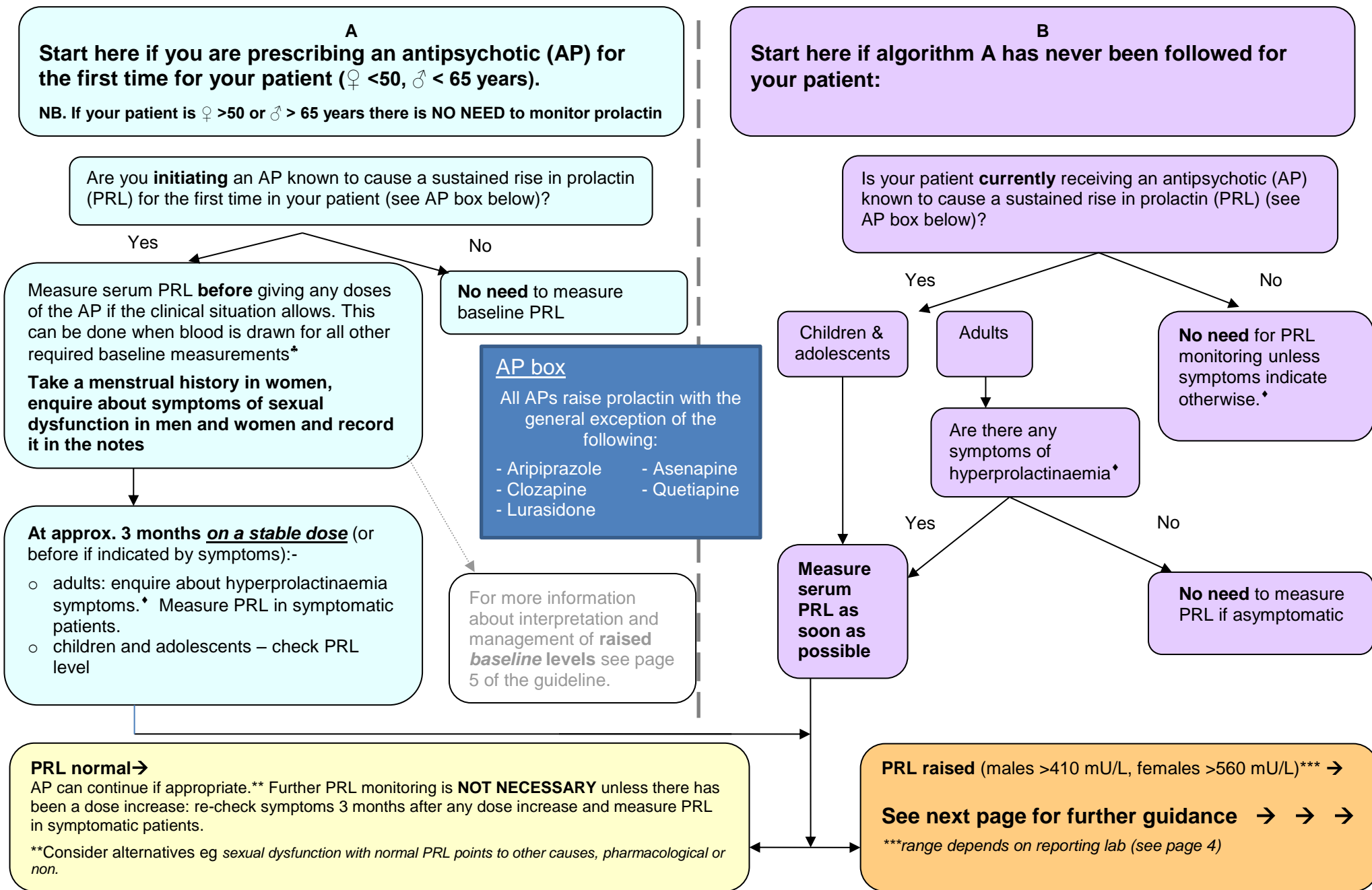


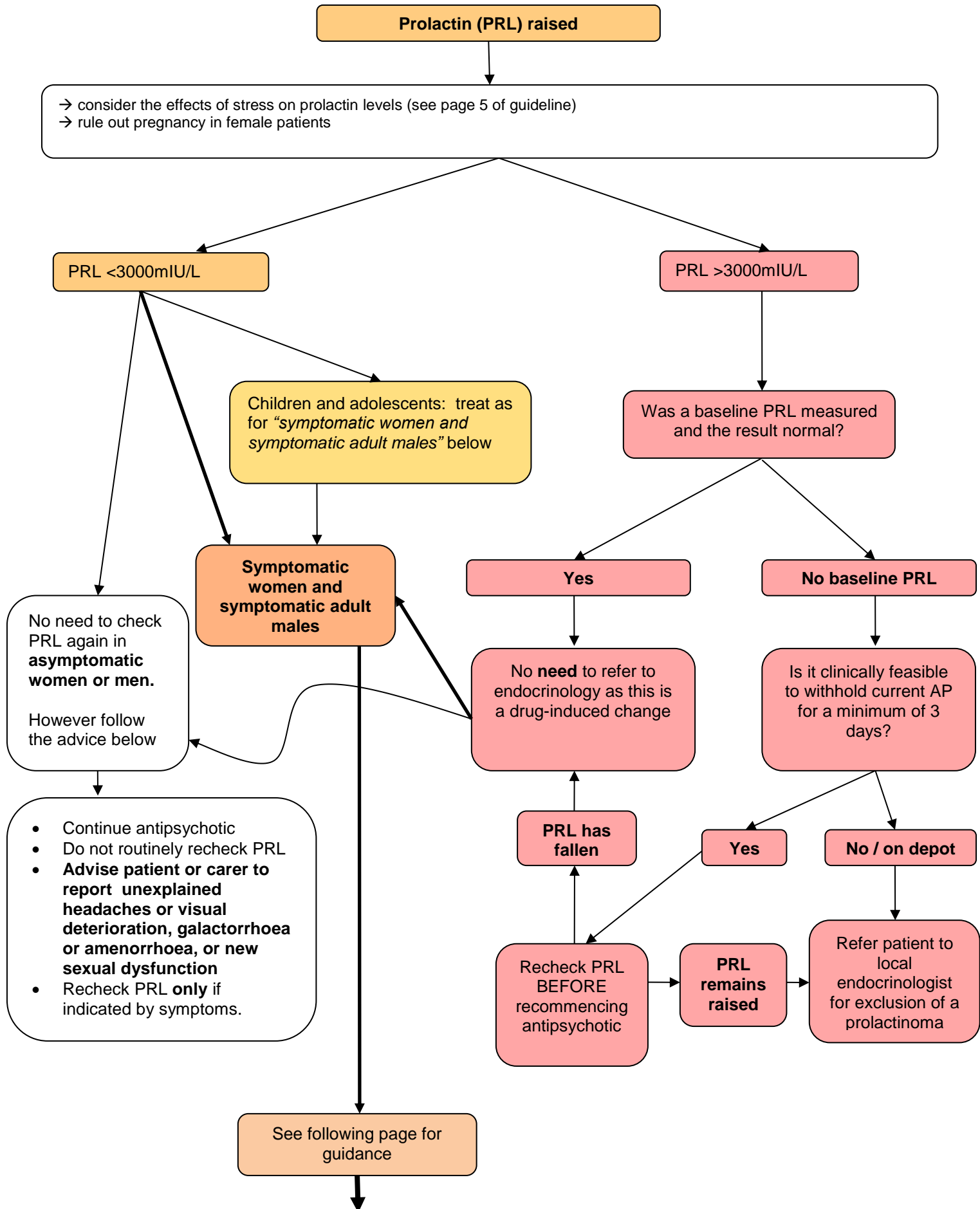
Antipsychotic-induced hyperprolactinaemia

- Trust guideline for identification, monitoring and management



♣ Oxford Health NHSFT Psychotropic Monitoring Guidelines

♦ Appendix 1: screening tool for the assessment of hyperprolactinaemic symptoms (see page 6). **Upload all completed questionnaires to the patient's notes.**





STEP 1: Consider a dose reduction or a switch to an antipsychotic with a lower potential to elevate PRL to alleviate symptoms if clinically appropriate (but see **NOTES** section below and [notes for primary care](#))

STEP 2: Follow the recommendations below to identify if your patient requires further investigation

- **Men age 18-65*** → Measure serum testosterone (**9 am sample**).
If 9 am testosterone is less than the lower limit of normal (<8.4 nmol/L) or borderline (8.4-12 nmol/L) repeat the level at least a week later. If both levels are below the lower limit of normal or borderline refer for further assessment (see appendix 2); If testosterone is above 12 nmol/L there is no need for further follow up of testosterone or prolactin levels unless the patient develops headache, deterioration in vision, or galactorrhoea. Recheck PRL only if indicated by symptoms and refer as appropriate.
- **Women age 18-50* with amenorrhoea for 3 months or longer** → discuss with Jan Brockie at the John Radcliffe Hospital to determine whether telephone advice is sufficient or if a referral appointment is necessary – see form in appendix 3 for more details
- **Children and adolescents** → if it is unwarranted to switch to a prolactin-sparing antipsychotic refer to a paediatric endocrinologist for advice (see appendix 4).

**a raised prolactin after the age of 50 in women and after the age of 65 in men will have no additional health consequences on bone health beyond those of age alone.*

NOTES

1. **Side effects must be balanced against the benefits of treatment. It may not be possible or appropriate to stop/switch existing antipsychotic treatment. Each case should be considered individually.**
2. Other risk factors for osteoporosis should be addressed e.g. smoking (see Oxford Health NHS FT smoking cessation guideline), sedentary lifestyle (see Oxford Health NHS FT weight management guideline), vitamin D deficiency and alcohol intake.
3. **A decrease in prolactin may result in the return of fertility even before the reappearance of periods:** contraceptive advice may be needed and recorded in the notes.
4. Prolactin levels should fall within days after dose reductions or switches, but a return to normal may take several weeks. Recheck prolactin monthly until normal.
5. Adjunctive aripiprazole could be used in some patients to reduce prolactin when switching to a prolactin-sparing antipsychotic is unwarranted (see page 5 of this guideline).
6. Dopaminergic drugs (cabergoline, bromocriptine), which are used to treat hyperprolactinaemia, carry the potential risk of inducing psychosis or worsening pre-existing psychosis and the British National Formulary advises caution in their use in patients with a history of serious mental disorders (especially psychotic disorders). The Trust would endorse the use of dopaminergic drugs only under special clinical circumstances and after contacting Pharmacy about the individual patient.

Notes for primary care

GPs should refer patients to Oxford Health NHS FT for a review of their antipsychotic medication if a dose reduction or switch is indicated. If appropriate, the psychiatrist will also initiate referral for further investigation, liaising with the GP about blood tests.

Guideline aims:

The purpose of this guideline is to provide prescribers with a comprehensive strategy for the investigation and management of hyperprolactinaemia, including:

- ⇒ clear cut-off points for the interpretation of prolactin results,
- ⇒ detailed information about the adverse effects and risks associated with a raised prolactin
- ⇒ a protocol for excluding other causes of hyperprolactinaemia
- ⇒ clear guidance about any necessary further investigations
- ⇒ clear criteria and referral pathways for the assessment of the potential risk to bone health

Background information

What is prolactin (PRL)?

PRL is a hormone synthesised in and secreted from lactotroph cells in the anterior pituitary gland. PRL production and secretion is predominantly controlled by dopamine and to a lesser extent thyrotropin-releasing hormone (TRH). Dopamine has an inhibitory effect - a reduction in dopaminergic input to the lactotrophs results in a rapid PRL increase.

PRL levels are highest during sleep and lowest whilst awake and there are approximately 10 peaks per day due to its pulsatile secretion.

PRL is the hormone that promotes milk secretion. Hyperprolactinaemia, both physiological (pregnancy and lactation) and pathological (neoplastic, iatrogenic etc), can inhibit the pulsatile secretion of gonadotrophin releasing hormone (GnRH). This in turn inhibits the release of both LH and FSH, thus blocking sex hormone secretion by the ovaries and the testes. This state of hypogonadism is characterised by menstrual disturbances, reduced fertility, sexual dysfunction and, in the longer term, osteoporosis and increased fracture risk.

The PRL assay is not standardised. The normal range varies slightly depending on the lab:

| | Oxfordshire | Buckinghamshire |
|-------------------------|----------------|-----------------|
| Males (adults) | 70 – 410 mU/L | 54-381 mU/L |
| Females (adults) | 110 – 560 mU/L | 25-628 mU/L |

What are the causes of hyperprolactinaemia?

Hyperprolactinaemia is one of the most common disorders of the hypothalamic-pituitary axis. The most common causes are listed below:

| Physiological causes: | Pharmacological causes: | Pathological causes: |
|--|--|--|
| <ul style="list-style-type: none"> • Pregnancy • Lactation • Stress (PRL levels of up to about 700 mU/L in men and 900 mU/L in women) • Macroprolactin (large molecular aggregates lacking biological activity but leading to falsely elevated PRL result). Screening for macroprolactin is routinely conducted by the lab if PRL is found to be raised. | <ul style="list-style-type: none"> • Antipsychotics • Antidepressants • Opiates • Peripheral dopamine receptor blockers e.g. metoclopramide, domperidone • Antihypertensives eg calcium channel blockers, methyl dopa • H2 antagonists e.g. cimetidine • Proton pump inhibitors e.g. omeprazole • Oestrogens | <ul style="list-style-type: none"> • Prolactinoma • Other pituitary or hypothalamic tumours or lesions • Hypothyroidism • Polycystic ovary syndrome • Severe renal or liver disease |

Which antipsychotics are associated with hyperprolactinaemia?

Given their antidopaminergic properties, all currently used APs can raise PRL. However, there are huge variations in the prevalence of hyperprolactinaemia and the degree of PRL elevation by individual drug, as shown by numerous studies and by an audit of 501 patients on APs of the Oxford Health NHS FT in whom PRL was measured one or more times. Although even minute doses of some APs (e.g. 50 mg amisulpride or 1 mg risperidone), can raise PRL levels, the degree of elevation in individual patients seems to be dose dependent. Despite not finding any cases of hyperprolactinaemia on aripiprazole (a partial dopamine agonist) in our audit, there are two published case reports of hyperprolactinaemia on this AP and there are have been other cases, albeit extremely infrequent, in clinical trials. Antipsychotic induced hyperprolactinaemia is more frequent in women than men.

Prevalence of hyperprolactinaemia in OH patients as % of number of PRL measurements and median (range) PRL levels by antipsychotic

| Antipsychotic | Women | | Men | |
|--|---------------------------|-----------------|---------------------------|----------------|
| | Hyperprolactinaemia % (n) | PRL mU/L | Hyperprolactinaemia % (n) | PRL mU/L |
| Amisulpride, sulpiride | 100 (63) | 2663 (670-7590) | 98 (49) | 956 (351-1811) |
| Risperidone oral | 98 (94) | 1404 (284-7074) | 79 (101) | 584 (58-2046) |
| Risperidone long acting injection | 91 (23) | 1399 (415-5947) | 56 (59) | 426 (158-1260) |
| Paliperidone long acting injection | 90 (29) | 1559 (366-4353) | 86 (29) | 801 (244-1513) |
| Haloperidol | 80 (20) | 1259 (274-2006) | 40 (5) | 290 (187-582) |
| Zuclopenthixol, flupentixol | 77 (114) | 933 (183-3470) | 69 (88) | 284 (120-1727) |
| Chlorpromazine, pipotiazine, trifluoperazine | 37 (16) | 576 (241-2675) | 67 (9) | 652 (95-1347) |
| Olanzapine | 33 (79) | 392 (69-3704) | 24 (108) | 271 (33-1076) |
| Quetiapine | 2 (65) | 203 (37-710) | 0 (23) | 172 (46-323) |
| Clozapine | 4 (94) | 321 (36-926) | 3 (133) | 142 (17-553) |
| Aripiprazole | 0 (35) | 167 (25-451) | 0 (30) | 52 (13-291) |
| All | 54.3 % | 544 (25-7590) | 45.0% | 300 (13-2046) |

What are the effects of hyperprolactinaemia?

Common symptoms

Some people with raised PRL are asymptomatic. Others may experience problems including breast enlargement, galactorrhoea, reduced libido, erectile dysfunction, amenorrhoea, or anorgasmia. In children and adolescents hyperprolactinaemia can lead to pubertal delay. Most hyperprolactinaemic women have reduced fertility, even if they continue to menstruate. AP induced hyperprolactinaemia is more severe in women than men. Whilst the percentage of men who develop hypogonadism (as defined by 9 am testosterone below the normal range) as a result of AP induced hyperprolactinaemia is uncertain but probably low, approximately just over two thirds of women with AP induced hyperprolactinaemia develop hypogonadism (as defined by amenorrhoea). The development of hypogonadism is related to the degree of hyperprolactinaemia, hence the APs inducing the greatest increases in PRL (amisulpride, sulpiride, risperidone, paliperidone and haloperidol), are those most likely to be associated with amenorrhoea and sexual dysfunction. However, sexual dysfunction is very common in patients with mental illness, and AP induced hyperprolactinaemia is only one of many causes.

Long term complications - osteoporosis

Osteoporosis leads to skeletal fragility, increasing the risk of fracture, particularly of hip, spine and wrist. Age-related osteoporosis is the commonest cause, however hypogonadism is an important secondary cause of fractures. Suppression of gonadal function is the main mechanism behind the development of osteoporosis with hyperprolactinaemia. A woman who is amenorrhoeic due to hyperprolactinaemia is more at risk of low bone mineral density (BMD) than someone who is menstruating despite hyperprolactinaemia, because amenorrhoea indicates very low oestrogen levels. The longer the duration of the amenorrhoea, the greater the BMD loss. For men, a 9am testosterone level below the normal range is the indicator of an increased risk of low BMD. Amenorrhoeic women and men with low testosterone should be referred for further investigation (see referral pathways in the following pages).

PRL normalisation prevents further bone loss, however BMD never returns to normal. Peak bone mass does not occur until a person's mid-20s therefore an AP affecting this process and prescribed before this age could have significant long-term implications.

Hormonal preparations (combined contraceptives or HRT in women and testosterone in men) may be used in those who are hypogonadal. Treatments for BMD loss may include bisphosphonates or denosumab and all patients with osteoporosis should take calcium and vitamin D supplements.

It costs the NHS £942 million to treat and manage osteoporotic fractures, with a fifth of all orthopaedic beds being occupied by patients with hip fractures. So, not only does osteoporosis lead to significant morbidity and mortality, there is also a significant financial burden.

Long term complications – tumours

Despite conflicting reports about cancer (ca) rates in AP treated patients, recent evidence suggests that hyperprolactinaemia is not associated with breast or prostate ca. If anything, the risk of prostate ca appears lower in hyperprolactinaemic men. An association with other types of ca, oropharyngeal and haematopoietic, has been suggested. However, current evidence is too weak to warrant an AP change in patients who develop asymptomatic hyperprolactinaemia. Manufacturers of amisulpride and sulpiride specifically contraindicate using their drugs when there is a concomitant PRL-dependent tumour and risperidone manufacturer advises caution.

Two pharmacovigilance studies suggest the possibility of an association between risperidone and amisulpride and the development of prolactinomas. However, the numbers were very small and the few clinical cases reported in the literature show reversibility of the lesions on AP change. In this guideline, we have taken this remote possibility into account by advising clinicians to ask patient or carer to report potential symptoms of prolactinoma such as unexplained headaches or visual deterioration.

What are the Trust's recommendations for prolactin monitoring?

The recommendations contained within this document are an update to guidelines on prolactin monitoring issued previously in 2013.

For a comprehensive guide on how to identify and manage antipsychotic-induced hyperprolactinaemia please follow the algorithms on the previous pages.®

⊗ Our recommendations for children and young people differ from the 2013 NICE guideline for psychosis and schizophrenia in this age group, which advises baseline PRL level and repeat at 12 weeks and then every 6 months thereafter.

A note about baseline prolactin levels

- Blood should be taken prior to any doses of antipsychotic because even a single dose can raise prolactin.
- If a baseline level is raised (and the patient was not being switched from another antipsychotic that could explain the level) and it is confirmed that no dose of the PRL-raising antipsychotic was taken prior to the blood being taken this could be explained by stress.
- Stress may cause slight increases in PRL to levels of up to about 700 mU/L in men and 900 mU/L in women.
- Levels higher than those explained by stress, *taken prior to the initiation of any antipsychotic*, warrant referral to the local endocrinology team for further investigation.

Aripiprazole as “add-on” to reduce prolactin

Several studies and clinical experience have shown adjunctive aripiprazole to be able to reduce or even normalize PRL in patients with hyperprolactinemia induced by haloperidol, risperidone, olanzapine, paliperidone or zuclopenthixol. However, no PRL reduction was seen when the cause of the hyperprolactinaemia was amisulpride. There is insufficient data for sulpiride. Thus, the Trust discourages the use of add-on aripiprazole for amisulpride induced hyperprolactinaemia, while for patients on sulpiride add-on aripiprazole could be tried after contacting Pharmacy. Patients on other antipsychotics should be treated with low dose aripiprazole (starting at 2.5- 5 mg daily or even less if there are pharmacological interactions, such as with fluoxetine) with dose increases at 4-8 weekly intervals according to response, and up to 10 mg maximum. Although add-on aripiprazole seems to have no deleterious metabolic side effects, this has not been tested in diabetic patients. In these patients, adjunctive aripiprazole should only be used under strict blood glucose monitoring. It should also be noted that combination antipsychotic treatment may increase the risk of other side effects and is likely to warrant the need for “high-dose” monitoring (see Oxford Health NHS FT High Dose Monitoring Guidelines). Clinicians are encouraged to contact Pharmacy should they wish to use add-on aripiprazole for the treatment of hyperprolactinaemia. It is crucial to bear in mind that the aim of adjunctive aripiprazole treatment is not to normalise PRL, but to reduce it sufficiently so that normal menses and normal testosterone and sexual function are restored. This would require a lower aripiprazole dose than full PRL normalisation.

Adjunctive aripiprazole should **not** be used to reduce PRL in women in whom restoration of fertility is unwarranted. In these women, a combined oral contraceptive should be used to combat the bone loss induced by amenorrhoea. If troublesome galactorrhoea is also present, add-on aripiprazole should be used only if accompanied by effective contraception. Further guidance can be obtained by contacting Dr Valeria Frighi or Pharmacy.

Appendix 1

Screening tool for the assessment of hyperprolactinaemia-related side effects.

Adapted with permission from the Glasgow Antipsychotic Side effect Scale (GASS) [Waddell L and Taylor M. Journal of Psychopharmacology 2008;22:238-243]

Name:.....

Age:.....

Sex: M / F

Please tick a column which best indicates the degree with which you have experienced the following side effects.

| Over the past week: | Yes | No |
|--|-----|----|
| The areas around my nipples have been sore and swollen | | |
| I have noticed fluid coming from my nipples | | |
| I have had problems enjoying sex or masturbating | | |
| Men only: I have had problems getting an erection | | |

| Tick yes or no for the following question about the last 3 to 6 months | Yes | No |
|---|-----|----|
| Women only: My periods have not been regular.* <i>*periods are regular when they occur about every month and last for 3-7 days.</i> | | |

Presence of any of the above symptoms may indicate hyperprolactinaemia.

Date completed:.....

Upload all completed questionnaires to the patient's notes

Appendix 2

For adult males with raised prolactin, sexual dysfunction and two low or borderline 9 am testosterone levels (<12 nmol/L)

Write a referral letter to the appropriate endocrinology service address (see below)

Please ensure that the following details are included in the referral letter:

- Medication list with start dates
- Results of the following tests:
 - Prolactin level
 - 9 am Testosterone levels
 - FSH, LH
 - Thyroid function tests
 - LFTs
 - U&Es
 - eGFR
 - FBC
- Any concerns that the psychiatrist has
- Whether the patient has had a fragility fracture
- Whether the patient has had a bone mineral density (BMD) scan
- Any caution/contra-indication to the use of testosterone

OXFORDSHIRE PATIENTS:

Refer to Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM) – send referral letter to the following address:

Consultant Endocrinologist
OCDEM
Churchill Hospital
Old Road
Headington
OX3 7LJ

BUCKINGHAMSHIRE PATIENTS:

Refer to Buckinghamshire Healthcare Endocrinology Service as appropriate:

Dr Stephen Gardner
Consultant Endocrinologist
Stoke Mandeville Hospital
Mandeville Road
Aylesbury, Bucks
HP21 8AL

OR

Dr Henrietta Brain
Consultant Endocrinologist
Wycombe Hospital
Queen Alexandra Road
High Wycombe, Bucks
HP11 2TT

For adult females with raised prolactin and amenorrhoea for 3 month or longer

For the attention of Jan Brockie

Jan works on Mon, Wed & Thurs and is happy to be contacted for advice and to discuss any potential referral. **Phone: 01865 221546**

Please complete steps 1 AND 2 below:

- Complete all sections of this form and then contact Jan Brockie, Advanced Nurse Practitioner, at the Menopause **Service by telephone** on the number above to discuss your patient management. Due to the previously high level of unattended appointments by our service users Jan is happy to discuss patients and give advice over the telephone where appropriate. Jan also offers appointments for further assessments if necessary and where there is a high likelihood of the patient attending the appointment.
- If a referral to Jan Brockie's clinic has been advised please send this form by **post AND fax** so that an appointment can be made to: **Jan Brockie, Menopause Service, Level 4, Women's Centre, John Radcliffe Hospital, Oxford, OX3 9DU, FAX: 01865 222070.**

| | | |
|---|--|----------------------------------|
| Referrer's name: | Signature: | Date: |
| Referrer's contact number(s): | | |
| Patient's Name and Surname | | |
| Address or Hospital & Ward | | |
| Date of birth | | |
| GP's name and practice address | | |
| Psychiatric diagnosis/es | | |
| Does the patient have any medical illnesses? | | |
| Has the patient ever had a venous thromboembolism? | | |
| Does the patient have any other significant past medical history? | | |
| Medication (stating doses) including contraception or HRT | | |
| Medication allergies | | |
| Compliance issues? | Y / N (circle) If yes, please state details below | |
| Recent prolactin levels (with dates) | | |
| Date of last menstrual period and age at the time | | |
| Is the patient a tobacco smoker? | Yes/No | Quantity: |
| Is the patient a cannabis smoker? | Yes/No | Quantity: |
| Does the patient drink alcohol? | Yes/No | Units/week: |
| Does the patient take physical exercise? | Yes/No | Details/frequency: |
| Has the patient ever had a fragility fracture? <i>A fracture without significant trauma, e.g a fall from standing height or less and not including fingers, toes or scaphoid</i> | Yes/No | Details including site and year: |

Appendix 4

For children and adolescents

Write a referral letter to the appropriate paediatric endocrinology service address (see below)

OXFORDSHIRE PAEDIATRIC PATIENTS:

Write a referral letter to:

Dr Fiona Ryan
Consultant in Paediatric Endocrinology and Diabetes
Paediatric Endocrinology Department
Oxford Children's Hospital,
Headington,
Oxford,
OX3 9DU

BUCKINGHAMSHIRE PAEDIATRIC PATIENTS:

Write a referral letter to:

For South and mid Bucks:

Dr Michelle Russell-Taylor
Consultant Paediatrician,
Wycombe Hospital,
Queen Alexandra Road,
Bucks,
HP11 2TT.

For Aylesbury and North bucks:

Dr Atanu Dutta,
Consultant Paediatrician,
Stoke Mandeville Hospital,
Mandeville Road,
Aylesbury,
Bucks,
HP21 8AL.

BANES PAEDIATRIC PATIENTS

Write a referral letter to:

Dr Amanda Billson
Consultant Paediatrician
Lead Paediatrician for Children & Young People with Diabetes in the Bath Clinical Area
Royal United Hospital,
Combe Park,
Bath BA1 3NG

WILTSHIRE PAEDIATRIC PATIENTS:

Write a referral letter to:

Dr Sanjay Rathi
Consultant Paediatrician
Great Western Hospital
Marlborough Road
Swindon
SN3 6BB.

SALISBURY PAEDIATRIC PATIENTS:

Dr Carl Taylor
Consultant Paediatrician
Salisbury NHS Foundation Trust,
Salisbury
SP2 8BJ

Latest edition by Rachel Brown, Clinical Lead Pharmacist, Oxford Health NHS FT and Dr Valeria Frighi, Senior Clinical Researcher and Honorary Consultant in Endocrinology and Diabetes, University Department of Psychiatry. April 2015. Approved by Oxford Health NHS FT Drugs and Therapeutics Group July 2015

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