

CLINICAL GUIDELINE

Guidance on Management of Antipsychotic Induced Hyperprolactinaemia

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Version History

Version	Date Issued	Reason for Change
V1	05/11/2020	Implementation of New Guideline
V2	31/01/2024	Information rearranged and edited to aid reading. Updated monitoring in line with latest guidance. Minor wording changes for clarity and addition of special consideration for older people

SUMMARY

This guideline aims to provide a comprehensive guidance on identification, investigation, monitoring and management of Hyperprolactinaemia induced by Antipsychotics.

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ABBREVIATIONS

<i>Abbreviation</i>	<i>Full Description</i>
GHC	Gloucestershire Health and Care NHS Foundation Trust
CAMHS	Child and Adolescent Mental Health Services
LD	Learning Disability
FSH	Follicle Stimulating Hormone
LH	Luteinising Hormone

1. INTRODUCTION

Hyperprolactinaemia is one of the side effects of antipsychotics prescribed in Mental Health and Learning Disability Services with significant short and long term impacts on physical health. It is therefore important for clinicians to be aware of the physical morbidities and therefore recognise the importance of identifying the symptoms, investigating, managing the symptoms or consider alternatives and when referral to Endocrinology would be indicated. This is the first guideline produced for the Trust.

2. PURPOSE

To provide guidance on management of hyperprolactinaemia induced by antipsychotics.

3. SCOPE

The guideline provides guidance and information to medical and non-medical prescribers who provide care to patients and service users who are prescribed antipsychotics.

4. DUTIES

4.1 General Roles, Responsibilities and Accountability

Gloucestershire Health and Care NHS Foundation Trust (GHC) aims to take all reasonable steps to ensure the safety and independence of its patients and service users to make their own decisions about their care and treatment.

In addition, **GHC** will ensure that:

- All employees have access to up to date evidence based policy documents.

- Appropriate training and updates are provided.
- Access to appropriate equipment that complies with safety and maintenance requirements is provided.

Managers and Heads of Service will ensure that:

- All staff are aware of, and have access to policy documents.
- All staff access training and development as appropriate to individual employee needs.
- All staff participate in the appraisal process, including the review of competencies.

Employees (including bank, agency and locum staff) must ensure that they:

- Practice within their level of competency and within the scope of their professional bodies where appropriate.
- Read and adhere to GHC policy
- Identify any areas for skill update or training required.
- Participate in the appraisal process.
- Ensure that all care and consent complies with the Mental Capacity Act (2005) – see section on [MCA Compliance below](#).

5. MENTAL CAPACITY ACT COMPLIANCE

Where parts of this document relate to decisions about providing any form of care treatment or accommodation, staff using the document must do the following: -

- Establish if the person able to consent to the care, treatment or accommodation that is proposed? (Consider the 5 principles of the Mental Capacity Act 2005 as outlined in section 1 of the Act. In particular principles 1,2 and 3) [Mental Capacity Act 2005 \(legislation.gov.uk\)](#).
- Where there are concerns that the person may not have mental capacity to make the specific decision, complete and record a formal mental capacity assessment.
- Where it has been evidenced that a person lacks the mental capacity to make the specific decision, complete and record a formal best interest decision making process using the best interest checklist as outlined in section 4 of the Mental Capacity Act 2005 [Mental Capacity Act 2005 \(legislation.gov.uk\)](#).
- Establish if there is an attorney under a relevant and registered Lasting Power of Attorney or a deputy appointed by the Court of Protection to make specific decisions on behalf of the person (N.B. they will be the decision maker where a relevant best interest decision is required. The validity of an LPA or a court order can be checked with the Office of the Public Guardian) [Office of the Public Guardian - GOV.UK \(www.gov.uk\)](#).
- If a person lacks mental capacity it is important to establish if there is a valid and applicable Advance Decision before medical treatment is given. The Advance Decision is legally binding if it complies with the MCA, is valid and applies to the specific situation. If these principles are met it takes precedence over decisions made in the persons best interests by other people. To be legally binding the person must have been over 18 when it was signed and had capacity to make, understand and communicate the decision. It must specifically state which medical treatments and in which circumstances the person refuses and only these must be considered. If a patient is detained under the Mental Health Act 1983 treatment can be given for a psychiatric disorder.
- Where the decision relates to a child or young person under the age of 16, the MCA does not apply. In these cases, the competence of the child or young person must be considered

under Gillick competence. If the child or young person is deemed not to have the competence to make the decision then those who hold Parental Responsibility will make the decision, assuming it falls within the Zone of Parental control. Where the decision relates to treatment which is life sustaining or which will prevent significant long-term damage to a child or young person under 18 their refusal to consent can be overridden even if they have capacity or competence to consent.

6. GUIDELINE DETAIL

Background

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

Plasma Prolactin elevation is linked to D2/D3 blockade and antipsychotics vary in their propensity for blocking these receptors. A reduction in dopaminergic input to lactotroph cells which is responsible for prolactin secretion will result in a rapid rise in prolactin level. Hyperprolactinaemia is defined as level of prolactin above the normal range. Sustained hyperprolactinaemia can have significant physical morbidities in the short term such as reduced fertility and sexual dysfunction and long-term osteoporosis even if asymptomatic and therefore requires identification, monitoring and management.

Causes of Hyperprolactinaemia

There are many causes of hyperprolactinaemia, including physiological, pathological and pharmacological. The scope of this guideline will only cover hyperprolactinaemia induced by antipsychotics.

These lists are not exhaustive ¹

Physiological	Pathological	Pharmacological
Pregnancy Lactation Stress Poor venepuncture technique Macroprolactin (prolactin aggregates with no active biological consequences)	Hypothyroidism Prolactinoma Chronic Renal Failure Polycystic Ovary Syndrome Liver Disease Other pituitary or hypothalamic tumours/lesions	Antipsychotics Antidepressants Opiates Dopamine Receptor Blockers e.g. metoclopramide Antihypertensive e.g. calcium channel blockers Proton-Pump Inhibitors High Dose Oestrogen

Consequences of Hyperprolactinaemia ^{2,3}

Asymptomatic hyperprolactinaemia is common and if service users are symptomatic, they may not link those to their medications or be too embarrassed to mention them. There can be short term symptoms and possibly long-term health consequences to hyperprolactinaemia and therefore important for clinicians to check for those.

Symptoms

In females:

- Oligomenorrhoea/amenorrhoea
- Galactorrhoea (when not pregnant or breast feeding)
- Vaginal dryness
- Acne
- Hirsutism

In males:

- Erectile dysfunction
- Decreased body and facial hair
- Gynaecomastia

In both sexes:

- Low bone density
- Reduction in other pituitary hormone production
- Decreased libido
- Headaches
- Visual disturbances
- Infertility

In children:

- Growth failure
- Delayed puberty

Potential Long Term Consequences¹²**• Osteoporosis**

Suppression of gonadal function is the main mechanism behind the development of osteoporosis in hyperprolactinaemia. Low levels of oestrogen and testosterone leading to low bone density increases the risks of fracture in both men and women. This is significant in those who have not reached their peak bone mass (under the age of 25) and careful consideration of antipsychotics and monitoring is essential as this process can be reversible and may have a partial restoration in bone mass even in those who have been hypogonadal for a long time. Amenorrhoea as a result of hyperprolactinaemia in women indicates a very low level of oestrogen compared to women who have hyperprolactinaemia and are menstruating. For men, sexual dysfunction and a low level of morning testosterone level is an indicator for compromised bone density mass. Amenorrhoeic women and men with low testosterone should be referred for investigations. There are other factors which affect the bone mass and service users should be given advice on sufficient diet for calcium, vitamin D and associated sunlight exposure, smoking cessation and exercise, weight management and intake of alcohol.

• Cancers / Tumours

There has been conflicting evidence on the link between Hyperprolactinaemia and Breast Cancer. In addition, hypogonadism is associated with lower risk of prostate and breast cancer and so hyperprolactinaemia could potentially be acting as a protective factor. Clinicians are advised to consider the benefits of antipsychotics against the insufficient evidence on risk of cancer when initiating and reviewing antipsychotics.

CAMHS Considerations:

- Due to developmental physiological changes that occur in childhood, children may be more susceptible to antipsychotic adverse effects than adults.
- Children who have diagnoses of autism and LD have an even greater propensity to experience adverse effects from antipsychotics.

Long Term Consequences in Children

Delayed Sexual Development in Adolescents

- Elevated serum prolactin inhibits the release of gonadotrophin-releasing hormone (GnRH) and thereby reduces the secretion of follicle stimulating hormone (FSH) and luteinising hormone (LH) from the pituitary.
- FSH and LH are important determinants of male and female gonadal maturation by their action on the testes and ovaries of the male and female.
- Hyperprolactinaemia in children and adolescents may therefore result in delayed sexual maturation or reduced bone development due to the dysfunction in the hypothalamic pituitary gonadal axis.

Antipsychotic Use in Children and Adolescents:

- Should antipsychotic use be likely to be long term, greater than 6 months in a growing young person, then an antipsychotic with a low potential risk of causing hyperprolactinaemia should be considered as a first line strategy.
- Two studies ^{7,8} have shown that Risperidone can elevate prolactin to a greater extent and more frequently than other second-generation antipsychotics in paediatric populations.
- Consideration of the use of antipsychotics long term in under 18-year-olds and the implications of potential hyperprolactinaemia must be communicated to the family and/or patients (if appropriate).

Antipsychotics and Hyperprolactinaemia

There is a huge variation between antipsychotics and prevalence of Hyperprolactinaemia. All first-generation antipsychotics and some second-generation antipsychotics are more likely than some to cause a rise in prolactin level. The extent of the prolactin level is related to the degree of D2 receptor occupancy and the degree of the rise in prolactin appears to be dose dependent. The rise in prolactin level after administration can occur within a few hours and the level usually starts to reduce within 3 days of stopping the antipsychotics and should be back within normal range within 3 weeks of cessation. For long acting/depot antipsychotics, levels may not return to normal for many months.

Antipsychotics Effect on Prolactin^{4, 5}

Drug	Effect on Prolactin
Amisulpride/Sulpiride	++ / +++
Aripiprazole	-
Clozapine	-
Lurasidone	+
Olanzapine	+
Quetiapine	- / +
Risperidone/Paliperidone	++ / +++
Thioxanthenes (Flupentixol, Zuclopenthixol)	+++ 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
Haloperidol	+++ Similar to phenothiazines

Initiation of antipsychotics (Baseline)

- A menstrual history when applicable should be taken and plans for pregnancy. A specific history about sexual function in men and women is important to establish a baseline.
- A baseline prolactin level, if possible, should be taken prior to initiation of an antipsychotic known to cause hyperprolactinaemia, as in some cases even a single dose can elevate prolactin levels.
- This can be done with other baselines tests such as thyroid function and renal function as prolactin level is partly controlled by TSH (Thyroid Stimulating Hormone) and renal insufficiency can result in reduced degradation of prolactin causing hyperprolactinaemia.

Sampling

- Avoid excessive stress during venepuncture which is one of the commonest causes of false elevations.
- Ideally samples should be collected at least 1 hour after waking and before eating as there can be a transient increase in response to food.
- If levels are higher than those explained by stress, taken prior to the initiation of any antipsychotic, then consider a referral to endocrinology.
- The baseline result may be influenced by previous antipsychotic use, if there is no gap in treatment. The morning dose should be omitted before the test if possible.

Diagnosis of Hyperprolactinaemia

- Usually based on a blood test showing an elevated prolactin level, or a high level together with symptoms. Factors outlined above need to be considered.
- The reference range should be <700 mIU/L
- 95% of female patients will have a prolactin result of <500 mIU/L and 95% of male patients will have a prolactin results of <325 mIU/L. Results of 500 - 700 mIU/L for female patients and 325 - 700 mIU/L for male patients are rarely pathological and are likely due to stress of venepuncture.

Monitoring

- Consider the choice of antipsychotics and their impact on Prolactin (table), whenever possible and appropriate, a baseline prolactin level should be completed.
- Once antipsychotics have been used for 3 months at a stable dose, an assessment for symptoms of hyperprolactinaemia should be completed including serum Prolactin level (or sooner if symptomatic). Assessment of symptoms should be repeated regularly, and serum level taken if hyperprolactinaemia is suspected thereafter.

Children and Adolescents:

- A repeat serum prolactin should be done at 3 months even if asymptomatic and every 6 months.
- If there are dose increases, prolactin levels should be repeated after 3 months.

Management of Hyperprolactinaemia¹⁵

- A thorough assessment to rule out other causes of raised prolactin levels.
- If prolactin is raised, but the patient is asymptomatic, continue with the antipsychotic and continue to monitor for symptoms and ensure that the patient is aware of long term complications.
- If prolactin is raised and the patient is symptomatic there are options to consider:

1. Reduce the dose or withdraw the antipsychotic

Certain antipsychotics are more prone to causing hyperprolactinaemia (see table 1), sensitivity varies between patients and this can be a dose-related effect. Therefore, wherever possible, consider reducing the dose of the antipsychotics raising prolactin levels. This may be associated with a risk of relapse therefore collaborative discussion with the patient of risk vs benefit is important.

2. Substitution of the antipsychotic

With one that has a lower potential to elevate prolactin. Studies show significant improvement of symptoms and normalisation of prolactin levels within a few weeks. The unpredictability of antipsychotic response to the change in drug needs to be considered.

3. Addition of low dose Aripiprazole

- Aripiprazole is a partial agonist at the D2/D3 receptors in the pituitary gland, it does not usually increase prolactin levels and tends instead to lower them.
- Before add on therapy is initiated, monotherapy with Aripiprazole should be considered.

- Note that Aripiprazole is not licensed for treating hyperprolactinaemia.
- The recommended dose can be 2.5 mg – 5 mg/day. Higher doses are not recommended for this indication and they might increase the risk of other side effects and lead to combinations constituting high dose antipsychotic therapy.
- If prolactin levels do not normalise after 4 weeks of treatment, Aripiprazole should be discontinued.
- When Aripiprazole augmentation has been successful, consider slowly reducing the dose of the antipsychotic raising prolactin levels if clinically appropriate.

4. Addition of Dopaminergic drugs

Treatment of hyperprolactinaemia with dopaminergic drugs such as Cabergoline, Bromocriptine or Amantadine is not usually advised and remains controversial. While this remains an option for those who need to remain on an antipsychotic and other options of managing the hyperprolactinaemia have failed, discussion with Endocrinologists and Pharmacists is recommended before treatment commences and acknowledge the risk of potentially worsening of psychosis.

5. Treatment with Hormones such as Oestrogen and Testosterone

Use of Oestrogen replacement in the form of HRT (Hormone Replacement Therapy) and oral contraceptive and exogenous Testosterone can be considered after consultation with specialists.

6. Metformin

A reduction in prolactin levels was achieved by taking high daily doses (2.5-3g) of Metformin in a study of diabetic women on antipsychotic medication.¹¹

7. Referrals to Endocrinologists:

Situations where a referral to Endocrinology may be considered:

- Unexplained prolactin level above 2500mIU/L
- Low testosterone/ undetectable LH/FSH
- Hyperprolactinaemia associated with symptoms suggestive of a pituitary lesion such as headache, visual disturbances etc. or other endocrinological problems.
- Persistent hyperprolactinaemia despite interventions
- Child / adolescent who cannot switch to prolactin sparing antipsychotic or not responding to antipsychotic dose reduction.

8. Learning Disability Consideration

1. In line with STOMP (stopping overmedication in people with learning disabilities), all antipsychotic use should be considered carefully before initiation including condition under which it is prescribed for, regular reviews to assess needs to continue treatment and alternatives if appropriate.
2. Capacity to consent to and cooperation with blood monitoring may require flexible approach when interpreting this guideline, where appropriate the Mental Capacity Act (MCA) principles should be followed.
3. Clinicians may need to actively ask about symptoms associated with hyperprolactinaemia due to impaired communication and possible lack of understanding of normal bodily functions.

8. Later Life Consideration

1. The evidence for some of the health risks is less clear in older patients but osteoporosis is a major concern, and it may be difficult to ascertain whether or not some relatively nonspecific symptoms are caused by hyperprolactinaemia – so, when reviewing patients on antipsychotic drugs, there should be a high index of clinical suspicion.
2. For patients without dementia who are expected to be, or have been, on antipsychotic drugs for at least one year, management should be the same as for younger patients.
3. For patients with dementia, a judgement should be made about whether to measure prolactin levels, considering expected lifespan, the previous and expected length of antipsychotic therapy and the stress/distress of venepuncture. (Consider whether blood samples are going to be taken for other purposes).

7. **PROCESS FOR MONITORING COMPLIANCE**

Are the systems or processes in this document monitored in line with national, regional, trust or local requirements?	NO
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8. **INCIDENT AND NEAR MISS REPORTING AND REGULATION 20 DUTY OF CANDOUR REQUIREMENTS**

To support monitoring and learning from harm, staff should utilise the Trust's Incident Reporting System, DATIX. For further guidance, staff and managers should reference the [Incident Reporting Policy](#). For moderate and severe harm, or deaths, related to patient safety incidents, Regulation 20 Duty of Candour must be considered and guidance for staff can be found in the [Duty of Candour Policy](#) and Intranet resources. Professional Duty of Candour and the overarching principle of 'being open' should apply to all incidents.

9. **TRAINING**

Medical and Non-medical prescribers should follow their professional development plans to maintain their registration.

10. **REFERENCES**

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