East Kent Hospitals University NHS Foundation Trust

Guidelines for management of hyperprolactinaemia in adults on antipsychotic drug therapy

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Version Control

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1	Nov 2017	Dr S Stock	archived	
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3	Mar 2022	Dr S Stock		Review and update template

Consultation Schedule

Name & Job Title of Individual / Meeting name	Date consulted
Mr Jagdip Bahia (Chief Pharmacist at Kent and Medway NHS and Social Care Partnership Trust.	May 2022
Dr H McGettigan (Lead Consultant Endocrinologist EKHUFT)	May 2022
Clinical Biochemistry senior staff	July 2022
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Ratification Schedule

Name of Meeting / Committee	Date approved / authorised
Version:	3
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Contents

1. Introduction, Background and Purpose

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 antipsychotic drugs 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 increase 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 drug 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)**

• Pregnancy
• Lactation
• Stress (including venepuncture)
• 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
		• 'blocking' pituitary tumour
		• 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 antipsychotic drugs have the potential to increase 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.

<table>
<tr><th>Prolactin-sparing (prolactin increase very rare)</th><th>Prolactin-elevating (low risk - minor changes only)</th><th>Prolactin-elevating (high risk- major changes)</th></tr>
<tr><td>Aripiprazole</td><td>Lurasidone</td><td>Amisulpride</td></tr>
<tr><td>Asenapine</td><td>Olanzapine</td><td>Paliperidone</td></tr>
<tr><td>Clozapine</td><td></td><td></td></tr>
<tr><td>Quetiapine</td><td></td><td>Risperidone</td></tr>
<tr><td></td><td></td><td>Sulpiride</td></tr>
<tr><td></td><td></td><td><u>First Generation Antipsychotics</u>

<table><tr><td>Thioxanthenes (Flupentixol, Zuclopenthixol)</td><td>Increase in prolactin 2-3 fold during the 1st month with reduction and normalisation after 6 months</td></tr><tr><td>Phenothiazines (Chlorpromazine, Fluphenazine, Pipotiazine, Trifluoperazine)</td><td>2-3 fold increase occurs within hours of treatment initiation with further 2 fold elevation in the following weeks</td></tr><tr><td>Butyrophenones (Haloperidol)</td><td>Similar to phenothiazines</td></tr></table></td></tr>
</table>

Table 2: Antipsychotic effect on prolactin concentration (Taylor D, et al 2021, Holt R. 2008, Bazire S 2020)

Contraindications

Drugs with a high-risk of elevating prolactin should, if possible, be avoided in the following patient groups:

- Patients under 25 years of age (i.e. before peak bone mass)
- Patients with osteoporosis
- Patients with a history of hormone-dependent breast cancer
- Young women (e.g. women of child bearing age where fertility required/desired)

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 prolactin changes observed with phenelzine and tranylcypromine	Very occasional reports of increased prolactin
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 and amenorrhoea reported with escitalopram and fluvoxamine Hyperprolactinaemia reported with sertraline
Serotonin-noradrenaline reuptake inhibitors (SNRI's)	Clear association observed between venlafaxine and duloxetine and prolactin elevation	Galactorrhoea reported with venlafaxine and duloxetine
Tricyclic antidepressants	Small mean changes in prolactin seen in some studies but no change in others	Symptomatic hyperprolactinaemia reported with imipramine, dosulepin and clomipramine Galactorrhoea reported with nortriptyline and when trazodone was added to citalopram Raised prolactin may be linked to response to amitriptyline
Mirtazapine	Strong evidence that mirtazapine has no effect on prolactin	Occasional reports of galactorrhoea and gynaecomastia
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. 2021)

2. 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 action limits 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 action limit.

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. Screening for macroprolactin may be indicated in the following situations:

- If serum prolactin concentration exceeds the action limit (see above) and a screen has not been performed previously
- If it is 5 years since previous screen was performed
- If a patient is known to have significant macroprolactinaemia. In this scenario, a screen would be performed each time prolactin is requested.

3. Scope

This guideline is for use when investigating hyperprolactinaemia in patients on antipsychotic drug therapy.

4. Guidance

4.1 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 checked 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 kidney disease 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 occasion 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)

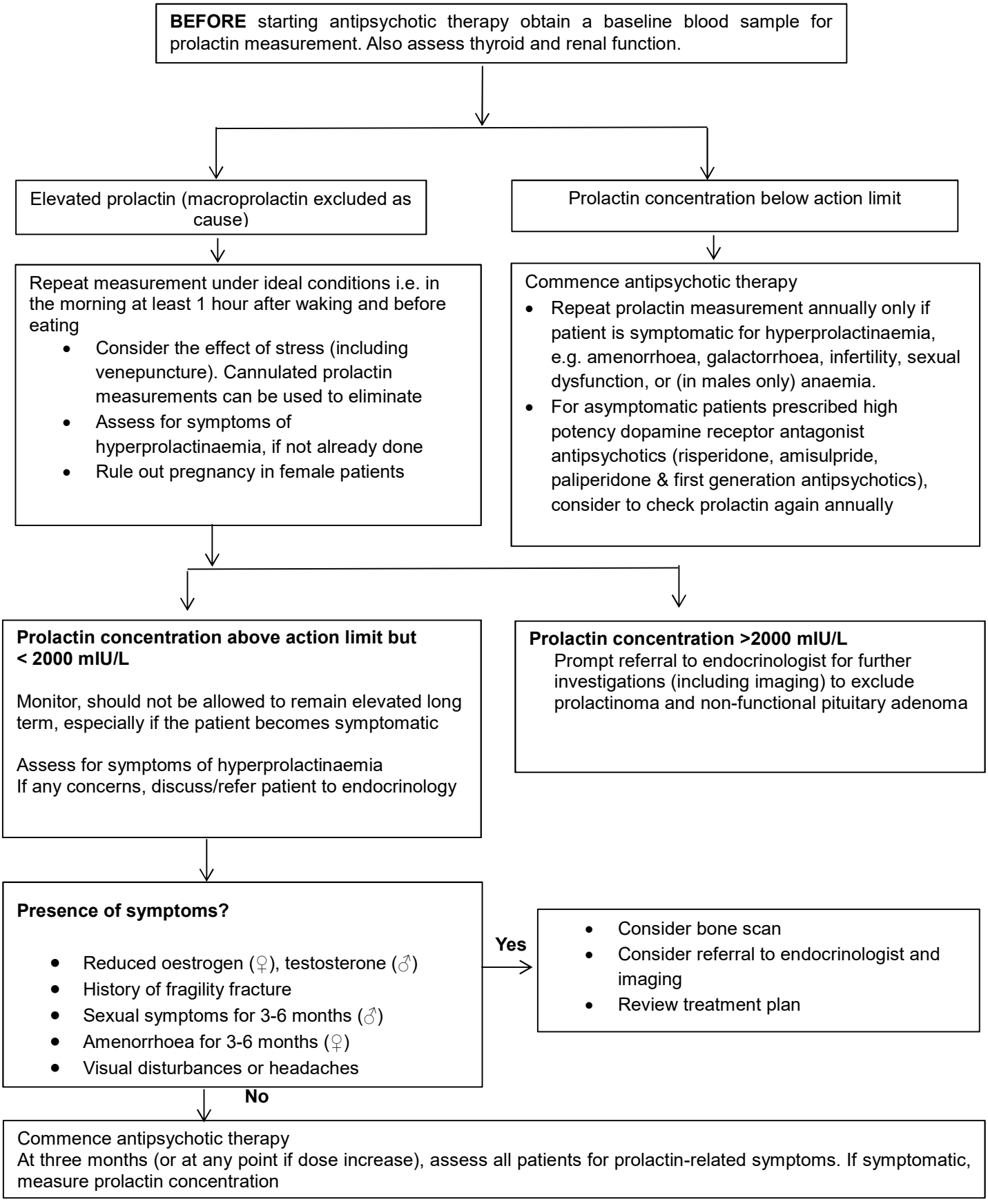
For concentrations >1000 mIU/L, taken prior to the initiation of any antipsychotic, the patient may need to be reviewed by endocrinology.

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.
Elevated prolactin (macroprolactin excluded as cause)
Prolactin concentration below action limit
Repeat measurement under ideal conditions i.e. in the morning at least 1 hour after waking and before eating
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
Commence antipsychotic therapy
Repeat prolactin measurement annually only if patient is symptomatic for hyperprolactinaemia, e.g. amenorrhoea, galactorrhoea, infertility, sexual dysfunction, or (in males only) anaemia.
For asymptomatic patients prescribed high potency dopamine receptor antagonist antipsychotics (risperidone, amisulpride, paliperidone & first generation antipsychotics), consider to check prolactin again annually
Prolactin concentration above action limit 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
Prolactin concentration >2000 mIU/L
Prompt referral to endocrinologist for further investigations (including imaging) to exclude prolactinoma and non-functional pituitary adenoma
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

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 action limit

Prolactin concentration below the action limit

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

Continue antipsychotic therapy

At one year, assess patient for prolactin-related symptoms. If symptomatic, and/or documented biochemical hypogonadism, measure prolactin concentration

Prolactin concentration above the action limit but <2000 mIU/L

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

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

Prolactin concentration >2000 mIU/L

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

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 i.e. low dose aripiprazole
- Consider dopamine agonist only if other options are not feasible. Do not use in severe mental illness.
- 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

4.2 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 treatment 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 2020, 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 increase 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 inducing antidepressant.
    3. If the above are not feasible, consider low dose aripiprazole as an add in to treat the hyperprolactinaemia. A dose of aripiprazole 2.5 mg to 5 mg might be sufficient, although higher doses might be needed in some patients. Monitor prolactin levels weekly to ascertain benefit. If prolactin concentrations do not normalise after 4 weeks of treatment, aripiprazole should be discontinued. Be aware that adding aripiprazole to treat hyperprolactinaemia is off-label. (Sommerfield et al, 2005); (Byerly et al, 2009); (Chang et al, 2010)
    4. For patients who need to remain on a prolactin-increasing antipsychotic, dopamine agonists 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.

5. Consultation and Approval

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

Consultation has been through e-mail communication between clinical biochemistry staff and the chief pharmacist (Mr Jagdip Bahia) at Kent and Medway NHS and Social Care Partnership Trust. Communication is stored on the S drive. The document was sent to Dr Mcgettigan, clinical lead for Endocrinology. Communication is stored on the S drive and on QPulse.

The document has been approved by senior clinical biochemistry staff and the Pathology Management and Governance Committee (PMGC), before being sent for Care Group approval.

6. Review and Revision Arrangements

Two years from implementation date, by author.

7. Training

Dissemination to relevant staff within Pathology via Q Pulse. Dissemination to users of the service via documentation hosted in the healthcare professional zone of Trustnet. Information may also be contained within the Pathology MicroGuide

8. Document Control including Archiving Arrangements

Dissemination to relevant staff within Pathology via Q Pulse. Dissemination to users of the service via documentation hosted in the healthcare professional zone of Trustnet. Information may also be contained within the Pathology MicroGuide

9. Monitoring

Compliance will also be subject to occasional audit within Clinical Biochemistry.

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