Sussex Partnership NHS
NHS Foundation Trust

# Guidance on the Treatment of Antipsychotic Induced Hyperprolactinaemia in Adults

# Version 1

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| GUIDELINE NO | |
| RATIFYING COMMITTEE | DRUGS AND THERAPEUTICS GROUP |
| DATE RATIFIED | April 2014 |
| DATE AVAILABLE ON INTRANET | |
| NEXT REVIEW DATE | April 2016 |
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## 1.0 Introduction

Prolactin is a hormone which is secreted from the lactotroph cells in the anterior pituitary gland under the influence of dopamine, which exerts an inhibitory effect on prolactin secretion[1].

A reduction in dopaminergic input to the lactotroph cells results in a rapid increase in prolactin secretion. Such a reduction in dopamine can occur through the administration of antipsychotics which act on dopamine receptors (specifically $D_2$) in the tuberoinfundibular pathway of the brain[2]. The administration of antipsychotic medication is responsible for the high prevalence of hyperprolactinaemia in people with severe mental illness[1]. Prolactin secretion is also controlled, but to a lesser extent, by thyrotropin- releasing hormone (TRH) [3].

| The normal range of prolactin is[4]: | | |
|---|---|---|
| Male: 0 - 424 mIU/L | (0-20 ng/ml) | |
| Female: 0 - 530 mIU/L | (0-25 ng/ml) | (not-pregnant or breast-feeding). |

Note that choice of antipsychotic should be based on the consideration of many factors and not just incidence of hyperprolactinaemia – eg. indication / efficacy, full side effect profile and patient choice (where appropriate).

## 2.0 Causes of Hyperprolactinaemia

There are many causes of hyperprolactinaemia, including the ones listed below (Table 1). The scope of this guideline will concentrate on antipsychotic induced hyperprolactinaemia.

| **Physiological causes** | **Pharmacological causes** | **Pathological causes** |
|---|---|---|
| (non-exhaustive list) | (non-exhaustive list) | (non-exhaustive list) |
| • Stress (Including poor venepuncture technique)<br>• Pregnancy<br>• Lactation<br>• Macroprolactin (Larger molecular forms of prolactin with no biological or pathological significance which may be detected in some assays) | • Antipsychotics<br>• Dopamine-receptor blockers<br>  o Metoclopramide<br>  o Domperidone<br>  o Cimetidine<br>• Antidepressants<br>  o Imipramine<br>  o Amitriptyline<br>  o Clomipramine<br>• Antihypertensives<br>  o α-methyldopa<br>  o Reserpine<br>• Oestrogens<br>• Opioids<br>• Calcium-channel blockers<br>  o Verapamil | • Microprolactinoma<br>• Macroprolactinoma<br>• Acromegaly<br>• Idiopathic<br>• Sarcoidosis<br>• Tuberculosis<br>• Cushing's disease<br>• Primary hypothyroidism<br>• Chronic renal failure<br>• Cirrhosis<br>• Untreated Parkinson's Disease |

Table 1: Causes of hyperprolactinaemia[3]

### 3.0 Antipsychotic Association with Hyperprolactinaemia

All antipsychotics have the potential to raise prolactin. All typical antipsychotics are associated with hyperprolactinaemia to varying degrees. Of the atypicals, the highest prevalence is with risperidone. It has been reported that 48%–93% of premenopausal women and 42%–47% of men taking antipsychotic medications have hyperprolactinemia[3]. The effect of antipsychotics on prolactin appears to be dose-related.

| Drug | Effect on Prolactin Levels |
|---|---|
| Amisulpride/Sulpiride | ++ / +++ |
| Aripiprazole | - |
| Clozapine | - |
| Olanzapine | + |
| Quetiapine | - / + |
| Paliperidone | ++ / +++ |
| Risperidone | ++ / +++ |
| Typical antipsychotics<br>• Thioxanthenes (Flupentixol, Zuclopenthixol) | +++<br>• Increase of prolactin 2-3 fold during the 1st month with reduction and normalisation after 6 months |
| • Phenothiazines (Chlorpromazine, Fluphenazine, Pipotiazine Trifluoperazine) | • 2-3 fold increase occurs within hours of treatment initiation with further 2 fold elevation in the following weeks |
| • Butyrophenones (Haloperidol) | • Similar to phenothiazines |

Key:

- = Very low elevation

+ = Low elevation

++ = Moderate elevation

+++ = High elevation

Table 2: Antipsychotic Effect on Prolactin[3,4,5]

The increase of prolactin can begin as early as a few hours after a dose and persists during the rest of the treatment, the total effect depending on therapy duration. In treatments of 3–9 weeks, the prolactin levels have been found to increase up to 10-fold from baseline, while during long-term treatment, partial tolerance may lead to prolactin normalization, though after long-term therapy prolactin levels remain above normal in most cases[1].

## 4.0 Effects of Hyperprolactinaemia [1,2]

Hyperprolactinaemia is often superficially asymptomatic and may well not affect the quality of life but persistent elevation of prolactin levels is associated with a number of adverse consequences.

| Male | Both sexes | Female |
|---|---|---|
| Diminished ejaculate volume | Loss of libido or sexual dysfunction | Oligorrhoea or Amenorrhea |
| Oligospermia | Galactorrhoea | Atrophic changes in vaginal mucosa |
| Gynaecomastia | Infertility | Reduced vaginal lubrication |
| | | Dyspareunia (pain during sexual intercourse) |
| | | Acne and hirsutism |

Table 3: Acute effects of Hyperprolactinaemia[3]

## 5.0 Long Term Complications of Hyperprolactinaemia[3]

### 5.1 Sexual Developments in Adolescents

Elevated serum prolactin inhibits the hypothalamus' pulsatile release of gonadotrophin-releasing hormone (GnRH), which in turn decreases the pituitary's secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH are important determinants of male and female gonadal maturation by their direct action on testes and ovaries within the hypothalamic-pituitary-gonadal axis. Therefore children and adolescents on prolactin elevating antipsychotics may have problems such as delayed sexual maturation or reduced bone growth because of hypothalamic-pituitary-gonadal axis (HPG) dysfunction.

### 5.2 Osteoporosis [6,7,8,9,10,11]

Osteoporosis is defined by the World Health Organization as a bone mineral density of more than 2.5 standard deviations below the mean value for peak bone mass in young adults when measured by dual-energy X-ray absorptiometry (DEXA).

Suppression of the gonadal axis appears to be one of the main mechanisms behind the development of osteoporosis with hyperprolactinaemia, though other factors such as the inhibitory effect of prolactin on osteoblasts may also be involved. It is established that hyperprolactinaemia causes suppression of the reproductive endocrine axis and consequent bone mineral density (BMD) loss. The propensity of antipsychotic agents to cause hyperprolactinaemia is related to their potency in antagonising DA-2 receptors on the anterior pituitary.

The patients greatest at risk are young women pre-puberty, due to HPG dysfunction (as mentioned above). Peak bone mass does not occur until a person's mid-20s

therefore an antipsychotic affecting this process and prescribed before this age could have significant long-term implications.

Bone strength is largely determined by calcium content and rate of bone loss, which in turn is determined by genetic factors, weight, ethnicity, diet, exercise, hormone status and gender.

A woman who is amenorrhoeic as a result of hyperprolactinaemia is more at risk of compromised bone mineral density (BMD) than someone who is not amenorrhoeic despite the hyperprolactinaemia, because amenorrhoea indicates very low levels of oestrogen. The longer the duration of the amenorrhoea, the greater the BMD loss.

For men, the indicator of an increased risk of compromised BMD is the presence of sexual dysfunction together with low testosterone and low gonadotrophin levels. Women with amenorrhoea and men with sexual dysfunction plus low testosterone that has been present for 3 to 6 months or more should be referred for further investigation.

Studies have reported that 25%–65% of patients with schizophrenia suffer from bone loss after taking antipsychotic drugs. Bone fractures in people with schizophrenia taking antipsychotics also occur more frequently than in the non-psychiatric population. Other established factors that can contribute to the high rates of osteoporosis in people with schizophrenia are high alcohol intake, cigarette smoking, and metabolic syndrome.

Normalisation of serum prolactin prevents further bone loss, however BMD never returns to normal.

It is encouraged that patients are provided with information on the importance of a well-balanced diet with appropriate intake of calcium and vitamin D, weight-bearing exercise, smoking cessation, limiting caffeine and alcohol intake, and ensuring adequate exposure to sunlight. In addition to monitoring BMD, bisphosphonates may be used as a preventive measure in patients at high risk for osteoporosis. Vitamin D therapy is also recommended in patients suffering from a decrease of bone mineral density. A prophylactic addition of vitamin D to the treatment of patients with schizophrenia who suffer from vitamin D deficiency could be considered to avoid loss of bone mineral density.

### 5.3 Breast Cancer

There is conflicting data on whether hyperprolactinaemia is a contributory factor in breast cancer. Some studies suggest that raised prolactin may have an aetiological role in breast cancer, whilst others have reported no increased risk. Furthermore, hyperprolactinaemia, is often associated with hypogonadism, which may protect against breast and prostate cancer. It seems likely that most people receiving antipsychotics will not develop cancer as a result of the drug and any potential risk should be balanced against the therapeutic benefits of the drugs.

## 6.0 Monitoring & Baseline Prolactin Levels

A baseline prolactin level should be taken prior to initiation of antipsychotics known to cause hyperprolactinaemia, as in some instances even a single dose can elevate prolactin[3].

Measuring a baseline prolactin level, and finding it is normal, can often prevent an MRI of the pituitary at a later stage if hyperprolactinaemia were to occur.

Thyroid function should be determined before initiation of antipsychotics and again if symptoms consistent of hyperprolactinaemia occur as prolactin is partly controlled by TSH as mentioned above[3].

Renal function should also be determined, as patients with renal insufficiency may have moderate hyperprolactinaemia caused by impaired renal degradation of prolactin and altered central prolactin regulation[3].

Levels of mild hyperprolactinaemia (up to about 1000mU/L) should have at least one repeated blood test before referral, assuming it is not drug related. In cases of only modest hyperprolactinaemia when the prolactin level remains persistently elevated and no cause is identified, pituitary imaging is indicated[3].

For levels > 1000mIU/L, taken prior to the initiation of any antipsychotic, the patient should be referred to an endocrinology department.

For levels >3000mIU/L (at any stage), the patient should be referred to endocrinology as such raised levels may indicate a prolactinoma.

## 7.0 Management of Hyperprolactinaemia

The diagnosis of hyperprolactinaemia should not be made based on a single blood test as stress can also elevate prolactin levels (as mentioned above), therefore venepuncture itself can sometimes result in high levels (usually <1000mU/L).

The ideal conditions for measuring prolactin levels are in the morning at least 1 hour after waking and before eating[3].

In cases where the patient has an elevated prolactin level which is due to antipsychotic treatment and where physiological causes have been ruled out, follow the suggested management steps below.

**Management Steps**[5,14,15]

- If the prolactin is raised but the patient is asymptomatic, continue antipsychotic and monitor for symptoms. Inform the patient and be aware of long term complications.
- If the prolactin is raised and the patient is symptomatic consider:
    1. A dose reduction or withdrawal of the antipsychotic
    2. Substitution of the current antipsychotic with one with a lower potential to elevate prolactin (See table 2). However, consider full profile of replacement drug to ensure benefits of the change exceed any new associated risk.
    3. If the above are not feasible, consider low dose aripiprazole as an add in to treat the hyperprolactinaemia
    4. If neither the above are appropriate, consider the cautious administration of dopamine agonists (they have the potential to worsen psychosis – see below for more information)

In a patient with suspected drug induced hyperprolactinaemia, where a baseline prolactin level was not obtained, consider stopping the antipsychotic, if appropriate, for 72 hours followed by re-measurement of the prolactin level[14,15].

If the raised prolactin does not coincide with therapy initiation, or the drug cannot be discontinued it is recommended to obtain a pituitary magnetic resonance image (MRI) to differentiate between medication-induced hyperprolactinaemia and symptomatic hyperprolactinaemia due to a pituitary or hypothalamic mass[15].

In cases where management step 2 (above) is followed and the causative antipsychotic is substituted, it is recommended to assess the side effects of the substituting drug. In some cases the risks may outweigh the benefits.

## 8.0 Pharmacological Treatment of Hyperprolactinaemia

The primary goal of therapy in patients with hyperprolactinaemia is to restore gonadal and sexual function, to prevent inappropriate lactation and bone demineralization from inadequate sex steroids by normalising prolactin concentration levels[15].

Only in cases where the causative agent cannot be reduced in dose, discontinued or switched to an alternative, should pharmacological treatment be employed.

### 8.1 Treatment with Aripiprazole

Before add-on therapy is considered, aripiprazole monotherapy should be evaluated and tried where possible.

There are a few studies which have demonstrated the effectiveness of aripiprazole as an add-on to normalise prolactin levels [5,16,17,18,19].

The evidence for this unlicensed indication is still incomplete, and therefore aripiprazole should not routinely be used in this way. However it might be a consideration for patients in whom the risks of switching to an alternative antipsychotic with a lower potential to raise prolactin are significant, and where the risks of maintaining a raised prolactin are also high.

In this instance, a risk benefit decision needs to be carefully considered on an individual patient basis. Combination antipsychotic treatment may increase the risk of other side effects and is likely to warrant the need for “high-dose” monitoring (See Trust Guidance on the use of antipsychotics).

It is also important to note that due to the partial agonism by aripiprazole at $D_2$ receptors, it has a very high affinity for these receptors. This can lead to competitive receptor occupancy and a reduced effectiveness of the original antipsychotic.

**Recommended Dose and Monitoring**

The dose of aripiprazole is 5mg with prolactin levels measured weekly to ascertain benefit. Higher doses than 5mg appear unnecessary[19]. If prolactin levels do not appear to be normalising after 4 weeks of treatment aripiprazole should be discontinued.

### 8.2 Treatment with Dopamine Agonists

Whether to treat a patient who has antipsychotic induced hyperprolactinaemia with a dopamine agonist remains controversial. Some studies suggest that dopamine agonist therapy will normalise prolactin levels in only up to 75% of such patients but may lead to exacerbation of the underlying psychosis[22,23,24].

The dopamine agonists available and licensed for use are bromocriptine, cabergoline (both ergot derived) and quinagolide (non ergot-derived). Of these, cabergoline should be used as first line in preference to other dopamine agonists because it has higher efficacy in normalizing prolactin levels and has a lower incidence of unpleasant side effects[14]. It also has a longer half life therefore it can be administered only once or twice a week.

Should the patient not tolerate or respond to cabergoline, bromocriptine should be used as second line. However, bromocriptine is generally considered to be contra-indicated in severe psychotic disorders[26].

Amantadine is a weak dopamine agonist which has been used to treat hyperprolactinaemia[24]. It is unlicensed for this indication, and perhaps has been used less. It is not contra-indicated in psychotic illness, but its use should be used with caution.

Quinagolide should only really be considered third line.

Prolactin levels should be measured a month after starting treatment with a dopamine agonist and monthly thereafter.

**Recommended Doses:**

- Cabergoline: 250 - 500 micrograms weekly as a single dose or as 2 divided doses on separate days. Increased at monthly intervals in steps of 500 micrograms until optimal response is achieved. Dose rage of 0.25-2mg weekly; (doses up to 4.5mg weekly have been used in hyperprolactinaemic patients)[25]
- Bromocriptine: 1-1.25mg at bedtime, increased gradually to 5mg every 6 hours[25]
- Quinagolide: 25 micrograms at bedtime for 3 days. Increased at intervals of 3 days in steps of 25 micrograms. Usual maintenance dose of 75-150micrograms daily [25]
- Amantadine: 100 mg/day for the first week. This can be increased by 100 mg weekly until a dose of 200-300 mg/day is reached. Max.400mg daily[25]

**The advice of a specialist should be sought whenever treatment with a dopamine agonist is considered**.

**Side effects and Cautions[25]:**

- Side effects: Nausea, constipation and headache are common. For a full list of side effects, please consult the manufacturer's leaflet.

- Cautions: **All dopamine agonists have the potential to worsen psychosis.**
- Cabergoline and bromocriptine should be used with caution in patients with a history of peptic ulcer.
- **Cabergoline and bromocriptine have been associated with fibrotic reactions.**

**Fertility and Pregnancy:**

- Successful treatment of hyperprolactinaemia in women of child-bearing age will restore periods and increase fertility.
- Informing patients of this is necessary, as contraception may be required.
- If a client is to become pregnant, their treatment with a dopamine agonist will need to be reviewed by their endocrinologist.

### 8.3 Treatment with Oestrogen and Testosterone

In patients with long term hypogonadism symptoms or bone loss, the use of oestrogen in women in the form of HRT or combined oral contraceptive, and exogenous testosterone in men can be considered. This should only be considered in conjunction with specialist advice [5,15,20.]

### 8.4 Herbal Remedies

Peony-glycyrrhiza decoction (PGD) in a small number of cases has been shown to be effective in reducing drug induced hyperprolactinaemia in patients with schizophrenia[26]. The data is limited, and therefore this herbal remedy should be used with caution.

Peony-glycyrrhiza decoction is not on the Trust Formulary and therefore is not available from pharmacy.

PGD is a mixture of Peony *(Paeonia lactiflora)* and Licorice *(Glycyrrhiza glabra)*. Interactions with drugs do exist, the most significant one being with warfarin.[20,26,27]. PGD may also interact with certain diseases or conditions such as bleeding disorders or heart disease[27].

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