Hyperprolactinaemia and psychotropics: endocrine effects and treatment

Hyperprolactinaemia is a common endocrine abnormality. Causes are multifactorial. Medication use contributes a considerable amount, with psychotropics often implicated, although underlying hypothalamic–pituitary pathology can co-exist. This article discusses the management of hyperprolactinaemia during psychotropic use.

Long-term psychotropic use, in addition to metabolic and cardiovascular effects, can result in endocrine alterations potentially leading to poor physical health in the mentally ill (Henderson and Doraiswamy, 2008). Hyperprolactinaemia is commonly associated with antipsychotic therapy and to a lesser extent with antidepressants. This article outlines the mechanisms, clinical consequences and management of psychotropic-induced hyperprolactinaemia. Antipsychotic-induced hyperprolactinaemia is given greater emphasis in this article because of its higher prevalence and greater clinical relevance.

Antipsychotic-induced hyperprolactinaemia

The lactotroph cells in the anterior pituitary synthesize and secrete human prolactin, controlled mostly by dopamine from the dopaminergic neurons in the hypothalamus. Dopamine exerts a tonic inhibitory effect on the pituitary lactotrophs by binding to the D_2 receptors. Any condition causing a reduction in dopamine effect undermines this tonic inhibition. Drugs like the first generation antipsychotics and some of the atypical antipsychotics suppress dopamine neurotransmission by D_2 receptor blockade in the pituitary, thereby causing increased release of prolactin.

Studies have shown that use of typical or conventional antipsychotics (e.g. phenothiazines or butyrophenones) caused hyperprolactinaemia in 40–90% of patients, while 50–100% of patients on 'newer' or atypical antipsychotics such as risperidone developed hyperprolactinaemia (Melmed et al, 2011). Prolactin often returns to normal within 3 weeks after discontinuation, depending on the type of antipsychotic drug and its half-life (Wieck and Haddad, 2002).

Antipsychotics: the potential for hyperprolactinaemia

The dopamine antagonistic effect of antipsychotics is dose-dependent, providing the basis for the concept of chlorpromazine equivalents. A linear or higher relation between dose and prolactin levels exists, irrespective of age, gender, race and reproductive age of women (Kinon et al, 2003).

The conventional antipsychotics frequently cause a significant rise in prolactin levels. They are listed in *Table 1*, with their chlorpromazine equivalents (American Psychiatric Association, 1997).

Risperidone, an atypical antipsychotic, has a greater likelihood of inducing hyperprolactinaemia than conventional antipsychotic medications. Similarly, even low doses of amisulpiride, another atypical antipsychotic, cause significant hyperprolactinaemia (Lee et al, 2012). The newer atypical antipsychotics (e.g. clozapine, olanzapine, quetiapine, ziprazidone and aripiprazole) produce little or no clinically significant hyperprolactinaemia, attributed to their lower dopamine D_2 receptor affinities (Woods, 2003).

Hyperprolactinaemia caused by antidepressants

Antidepressants with serotoninergic activity, including selective serotonin-reuptake inhibitors, monoamine oxidase inhibitors and some tricyclic antidepressants, can cause modest and mostly asymptomatic hyperprolactinaemia (Wieck and Haddad, 2003). The mechanism is not clearly understood and the data available are conflicting.

Table 1. Chlorpromazine equivalents of conventional or typical antipsychotics

Generic name	Equivalent dose (mg)
Haloperidol	2
Fluphenazine (oral)	2
Trifluoperazine	2
Thiothixene	4
Perphenazine	8
Loxapine	10
Prochlorperazine	15
Mesoridazine	50
Thioridazine	100
Chlorpromazine	100

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Hyperprolactinaemia reported with antidepressants is considerably less prevalent than that with antipsychotics. A French pharmacovigilance database analysis showed that 186 out of 11 863 (1.5%) reported users of selective serotonin-reuptake inhibitors were found to have hyperprolactinaemia as an adverse drug reaction – fluvoxamine, citalopram, fluoxetine and paroxetine were implicated (Trenque et al, 2011). Duloxetine and sertraline were not associated with a rise in prolactin levels.

A review of antidepressant-mediated hyperprolactinaemia concluded that the symptoms were rare and the routine monitoring of prolactin levels in antidepressant use was inappropriate unless symptomatic (Coker and Taylor, 2010).

Hyperprolactinaemia caused by other psychotropic drugs

Lithium, valproic acid, buspirone, carbamazepine and benzodiazepines rarely produce clinically relevant increases in prolactin levels (Marken et al, 1992).

Endocrine consequences of hyperprolactinaemia

Clinical manifestations of hyperprolactinaemia arise from the direct action of excessive prolactin on its target tissues and from the sequelae of hypogonadism secondary to hyperprolactinaemia. It is prudent to avoid prolactin-elevating antipsychotics in adolescents and young adults who are yet to reach their peak bone mass. In women planning pregnancy, an alternative should be considered because of the impact of hyperprolactinaemia on fertility.

Short-term effects of hyperprolactinaemia

Galactorrhoea and gynaecomastia

A direct effect of hyperprolactinaemia is galactorrhoea; this is a common presenting complaint in women. In men, galactorrhoea is less common, but gynaecomastia is well documented.

Hypogonadism, loss of libido and impotence

Hyperprolactinaemia inhibits the pulsatile secretion of gonadotrophin-releasing hormone, alters the pattern of follicle-stimulating hormone and luteinizing hormone secretion, and suppresses gonadal steroidogenesis. Collectively, these hormonal changes result in hypogonadism. This can result in reversible loss of libido in men and women. Erectile dysfunction in men and its relation to hyperprolactinaemia is poorly understood; however, testosterone replacement for treatment of impotence may only become effective when hyperprolactinaemia is corrected.

Infertility and amenorrhoea

Infertility can be a presenting feature of hyperprolactinaemia. In men and women, the loss of gonadotrophin-releasing hormone pulsatile secretion results in the loss of follicle-stimulating hormone, luteinizing hormone and testosterone pulsatility. The loss of normal pulsatile secretion of luteinizing hormone and follicle-stimulating hormone inhibits the mid-cycle luteinizing hormone surge in women, resulting in anovulation and amenorrhoea. The loss of pulsatile testosterone secretion results in impaired spermatogenesis, impaired sperm quality and motility, and changes in the testicular morphology similar to those observed in pre-pubertal testes.

Long-term effects of hyperprolactinaemia

Accelerated bone turnover is a common feature of physiological and pathological hyperprolactinaemia. The pathophysiology is largely related to the osteopaenic effect of hyperprolactinaemia-induced hypogonadism. Most studies confirmed oestrogen-dependent bone loss in women (Wieck and Haddad, 2003). Direct bone resorptive mechanisms may play a role, although this remains unproven. Similarly, androgen-dependent bone loss has been reported in men (Kinon et al, 2013). Osteopaenia has been found to affect both cortical and trabecular bone compartments, and progressive bone loss has been demonstrated in untreated patients.

Patients with mental illness are at higher risk for bone mineral loss irrespective of treatment (Howard et al, 2007). In these patients, co-existent hyperprolactinaemia and its impact on the hypothalamic–pituitary–gonadal axis adds to the risk. Reversal of the hyperprolactinaemic state has been associated with improvement in bone mineral density.

Diagnosis

Diagnosing antipsychotic-induced hyperprolactinaemia requires the exclusion of hypothalamic–pituitary pathology. Prolactin-secreting pituitary adenomas and non-functioning pituitary adenomas as well as non-pituitary lesions involving the sella (e.g. craniopharyngioma, Rathke's cleft cyst and parasellar meningioma causing pituitary stalk compression) can cause hyperprolactinaemia. Other endocrine conditions such as hypothyroidism or polycystic ovary syndrome, and non-endocrine causes, such as chest wall trauma, renal failure and cirrhosis, can also result in increased levels of serum prolactin.

The use of prolactin-elevating antipsychotics should prompt the clinician to enquire about galactorrhoea and breast changes, loss of libido and erectile dysfunction, and amenorrhoea, and to check prolactin level.

Serum prolactin measurements and important cut-off points

Serum prolactin measurements are assay-dependent and vary with the laboratories used. There is gender variation too, men having lower prolactin levels than women. Owing to these variations, instead of using specific result cut-off points, multiples of the upper limits of the normal range are used to ascertain clinical relevance.

Identifying the cause of the hyperprolactinaemia

1. If the prolactin level is less than twice the upper limit, repeat the test. If the prolactin level normalizes, the transient rise is likely to be physiological and no further action is necessary (Rhoden et al, 2003)
2. If the prolactin level remains elevated, consider stopping the antipsychotic for 3 days or switching to a prolactin-sparing antipsychotic and repeat the test (Melmed et al, 2011). If unable to stop or the prolactin level is unchanged after stopping, the patient must be referred for further assessment of hyperprolactinaemia, before labelling as antipsychotic-induced hyperprolactinaemia – complete pituitary function tests and magnetic resonance imaging of the pituitary gland with gadolinium contrast enhancement are often required
3. If the prolactin level is more than five times the upper limit, a hypothalamic–pituitary lesion must be excluded and a referral to endocrinology is recommended.

Management of psychotropic-induced hyperprolactinaemia

Antipsychotic medications account for the overwhelming majority of cases of drug-related hyperprolactinaemia in psychiatry. Symptomatic hyperprolactinaemia is rare with antidepressants and routine monitoring is not recommended.

Treatment considerations in antipsychotic-induced hyperprolactinaemia

There are two facets to managing the condition: measures to reduce the prolactin levels and treating the effects of hyperprolactinaemia.

Treating the hyperprolactinaemia

When pituitary pathology has been ruled out, symptomatic hyperprolactinaemia warrants treatment.

If the patient has short-term or long-term adverse effects of hyperprolactinaemia, reducing or stopping the offending psychotropic medication must be the first step. The patient's own psychiatrist must be involved in any proposed treatment change and the decision should be made with careful consideration of the potential effect on the mental health of the patient.

If such treatment change is not clinically feasible, substituting with an antipsychotic that does not induce hyperprolactinaemia may be considered. Aripiprazole, a partial dopamine agonist, deserves special mention as there is increasing evidence favouring its use as first line or as adjuvant antipsychotic therapy (Hoffer et al, 2009; Yasui-Furokori et al, 2010).

If substitution is not an effective alternative, cautious introduction of dopamine agonists can be instituted, under supervision of an endocrinologist and a psychiatrist. Cabergoline is the preferred first-line therapy; bromocriptine and less commonly quinagolide are also used. These patients should be monitored frequently for any worsening of psychotic symptoms.

Treating the effects of hyperprolactinaemia

Symptomatic hypogonadism should be treated with oestrogen or testosterone replacement. Women with amenorrhoea and subfertility will need further assessment if they wish to conceive.

Bone mineral density scanning by dual-energy X-ray absorptiometry should be offered to those with other risk factors, in addition to hyperprolactinaemia. Oestrogen replacement in hypo-oestrogenic female patients and testosterone replacement in hypogonadal men are the mainstays of therapy to treat and prevent bone loss (Haddad and Wieck, 2004). In patients with established osteoporosis, treatment includes bisphosphonates in addition to calcium and vitamin D replacement.

KEY POINTS

- Hyperprolactinaemia is common in patients taking all conventional antipsychotic medications (40–70%) and the atypical antipsychotic risperidone (50–100%).
- Hyperprolactinaemia can cause breast and gonadal effects, in addition to reduced bone mineral density in the medium to long term.
- Co-existing hypothalamic–pituitary pathology needs to be excluded if prolactin levels are repeatedly more than twice the upper limit of normal, particularly when a patient has stopped taking prolactin-elevating antipsychotic therapy.
- In confirmed antipsychotic-induced hyperprolactinaemia, the first-line approach is to substitute with prolactin-sparing antipsychotic therapy. If substitution is not possible, careful use of dopamine agonists under joint specialist monitoring should be considered.
- In hypogonadal, hyperprolactinaemic patients, oestrogen or testosterone replacement can be beneficial, not only for hypogonadism but also for preserving bone mineral density.

Conclusions

Hyperprolactinaemia often goes undetected in patients who are on psychotropic medications, as the symptoms can be subtle and not often discussed during clinical consultations. Hyperprolactinaemia can adversely impact on the physical health and quality of life of mentally ill patients. Clinicians should be more aware of antipsychotic-induced hyperprolactinaemia, especially given the availability of prolactin-sparing antipsychotics. Appropriate investigations and effective management can reduce the burden of adverse effects and prevent long-term consequences. Psychiatrists, GPs and endocrinologists need to work closely together to provide the best possible care for these patients. **BJHM**

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