



Antipsychotic-Induced Hyperprolactinaemia: The risks explained and new guidelines.

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Presentation

- Clinical scenario
- Prolactin refresher course
- Hyperprolactinaemia: effects and prevalence
- Are we following guidelines? Audit findings
- **NEW GUIDELINES**

Clinical scenario

- 35 year old woman
- Schizophrenia
- On depot medication, risperidone
- Amenorrhoea
- Prolactin 1032 mIU/L (60-620)

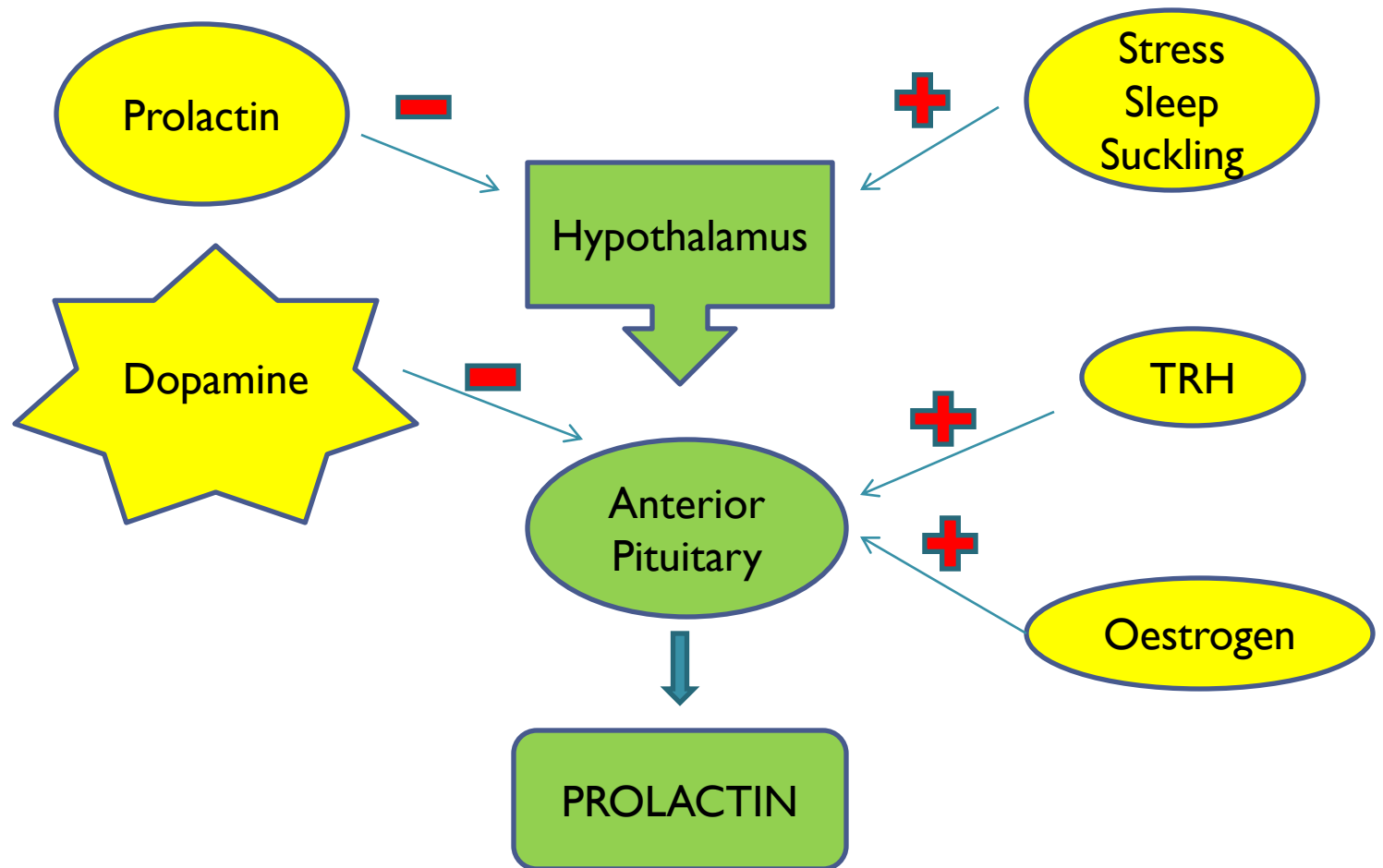
Questions:

1. What are the effects of raised prolactin in short and long term?
2. How common is antipsychotic induced hyperprolactinaemia?
3. Are we monitoring for hyperprolactinaemia and discussing side effects with patients?
4. Do we have comprehensive guidelines?

Bear in mind:

- Antipsychotics prescribed for a wide range of psychiatric disorders
- Treatment may start in late teens and continue indefinitely
- Most potent prolactin elevating antipsychotics:
 - risperidone, typicals, ami/sulpiride

Secretion of Prolactin



Actions of Prolactin

- Stimulation of breast growth (gynaecomastia)
- Initiation and maintenance of breast feeding (galactorrhoea)
- Suppresses FSH and LH (amenorrhoea, reduced fertility, sexual dysfunction)
- Role less clear in men, decreases gonadotrophin release (sexual dysfunction, reduced fertility)

Causes of Hyperprolactinaemia

- Physiological
 - Pregnancy, lactation, stress
- Pathological
 - Parkinson's disease, pituitary tumour, hypothyroidism
- Pharmacological

Pharmacological Causes of Hyperprolactinaemia

- Antipsychotics (D2 blockade)
 - ANY antipsychotic except clozapine
 - Especially typicals, risperidone, amisulpiride, sulpiride
- Antidepressants (tricyclics)
- Antihypertensives
- Dopamine Receptor blockers
- Opiates

Question 1

What are the effects of raised prolactin in the short and long term?



Literature Review

Effects of Hyperprolactinaemia in short-term (weeks to months)

- Gynaecomastia, galactorrhoea
- Oligo/amenorrhoea
- Impaired libido
- Sexual dysfunction



Effects of Chronic Hyperprolactinaemia

OSTEOPOROSIS

(Klibanski et al, 1980)

Mechanism:

- Suppression of gonadal axis
- Prolactin has inhibitory effect on osteoblasts (Howard et al, 2007)

Why is osteoporosis a problem?

- Skeletal fragility
- Fractures (hip, spine, wrist)
- Cost to patients and the NHS
- Peak bone mineralisation at 25 years old

Other Effects of Chronic Hyperprolactinaemia

- **Breast cancer**
 - 16% increase (Wang, 2002; Tworoger et al, 2007)
- **Pituitary tumours**
 - adenomas, adenocarcinomas (Szarfman et al, 2006)
- **Prostate Cancer**
 - Prolactin possible tumour promoter in animal models (Harvey et al, 2008)

Question 2


- How common is antipsychotic-induced hyperprolactinaemia?

Prevalence of antipsychotic-induced hyperprolactinaemia?

- 80-90% in women taking amisulpiride/risperidone (Bushe et al, 2008)
- 20-90% all patients taking ANY antipsychotic medication (Kinon 2003; Marder 2004; Wieck and Haddad 2003)
- 75% women and 33% of men taking typical antipsychotics have prolactin concentrations above ULN (Smith et al, 2002)

Rates of prolactin-related side effects

- Over 40% of patients taking prolactin raising antipsychotics show osteopaenia associated with hypogonadism (Meaney et al, 2001)
- Hyperprolactinaemia is an important secondary cause of osteoporosis (Javaid & Holt, 2008)
- 68% males, 52% females on antipsychotic medication report sexual side effects (Howes & Smith, 2002)
- Hyperprolactinaemia principal cause of sexual dysfunction in women taking antipsychotic medication (Smith et al, 2002)
- Clinicians underestimate the prevalence of these side effects (Malik et al, 2007)



“There is good consistent evidence that in any clinically treated population almost half the patients will have hyperprolactinaemia and that persistent hyperprolactinaemia will not be benign”

Dursun et al, 2008



Question 3.

Are we monitoring for hyperprolactinaemia and discussing side effects with patients?

OBMH guidelines:

- Baseline prolactin to be taken in any patient being commenced on risperidone, ami/sulpiride, typicals
- Further measurement only required if symptoms of hyperprolactinaemia are present

Audit:

To establish if the group of consultant General Adult psychiatrists in Oxford regularly:

- 1) Follow OBMH Trust Guidelines for screening for hyperprolactinaemia
- 2) Educate patients about potential side effects

Results

- Baseline prolactin measurement 17% (34%)
- If symptomatic 75% (75%)
- Screening for >1 side effect 37% (58%)
- Discussion of risks of raised PRL 21% (62%)
- Use of Trust guidelines 17% (58%)

Barriers to discussion of side-effects

- Embarrassment of discussing sexual symptoms
- Concerns about compliance
- Time limitations
- Lack of knowledge

SUMMARY

- Hyperprolactinaemia is a common side effect
- Negative patient experience
- Established risks in long term
- Lack of clinician awareness
- Patients not receiving optimal care
- Legal implications?

Question 4

Do we have comprehensive guidelines?

Aims:

- Comprehensive guidelines:
 - Accurate measurement of prolactin
 - Clear cut-off points for interpretation of prolactin results
 - Severity and duration of side effects predisposing to harm
 - Protocol for excluding other causes
 - Notes for GPs
 - Further investigations
 - Clear referral pathways

OBMH guidelines:

- Baseline prolactin to be taken in any patient being commenced on risperidone, ami/sulpiride, typicals
- Further measurement only required if symptoms of hyperprolactinaemia are present

New guidelines

- Working group:
 - Rachel Brown, Phil Davison
- Developed with:
 - Professor Margaret Rees (Reader in Reproductive Medicine and Honorary Consultant in Medical Gynaecology)
 - Professor John Wass (Consultant Endocrinologist and Professor of Endocrinology)
 - Dr Kassim Javaid (Lecturer in Metabolic Bone Disease and Honorary Consultant Rheumatologist)
 - Dr Brian Shine (Consultant Chemical Pathologist)

Prolactin monitoring guidance for patients being started on an antipsychotic

For patients already taking an antipsychotic see following page

Are you initiating an antipsychotic known to cause a sustained rise in prolactin for the first time in your patient? (ie this is their first antipsychotic or their first prolactin-raising antipsychotic)

YES

NO

Take a prolactin level **before** giving any doses of the antipsychotic. The level can be taken when blood is drawn for all other required baseline measurements (see OBMH Psychotropic Monitoring Guidelines)

There is no need to take a baseline prolactin level. Check prolactin only if symptoms of hyperprolactinaemia develop (the questions in appendix 1 may be a useful screening tool).

Recheck prolactin after 3 months on a stable dose (or before if indicated by symptoms)

For information about interpretation and management of raised *baseline* levels see main guideline

Prolactin raised Prolactin normal

Continue antipsychotic. Further prolactin level monitoring is not necessary unless there has been a dose increase (re-check 3 months after any dose increase) or if symptoms indicate a need.

- consider repeating under approximately ideal conditions ie in the morning at least 1 hour after waking and before eating
- see notes in main guidance about the effects of stress on prolactin
- rule out pregnancy in female patients
- assess for any symptoms of hyperprolactinaemia (see guide in appendix 1)

Prolactin <3000mIU/L

Prolactin >3000mIU/L

asymptomatic

symptomatic

1. Consider dose reduction or a switch to an antipsychotic with a lower potential to

Prolactin <3000mIU/L

symptomatic

Prolactin >3000mIU/L

asymptomatic

Continue antipsychotic and monitor for symptoms (see appendix 1). Recheck prolactin only if indicated by symptoms.

1. Consider dose reduction or a switch to an antipsychotic with a lower potential to elevate prolactin (but see **NOTES** section below and [notes for primary care](#))

2. In addition, follow the recommendations below to identify which patients require further investigation into the adverse effect of raised prolactin on bone:

MALES

In males *without* a history of fragility fracture[†] who have had sexual symptoms present for 3-6 months (or longer) → Take a testosterone level (take at 9 am). If the testosterone level is less than 8.4nmol/L, follow the instructions in [box.1](#) below.

In males *with* a history of >1 fragility fracture[†] → Follow the advice in [box.1](#) below. NB there is no need to take a testosterone level.

BOX 1 Conduct the following blood tests: FBC, ESR, [U&Es](#), Cr, Ca, PO4, Albumin, ALP, ALT, and TSH.

Then refer for further assessment to Prof Wass/Dr [Jayaid's](#) clinic at the NOC using the referral form in [appendix 2](#).

FEMALES

In females *with* a history of >1 fragility fracture[†] → follow the advice in [box.1](#) above.

In females *without* a history of >1 fragility fracture[†] but who have had amenorrhoea present for 3-6 months (or longer) → refer all females, *except* those who are receiving combined oral contraception (the OCP provides enough oestrogen to protect bones), for further assessment to Prof Margaret Rees' clinic at the JR using the referral form in [appendix 3](#) [note, referral *includes* women who use progesterone only methods of contraception and women who are [peri- or post-menopausal](#)].

NB. For patients not meeting the referral criteria above who continue to have a raised prolactin (eg if antipsychotic dose reduction is not possible/does not result in normalisation of prolactin & for a switch is not possible) consideration should be given to the following: men - repeat testosterone level at 6-monthly intervals, women establish whether [amenorrhoeic](#) at 6 monthly intervals and follow referral criteria as above, if appropriate.

Consider [prolactinoma](#) – refer to endocrinologist (at the Churchill Hospital) for further investigation and consider switching to an antipsychotic with a lower potential to elevate prolactin (but see notes below)

Notes for primary care

GPs should refer patients to OBMH for a review of their antipsychotic medication if a dose reduction or switch appears to be indicated. If appropriate the psychiatrist will also initiate referral for further investigation of bone risk, liaising with the GP about blood tests.

Fragility fracture definition:

A type of (pathological) fracture occurs as a result of a trauma – typically from a fall. Exclusions are major RTAs, falls from more than 10 feet, and the following fracture sites: fingers, toes, scapoid and skull.

NOTES

1. Side effects must be balanced against the benefits of treatment.
2. Other risk factors for osteoporosis should be addressed eg smoking (see OBMH smoking cessation guideline), sedentary lifestyle (see OBMH weight management guideline), and alcohol intake.
3. A normalisation in prolactin may result in the return of fertility. Contraceptive advice may need to be offered.
4. Prolactin levels should fall fairly quickly after dose reductions or switches, but a return to normal may take several weeks. Recheck prolactin monthly until normal.
5. Dopamine agonists to treat hyperprolactinaemia should only be considered in exceptional circumstances due to the serious risk of worsening the psychosis.
6. There are a handful of case reports and 1 RCT of aripiprazole being used as "add-on" therapy to reduce prolactin when switching

Conclusions I

- Recent data suggest hyperprolactinaemia is a common SE of antipsychotic medication
- Side effects are experienced as severe by patients and may affect compliance
- Lack of clinician awareness
- Antipsychotics used in a wide range of psychiatric disorders
- Long term complications include osteoporosis and possibly breast cancer

Conclusions 2

- Existing guidelines for measurement of prolactin and management of hyperprolactinaemia not comprehensive
- New guidelines provide comprehensive strategy for investigation and management of hyperprolactinaemia
- Improved patient experience and outcomes