NHS
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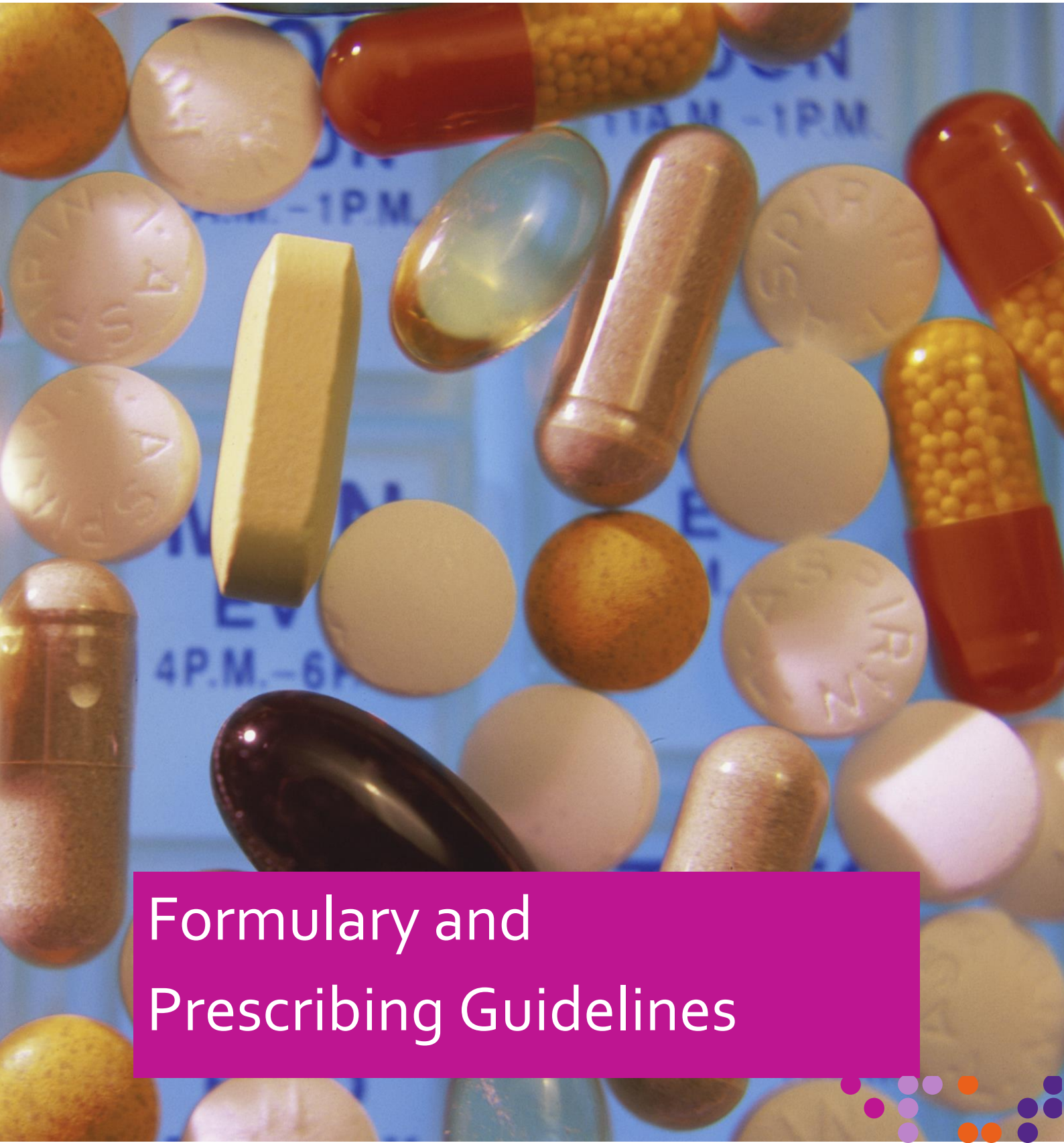
SECTION 22: THE TREATMENT OF HYPERPROLACTINAEMIA



Formulary and Prescribing Guidelines

22.1 Introduction

Prolactin, also known as lactotrophin, is a hormone which is secreted by the lactotroph cells in the anterior pituitary gland, a small gland located at the bottom of the brain. Prolactin causes breasts to grow and enables milk production during pregnancy and after birth. Levels are raised in women during pregnancy and when breast-feeding. Prolactin levels can be influenced by dopamine as it will exert an inhibitory effect, so a presence of dopamine in the lactotroph inhibits the release of prolactin. (13)(2)

Administration of antipsychotics can act on the dopamine receptors, specifically the D_2 receptors in the tuberinfundibular pathway of the brain, can lead to a dopamine inhibition, hence leading to raised levels of prolactin. Certain antipsychotics have a higher prevalence for D_2 receptors, hence choice of antipsychotics should be considered on an individual patient basis (13).

22.2 Interpretation of Prolactin concentration[1]

Normal prolactin levels are dependent on gender, with levels being higher in females. Generally normal prolactin levels are:

- 210-420 mIU/L for men (approximately 10-20 ng/mL)
- 210-530 mIU/L for women (approximately 10-25 ng/mL).

Table 1*- lists the causes of hyperprolactinaemia, however in patients with serious mental illness most cases are due to antipsychotics.*

Pituitary Disorders	Systemic Disorders	Physiological	Medication
Prolactinomas: Microadenomas (<10 mm): 90% Macroadenomas (>10 mm): 10%	Hypothyroidism	Pregnancy	Antipsychotics
Cushing's Disease	Chronic Renal Failure	Breastfeeding	Tricyclic Antidepressants
Acromegaly	Liver Failure	REM Sleep	Monoamine Oxidase Inhibitors
Empty Sella Syndrome	Seizures	Stress	Metoclopramide
Cranial Irradiation	Sarcoidosis		Verapamil

	Polycystic Ovary Disease		Methyldopa
	Oestrogen-secreting Tumours		
	Chest Wall Lesions		

The degree of hyperprolactinaemia will influence the severity and type of clinical symptoms the patient may experience. The following is a guide for premenopausal women:

- Serum prolactin levels between 657 and 1060 mIU/L (30.9-49.8 ng/mL) are associated with reduced libido
- Serum prolactin levels between 1081 and 1590 mIU/L (50.8-74.7 ng/mL) are associated with oligomenorrhea (infrequent menstrual periods).
- Serum prolactin levels above 2120 mIU/L (99.6 ng/mL) are associated with hypogonadism and menstrual dysfunction, including amenorrhoea and galactorrhoea.

22.3 Monitoring and Baseline Prolactin Levels[1]

- Many patients with hyperprolactinaemia are asymptomatic; however a history should still be taken for hypothyroidism, gynaecomastia and galactorrhoea. Any patient presenting with these symptoms should be investigated with a serum prolactin level.
- Regarding serum prolactin testing, the general principles are:
    - Check serum prolactin levels before starting an antipsychotic and before switching to a new antipsychotic. Consider rechecking once optimal antipsychotic dose has been reached and annually for patients on established antipsychotic treatment.
    - Stress can raise prolactin levels, therefore to confirm hyperprolactinaemia, repeat testing of prolactin is recommended for modest increases of prolactin (<1000 mIU/L).
    - Women of child bearing potential should have pregnancy ruled out.
    - Enquire about visual disturbance and headache (pituitary adenoma) or symptoms of hypothyroidism.
    - Check thyroid function before initiation of antipsychotics and if symptoms of hyperprolactinaemia occur as prolactin is partly controlled by TSH.[3]
    - Check renal function as renal insufficiency may cause moderate hyperprolactinaemia due to impaired renal degradation of prolactin and altered regulation of central prolactin.[3]

- Consider also checking liver function.

- If prolactin levels are persistently high and there is no obvious cause, a pituitary MRI and discussion with endocrinology is indicated.

- Prolactin levels above 1000 mIU/L before initiation of antipsychotics should be investigated and discussed with endrocrinology.

- Hyperprolactinaemia below 2500 mIU/L for asymptomatic patients which is most likely caused by antipsychotics does not necessarily require investigation or treatment. The patient should be informed and there should be regular enquiry for symptoms. If hypogonadism, gynaecomastia or galactorrhoea develop then a repeat serum prolactin test should be taken and intervention offered. If unsure if intervention is required then a discussion with endocrinology is recommended.

- Prolactin levels above 2500 mIU/L should be discussed with endocrinology after history and examination of the patient. This is regardless of whether the patient is taking antipsychotics as this level may indicate prolactinoma.

22.4 Long Term Complications of Hyperprolactinaemia

Osteoporosis[1,6,7,8,9,10,11]

Hyperprolactinaema suppresses hypothalamic-pituitary-gonadal axis, which when prolonged reduces bone mineral density and increases chance of osteoporosis. People with schizophrenia are 2.5 times more likely to have to osteoporosis than the general population. This is partly due to lifestyle factors such as increased smoking and alcohol intake, low vitamin D levels and sedentary behaviour. Schizophrenia and related psychosis is usually diagnosed between 16 and 30, and often before the patient reaches peak bone mass. Taking prolactin-raising medication at an early age, alongside the lifestyle factors, may prevent development of optimum peak bone mass. This will reduce life-long bone mineral density (BMD) and increase chance of osteoporosis.

A woman that has amenorrhoea due to hyperprolactinaemia is more at risk of reduced BMD than someone who is not amenorrhoeic, because amenorrhoea suggests very low oestrogen levels. The longer the duration of amenorrhoea the greater the loss of BMD. For men, sexual dysfunction and low testosterone and gonadotrophin levels increases the risk of compromised BMD. If these patients have these symptoms for 3-6 months then they should be referred for further investigation.

Serum prolactin levels returning to normal levels will prevent further bone loss, but the BMD will never return to normal. Patients should be advised on the importance of a well-balanced diet, an appropriate intake of Vitamin D and calcium, smoking cessation, limiting alcohol and caffeine intake, carrying out weight-bearing exercise and adequate exposure to sunlight. Patients that are high risk for osteoporosis may have bisphosphonates prescribed as a preventive measure as well as the BMD monitoring. Vitamin D therapy is recommended for patients that have reduced BMD and as prophylaxis for schizophrenics with vitamin D deficiency to prevent loss of BMD.

Cancer Risk[1]

Hyperprolactinaemia has been implicated in an increased risk of malignancy, especially breast cancer. Although female schizophrenics have a higher chance of breast cancer, it is

unclear if antipsychotic induced hyperprolactinaemia contributes to this. There needs to be further work to determine if moderating hyperprolactinaemia will reduce rates of malignancy.

Adolescent Sexual Development[3]

Increased prolactin levels inhibits release of gonadotrophin-releasing hormone (GnRH) from hypothalamus. This reduces the pituitary's secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which are important in male and female gonadal maturation, by their direct action on testes and ovaries. This means adolescents and children who take antipsychotics which increase prolactin may suffer from delayed sexual maturation or reduced bone growth due to dysfunction of their hypothalamic-pituitary-gonadal axis (HPG).

22.5 Antipsychotics inducing hyperprolactinemia

The majority antipsychotics have the potential to raise the levels of prolactin, with all typical antipsychotics having some form of effect on prolactin levels. Risperidone has the highest prevalence among atypical antipsychotic, with doses greater than 6mg/day causing sexual dysfunction in non-psychiatric patients (13)(19). However, the degree of hyperprolactinaemia elevation is not only dependent on the medication dose, but the occupancy of D2 receptors, as certain antipsychotics therapeutic efficacy is close to causing an increase in prolactin (2).

Table 2*- shows individual antipsychotics and the effect on prolactin concentrations* (2)

Prolactin-sparring (prolactin increase very rare)	**Prolactin-elevating (low risk; minor changes only)**	**Prolactin-elevating (high risk; major changes)**
Aripiprazole	Lurasidone	Amisulpride
Asenapine[1]	Olanzapine	Paliperidone
Clozapine	Ziprasidone	Risepridone
Quetiapine		Sulpiride
		FGA's (e.g. haloperidol & chlorpromazine)

[1] *Antipsychotic is only licensed to be utilised in bipolar disorder under Trust Formulary*

The majority of antipsychotics work by acting as a dopamine antagonist which hence, increases prolactin. The exception being aripiprazole, which not only acts as an antagonist, but also as a partial D2 agonist, hence studies have shown the use for treatment in hyperprolactinaemia (4).

The majority of patients with hyperprolactinaemia are asymptomatic and there is no correlation between patients quality of life and hyperprolactinaemia (2). However, persistently raised prolactin levels can suppress the hypothalamic-pituitary-gonadal axis, resulting in deteriorations to patients mental health and physical health changes such as sexual dysfunction, menstrual disturbances, gynaecomastia and galactorrhoea (2)(5). Hence, it is vital to obtain patients prolactin levels before initiating any treatment with antipsychotics and after 3 months to ensure that, so recommended changes can take place and ensuring that the raise in prolactin is due to the antipsychotic. After 3 months, all patients should be asked on any prolactin related symptoms and the plasma prolactin levels should be obtained to compare levels prior treatment and after treatment (2).

22.6 Management of hyperprolactinemia

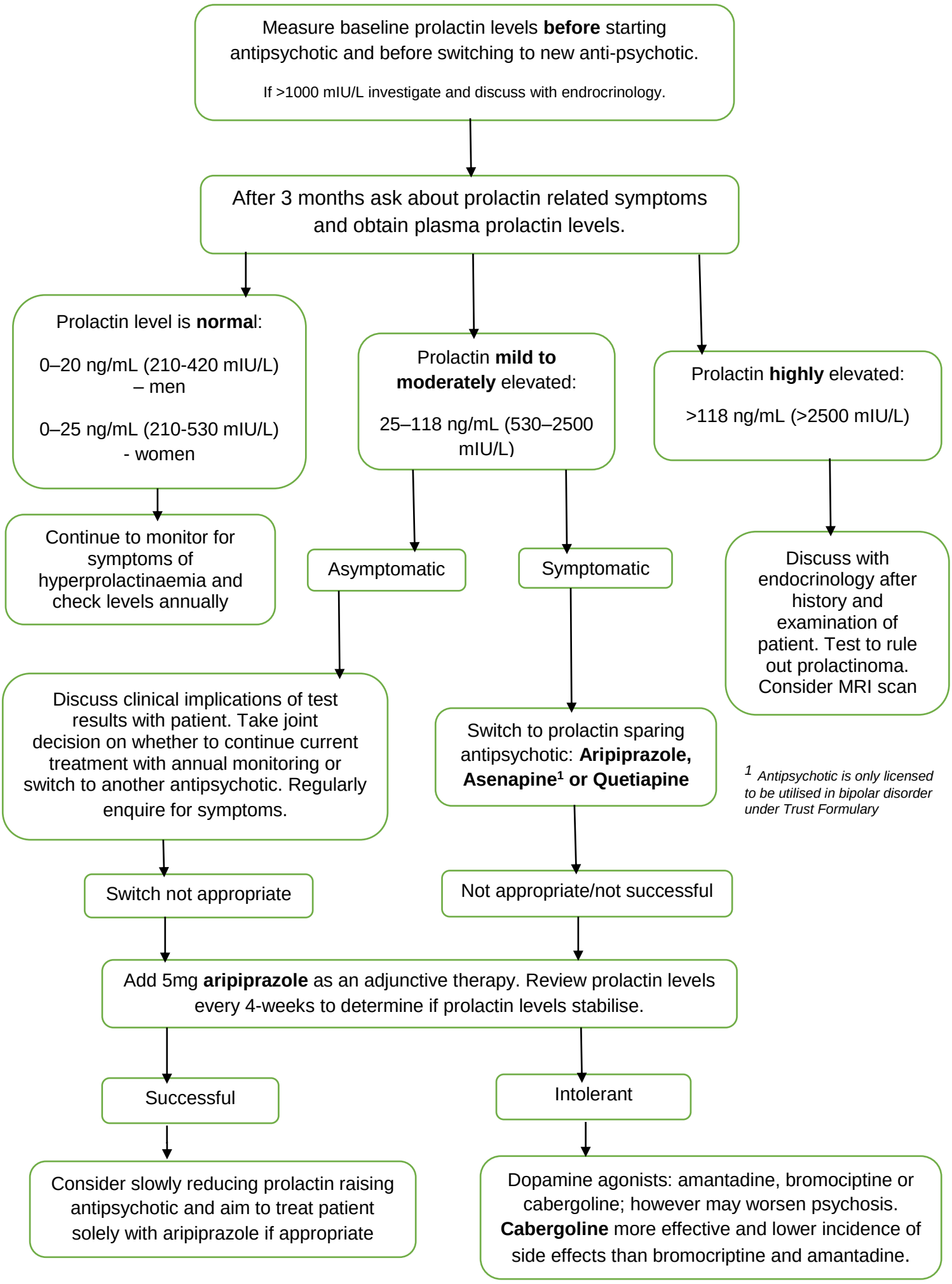
Although patients can be switched to antipsychotics with a lower risk of prolactin elevation (see table 1.1). Treatment for hyperprolactinaemia should be individually tailored to the patients symptoms, long term risk of hyperprolactinaemia and the potential effects to their mental health (2)(12), as changes to the patients treatment can destabilise their mental health illness and may result in a relapse (2).
Treatment of hyperprolactinaemia for asymptomatic patients should always be include the patient, to ensure they are aware of the potential clinical implications of hyperprolactinaemia and make an informed decision to continue their current treatment regimen with increased regular prolactin blood levels monitoring, or to switch to an alternative antipsychotic (-refer to ***table 2***).

Where substitution to an antipsychotic with a lower potential of elevating prolactin levels is not feasible, adding low dose aripiprazole (5mg) as an adjunctive therapy to patients existing antipsychotic treatment should be considered, as it has shown to be high effective (2)(13). However, studies have shown by increasing dosage of aripiprazole does not necessary prove to be effective in reducing levels of prolactin (2)(13)(14)(4)(15)(5). As this is currently an unlicensed form of treatment, prolactin levels should also be reviewed on 4-weekly basis to see if prolactin levels stabilise. (2)(12)(14)(15). Where aripiprazole adjunct therapy is effective, clinicians should also considering slowly reducing the dose of antipsychotic that raised prolactin levels, with an aim of treating the patient solely with aripiprazole if appropriate (2)(12).

If after 4-week monitoring of prolactin levels, the levels do not subside, aripiprazole treatment should be discontinued and other forms of treatment should be explored. Clinicians should also take into consideration
aripiprazole's mode of action as a partial agonist at D2 receptors with high receptor affinity, as it could lead to reduce effectiveness in comparison to the original antipsychotic.

In cases where patients need to remain on a prolactin-elevating antipsychotic and are intolerant to aripiprazole, dopamine agonists can be considered (2)(12)(5). Amantadine, bromociptine and cabergoline have shown to be effective in treatment of elevated prolactin, however each of these treatment has the potential to worsen the psychosis theoretically (2)(16)(17)(18). Studies have indicated that Cabergoline being slightly more

effective in treatment of hyperprolactinemia in comparison to the other dopamine agonists and patients having lower incidence of side effects from the medication (12)(16)(18). When considering dopamine agonist as a choice of treatment, the side-effects of the medication should be considered as cabergoline and bromocriptine have been associated with fibrotic reactions and patients who have history of peptic ulcer issue (12).



Approved by Medicines Management Group September 2021

References

1. D.Taylor, F.Gaughran, T.Pillinger, *Maudsley Practice Guidelines for Physical Health Conditions in Psychiatry*, Wiley Blackwell, 2020, Pages 117-123

2. Tomova N, Whale D. Guidance on the Treatment of Antipsychotic Induced Hyperprolactinaemia in Adults [Internet]. 1st ed. Sussex Partnership NHS Foundation Trust; 2021 [cited 1 July 2021]. Available from: http://www.sussexpartnership.nhs.uk/sites/default/files/documents/hyperprolactinaemia_glines_-_final_-_0414.pdf

3. Holt R. Medical causes and consequences of hyperprolactinaemia. A context for psychiatrists. Journal of Psychopharmacology 22(2) Supplement (2008) 28–37

4. Shim J, Shin J, Kelly D, Jung D, Seo Y, Liu K et al. Adjunctive Treatment With a Dopamine Partial Agonist, Aripiprazole, for Antipsychotic-Induced Hyperprolactinemia: A Placebo-Controlled Trial. American Journal of Psychiatry [Internet]. 2007 [cited 1 July 2021];164(9):1404-1410. Available from: https://pubmed.ncbi.nlm.nih.gov/17728426/

5. PETTY R. Prolactin and antipsychotic medications: mechanism of action. Schizophrenia Research [Internet]. 1999 [cited 1 July 2021];35:S67-S73. Available from: https://pubmed.ncbi.nlm.nih.gov/10190227/

6. Meanie AM et al. Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia. *BJP* 2004, 184:503-508.

7. Antipsychotic-Induced Hyperprolactinemia. JR Bostwick et al. Pharmacotherapy. 2009;29 (1):64-73.

8. Sherman S,.Preventing and treating osteoporosis: strategies at the millennium.*Annals of the New York Academy of Sciences*. 2001; 949:188–197.

9. Watts NB. Therapies to improve bone mineral density and reduce the risk of fracture: clinical trial results.*Journal of Reproductive Medicine for the Obstetrician andGynecologist*.2002;47(1):82–92.

10. Rodriguez-Martinez MA & Garcia-Cohen EC. Role of Ca(2+) and vitamin D in the prevention and treatment of Osteoporosis. *Pharmacology & Therapeutics*.2002;93(1): 37–49.

11. Antipsychotic-induced hyperprolactinaemia, hypogonadism and osteoporosis in the treatment of schizophrenia. Journal of Psychopharmacology. 2008;22(2):70-75

12. Tollin S. Use of the dopamine agonists bromocriptine and cabergoline in the management of risperidone-induced hyperprolactinemia in patients with psychotic disorders. Journal of Endocrinological Investigation [Internet]. 2000 [cited 1 July 2021];23(11):765-770. Available from: https://pubmed.ncbi.nlm.nih.gov/11194712/

13. Taylor D, Barnes T, Young A. The Maudsley prescribing guidelines in psychiatry|Prescribing guidelines in psychiatry. 13th ed. Hoboken, NJ: Wiley-Blackwell; 2018.

14. Melmed S, Casanueva F, Hoffman A, Kleinberg D, Montori V, Schlechte J et al. Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism [Internet]. 2011 [cited 1 July 2021];96(2):273-288. Available from: https://academic.oup.com/jcem/article/96/2/273/2709487

15. Cohen L, Biederman J. Treatment of Risperidone-Induced Hyperprolactinemia with a Dopamine Agonist in Children. Journal of Child and Adolescent Psychopharmacology [Internet]. 2001 [cited 1 July 2021];11(4):435-440. Available from: https://pubmed.ncbi.nlm.nih.gov/11838826/

16. Chen C, Huang Y, Ree S, Hsiao C. Differential add-on effects of aripiprazole in resolving hyperprolactinemia induced by risperidone in comparison to benzamide antipsychotics. Progress in Neuro-Psychopharmacology and Biological Psychiatry [Internet]. 2010 [cited 1 July 2021];34(8):1495-1499. Available from: https://pubmed.ncbi.nlm.nih.gov/20732372/

17. Cavallaro R, Cocchi F, Angelone S, Lattuada E, Smeraldi E. Cabergoline Treatment of Risperidone-Induced Hyperprolactinemia. The Journal of Clinical Psychiatry [Internet]. 2004 [cited 1 July 2021];65(2):187-190. Available from: https://pubmed.ncbi.nlm.nih.gov/15003071/

18. Byerly M, Marcus R, Tran Q, Eudicone J, Whitehead R, Baker R. Effects of aripiprazole on prolactin levels in subjects with schizophrenia during cross-titration with risperidone or olanzapine: Analysis of a randomized, open-label study. Schizophrenia Research [Internet]. 2009 [cited 1 July 2021];107(2-3):218-222. Available from: https://pubmed.ncbi.nlm.nih.gov/19038534/

19. Aboraya A, Fullen J, Ponieman B, Makela E, Latocha M. Hyperprolactinemia Associated with Risperidone. Edgmont Psychiatry [Internet]. 2004 [cited 1 July 2021];. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3010960/