PROLACTIN AND ANTIPSYCHOTIC DRUG THERAPY: GUIDELINES FOR MANAGEMENT OF HYPERPROLACTINAEMIA IN ADULTS

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Name of originator/author:	Dr Sally Stock
Director responsible for implementation:	Dr Edmund Lamb
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Target audience:	Clinical staff (medical, nursing and scientific), Trust wide and primary care

Version Control Schedule

Version	Date	Author	Status	Comment
1.0	Nov 2017	Dr S Stock	archived	

Contents

1 Policy Summary

This policy gives guidance to clinicians and healthcare professionals investigating and managing hyperprolactinaemia in adult patients receiving antipsychotic therapy.

2 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 (La Torre D, Falorni A. 2007).

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 (Stahl SM. 2009). The administration of antipsychotic medication is responsible for the high prevalence of hyperprolactinaemia in people with severe mental illness (La Torre D, Falorni A. 2007). Prolactin secretion is also controlled, but to a lesser extent, by thyrotropin- releasing hormone (TRH) (Holt R. 2008).

Hyperprolactinaemia is often asymptomatic. Prolactin concentrations can rise after exercise, meals, sexual activity, during REM sleep and in the early morning. Persistent elevation is associated with a number of adverse consequences:

Men

- Hypogonadism
- Infertility
- Erectile dysfunction
- Gynaecomastia
- Galactorrhoea (rare)
- Reduced libido
- Decreased sperm production
- Reduced bone density

Women

- Breast enlargement
- Galactorrhoea
- Disrupted menstrual cycle
- Infertility
- Reduced libido
- Atrophic changes in the vaginal mucosa
- Reduced vaginal lubrification
- Dyspareunia (pain during sexual intercourse)

Chronic hyperprolactinaemia may lead to a decrease in bone mineral density. It is thought to be due to a combination of the inhibitory action of prolactin on osteoblast activity and the prolactin-induced hypogonadism (Lozano R, Marin R 2013). A history of antipsychotic use constitutes a risk factor for hip fracture (Howard L *et. al.* 2007).

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 (non exhaustive list)	Pharmacological causes (non-exhaustive list)	Pathological causes (non-exhaustive list)

• Stress (including venepuncture)
• Pregnancy
• Lactation
• Macroprolactin (larger molecular forms of prolactin with no biological significance which may be detected in some assays)
	• Antipsychotics
	• Dopamine-receptor blockers
	  ○ Metoclopramide
	  ○ Domperidone
	  ○ Cimetidine
	• Antidepressants
	  ○ Imipramine
	  ○ Amitriptyline
	  ○ Clomipramine
	• Antihypertensives
	  ○ α-methyldopa
	• Oestrogens
	• Opioids
	• Calcium channel blockers
	  ○ Verapamil
		• Microprolactinoma
		• Macroprolactinoma
		• Acromegaly
		• Idiopathic
		• Sarcoidosis
		• Tuberculosis
		• Cushing's disease
		• Primary hypothyroididsm
		• Chronic renal failure
		• Cirrhosis
		• Untreated Parkinson's disease

Table 1: Causes of hyperprolactinaemia (Holt R. 2008)

The use of antipsychotic medication is the second most common cause of hyperprolactinaemia after pregnancy. All antipsychotics have the potential to elevate prolactin concentration. All typical antipsychotics are associated with hyperprolactinaemia to varying degrees. Those associated with the highest prevalence of hyperprolactinaemia are risperidone, amisulpride and paliperidone (Bushe C *et. al.* 2008). It has been reported that 48%-93% of premenopausal women and 42%-47% of men taking antipsychotic medications have hyperprolactinaema (Holt R. 2008). The effect appears to be dose related.

Drug	Effect on prolactin concentration
Amisulpride/Sulpiride	++/+++
Aripiprazole	-
Clozapine	-
Olanzapine	+
Quetiapine	+/-
Paliperidone	++/+++
Risperidone	++/+++
Lurasidone	+/-
Typical antipsychotics • Thioxanthenes (Flupentixol, Zuclopenthixol)	+++ • Increase in 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

Table 2: Antipsychotic effect on prolactin concentration (Holt R. 2008, Taylor *et. al.* 2012, Bazire S 2012)
Key: - = Very low elevation + = Low elevation ++ = Moderate elevation +++ = High elevation

Antidepressants are considered to have less effect on prolactin concentration. Reported associations can be found in table 3.

Drug/ group	Prospective studies	Case reports/ series
Agomelatine	No mention of prolactin changes in clinical trials.	None
Monoamine Oxidase inhibitors	Small mean changes observed with phenelzine and tranylcypromine	None
Selective serotonin reuptake inhibitor (SSRI's)	Prospective studies generally show no change in prolactin. Some evidence from prescription event monitoring that SSRI's are associated with high risk of non-puerperal lactation. In a French study, 1.6% of adverse effect reports for SSRI were of hyperprolactinaemia.	Galactorrhoea reported with fluoxetine and paroxetine. Euprolactinaemic galactorrhoea reported with escitalopram Hyperprolactinaemia reported with sertraline
Tricyclic antidepressants	Small mean changes seen in some studies but no change in others	Symptomatic hyperprolactinaemia reported with imipramine, dosulepin and clomipramine
Vortioxetine	No mention of prolactin changes in clinical trials	None, although clinical experience is limited.

Table 3. Reported associations between antidepressants and changes in prolactin concentrations. (Taylor D, et. al. 2015)

3 Purpose and Scope

This policy outlines the procedure to investigate and manage patients with hyperprolactinaemia receiving antipsychotic therapy. It may be used for patients both within the Trust and in primary care and the community.

4 Definitions

Prolactin is a peptide hormone synthesised and secreted from lactotroph cells in the anterior pituitary gland. It is primarily associated with lactation and plays a vital role in breast development during pregnancy.

The prolactin reference ranges in place at East Kent Hospitals University Foundation Trust are as follows:

- male < 700 mIU/L
- female <1000 mIU/L

Hyperprolactinamia is the presence of blood prolactin concentrations exceeding the reference range. hyperprolactinaemia may cause galactorrhoea and disruptions to the normal menstrual cycle in women, and hypogonadism, erectile dysfunction and infertility in men. Hyperprolactinaemia can be due to physiological and pathological causes.

Macroprolactin is a high molecular mass (Mr) form of prolactin bound to IgG. Although it is thought to be physiologically inactive it can be detected by most prolactin clinical assays and give rise to increased serum prolactin concentrations. Hyperprolactinaemia due to macroprolactin can lead to misdiagnosis and clinical suspicion alone is not a satisfactory approach to detecting macroprolactin. Therefore depending on the clinical situation laboratory screening for macroprolactin may be indicated when a serum prolactin concentration exceeds the reference range on the first occasion or when the patient is known to have significant macroprolactinaemia.

5 Duties

All staff involved in the investigation of patients with hyperprolactinaemia, whether clinical or laboratory, must adhere to this policy.

6 Hyperprolactinaemia due to antipsychotic therapy

6.1 Monitoring and baseline prolactin concentration

Flow diagram A – Patients in which antipsychotic therapy is being considered
Flow diagram B – Monitoring patients on antipsychotic therapy

A baseline blood prolactin measurement should be taken prior to initiation of antipsychotics known to cause hyperprolactinaemia, as in some instances even a single dose can increase prolactin concentration (Holt R. 2008).

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

Thyroid function should be determined before initiation of antipsychotics and again if symptoms consistent of hyperprolactinaemia occur as prolactin is partly controlled by TSH. Inadequately controlled hypothyroidism can contribute to hyperprolactinaema.

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 (Holt R. 2008).

Mild hyperprolactinaemia should be confirmed on at least one occassion before referral, assuming it is not drug related. In cases of only modest hyperprolactinaemia when the prolactin concentration remains persistently elevated and no cause is identified, pituitary imaging is indicated (Holt R. 2008)

For concentrations > 1000 mIU/L, taken prior to the initiation of any antipsychotic, the patient may need to be reviewed by endocrinology.

For concentrations >2000 mIU/L (at any stage), the patient must be referred to endocrinology as such raised concentrations may indicate the co-existence of underlying structural pituitary pathology.

At 3 months all patients should be asked about prolactin-related symptoms such as sexual side effects, amenorrhoea, headaches and visual disturbances. In the presence of these symptoms or documented biochemical hypogonadism, prolactin concentration should be measured.

In presence of hyperprolactinaemia, prolactin concentration should be monitored 3-6 monthly

A

BEFORE starting antipsychotic therapy obtain a baseline blood sample for prolactin measurement. Also assess thyroid and renal function.

Raised prolactin concentration

Repeat measurement under ideal conditions i.e. in the morning at least 1 hour after waking and before eating

- Exclude macroprolactin
- Consider the effect of stress (including venepuncture). Cannulated prolactin measurements can be used to eliminate
- Assess for symptoms of hyperprolactinaemia, if not already done
- Rule out pregnancy in female patients

Prolactin concentration above the gender specific reference range but < 2000 mIU/L

Monitor, should not be allowed to remain elevated long term, especially if the patient becomes symptomatic

Assess for symptoms of hyperprolactinaemia
If any concerns, discuss/refer patient to endocrinology

Presence of symptoms?

- Reduced oestrogen (♀), testosterone (♂)
- History of fragility fracture
- Sexual symptoms for 3-6 months (♂)
- Amenorrhoea for 3-6 months (♀)
- Visual disturbances or headaches

Yes

- Consider bone scan
- Consider referral to endocrinologist and imaging
- Review treatment plan

No

Commence antipsychotic therapy
At three months (or at any point if dose increase), assess all patients for prolactin-related symptoms. If symptomatic, measure prolactin concentration

Prolactin concentration within reference range

Commence antipsychotic therapy
Re-check prolactin concentration at three months (if symptomatic e.g. amenorrhoea, headaches and visual disturbances), documented biochemical hypogonadism, or following a dose increase

Prolactin concentration >2000 mIU/L

Prompt referral to endocrinologist for further investigations (including imaging) to exclude prolactinoma and non-functional pituitary adenoma

B

Is the patient currently receiving an antipsychotic known to cause a sustained rise in prolactin concentration?

YES

Are there any symptoms of hyperprolactinaemia? Has there been a dose increase?

NO

There is no need for prolactin concentration to be monitored unless symptoms indicate otherwise

YES

Obtain a blood sample for prolactin measurement

Prolactin concentration above the gender specific reference range

Repeat measurement under ideal conditions i.e. in the morning at least 1 hour after waking and before eating

- Exclude macroprolactin
- Consider the effect of stress (including venepuncture) and use of cannulated prolactin measurements
- Assess for symptoms of hyperprolactinaemia
- Rule out pregnancy in female patients

Prolactin concentration above the gender specific reference range but < 2000 mIU/L

Monitor, should not be allowed to remain elevated long term, especially if the patient becomes symptomatic

Assess for symptoms of hyperprolactinaemia
If any concerns, discuss/refer patient to endocrinology

Presence of symptoms?

- Reduced oestrogen (♀), testosterone (♂)
- History of fragility fracture
- Sexual symptoms for 3-6 months (♂)
- Amenorrhoea for 3-6 months (♀)
- Visual disturbances or headaches

Yes

Consider bone scan and referral to endocrinologist
Consider a dose reduction or withdrawal of the antipsychotic after consideration of the risk/benefit ratio
Consider supplementation of current antipsychotic with one with a lower potential to elevate prolactin concentration
Consider low dose aripiprazole or dopamine agonist
Consider offering bone protection

No

Continue antipsychotic therapy
At three months (or at any point if dose increase), assess for prolactin-related symptoms. If symptomatic, measure prolactin concentration

Prolactin concentration within gender specific reference range

Continue antipsychotic therapy

At three months (or at any point if dose increase), assess patient for prolactin-related symptoms. If symptomatic, and/or documented biochemical hypogonadism, measure prolactin concentration

Prolactin concentration >2000 mIU/L

Prompt referral to endocrinologist for further investigations (including imaging) to exclude prolactinoma and non-functional pituitary adenoma

6.2 Management of Hyperprolactinaemia

The diagnosis of hyperprolactinaemia should not be made based on a single blood test as stress can also elevate prolactin concentrations (as mentioned above), therefore venepuncture itself can sometimes result in high concentrations. Cannulated prolactin measurements can be used to eliminate the possibility of venepuncture/stress induced hyperprolacinaemia.

The ideal conditions for measuring prolactin levels are in the morning at least 1 hour after waking and before eating (Holt R. 2008).

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

- If the prolactin concentration is increased but the patient is asymptomatic, continue antipsychotic and monitor for symptoms. Inform the patient and be aware of long term complications.
- If the prolactin concentration is increased and the patient is symptomatic consider (Bazire S 2012, Bleakly S 2009, Melmed S, 2011):
    1. A dose reduction or withdrawal of the antipsychotic after consideration of the risk/benefit ratio
    2. Substitution of the current antipsychotic with one with a lower potential to elevate prolactin concentration (see table 2). However, consider full profile of replacement drug to ensure benefits of the change exceed any new associated risk. Antipsychotics not associated with hyperprolactinaemia include aripiprazole, olanzapine, clozapine, quetiapine. Mirtazapine is a non-prolactin elevating antidepressant.
    3. If the above are not feasible, consider low dose aripiprazole as an add in to treat the hyperprolactinaemia
    4. For patients who need to remain on a prolactin-increasing antipsychotic, dopamine agonsists may be effective. Amantadine, cabergoline and bromocriptine have been used, but each has the potential to worsen psychosis, so risk/benefit must be assessed. Patients who need to remain on a prolactin-increasing antipsychotic should be offered bone protection.

7 Key Stakeholders, Consultation, Approval and Ratification Process

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this policy.

Consultation has been through e-mail communication between clinical biochemistry staff and the chief pharmacist (Mr Jon Stock) at Kent and Medway NHS and Social Care Partnership Trust. Communication is stored on the S drive. The document was also circulated to all Consultant Endocrinologists at EKHUFT via the Endocrine lead. Comments were received from Dr Joseph and Dr Faghahati. Communication is stored on the S drive.

8 Review and Revision Arrangements

Three years from implementation date, by author.

9 Dissemination and Implementation

Via QPulse, Trustnet and communiation via EKHUFT endocrine lead clinician.

10 Document Control including Archiving Arrangements

Archive of this document will be through QPulse.

11 Monitoring Compliance

Within the Trust, compliance with this policy must rest with the requesting Divisions with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry.

12 References

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Psychosis and schizophrenia in adults: prevention and management Clinical guideline Published: 12 February 2014 nice.org.uk/guidance/cg178

Bipolar disorder: assessment and management Clinical guideline Published: 24 September 2014 nice.org.uk/guidance/cg185

13 Associated Documentation

Not applicable

Appendix A - Equality Impact Assessment

Equality and Human Rights Impact Analysis (EHRIA)

Part One – Screening Tool

Name of the policy, strategy, function or methodology:	Prolactin and antipsychotic drug therapy: guidelines for management of hyperprolactinaemia in adults

Details of person completing the EHRIA	
Name	Dr Sally Stock
Job Title	Consultant Clinical Scientist
Department/Specialty	Clinical Biochemistry
Telephone Number	01233 616025

1. Identify the policy, strategy, function or methodology aims

What are the main aims, purpose and outcomes of the policy, strategy, function or methodology?
To guide staff on the appropriate management of hyperprolactinaemia in patients receiving antipsychotic therapy
Does it relate to our role as a service provider and/or an employer?
Service provider.

2. Assess the likely impact on human rights and equality

Use this table to check if the policy, strategy, function or methodology:

- could have a negative impact on human rights or on any of the equality groups, or
- could have a positive impact on human rights, contribute to promoting equality, equal opportunities or improve relations.

It is not necessary to complete each box, nor to mark whether it is positive or negative, although you can do this if you find it helpful.

	Protected Characteristic								
	Race	**Sex**	**Disability**	**Sexual Orientation**	**Religion or belief**	**Age**	**Gender reassignment**	**Marriage & Civil Partnership**	**Pregnancy & Maternity**
Could this policy, procedure, project or service affect this group differently from others? **YES/NO**									
Could this policy, procedure, project or service promote equal opportunities for this group? **YES/NO**									
Right to life *e.g. decisions about life-saving treatment, deaths through negligence in hospital*									
Right not to be tortured or treated in an inhuman or degrading way *e.g. dignity in care, abuse or neglect of older people or people with learning disabilities.*									
Right to respect for private and family life e.g. *respecting lgb relationships, confidentiality*									
Right to freedom of thought, conscience and religion *e.g. respect for cultural and religious requirements*									
Right to freedom of expression *e.g. access to appropriate communication aids*									
Right to freedom of assembly and association *e.g., right to representation, to socialise in care settings*									
Right to education *e.g. access to basic knowledge of hygiene and sanitation*									
Right to liberty e.g. informal detention of patients who do not have capacity									

3. How does it impact on people's human rights and equality?

Using the table above, explain anticipated impacts. If a full EHRIA is recommended, you can summarise the impacts - it is not necessary to set these out in detail,

Could people's human rights be impacted negatively? Could the policy, strategy, function or methodology result in inequality or discrimination?
No.
Could this policy, strategy, function or methodology result in positive impacts on people's human rights or equality? Could it present opportunities to promote equality?
No

4. Recommendations

Is a full EHRIA recommended? If not, give reasons
No. The policy has equal impact.

5. Publication of EHRIA

Give details of where Screening Tool or the full EHRIA will be published and when this will take place
With document.

Details of person completing the EHRIA	
Name	Dr Sally Stock

Signed …… Date: ……

Approval and sign-off	Name
Head of Department/Director	Mr Edward Kearney, Head of Service Clinical Biochemistry

Signed …… Date: ……

	Name
Trust Board approval and sign-off	not applicable

Signed …… Date: ……

Appendix B – Author's Checklist of compliance with the Policy for the Development and Management of Organisation Wide Policies and Other Procedural Documents

POLICY:

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

	Requirement:	Compliant Yes/No/ Unsure	Comments
1.	**Style and format**	Yes	
2.	**An explanation of any terms used in documents developed**	Yes	
3.	**Consultation process**	Yes	
4.	**Ratification process**	Yes	
5.	**Review arrangements**	Yes	
6.	**Control of documents, including archiving arrangements**	Yes	
7.	**Associated documents**	n/a	
8.	**Supporting references**	Yes	
9.	**Relevant NHSLA criterion specific requirements**	n/a	
10.	**Any other requirements of external bodies**	n/a	
11.	**The process for monitoring compliance with NHSLA and any other external and/or internal requirements**	n/a	

Appendix C – Plan for Dissemination of Policies

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

Acknowledgement: University Hospitals of Leicester NHS Trust (Amended)

Title of document:	Prolactin and antipsychotic drug therapy: guidelines for management of hyperprolactinaemia in adults		
Version Number:	1.0		
Approval Date:	November 2017	**Dissemination lead:**	Dr Sally Stock
Previous document already being used?	No		
If yes, in what format (paper / electronic) and where (e.g. Directorate / Trust wide)?	Electronic version hosted on Q pulse (document management system within pathology) and within the healthcare professionals zone of Trustnet		
Proposed instructions regarding previous document:			

To be disseminated to:	**How will it be disseminated, who will do it and when?**	**Format (i.e. paper or electronic)**	**Comments:**
Trust clinical staff	TrustNet	electronic	
Primary care	TrustNet	electronic	
Clinical Biochemistry staff	QPulse	electronic	

Author's Dissemination Record - to be used once document is approved – to be kept with the master document

Date document forwarded to be put on the Trust's central register / in SharePoint:		**Date document put on Directorate register (if appropriate) / on Directorate webpage (if applicable)**	

Disseminated to: (either directly or via meetings, etc.)	**By Whom?**	**Format (i.e. paper or electronic)**	**Date Disseminated:**