsychotics is shown in Table 1.

When considering the effect of these medications it is worth noting evidence that some antipsychotic-naïve people have raised prolactin at baseline (Pérez-Iglesias 2012; González-Blanco 2016). This finding is supported by a meta-analysis by González-Blanco et al (2016), who found significantly raised prolactin levels in both male and female antipsychotic-naïve patients with schizophrenia and related disorders. This was considered to be related to stress response, and González-Blanco et al further linked raised prolactin to biochemical alterations, including TRH, ghrelin and interleukins.

Rates of hyperprolactinaemia vary, with reports of 40–90% for typical antipsychotics (Melmed 2011), 40–93% for any antipsychotic (Shim 2007; Cookson 2012) and 50–100% for risperidone specifically (Melmed 2011; Pérez-Iglesias 2012). There are a variety of reasons underlying the varied effect

of antipsychotics on prolactin levels, as summarised in Fig. 3. It is therefore not surprising that there are differences in effect size noted across the literature.

Discontinuation risks

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study involved 1493 participants with schizophrenia. In phase 1, participants were randomly assigned to receive olanzapine, perphenazine, quetiapine, risperidone or ziprasidone. Overall, 74% discontinued their medication within 18 months owing to inefficacy or intolerable side-effects. Interestingly, despite risperidone being the only drug in this trial associated with a substantial increase in prolactin it had the lowest rate of discontinuation because of intolerable side-effects (10%, compared with the highest rate of 18% with olanzapine) (Lieberman 2005).

Prolactin-sparing antipsychotics similarly differ in effect. For example, Crespo-Facorro et al (2017) demonstrated that aripiprazole had a lower risk of prolactin excess (14.3% showed mild excess, 5.4% marked) compared with two other prolactin-sparing antipsychotics: quetiapine (36.1% mild, 5.6% marked) and ziprasidone (18.4% mild, 8.2% marked) after 1 year of treatment. Over the year, participants on aripiprazole showed an overall decrease in prolactin levels, whereas a progressive increase was seen in those on quetiapine and ziprasidone.

Adaptation

Eberhard et al (2007) focused on risperidone therapy in a longitudinal study over 5 years,
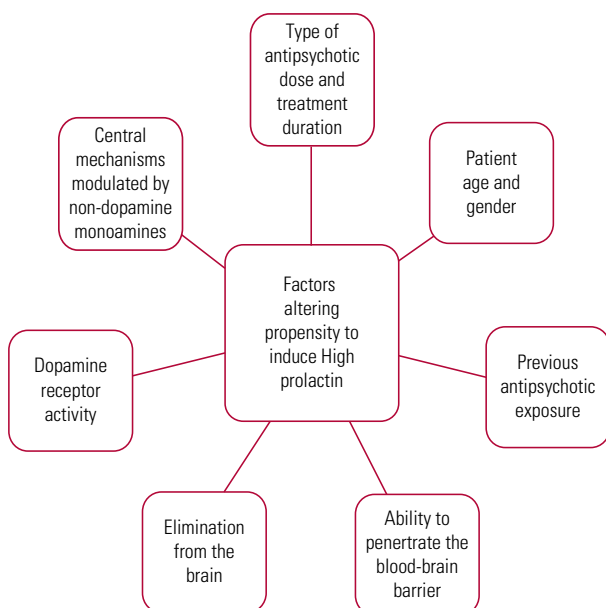
FIG 3 Differences in antipsychotic effect on prolactin (Cookson 2012; Pérez-Iglesias 2012).

finding that the increase in prolactin was linked to the metabolite 9-OH risperidone and that this prolactin effect was more pronounced in women. However, in those who took risperidone monotherapy over the 5 years a linear reduction in prolactin was noted later on, suggesting this adaptation over time. Corroborating this was work by Pérez-Iglesias et al (2012), who found a tendency for prolactin levels to decrease at 1 year for those on risperidone. However, they noted that 71% of values remained above the normal range.

Confounders

When considering medication-induced hyperprolactinaemia, it is important to remember that medications other than antipsychotics can be a potential cause. Other psychotropics, including tricyclic antidepressants and monoamine oxidase inhibitors, as well as a number of physical health medications, such as anti-emetics, opiates and antihypertensives, potentially cause or worsen hyperprolactinaemia. Some key examples are listed in Box 4.

Treatment of antipsychotic-induced hyperprolactinaemia

Once high prolactin has been established, alternatives have been ruled out and symptoms assessed, if the antipsychotic is identified as the cause, treatment must be reviewed (Grigg 2017). Options given in the Maudsley Prescribing Guidelines (Taylor 2018) and the Endocrine Society's clinical practice guideline (Melmed 2011) include: continuing the antipsychotic and monitoring; stopping/reducing the antipsychotic; switching to a prolactin-sparing antipsychotic; or considering adjunctive therapy (Fig. 4). Prolactin-sparing antipsychotics include aripiprazole, asenapine, quetiapine and clozapine (Haddad 2004; Taylor 2018).

When considering these options, it is important to balance carefully the benefits of antipsychotic medication against the risk of relapse if altered, as well as the distress reported regarding side-effects (De Hert 2014; Grigg 2017). Prolactin-sparing antipsychotics will have their own side-effect profiles and so it may instead be preferable to decrease the current antipsychotic rather than attempting a switch (De Hert 2014).

If the patient is asymptomatic, the Maudsley guidelines suggest that a joint decision should be taken as to whether to treat the high prolactin or continue the current antipsychotic regimen with monitoring. Strategies such as stopping smoking and ensuring adequate calcium and vitamin D intake can be used to help with the risk of altered bone mineral density if this is a concern (Taylor 2018).

BOX 4 Common medications that can cause hyperprolactinaemia

- Antipsychotics: amisulpride, risperidone, paliperidone, sulpiride, haloperidol and chlorpromazine
- Tricyclic antidepressants: amitriptyline, clomipramine
- Monoamine oxidase inhibitors
- Anti-emetics: metoclopramide
- Opiates: morphine
- Antihypertensives: methyldopa, verapamil

(Melmed 2011; Samperi 2019)

Switching antipsychotics

Given the evidence showing a decrease in prolactin with aripiprazole it is logical to switch to this medication when prolactin presents a problem. However, Grigg et al (2017) advise that switching those already stabilised on antipsychotics should be done with extreme caution and only if symptoms of hyperprolactinaemia are present and other interventions are inappropriate or unsuccessful.

Byerly et al (2009) studied switching to aripiprazole from risperidone or olanzapine. They investigated three methods: aripiprazole initiation with immediate olanzapine/risperidone discontinuation; initiating aripiprazole while tapering off olanzapine/risperidone; and titrating up aripiprazole while tapering off olanzapine/risperidone. When switching either olanzapine or risperidone to aripiprazole, prolactin significantly decreased in all

---

Hyperprolactinaemia identified

Assess symptoms and rule out alternative causes

Antipsychotic-induced hyperprolactinaemia confirmed

Consider: reducing dose, stopping antipsychotic, switching antipsychotic or continuing the medication with appropriate monitoring

Consider adjunctive medications - aripiprazole, metformin, dopamine agonists, PGD, hormone therapy
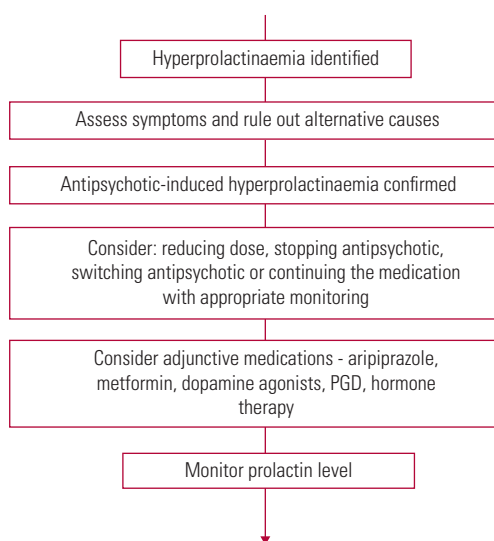
Monitor prolactin level

FIG 4 Summary of treatment of antipsychotic-induced hyperprolactinaemia (Haddad 2004; Melmed 2011; Cookson 2012; Grigg 2017; Taylor 2018). PGD, peony-glycyrrhiza decoction.

groups at 1 week and no switching strategy was evidently superior.

Adjunctive aripiprazole

If switching the antipsychotic to a prolactin-sparing form is not appropriate or is not successful, adjunctive aripiprazole can be considered, since adjunctive aripiprazole has been shown to be successful in reducing prolactin to normal levels (Cookson 2012; Taylor 2018).

Shim et al (2007) demonstrated that when aripiprazole was added to haloperidol, prolactin was reduced without significant effects on psychopathology, although it is worth noting that the study was conducted in a stable clinical group. Prolactin levels decreased by 76.5% at 4 weeks and 84.2% at 8 weeks of adjunctive aripiprazole. Furthermore, 84.6% of participants had normal prolactin ranges at 8 weeks of aripiprazole treatment, compared with only 3.6% in the placebo group (Shim 2007). Interestingly, Hoffer et al (2009) concluded in their review that aripiprazole can lower prolactin in those with both iatrogenic and tumorigenic hyperprolactinaemia.

It is important to consider the effect of adding aripiprazole on the initial antipsychotic. It is possible that it could displace other antipsychotics from the dopamine D_2 receptor, altering their effect (Hoffer 2009; Grigg 2017). Furthermore, aripiprazole itself is still linked with symptoms of sexual dysfunction, despite having the most favourable prolactin profile, and there are concerns about potential adverse effects of antipsychotic polytherapy (De Hert 2014; Grigg 2017). Comparatively, of the second-generation antipsychotics the one thought to have the lowest impact on sexual function is quetiapine (De Hert 2014).

Alternative adjuncts

If aripiprazole is not tolerated, alternative adjuncts could be discussed. The Endocrine Society explains that cautious administration of a dopamine agonist can be considered. In the case of antipsychotic use, adding a dopamine agonist may help with high prolactin effects by normalising levels (in around 75% of individuals) but this risks worsening any existing psychotic symptoms and precipitating other side-effects (Melmed 2011). These are further considered below. Grigg et al (2017) reviewed multiple global guidelines and similarly express a concern that dopamine agonists could worsen psychotic symptoms, and currently do not endorse this approach.

Other options reported in the Maudsley guidance include adjunctive metformin or peony-glycyrrhiza decoction (PGD) (Taylor 2018). PGD, a herbal remedy, has been compared with dopamine agonists and was found to have a similar effect on prolactin as bromocriptine but without exacerbating psychosis. Interestingly, a greater proportion of those on PGD showed improvement in prolactin-related side-effects (56% v. 17%) (De Hert 2014). Metformin is an emerging possibility, with some evidence suggesting a role in reducing effects such as weight gain, insulin resistance and prolactin levels; however, these emerging treatments need further study (Grigg 2017).

Grigg et al (2017) further recognise the importance of ensuring hormone balance in antipsychotic-related hyperprolactinaemia and suggest testosterone therapy to protect bone health in men who are persistently hypogonadal. In premenopausal women they suggest the oral contraceptive pill to help regulate menstrual cycles. In postmenopausal women they suggest that there may be a role for selective oestrogen-receptor modulators, again to help protect bone health.

The various adjunct options are summarised in Fig. 5.

Management of prolactinoma

Prolactinoma management does not fall naturally within the remit of psychiatrists, but the impacts of treatment on psychiatric patients are of significant importance – thus an awareness of treatments is helpful.

Dopamine agonists are the first-line treatment for prolactinoma, resulting in prolactin normalisation and symptom suppression in 90% of cases, thankfully with low doses required: as much as ten times lower than usually required in the management of Parkinson's disease (Webster 1994; Melmed 2011; Wang 2012). Monitoring includes periodic prolactin
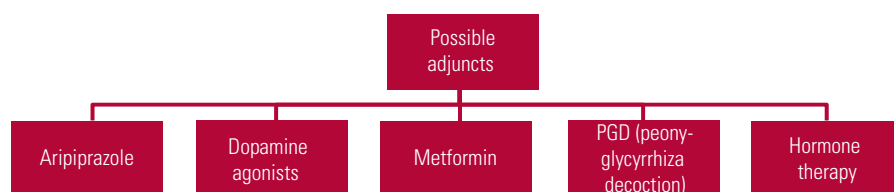
FIG 5 Summary of possible adjuncts to address hyperprolactinaemia (Shim 2007; Melmed 2011; Cookson 2012; Grigg 2017; Taylor 2018).

measurements, repeated MRI, visual field checks and comorbidity assessment. There is also the possibility of tapering and stopping the dopamine agonists after 2 years, if prolactin levels and MRI scans remain normal (Melmed 2011).

Other management options include surgical interventions and radiotherapy. However, these have comparatively poorer outcomes, carry more risk and are less cost-effective (Bloomgarden 2014). They may be used in specific circumstances, such as when dopamine agonists are contraindicated, there is treatment resistance to less invasive methods or in malignancy (Casanueava 2006; Melmed 2011; Tirosh 2015). Unfortunately, there are no biomarkers to predict whether a benign prolactinoma will progress to a malignancy. Carcinomas or aggressive pituitary adenomas should be treated at a tertiary centre by a multidisciplinary team, but these are comparatively rare diagnoses. Treatment options include radiation therapy or the chemotherapeutic alkylating agent temozolomide, particularly if conventional medical or surgical treatment has not controlled the tumour (Olarescu 2019).

Effects of prolactinoma treatments relevant to mental health

Although the adverse psychiatric effects of dopamine agonists are infrequent, especially in the low doses recommended for prolactinoma treatment, there are several that can be severe, and an awareness of their impact is crucial (Melmed 2011; Wang 2012). The key adverse effects relevant to mental health (Box 5) are as follows.

Exacerbation of psychosis

In the British National Formulary (BNF), serious mental health problems – particularly psychosis – are listed as cautions for cabergoline and bromocriptine, the two most commonly used dopamine agonists (Joint Formulary Committee 2019a, 2019b). Common side-effects of cabergoline include hallucinations and delusions, with psychotic disorder noted as a less common effect (Joint Formulary

Committee 2019a). Contrasting this, bromocriptine also has hallucinations listed as a common side-effect, but psychotic disorder and neuroleptic malignant-like syndrome are listed as rare effects (Joint Formulary Committee 2019b). Importantly, neuroleptic malignant syndrome is linked with withdrawal of bromocriptine rather than commencement (electronic medicines compendium 2018). Contextualising these risks in psychiatric patients is difficult, as many studies into dopamine agonists involve patients being treated for Parkinson's disease rather than a general population.

Impulse control disorders

Evidence suggests that people may exhibit hypersexuality, pathological gambling, compulsive overspending and compulsive eating with dopamine agonist treatment (electronic medicines compendium 2016; Grall-Bronnec 2018; Shimon 2019). Grall-Bronnec et al (2018) conducted a large systematic review that reported a prevalence of 10–25% for impulse control disorders in people being treated with dopamine agonists for prolactinoma.

From a psychiatric viewpoint it is important to note that mental illness – particularly depression with anxiety and traits of impulsivity and neuroticism – correlates with development of impulse control disorders in those being treated with dopamine agonists for Parkinson's disease or restless legs syndrome. Mixed data were also reported regarding pre-existing addiction disorders and development of impulse control disorders with dopamine agonist therapy (Grall-Bronnec 2018).

Sleep attacks

A potential side-effect of dopamine agonist treatment is the development of sleep attacks – sudden, irresistible urges to sleep – found to occur in around 6.6% of people with Parkinson's disease taking dopamine agonists (Homann 2002; electronic medicines compendium 2016). These effects occurred at both high and low doses, with different durations of treatment and across the medications in this drug class, making this side-effect difficult to predict.

Metabolic effects

In a non-psychiatric population, Auriemma et al (2013) concluded that treatment of a prolactinoma with cabergoline significantly reduced the prevalence of metabolic syndrome. This effect is believed to be due to hyperprolactinaemia being linked to glucose intolerance and the development of an impaired metabolic profile. This is positive news, as not only could psychiatrists use cabergoline to relieve troubling symptoms in patients prescribed

> **BOX 5** Potential effects of dopamine agonists relevant to mental health
>
> - Exacerbation of psychosis
> - Impulse control disorders
> - Sleep attacks
> - Metabolic effects
> - Valvular heart disease

> **BOX 6** Key practice points for mental health clinicians
>
> - Baseline prolactin level should be measured on commencement of antipsychotics
> - Where possible, choose a prolactin-sparing medication
> - Where possible, take a collaborative treatment planning approach and discuss with the patient the potential side-effects of antipsychotics, including risk of hyperprolactinaemia
>
> - Ensure adequate medication and prolactin-level monitoring to reduce physical health risks
> - When hyperprolactinaemia is evident, consider physiological, analytical and pathological differentials
> - For those receiving dopamine agonist treatment, monitor for psychiatric side-effects

MCQ answers
1 c 2 b 3 a 4 b 5 d

psychotropics, but they could also potentially reduce metabolic risk factors by responding to raised prolactin appropriately. Conversely, however, it is possible for cabergoline to cause compulsive eating, linking back to impulse control disorders (electronic medicines compendium 2016).

Valvular heart disease

A possible effect of cabergoline is the development of valvular heart disease, particularly regurgitation, with some evidence demonstrating this effect in both Parkinson's and hyperprolactinaemia patient populations (De Vecchis 2013). However, cabergoline is used in much lower doses in treating prolactinomas, and contrasting evidence reported by Melmed et al (2011) and Shimon (2019) did not suggest an association with increased risk of valvular disease in this group. Therefore, the evidence is not yet conclusive in this regard.

Conclusions

Throughout this narrative review we have considered the underlying physiology of prolactin and hyperprolactinaemia and given an overview of investigation and management options. On the basis of this we have devised the key practice points contained in Box 6. Overall, hyperprolactinaemia is a significant risk to both patient well-being and concordance with antipsychotic medication; and it is hoped that the key practice points described will help clinicians to best identify and treat abnormal prolactin levels and take a collaborative approach when making treatment decisions (Grigg 2017).

Acknowledgements

We thank the Coventry and Warwickshire Partnership NHS Trust library team for their assistance in obtaining the necessary literature for this review.

Author contributions

K.R. was the lead author on this project. Otherwise, equal contributions to the manuscript content were made by all authors.

Declaration of interest

None.

ICMJE forms are in the supplementary material, available online at https://doi.org/10.1192/bja.2020.36.

References

Joint Formulary Committee (2019a) Cabergoline. In British National Formulary Online. BMJ Publishing Group/Royal Pharmaceutical Society. Available from: https://bnf.nice.org.uk/drug/cabergoline.html#cautions [accessed 13 Jun 2019].

Abubakr A, Wambacq I (2016) Diagnostic value of serum prolactin levels in PNES in the epilepsy monitoring unit. *Neurology: Clinical Practice*, **6**: 116–9.

Ahmad A, Ijaz F, Tauseef A, et al (2019) Role of prolactin: a comparative study between grand mal epileptic and pseudo-seizures patients. *Indo American Journal of Pharmaceutical Sciences*, **6**: 11344–8.

Auriemma RS, Granieri L, Galdiero M, et al (2013) Effect of cabergoline on metabolism in prolactinomas. *Neuroendocrinology*, **98**: 299–310.

Bahar A, Akha O, Vesgari Z (2011) Hyperprolactinaemia in association with subclinical hypothyroidism. *Caspian Journal of Internal Medicine*, **2**: 229–33.

Bloomgarden E, Molitch ME (2014) Surgical treatment of prolactinomas: cons. *Endocrine*, **47**: 730–3.

Bushe C, Shaw M, Peveler RC (2008) A review of the association between antipsychotic use and hyperprolactinaemia. *Journal of Psychopharmacology*, **22**(suppl 2): 46–55.

Byerly MJ, Marcus RN, Tran Q, et al (2009) Effects of aripiprazole on prolactin levels in subjects with schizophrenia during cross-titration with risperidone or olanzapine: analysis of a randomised, open-label study. *Schizophrenia Research*, **107**: 218–22.

Casanueva FF, Molitch ME, Schlechte JA, et al (2006) Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. *Clinical Endocrinology*, **65**: 265–73.

Chen Y, Wang H, Yang W, et al (2016) A new method of using polyethylene glycol (PEG) precipitation of macroprolactin to detect genuine hyperprolactinaemia. *Journal of Clinical Laboratory Analysis*, **30**: 1169–74.

Cookson J, Hodgson R, Wildgust HJ (2012) Prolactin, hyperprolactinaemia and antipsychotic treatment: a review and lessons for treatment of early psychosis. *Journal of Psychopharmacology*, **26**(suppl 5): 42–51.

Crespo-Facorro B, Ortiz-Garcia de la Foz V, Suarez-Pinilla P, et al (2017) Effects of aripiprazole, quetiapine and ziprasidone on plasma prolactin levels in individuals with first episode nonaffective psychosis: analysis of a randomised open-label 1-year study. *Schizophrenia Research*, **189**: 134–41.

De Hert M, Detraux J, Peuskens J (2014) Second-generation and newly approved antipsychotics, serum prolactin levels and sexual dysfunctions: a critical literature review. *Expert Opinion on Drug Safety*, **13**: 605–24.

Dekkers OM, Ehrenstein V, Bengtsen M, et al (2015) Breast cancer risk in hyperprolactinaemia: a population-based cohort study and metal-analysis of the literature. *European Journal of Endocrinology*, **173**: 269–73.

De Vecchis R, Esposito C, Ariano C (2013) Cabergoline use and risk of fibrosis and insufficiency of cardiac valves: meta-analysis of observational studies. *Herz*, **38**: 868–80.

Eberhard J, Lindström E, Holstad M, et al (2007) Prolactin level during 5 years of risperidone treatment in patients with psychotic disorders. *Acta Psychiatrica Scandinavica*, **115**: 268–76.

Ecker D, Unrath A, Kassubeck J, et al (2009) Dopamine agonists and their risk to induce psychotic episodes in Parkinson's disease: a case-control study. *BMC Neurology*, **9**: 23.

electronic medicines compendium (2016) *Dostinex tablets:* SmPC. emc. Available from: https://www.medicines.org.uk/emc/product/1691/smpc [accessed 31 Dec 2019].

electronic medicines compendium (2018) *Bromocriptine 2.5mg tablets:* SmPC. emc. Available from: https://www.medicines.org.uk/emc/product/1202/smpc [accessed 31 Dec 2019].

Ferriani RA, Silva de Sá MF (1985) Effect of venipuncture stress on plasma prolactin levels. *International Journal of Gynecology and Obstetrics*, **23**: 459–62.

González-Blanco L, Greenhalgh AMD, Garcia-Rizo C, et al (2016) Prolactin concentrations in antipsychotic-naïve patients with schizophrenia and related disorders: a meta-analysis. *Schizophrenia Research*, **174**: 156–60.

Grall-Bronnec M, Victorri-Vigneau C, Donnio Y, et al (2018) Dopamine agonists and impulse control disorders: a complex association. *Drug Safety*, **41**: 19–75.

Grigg J, Worsley R, Thew C, et al (2017) Antipsychotic-induced hyperprolactinaemia: synthesis of world-wide guidelines and integrated recommendations for assessment, management and future research. *Psychopharmacology*, **234**: 3279–97.

Haddad PM, Wieck A (2004) Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs*, **64**: 2291–314.

Hoffer ZS, Roth RL, Mathews M (2009) Evidence for the partial dopamine-receptor agonist aripiprazole as a first-line treatment of psychosis in patients with iatrogenic or tumorogenic hyperprolactinaemia. *Psychosomatics*, **50**: 317–24.

Homann CN, Wenzel K, Suppan K, et al (2002) Sleep attacks in patients taking dopamine agonists: review. *BMJ*, **324**: 1483–7.

Howard L, Kirkwood G, Leese M (2007) Risk of hip fracture in patients with a history of schizophrenia. *British Journal of Psychiatry*, **190**: 129–34.

Jha SK, Kannan S (2016) Serum prolactin in patients with liver disease in comparison with healthy adults: a preliminary cross-sectional study. *International Journal of Applied and Basic Medical Research*, **6**: 8–10.

Johnston AN, Bu W, Hein S, et al (2018) Hyperprolactinaemia-inducing antipsychotics increase breast cancer risk by activating JAK-STAT5 in precancerous lesions. *Breast Cancer Research*, **20**(1): 42.

Joint Formulary Committee (2019b) Bromocriptine. In British National Formulary Online. BMJ Publishing Group/Royal Pharmaceutical Society. Available from: https://bnf.nice.org.uk/drug/bromocriptine.html#cautions [accessed 13 Jun 2019].

Kyritsi EM, Dimitriadis GK, Angelousi A, et al (2018) The value of prolactin in predicting prolactinoma in hyperprolactinaemic polycystic ovarian syndrome. *European Journal of Clinical Investigation*, **48**(7): e12961.

Lieberman JA, Stroup TS, McEvoy JP, et al (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia: CATIE trial. *New England Journal of Medicine*, **353**: 1209–23.

Majumdar A, Mangal NS (2013) Hyperprolactinemia. *Journal of Human Reproductive Sciences*, **6**: 168–75.

McCabe R, Priebe S (2008) Communication and psychosis: it's good to talk, but how? *British Journal of Psychiatry*, **192**: 404–5.

McCabe R, Healey PGT (2018) Miscommunication in doctor-patient communication. *Topics in Cognitive Science*, **10**: 409–24.

Melmed S, Casanueva FF, Hoffman AR, et al (2011) Diagnosis and treatment of hyperprolactinaemia: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*, **96**: 273–88.

Milano W, Colletti C, Capasso A (2017) Hyperprolactinemia induced by antipsychotics: from diagnosis to treatment approach. *Endocrine, Metabolic & Immune Disorders – Drug Targets*, **17**: 38–55.

Miyamoto BE, Galecki M, Francois D (2015) Guidelines for antipsychotic-induced hyperprolactinaemia. *Psychiatric Annals*, **45**: 266–72.

National Institute for Health and Care Excellence (2014) *Psychosis and Schizophrenia in* Adults: Prevention *and* Management (Clinical Guideline CG178). NICE.

Ni L, Wu J, Long Y, et al (2019) Mortality of site-specific cancer in patients with schizophrenia: a systematic review and meta-analysis. *BMC Psychiatry*, **19**(1): 323.

Olarescu NC, Perez-Rivas LG, Gatto F, et al (2019) Aggressive and malignant prolactinomas. *Neuroendocrinology*, **109**: 57–69.

Pérez-Iglesias R, Mata I, Martinez-Garcia O, et al (2012) Long-term effect of haloperidol, olanzapine, and risperidone on plasma prolactin levels in patients with first-episode psychosis. *Journal of Clinical Psychopharmacology*, **32**: 804–8.

Rand T, Kink E, Sator B, et al (1996) MRI of microadenomas in patients with hyperprolactinaemia. *Neuroradiology*, **38**: 744–6.

Riecher-Rössler A, Rybakowski JK, Pflueger MO, et al (2013) Hyperprolactinemia in antipsychotic-naive patients with first-episode psychosis. *Psychological Medicine*, **43**: 2571–82.

Saleem M, Martin H, Coates P (2018) Prolactin biology and laboratory measurement: an update on physiology and current analytical issues. *Clinical Biochemist Reviews*, **39**: 3–16.

Samperi I, Lithgow K, Karavitaki N (2019) Hyperprolactinaemia. *Journal Clinical Medicine*, **8**(12): 2203.

Sethi BK, Chanukya GV, Nagesh VS (2012) Prolactin and cancer: has the orphan finally found a home? *Indian Journal of Endocrinology and Metabolism*, **16**(suppl 2): S195–8.

Shim J, Shin J, Kelly DL, et al (2007) Adjunctive treatment with a dopamine partial agonist, aripiprazole, for antipsychotic-induced hyperprolactinaemia: a placebo-controlled trial. *American Journal of Psychiatry*, **164**: 1404–10.

Shimon I (2019) Giant prolactinomas. *Neuroendocrinology*, **109**: 51–6.

Taylor DM, Barnes TRE, Young AH (2018) *The Maudsley Prescribing Guidelines in Psychiatry* (13th edn). Wiley Blackwell.

Tirosh A, Shimon I (2015) Management of macroprolactinomas. *Clinical Diabetes and Endocrinology*, **1**: 5.

Trimble MR (1978) Serum prolactin in epilepsy and hysteria. *BMJ*, **2**: 1682.

Wang AT, Mullan RJ, Lane MA, et al (2012) Treatment of hyperprolactinaemia: a systematic review and meta-analysis. *Systematic Reviews*, **1**: 33.

Wang M, Wu X, Chai F, et al (2016) Plasma prolactin and breast cancer risk: a meta-analysis. *Scientific Reports*, **6**: 25998.

Webster J, Piscitelli G, Polli A, et al (1994) A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea: Cabergoline Comparative Study Group. *New England Journal of Medicine*, **331**: 904–9.

World Health Organization (2018) *Schizophrenia: Key Facts*. WHO. Available from: https://www.who.int/en/news-room/fact-sheets/detail/schizophrenia [accessed 2 Jun 2020].

MCQs

Select the single best option for each question stem

1 The most common neuropsychiatric effect of the dopamine agonists cabergoline and bromocriptine is:
a delusions
b pathological gambling
c hallucinations
d neuroleptic malignant syndrome
e psychotic disorder.

2 Which of the following is not a pathological cause of hyperprolactinaemia?
a pituitary stalk damage
b pregnancy
c pituitary hypersecretion
d antipsychotic medication
e systemic disorder.

3 The population thought to be at higher risk of significant adverse effects of hyperprolacti-naemia is:
a people under 25
b people under 35
c people under 45
d people under 55
e people under 65.

4 An indication for head MRI would be:
a mildly raised asymptomatic hyperprolactinaemia
b if high prolactin does not appear linked with medication
c physiological hyperprolactinaemia in pregnancy
d prescription review for antipsychotic therapy
e prescription review for antidepressant therapy.

5 Of the following medications, the one most likely to raise prolactin levels is:
a aripiprazole
b quetiapine
c asenapine
d risperidone
e clozapine.