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EDITORIAL

Product familiarisation programs

Greg Kyle
Professor of Pharmacy
Director International Engagement and Recruitment
School of Clinical Sciences
Queensland University of Technology
Brisbane

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dabigatran, drug promotion, medicine access programs, Pharmaceutical Benefits Scheme

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Product familiarisation programs (sometimes also called 'patient familiarisation programs') are provided by pharmaceutical companies and are designed to familiarise prescribers with a newly approved medicine while Pharmaceutical Benefits Scheme (PBS) listing is pending.[1] They are usually targeted at specialists and, according to Medicine Australia's Code of Conduct, each individual prescriber can only enrol up to ten patients in a program. The enrolment period is limited to six months, however extensions are allowed if there is a strong clinical or equity rationale.[2]

Probably the biggest product familiarisation program in Australia was conducted by Boehringer Ingelheim for the anticoagulant dabigatran (Pradaxa). Specialists and GPs were approached starting from June 2011 and around 25 000 patients were enrolled in total.[3] The program was extended from June 2012 to December 2013 because the Government delayed PBS listing to review a report on anticoagulant therapies.[4]

Supporters of these programs argue that they increase patient access to medicines and assist with the affordability of new medicines. Prescribers can gain experience with a new drug in 'real world' patients at no financial risk to the patient. Such use allows specialists and GPs to test and monitor patients enrolled in the program, thereby increasing their experience with the new drug and enabling earlier reporting of any adverse drug reactions in 'real world' as opposed to clinical trial patients.

Another advantage is cost. Because the drug's sponsor bears the cost of the product supplied during the program, treatment is free for the patient. This also represents a significant saving to the Government. When listed on the PBS for non-valvular atrial fibrillation on 1 September 2013, the dispensed price for the maximum quantity of dabigatran 110 mg or 150 mg was $96.12. Using this (imperfect) measure for simplicity, the dispensed-price cost would have been $2 403 000 per month for 25 000 patients.

Opponents of product familiarisation programs argue that they are thinly disguised marketing exercises that could increase the net cost of the PBS to the Australian Government. Pharmaceutical companies could use them to gain early exposure to prescribers with their newest drug.

Sponsors will report the headline cost to demonstrate their generosity. However, the dispensed price does not represent the true cost of the drug to the sponsor. While the Government does save money when the product familiarisation program is running, it can be argued that the sponsor is building a ready supply of patients once PBS listing is achieved. In the dabigatran case, there were approximately 25 000 patients ready to continue their prescription on the PBS.

There is also a societal cost to consider, especially with a paucity of head-to-head clinical trials between any new drug and existing therapy. The short-term effect of a familiarisation program may save the Government money, but what is the long-term impact? If the new drug has only marginal incremental patient benefit, but with greater cost, it can sequester PBS money that could have been used for a different drug with a larger incremental benefit.

The big question on most practitioners' minds will probably be 'should I participate or not?' However, it is important to recognise the marketing aspect of these programs that will not be mentioned by company representatives. The overarching aim of sponsors is to sell their drugs.

The decision to enrol a patient in a program should be based on what is best for them. Often newer drugs will not have large amounts of postmarketing experience of their use, and familiarisation programs can provide some experience. It may also be difficult to obtain independent information about the new drug and determine its place in therapy to make an evidence-based prescribing decision. All these factors need to be considered in the decision making.

This is another of the vexed issues in medicine – there are patient benefits, but there is also no such thing as a free lunch … for prescribers or for patients. <

Conflict of interest: none declared

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LETTERS

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

Letters to the Editor

Acupuncture and low back pain

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I was reading the article 'Managing low back pain in primary care'.[1] It included acupuncture as one of the few effective physical therapies. The supporting evidence for this statement was published by the UK National Institute for Health and Care Excellence in 2009. I would like to inform readers that the guidance has been updated. The new guidance states 'Do not offer acupuncture for managing low back pain with or without sciatica'.[2]

Jeremy Laidman
Melbourne

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ARTICLE

Functional dyspepsia

SUMMARY

Functional dyspepsia is characterised by troublesome early satiety, fullness, or epigastric pain or burning. It can easily be overlooked as the symptoms overlap with gastro-oesophageal reflux disease and irritable bowel syndrome.

Diagnosis is clinical, however it requires exclusion of structural gastrointestinal disease. The presence of red flags, such as weight loss or anaemia, should prompt investigation including gastroscopy.

The pathophysiology of functional dyspepsia is not completely understood. It is thought to be associated with upper gastrointestinal inflammation and motility disturbances, which may be triggered by an infectious or allergenic agent, or a change in the intestinal microbiome. Slow gastric emptying occurs in 20% of cases.

While functional dyspepsia is distressing and affects quality of life, it has no long-term impacts on mortality.

There are many treatment options available, with varying levels of evidence of efficacy. These include reassurance, dietary modification, acid suppression, prokinetic drugs including fundic relaxors, tricyclic antidepressants, rifaximin and psychological therapy.

Nicholas J Talley
Laureate professor[1]
Pro-vice-chancellor[1]

Thomas Goodsall
Conjoint research fellow[1]
Registrar[2]

Michael Potter
Conjoint research fellow[1]
Registrar[2]

[1] Global Research University of Newcastle
[2] Department of Gastroenterology John Hunter Hospital Newcastle New South Wales

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dyspepsia, endoscopy, gastro-oesophageal reflux, H_2 receptor antagonists, proton pump inhibitors

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Introduction

Functional dyspepsia is a common problem in Australia and often impacts on quality of life and work productivity.[1,2] It affects 10% of the population and is more prevalent in women.[3-5]

Functional dyspepsia refers to troublesome upper gastrointestinal symptoms including inability to finish a meal (early satiety), postprandial fullness, and epigastric pain or burning.[6] Some patients also complain of nausea, heartburn (although this is not the predominant complaint) and even weight loss (few patients with functional dyspepsia are obese). Peptic ulceration, reflux oesophagitis and gastric cancer may present with identical complaints but the vast majority of patients with these symptoms have functional dyspepsia.

There are two subtypes of functional dyspepsia, although these often overlap in practice (see Box).[6] The largest group (70%) have early satiety or postprandial fullness, termed postprandial distress syndrome. The other group experience ulcer-like pain or burning, termed epigastric pain syndrome.

Early satiety is a prevalent symptom in population-based surveys (5–11%).[3,4] Unless specifically asked about, it may often be missed or misinterpreted as bloating, discomfort or fullness after eating. These are also very common complaints even if meal size is not affected.[3,4] Most patients with these symptoms have no serious pathology on routine testing including gastroscopy, and are labelled as having functional or non-ulcer dyspepsia.[4,6]

Correctly diagnosing functional dyspepsia is important to guide appropriate therapy and reduce unnecessary procedures or treatments.

Differential diagnosis

Distinguishing functional dyspepsia from gastro-oesophageal reflux disease (GORD) without oesophagitis has been an area of clinical confusion, as early satiety can occur in both conditions.[4,6]

Box Rome IV diagnostic criteria for functional dyspepsia subtypes

Postprandial distress syndrome

Bothersome postprandial fullness or early satiety severe enough to impact on regular activities or finishing a regular-size meal for 3 or more days per week in the past 3 months, with at least a 6-month history.

Epigastric pain syndrome

Bothersome epigastric pain or epigastric burning 1 or more days per week in the past 3 months, with at least a 6-month history.

Note: both require the absence of evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy).
Source: Reference 6

Recent evidence suggests GORD is often the diagnostic label applied to patients even if they have typical symptoms of functional dyspepsia with little or no heartburn.[7] In patients with functional dyspepsia and no reflux symptoms, there is a substantially increased risk of GORD developing over the next 10 years.[4,8] Some patients with GORD who fail to respond to acid suppression with proton pump inhibitors may have functional dyspepsia so they should be asked about their symptoms.[4] Emerging data suggest GORD and functional dyspepsia are part of the same disease spectrum.

Symptoms of irritable bowel syndrome often overlap with those of functional dyspepsia, with epigastric pain and postprandial fullness often occurring with lower abdominal pain and bloating (diagnostic criteria in irritable bowel syndrome). However, unlike in irritable bowel syndrome, the symptoms of functional dyspepsia alone are not associated with a change in bowel habit. Both can arise after acute infectious gastroenteritis.[4]

Gastroparesis is often confused with functional dyspepsia but is rare.[4,6] This should be considered in patients with persistent vomiting or weight loss associated with dyspepsia.[4,6] A nuclear medicine gastric-emptying test can be helpful in this setting.

Pathophysiology

Functional dyspepsia has been considered an idiopathic disorder but this view is changing. In some cases, functional dyspepsia develops after acute infectious gastroenteritis, suggesting acute intestinal inflammation may play a role.[4,6]

Helicobacter pylori is a recognised cause of functional dyspepsia.[9] Most patients with *H. pylori* do not develop functional dyspepsia so in many of these cases it is an incidental finding. However in a minority, eradicating the infection cures dyspepsia long term, especially in those with epigastric pain as the main problem.[4,9]

Gastric and duodenal motility disturbances have been observed in functional dyspepsia. Gastric emptying is often normal but may be slow in 25% of patients or occasionally fast.[10] However, symptoms have generally not correlated with slow gastric emptying in functional dyspepsia.[4] Other abnormalities include failure of the gastric fundus to relax normally after eating. This occurs in up to 40% of patients and is linked to early satiety.[4,10] Hypersensitivity to distension of the stomach or duodenum (visceral hypersensitivity) occurs in about one-third of cases.[4,11]

People with postprandial distress have unique duodenal pathology, namely increased duodenal eosinophils that may degranulate.[11-15] Duodenal eosinophils have been linked to increased mucosal permeability, submucosal neuronal structural and functional changes, and symptoms.[12,13] They may reflect an infectious or allergenic trigger. In functional dyspepsia, the duodenal microbiome is also abnormal with increased oral streptococci.[16]

Psychological distress is common in patients with functional dyspepsia but may begin after the gut symptoms manifest.[3,8,17] Anxiety is prevalent but depression can occur and should not be missed.

Proposed disease model

Recently a unifying disease model has been proposed for functional dyspepsia.[4] Either an infection, microbiome alteration or a food allergen, such as wheat, induces increased duodenal permeability and duodenal eosinophilia with or without increased mast cells. This activates a mucosal immune response. Local duodeno-gastric reflex responses to low-grade inflammation alter gastroduodenal function, including impaired fundic relaxation in a subset of patients. Circulating cytokines such as tumour necrosis factor alpha may lead to systemic and central nervous system symptoms such as anxiety.[18]

These concepts are all supported by experimental evidence and, if correct, the model represents a paradigm shift with profound treatment implications.

Diagnosis

A typical history of long-standing troublesome early satiety and postprandial fullness is sufficient to make a clinical diagnosis and commence treatment, but often gastroscopy is required.[4,6] Any of the following red flag symptoms should prompt endoscopy:

- new onset in older age
- unintended weight loss
- vomiting
- bleeding
- iron deficiency anaemia
- family history of upper gastrointestinal cancer
- progressive dysphagia or odynophagia.

It is otherwise reasonable to screen for *H. pylori* infection by breath or stool antigen test and treat positive cases. Non-steroidal anti-inflammatory drugs should be stopped before either investigation or an empiric trial of therapy, usually a proton pump inhibitor for 2–4 weeks, in those who are still symptomatic.[4,6]

If gastroscopy is required, biopsies can be obtained from the duodenum as well as stomach to look for coexistent pathology even if the mucosa looks normal.

Treatment

There are many treatment options available for functional dyspepsia, with some being more effective than others (see Table). Many patients will respond to non-pharmacological management and drug therapy should be reserved for refractory cases.

Reassurance and explanation

Making a firm diagnosis even in the absence of endoscopy is sound medical practice and probably therapeutic. Functional dyspepsia is common and impacts on quality of life, but the good news is there is no associated increased mortality.[19] Reassurance, explanation and advice to reduce stress should be routine. Depression should be excluded by asking simple screening questions.[20]

Diet

Traditionally eating smaller regular low-fat meals is the advice offered, as the stomach and duodenum can process these more easily (a high fat intake slows gastric emptying)[21] and gastric distension is minimised. Wheat may induce typical dyspepsia symptoms. Eliminating it may provide relief in some patients although strong empirical evidence is lacking.[22] Theoretically a low FODMAP diet, an established therapy for irritable bowel syndrome, may help by reducing upper intestinal distension but there is no empirical evidence in functional dyspepsia.[22] Other triggers have been identified, including fatty, fried or spicy foods, and carbonated drinks, and avoiding these may be of benefit.[23]

Table **Usefulness of therapies for functional dyspepsia**

Therapy	Functional dyspepsia subtypes	
	Epigastric pain syndrome	Postprandial distress syndrome
Reassurance	+	+
Diet	+	+
Acid suppression	++	+
Prokinetics	+	++
Fundic relaxors	-	+
Tricyclic antidepressants	++	+
Rifaximin	+	+
Psychological therapy	+	+

- not useful
+ limited evidence of efficacy
++ efficacious

Acid suppression

Reducing the amount of acid bathing the duodenum may be helpful.[4] Proton pump inhibitors are superior to placebo in functional dyspepsia. However, they have risks with long-term use. The majority of patients do not respond to this therapy, and it is most useful in those with epigastric pain.[24] An alternative is H_2 receptor antagonist therapy, which is also superior to placebo. Some patients find this helpful even if proton pump inhibitors have failed.[24] Antacids and sucralfate are not efficacious.[24]

Prokinetics

In Australia, domperidone is sometimes prescribed but the evidence for efficacy in functional dyspepsia is very limited.[24] Cisapride has a better evidence base and is available from compounding chemists.[24] Both of these drugs prolong the QT interval and must be used with caution. ECG monitoring is recommended. Prokinetics help postprandial distress more than pain. Metoclopramide should be avoided unless nausea is a serious issue as irreversible tardive dyskinesia is a concern. For nausea in such cases a $5HT_3$ antagonist (ondansetron) is preferred.[24]

Fundic relaxors

Fundic relaxors can be considered for people unresponsive to prokinetics. Cisapride relaxes the gastric fundus, but alternative options include the anti-anxiety drug buspirone[25] or the over-the-counter product Iberogast.[26]

Antidepressants

Low-dose tricyclic antidepressants are superior to placebo for functional dyspepsia, but they are probably most helpful for those with epigastric pain.[27,28] Consider amitriptyline 10–25 mg at night increasing to 50 mg if tolerated after 2–4 weeks. Some people may need doses up to 100 mg. These doses may be associated with adverse effects, especially in older patients.

Selective serotonin reuptake inhibitors and selective noradrenaline reuptake inhibitors are reported to be no better than placebo.[27] Mirtazepine may have some efficacy particularly if nausea is associated.[29]

Non-absorbable antibiotic rifaximin

The microbiome is disturbed in functional dyspepsia. One randomised controlled trial from Hong Kong has reported rifaximin was superior to placebo, although this is currently an expensive off-label therapy and data

on relapse and retreatment are not available.[30] While rifaximin's predominant effect in functional dyspepsia is believed to be antibiotic, its anti-inflammatory properties may contribute to symptom relief.[30]

Psychological therapy

Evidence for psychological therapy in functional dyspepsia is limited. However, for patients with a strong psychological component, offering cognitive behavioural therapy is reasonable.[4,6]

The future

Low-grade duodenal inflammation may be amenable to anti-inflammatory therapy and possible cure. An eosinophil-stabilising drug montelukast appeared to have efficacy in children with functional dyspepsia.[31]

Conclusion

Functional dyspepsia is common, and the diagnosis can be made clinically in the absence of red flags. Concerning features on history or physical examination should prompt referral to a gastroenterologist for consideration of gastroscopy. Although symptoms can be significantly troublesome or disabling, there is no long-term effect on mortality. Multiple pharmacological and non-pharmacological therapies are available for patients with functional dyspepsia, giving clinicians several options for managing patients with this condition. <

Nicholas Talley has received grants and research support from: Abbott Pharmaceuticals (IBS), Commonwealth Diagnostics (International), Janssen (constipation), Prometheus (IBS), Pfizer (at Mayo Clinic), Rome Foundation and Salix (at Mayo Clinic). He has patents on: biomarkers of irritable bowel syndrome, licensing questionnaires (Mayo Clinic), Nestec European Patent Application No. 12735358.9 and New Singapore 'Provisional' Patent NTU Ref: TD/129/17 'Microbiota Modulation of BDNF Tissue Repair Pathway'. He has been involved with the following consultancies: Adelphi Values (functional dyspepsia working group to develop a symptom-based PRO instrument), Allergens PLC (GI development programs), GI therapies (non-invasive device company, consultant and options), Napo Pharmaceutical, Outpost Medicine, Samsung Bioepis and Yuhan (IBS).

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ARTICLE

Thyroid disorders in pregnancy and postpartum

Ashleigh Smith
Obstetrics and gynaecology registrar[1]

Jade Eccles-Smith
Basic physician trainee[2]

Michael D'Emden
Consultant endocrinologist[2]
Director
Endocrinology and Diabetes[2]

Karin Lust
Consultant obstetric and General physician[2]
Interim clinical director
Obstetrics and Gynaecology[2]

[1] Obstetrics and Gynaecology
Mater Mothers' Hospital
South Brisbane

[2] Royal Brisbane and Women's Hospital
Brisbane

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SUMMARY

Thyroid dysfunction in pregnancy has consequences for mother and baby. Potential problems include pre-eclampsia, prematurity and congenital abnormality.

For women known to have hypothyroidism, an increase in thyroxine dose by 20–40% when pregnancy is confirmed usually ensures they remain euthyroid. Treatment of subclinical hypothyroidism is recommended if the woman has antithyroid antibodies.

Treatment of hyperthyroidism, unless it is related to human chorionic gonadotrophin, involves propylthiouracil in the first trimester. Carbimazole may be used in the second trimester. Thyroid function tests are checked every month and every two weeks following a change in dose.

Women with a current or a past history of Graves' disease who have thyrotropin receptor antibodies require early specialist referral as there is a 1–5% risk of fetal hyperthyroidism.

Women with thyroid disorders in pregnancy should be followed up by their GP in the postpartum period. Postpartum thyroiditis may present months after delivery.

Introduction

Normal thyroid function is essential for fetal development. A deficiency or an excess of thyroid hormone can occur in pregnancy. Thyroid dysfunction can cause problems for both the mother and baby.[1-3] Sometimes the hypothyroidism or hyperthyroidism is subclinical (Table 1).[2,4-6]

Universal screening in pregnancy is currently not recommended, but is recommended for women with a higher risk of thyroid dysfunction (Box 1).[1,7] Women with known thyroid disease will need to have their treatment adjusted and more frequently monitored during pregnancy (see Fig.).

Physiology

During pregnancy the thyroid gland undergoes hyperplasia and increased vascularity. Circulating iodine is reduced and thyroid-binding globulin increases.

The rising concentration of beta-human chorionic gonadotrophin (HCG) in the first trimester can directly stimulate the thyroid stimulating hormone (TSH) receptor as HCG has structural similarities to TSH. This in turn leads to increased free triiodothyronine (fT3) and free thyroxine (fT4), suppressing TSH secretion. A serum TSH below 0.1 mIU/L may be present in 5% of women by the 11th week of pregnancy.

Table 1 **Prevalence of thyroid disorders in pregnancy**

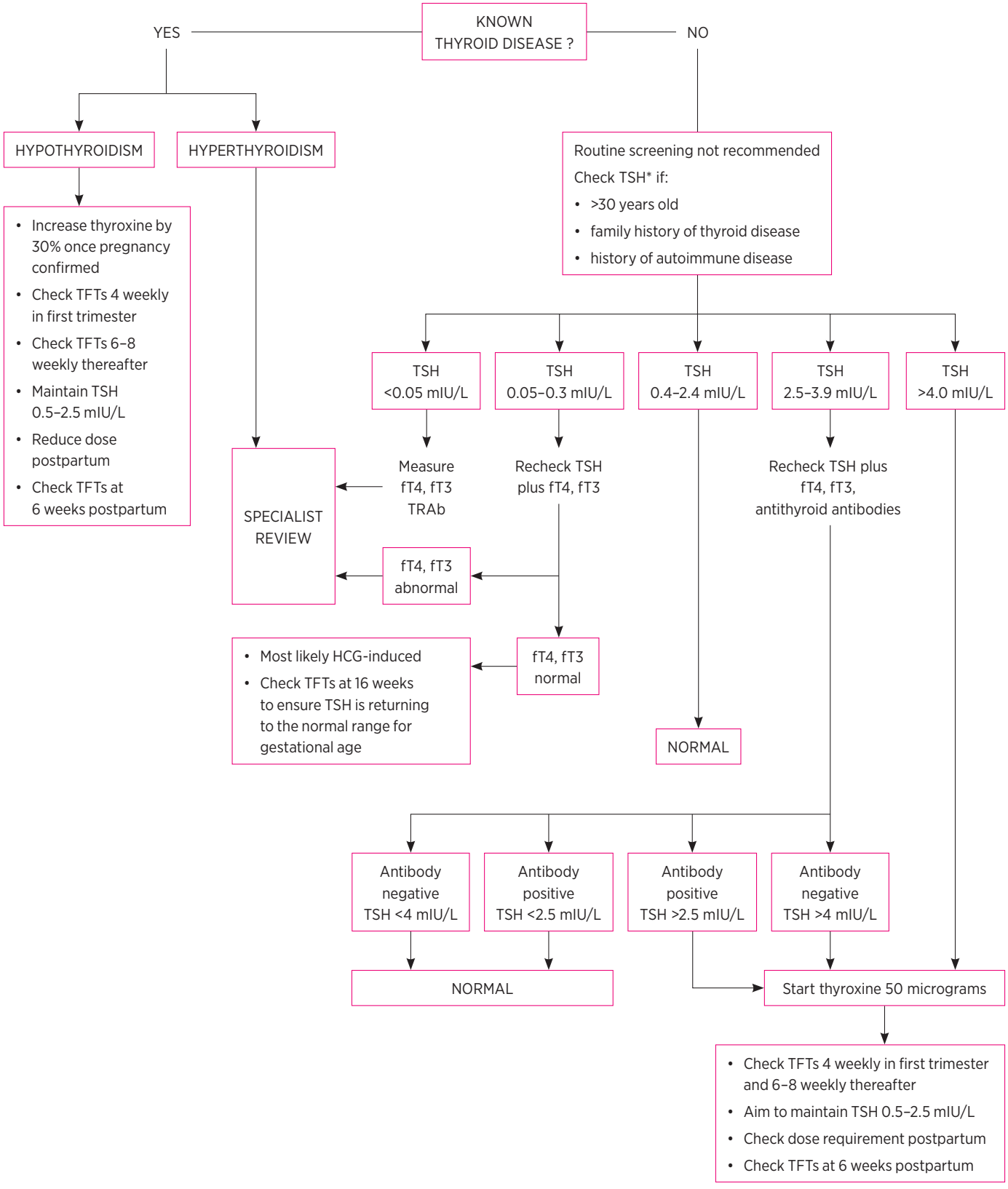
Disorder	Prevalence in screened pregnancies
Overt hypothyroidism	0.3–0.5%[2]
Subclinical hypothyroidism + antithyroid peroxidase antibodies negative	Total 2–3%[2]
Subclinical hypothyroidism + antithyroid peroxidase antibodies positive	Total 2–3%[2]
Overt hyperthyroidism	0.1–0.4% (Graves' disease accounts for 85% of these cases)[1]
Human chorionic gonadotropin-mediated hyperthyroidism	1–3%[4,5]
Subclinical hyperthyroidism	2–5%[4]
Thyroid nodules	3–21%[6]

Box 1 **Recommendations for thyroid function screening in pregnancy**

- Women from an area with moderate to severe iodine insufficiency
- Symptoms of hypothyroidism
- Family or personal history of thyroid disease
- Family or personal history of thyroid peroxidase antibodies
- Type 1 diabetes
- History of head and neck radiation
- Recurrent miscarriage or impaired fertility
- Morbid obesity
- Hyperemesis gravidarum and clinical features suggestive of hyperthyroidism
- Clinical symptoms or signs suggestive of thyrotoxicosis

Source: References 1, 7

Fig. **Thyroid management in pregnancy**



TFT thyroid function test
fT3 free triidothyronine
TSH thyroid stimulating hormone
TRAb thyrotropin receptor antibodies
fT4 free thyroxine
HCG human chorionic gonadotrophin
* TSH concentration varies with gestational age

The TSH subsequently normalises as beta-HCG falls in the second and third trimesters.

In view of these physiological changes, consult gestation-specific TSH concentration ranges when interpreting thyroid function tests. These reference ranges differ from non-pregnant ranges (Table 2).[7,8]

The fetal thyroid starts functioning at 10–12 weeks gestation but does not fully mature until the third trimester. Before then the fetal metabolic requirements are met by maternal thyroxine.

Iodine supplementation

Women have an increased iodine requirement during pregnancy and lactation due to increased thyroid hormone production, increased renal iodine excretion and fetal iodine requirements. The National Health and Medical Research Council recommends pregnant and breastfeeding women take a daily supplement of iodine 150 micrograms. The recommended total daily intake of iodine in pregnancy is 250 micrograms.[9]

Women with hypothyroidism

For women with overt hypothyroidism who are planning pregnancy, guidelines recommend optimisation of TSH before conception. Thyroid dysfunction in pregnancy is clinically important as insufficient thyroxine is associated with an increased risk of premature birth, low birth weight and miscarriage.[2,4,5]

After conception, an increase in thyroxine as soon as possible is recommended with the goal of normalising the TSH concentration. An easy approach is to increase the total weekly thyroxine dose by an extra two tablets per week or by 20–30% of the baseline dose when pregnancy is confirmed.[6,8,10]

Serum TSH should be monitored every four weeks in the first trimester to ensure the woman is euthyroid, and then six to eight weekly therafter.[11] Thyroid function tests should be rechecked four weeks after any dosage adjustments to ensure euthyroid levels are maintained. Aim to maintain TSH in the range 0.5–2.5 mIU/L.

Failure to achieve a euthyroid state despite appropriate therapy necessitates investigation into causes for a lack of thyroxine uptake. This can result from poor adherence to therapy or impaired absorption. Women should be advised to take their thyroxine on an empty stomach before breakfast. There should be a 4–5 hour gap before taking medicines such as vitamins, calcium and iron tablets as interactions in the gastrointestinal tract can reduce thyroxine absorption.

Following delivery, the thyroxine dose should be reduced to the patient's preconception dose, assuming the woman was euthyroid on that dose. Check thyroid function tests 4–6 weeks after their dose has been reduced postpartum.[8]

Table 2 **Normal thyroid stimulating hormone concentrations in pregnancy**

Gestation	Thyroid stimulating hormone (mIU/L)
First trimester	0.1–2.5
Second trimester	0.2–3.0
Third trimester	0.3–3.0

Note that individual laboratories may have slightly different pregnancy-specific ranges and it is important to confirm ranges with your local pathologist.
Source: Reference 7

Hypothyroidism diagnosed during pregnancy

A new diagnosis of overt hypothyroidism should warrant immediate thyroxine replacement and further investigation for the presence of thyroid auto-antibodies:

- antithyroid peroxidase antibodies (antiTPO)
- antithyroglobulin antibodies (TgAb)
- thyrotropin receptor antibodies (TRAb) (if there is a history of treated Graves' disease).

The usual starting dose of thyroxine is at least 50 micrograms per day with maintenance between 100 and 150 micrograms per day.[11,12] The starting dose of thyroxine will depend on the degree of hypothyroidism,[13] the size of the patient and the presence of other medical problems. If unsure, the most important thing is to check thyroid function soon after starting therapy (e.g. at 4 weeks) and up-titrate the dose aiming to achieve a TSH below 2.5 mIU/L as quickly as possible.

Subclinical hypothyroidism

Subclinical hypothyroidism in pregnancy is associated with an increased risk of recurrent miscarriage, intrauterine growth restriction, preterm birth, low birth weight, perinatal mortality and pre-eclampsia.[14-17] Thyroxine may reduce associated risks.[18] Recent studies support thyroxine replacement in women with subclinical hypothyroidism undergoing assisted reproduction technologies, to improve pregnancy outcome.[6,19,20] The aim of treatment is to achieve a TSH less than 2.5 mIU/L.

Women with subclinical hypothyroidism should be tested for antithyroid antibodies as this impacts on the effects in pregnancy and may also be associated

with other autoimmune conditions such as type 1 diabetes.[6,7] At present there are no data to support treating pregnant women who have subclinical hypothyroidism if they do not have antibodies.

Previous guidelines recommended giving thyroxine to all women with subclinical hypothyroidism, regardless of their antibody status.[11] This was due to research which reported multiple maternal and neonatal adverse outcomes associated with subclinical hypothyroidism, however the role of thyroxine therapy in preventing these outcomes was unclear.[21]

The American Thyroid Association in 2017 updated its guidelines for the management of thyroid disease in pregnancy following new research. Thyroxine should be given if there are antithyroid antibodies and the initial TSH is 2.5–4 mIU/L. If the initial TSH is 4 mIU/L or more, start thyroxine irrespective of antibody status.[6]

If a decision is made to treat subclinical hypothyroidism, the suggested starting dose of thyroxine is 50 micrograms per day. Thyroid function tests are checked within four weeks of starting therapy.[11,12]

In the postpartum period the ongoing need for thyroxine needs to be reassessed. The concentrations of thyroid hormones that prompted treatment during pregnancy may be satisfactory in a non-pregnant woman. If the woman had antithyroid antibodies but the initial TSH was less than 4 mIU/L, cease thyroxine and recheck thyroid function at six weeks. If the TSH was greater than 4 mIU/L continue thyroxine. In women who did not have antithyroid antibodies but had TSH greater than 4 mIU/L, cease thyroxine and check thyroid function in six weeks.[6]

Targeted screening is reported to miss up to 30% of cases of thyroid dysfunction. A recent study reported 9.6% of cases of subclinical hypothyroidism would have been missed by targeted screening. If prospective trials find that treating subclinical hypothyroidism in pregnancy is beneficial, this would support universal screening in future.[22]

Hyperthyroidism

Women with a history or new diagnosis of hyperthyroidism in pregnancy should be referred for specialist review (Box 2).[11]

Overt hyperthyroidism in pregnancy has a prevalence of 0.1–0.4%.[1] Graves' disease accounts for 85% of these cases, followed by HCG-mediated hyperthyroidism.[1] Rarer causes include toxic multinodular goitre, thyroiditis and toxic adenoma.[2,23] The presence of thyrotropin receptor antibodies distinguishes Graves' disease from HCG-mediated hyperthyroidism. This is important as they have different risks of fetal hyperthyroidism and require different management.

Nuclear medicine thyroid radioiodine scans are contraindicated in pregnancy due to the risk to the fetus. They should not be used to investigate hyperthyroidism in pregnancy.

HCG-mediated hyperthyroidism (TRAb negative) is usually transient and related to the physiological changes of pregnancy. Treatment is not generally required.[10] Similarly, at present there is no evidence to support the treatment of subclinical hyperthyroidism in pregnancy.[2] Observation with measurements of TSH and fT4 every four to six weeks is recommended as best practice.[2]

The circulating maternal thyrotropin receptor antibodies in Graves' disease have the potential to cross the placenta and cause fetal hyperthyroidism.[2] Maternal antibodies should be checked when pregnancy is confirmed, at 18–22 weeks and again at 30–34 weeks to evaluate the need for neonatal and postnatal monitoring. If the antibodies are elevated, the fetus will require monitoring for thyroid dysfunction with serial ultrasounds for fetal growth and signs of fetal hyperthyroidism.[2,6,23]

Antithyroid therapy

Medical therapy is recommended in women with overt hyperthyroidism due to Graves' disease, toxic adenoma or toxic multinodular goitre.[6] For these women the aims of therapy are to use the lowest dose of antithyroid drugs to minimise maternal and fetal adverse effects.[6] The dose should be adjusted to keep maternal serum fT4 at the upper limit of the normal range to minimise the risk of fetal hypothyroidism.[23]

Both propylthiouracil and carbimazole cross the placenta and have implications in fetal development. The risks include fetal goitre and transient hypothyroidism.[2,24] Both drugs can cause maternal agranulocytosis.[24]

Propylthiouracil is recommended as the first-line antithyroid drug in the first trimester as carbimazole is associated with congenital abnormalities.

Box 2 Pregnant women with thyroid dysfunction

Women who require early referral to an obstetrician and endocrinologist or obstetric medicine physician include those with:

- current Graves' disease
- a history of Graves' disease and treatment with radioactive iodine or thyroidectomy pre-pregnancy
- a previous neonate with Graves' disease
- previously elevated thyrotropin receptor antibody
- a new diagnosis of hyperthyroidism.

Source: Reference 11

Start propylthiouracil at a dose appropriate for the severity of the hyperthyroidism after discussion with an endocrinologist or physician with experience in managing thyroid disease.[2,6,23-24]

If antithyroid medication is required after the first trimester, there is insufficient evidence at present to determine whether propylthiouracil should be changed to carbimazole. Both drugs are associated with rare but significant long-term adverse effects and it is unclear which has the greatest risk in the second trimester. Individual units may have specific management strategies. All women with Graves' disease in pregnancy should be managed by a specialist in this area.[2,6,23-24] If changing an antithyroid drug, assess thyroid function after two weeks, then return to four-weekly monitoring.[2,23,24]

Symptomatic treatment of tachycardia and tremors can be achieved with short-term use of a beta blocker (e.g. propranolol). As pregnancy progresses the dose of the antithyroid drug may be reduced and it can often be stopped.[23]

If the woman cannot be treated with antithyroid drugs, surgery may be indicated. It can be considered for women who are not adherent to the drugs, or who have had a severe adverse reaction and for those who require high doses (consider specialist referral at doses >30 mg/day carbimazole or >450 mg/day propylthiouracil). Ideally, surgery is performed in the second trimester.[4]

At delivery the paediatrician should be informed that the mother has been on antithyroid drugs, or has thyrotropin receptor antibodies as the neonate will require thyroid function monitoring.[23] There is an increased risk of a recurrence of Graves' disease in the postpartum period in women who ceased their antithyroid drug during pregnancy.[23] Women can continue to use thyroxine or antithyroid drugs while breastfeeding.[25]

Thyroid nodules

When a pregnant woman is found to have a thyroid nodule on examination it can be investigated with ultrasound. Imaging with radioactive iodine is contraindicated in pregnancy.

If the woman has a solid nodule smaller than 10 mm, it can usually be investigated after delivery. Ultrasound-guided fine-needle aspiration for cytology is indicated for larger lesions. Fine-needle aspiration should be considered for a nodule of 5 mm or more if the woman has a high risk of thyroid cancer or the ultrasound findings are suspicious for malignancy. Complex nodules 15 mm or larger also require fine-needle aspiration.

Some authors recommend that women near term (i.e. delivery in <4 weeks) could have fine-needle aspiration delayed until postpartum with probable safety.

If the biopsy is diagnostic or highly suspicious of malignancy, postponing surgery until postpartum is unlikely to change disease-specific survival in women with papillary or follicular neoplasm without evidence of advanced disease. However surgery could still be offered in the second trimester.[2,23,26]

Immediate surgery is indicated if the nodule causes tracheal obstruction.

Postpartum thyroiditis

Postpartum thyroiditis is defined as the development of hypothyroidism, thyrotoxicosis or both in the year following delivery, in any woman who did not have clinical evidence of thyroid disease before pregnancy.[2] It occurs in 7–10% of postpartum women, although this varies depending on iodine intake and genetic factors.[2]

Investigation for postpartum thyroiditis is recommended if there is a clinical suspicion and it should be considered as a differential diagnosis in women presenting with depressive symptoms in the postpartum period. Almost 50% of women with antithyroid peroxidase antibodies in early pregnancy will develop postpartum thyroiditis, therefore it is the most useful marker identifying those at risk.[27] Thyroid function tests are indicated at three and six months postpartum in these women and those with known autoimmune disease, previous postpartum thyroiditis or chronic viral hepatitis.[2]

Annual TSH tests for 5–10 years are recommended for women with a history of postpartum thyroiditis. They have an increased risk of developing permanent overt hypothyroidism.[2]

Conclusion

Thyroid dysfunction during pregnancy and the postpartum period is a common obstetric problem primarily managed by GPs. At-risk women are screened, but universal thyroid function screening is currently not recommended during pregnancy or postpartum.

Thyroxine is used for treating overt hypothyroidism and is recommended in antibody positive subclinical hypothyroidism. For hyperthyroidism, propylthiouracil is the preferred antithyroid drug in the preconception and first trimester to reduce the risk of teratogenicity.[1] Carbimazole may be used in the second trimester. <

Conflict of interest: none declared

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ARTICLE

Hyperprolactinaemia

Angela X Chen
Endocrine advanced trainee[1]
Associate lecturer[2]
Morton G Burt
Endocrinologist[1]
Associate professor[2]

[1] Southern Adelaide Diabetes and Endocrine Services
Repatriation General Hospital
[2] School of Medicine
Flinders University
Adelaide

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SUMMARY

Serum prolactin should only be measured in patients with a pituitary mass or the clinical symptoms and signs of hyperprolactinaemia.

There are many causes of hyperprolactinaemia, including drugs. It is important to identify the underlying cause to guide appropriate treatment.

Hyperprolactinaemia can cause galactorrhoea and impair reproductive function. It can accelerate bone loss if it is associated with sex hormone deficiency.

Most prolactinomas are microprolactinomas. They usually do not grow sufficiently to cause hypopituitarism or visual field loss.

Patients with a prolactinoma are usually successfully treated with a dopamine agonist such as cabergoline.

Introduction

A high prolactin concentration in blood (hyperprolactinaemia) is a relatively common endocrine abnormality. The causes range from benign conditions requiring no treatment to major medical problems necessitating immediate therapy. Hyperprolactinaemia can also be an adverse effect of some drugs.

Physiology

Prolactin is a polypeptide hormone that is synthesised and secreted by lactotroph cells in the anterior pituitary gland. The secretion of prolactin is primarily regulated by dopamine, which is produced in the hypothalamus and inhibits prolactin secretion. The hypothalamic hormone thyrotropin-releasing hormone stimulates prolactin secretion.

Prolactin exerts its effects by binding to prolactin receptors. These are located on the cell membrane of many cells, particularly in the breast and pituitary. In the breast, prolactin stimulates glandular proliferation during pregnancy and breast milk production postpartum. In the pituitary gland, prolactin inhibits gonadotrophin secretion.

Aetiology of hyperprolactinaemia

There are physiological, pathological and drug-related causes of hyperprolactinaemia (Table 1).

Physiological causes

Pregnancy, suckling and lactation, exercise, coitus and stress can all increase prolactin. These increases are transient, and usually do not exceed twice the upper limit of normal reference ranges.

Estimates suggest that at least 10% of hyperprolactinaemia is secondary to macroprolactinaemia.[1] This arises when immunoglobulins in serum bind prolactin to create high-molecular-weight forms of prolactin. As clearance of these macroprolactin molecules is slower than monomeric prolactin, the serum prolactin concentration increases. Macroprolactin is largely biologically inactive, so most patients with macroprolactinaemia are asymptomatic.

Pathological causes

Prolactinomas are tumours arising from the prolactin-secreting cells in the pituitary. Most prolactinomas (90%) are microadenomas (<1 cm in diameter), which are 10 times more common in women than in men. Microadenomas cause a moderate elevation in prolactin that can be associated with symptoms of hyperprolactinaemia, but they usually do not grow and cause a mass effect or hypopituitarism.[2]

Macroadenomas (>1 cm in diameter) are less common and giant prolactinomas (>4 cm in diameter) are rare. Compared with women, men are nine times more likely to present with a macroadenoma. These tumours cause marked hyperprolactinaemia – a prolactin concentration more than 10 000 mIU/L almost always indicates a macroprolactinoma. They can cause hypopituitarism and visual field loss or ocular palsies by compressing the optic chiasm or the cranial nerve nuclei.

Other hypothalamic and pituitary masses can also cause hyperprolactinaemia. As dopamine inhibits prolactin secretion, any mass or infiltrative lesion that compresses the pituitary stalk can attenuate dopamine's action and cause hyperprolactinaemia.

However, hyperprolactinaemia from stalk compression is usually below 2000 mIU/L, allowing distinction from a macroprolactinoma.[3]

Several illnesses can cause hyperprolactinaemia. Prolactin is predominantly renally cleared, so renal impairment can increase prolactin concentration. As thyrotropin-releasing hormone stimulates prolactin secretion, hypothyroidism can also cause hyperprolactinaemia. Seizures can cause a transient increase in prolactin.

Drug-related causes

A number of drugs impair hypothalamic dopamine release leading to increased secretion of prolactin (prolactin 500–4000 mIU/L). Hyperprolactinaemia develops in patients taking antipsychotics such as risperidone. It can also develop, to a lesser extent, with some selective serotonin reuptake inhibitors.[4,5] Other drugs may cause hyperprolactinaemia less frequently (Table 1). If hyperprolactinaemia is drug-induced, concentrations usually normalise if the drug is ceased for 72 hours.

Clinical features

In some patients hyperprolactinaemia causes no symptoms, but it can affect breast and reproductive function (Table 2 and Fig. 1). In women, it can cause oligo-amenorrhoea, infertility and galactorrhoea. In men, hyperprolactinaemia can result in erectile dysfunction, infertility and gynaecomastia. Galactorrhoea is much less common in men than in women.[6] In both sexes, gonadal hormone deficiency can accelerate bone loss. Patients may present with symptoms or signs associated with the underlying cause of hyperprolactinaemia. For example, headache and visual loss in a patient with a pituitary mass, and fatigue and cold intolerance in a patient with hypothyroidism.

Investigation

It should be emphasised that prolactin should only be measured in patients with clinical symptoms or signs of hyperprolactinaemia or patients with a known pituitary mass.

The diagnosis of hyperprolactinaemia can be based on a single measurement of serum prolactin that is above the upper limit of normal. The venepuncture must be performed without excessive stress.[5]

Macroprolactinaemia should be excluded, especially in asymptomatic patients, by adding polyethylene glycol to a serum sample to precipitate macroprolactin.[5] Many laboratories in Australia routinely screen for macroprolactin in cases of apparent hyperprolactinaemia. Polyethylene glycol precipitation also allows for the measurement of monomeric prolactin, which is usually normal in patients with macroprolactinaemia.

Once the diagnosis of hyperprolactinaemia has been made, investigations are required to identify the underlying cause and associated complications. Women and men should have oestrogen and morning testosterone measured respectively along with gonadotrophins. Thyroid and renal function should be assessed and pregnancy excluded in women of childbearing age.

Table 1 **Causes of hyperprolactinaemia**

Cause	Examples
Physiological (transient hyperprolactinaemia)	Pregnancy Lactation Excercise Coitus Chest wall/nipple stimulation Stress Seizure
Macroprolactinaemia	Immunoglobulin (IgG) binding prolactin
Hypothalamic/ pituitary lesions	Prolactinoma Non-functioning masses: • adenoma • craniopharyngioma • meningioma • Rathke's cleft cyst Inflammatory/infiltrative lesions: • lymphocytic hypophysitis • Langerhan's cell histiocytosis
Other illness	Hypothyroidism Chronic renal failure
Drugs	Antipsychotics (risperidone, amisulpride, paliperidone, haloperidol) Antiemetics (metoclopramide, domperidone) Antidepressants (uncommon) Opioids Oestrogens Antihypertensives (verapamil)

Table 2 **Clinical features of hyperprolactinaemia**

	Women	Men
Breast	Galactorrhoea	Gynaecomastia Galactorrhoea
Reproductive	Oligo-amenorrhoea Infertility Osteopenia/osteoporosis	Erectile dysfunction Infertility Osteopenia/osteoporosis

Unless another clear cause is identified, MRI of the pituitary is indicated. Patients with a pituitary mass more than 1 cm in diameter should have investigations assessing other pituitary hormones and have visual field testing. Measure the bone mineral density of hypogonadal patients.

Management

Some patients do not require treatment.
Patients with physiological hyperprolactinaemia, macroprolactinaemia, asymptomatic microprolactinoma or drug-induced hyperprolactinaemia usually do not require treatment. If hyperprolactinaemia is secondary to hypothyroidism, treating the patient with thyroxine should normalise prolactin.

Drug-induced hyperprolactinaemia

In patients with symptomatic drug-induced hyperprolactinaemia the first consideration is whether the drug can be withdrawn, or replaced with an alternative that does not cause hyperprolactinaemia. If the risks of stopping the drug are greater than the potential benefits, any hypogonadism can be treated with appropriate sex hormone replacement. Occasionally patients with galactorrhoea can be prescribed a dopamine agonist, but this may impair the primary action of the drug which has caused the hyperprolactinaemia. For example, prescribing a dopamine agonist to a patient taking an antipsychotic drug could exacerbate their psychiatric condition.

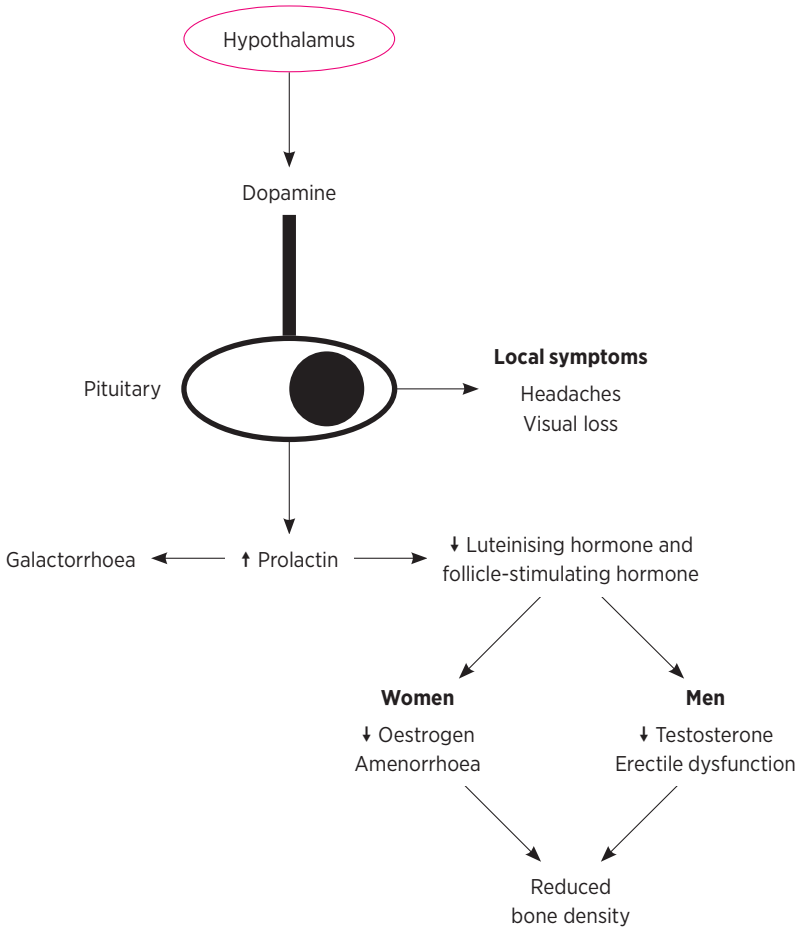
Prolactinoma

The first-line treatment of a prolactinoma is a dopamine agonist. These are recommended in all patients with a macroprolactinoma and most patients with a symptomatic microprolactinoma. The two most commonly used dopamine agonists in Australia are cabergoline and bromocriptine. Both drugs should be started at a low dose and titrated up as required to minimise gastrointestinal adverse effects and orthostatic hypotension. A third option, quinagolide, is a non-ergot-based dopamine agonist that is also available in Australia.

Bromocriptine is a non-selective dopamine agonist that binds to D1 receptors in the gut and D2 receptors in the pituitary. Cabergoline has a longer half-life and is more specific for the D2 receptors. Consequently, cabergoline is more effective and better tolerated than bromocriptine and is the recommended first-line treatment.[5,7] Cabergoline normalises prolactin in up to 95% of patients, reduces tumour size in about 90% and controls symptoms in the majority of patients.[5] It can be extremely effective, even in a patient with a giant prolactinoma (Fig. 2). Correction of sex hormone deficiency also improves bone mineral density, although bisphosphonate therapy can occasionally be required.

Treatment resistance is defined as a less than 50% reduction in tumour size or a prolactin concentration that does not return to normal with dopamine agonist therapy. It occurs in 10% of patients with a prolactinoma treated with cabergoline and in 25% of those treated with bromocriptine.[5] In these patients, an alternative dopamine agonist or higher than usual doses can be trialled. Patients with persistent visual field defects, dopamine agonist resistance and pituitary apoplexy* often require transsphenoidal surgery, radiotherapy or both. Following surgery, prolactin normalises in approximately 90% of patients with microadenomas but in less than 50% of patients with macroadenomas.[5]

Fig. 1 **Clinical and endocrine effects of a prolactinoma at diagnosis**



* Pituitary apoplexy is an emergency caused by acute haemorrhage or infarction in the pituitary gland. Symptoms may include severe headache and altered vision.

Safety of dopamine agonists

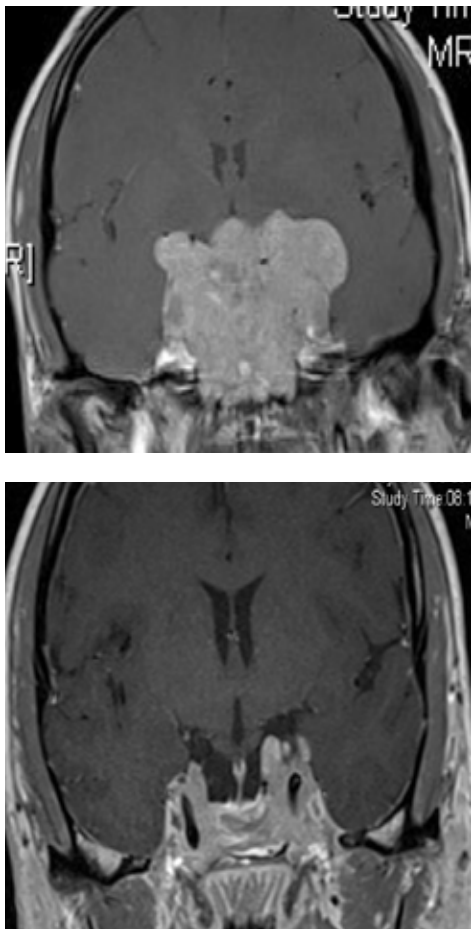
In addition to D2 receptors, cabergoline has high affinity for serotonin 2B (5-HT_{2B}) receptors on cardiac valves. Consequently, cabergoline has been associated with cardiac valvulopathy in patients with Parkinson's disease,[8] but this adverse effect is mainly when daily doses are above 3 mg.[8] Most patients with prolactinoma require much lower doses, for example less than 2 mg/week. The available evidence suggests that these lower doses of cabergoline do not cause valvulopathy.[5] Bromocriptine does not activate the 5-HT_{2B} receptor so does not cause valvulopathy.

Monitoring and withdrawal

Prolactin should be measured one month after starting a dopamine agonist and periodically thereafter. Pituitary MRI is often repeated after one year of therapy in patients with a microprolactinoma.[5] It should be repeated earlier in patients with a macroprolactinoma, new symptoms or a progressive increase in prolactin concentration despite treatment. Visual fields and bone density should be reassessed if they were abnormal before treatment.

Dopamine agonists can often be stopped after 2–3 years of dopamine agonist treatment in patients who maintain a normal prolactin concentration during gradual tapering of the dopamine agonist dose, especially if there is no visible adenoma on MRI.[5] However, the risk of recurrent hyperprolactinaemia ranges from 26–69%. Recurrence is usually during the first 12 months after treatment cessation, therefore serum prolactin must be regularly monitored after treatment withdrawal.[6,9]

Fig 2. **MRI showing shrinkage of a giant prolactinoma**



a Tumour at diagnosis
b After two months of cabergoline treatment

Pregnancy

In women, dopamine agonist therapy usually restores ovulation and fertility. The oestrogen concentration increases during pregnancy and causes clinically significant growth in 20–25% of macroprolactinomas. However, the risk of significant enlargement of a microprolactinoma is only about 3%.

There is no evidence that bromocriptine or cabergoline are associated with adverse outcomes in pregnancy, however in women with a microadenoma, dopamine agonists are usually stopped when pregnancy is confirmed. As the prolactin concentration rises during normal pregnancy, serial prolactin measurement is not informative. Patients should be monitored for clinical signs, such as visual field loss, which suggest the tumour is growing. MRI and visual field testing can be performed if there are concerns.

In patients with a macroadenoma the decision whether to stop a dopamine agonist during pregnancy should be individualised. They should undergo regular clinical review and visual fields should be formally assessed every three months.

Conclusion

Hyperprolactinaemia is a common occurrence encountered in clinical practice. Investigations are needed to find the cause of hyperprolactinaemia to guide appropriate treatment. Symptomatic patients with a prolactinoma are usually treated with the dopamine agonist cabergoline. This effectively normalises prolactin and reduces the size of the prolactinoma in the majority of patients. ≺

Morton Burt was previously awarded a competitive Pfizer cardiovascular lipid research grant.

Q:

SELF-TEST QUESTIONS

True or false?

1. Macroprolactinaemia requires treatment with transsphenoidal surgery.
2. Dopamine inhibits the secretion of prolactin.

Answers on page 247

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ARTICLE

Surgical antimicrobial prophylaxis

SUMMARY

Surgical antimicrobial prophylaxis is the most common indication for antimicrobial use in Australian hospitals. However, it is associated with high rates of inappropriate use.

Effective use of antimicrobials to prevent infection is essential to reduce risks associated with surgical procedures. Efforts need to be made to maximise the quality of surgical antimicrobial prophylaxis prescribing.

Procedural prophylaxis (before or during surgery) is not indicated for all surgeries, especially minor procedures. Post-procedural prophylaxis, including the use of topical antimicrobials, is rarely indicated yet frequently prescribed.

The Therapeutic Guidelines: Antibiotic is a key reference for all Australian prescribers.

GPs can have a significant role in optimising surgical antimicrobial prophylaxis and reducing the burden of inappropriate antimicrobial use.

Courtney Ierano
PhD Fellow[1]

Jo-Anne Manski-Nankervis
General practitioner[2]
Lecturer in primary care[2]

Rod James
Project officer[1]

Arjun Rajkhowa
Centre manager[1]

Trisha Peel
Chief investigator[1]
Infectious diseases and antimicrobial stewardship physician[3]

Karin Thursky
Director[1]
Deputy head[4]

[1] National Centre for Antimicrobial Stewardship
Doherty Institute
Royal Melbourne Hospital/ University of Melbourne

[2] Department of General Practice
University of Melbourne

[3] Department of Infectious Diseases
Alfred Health and Monash University

[4] Department of Infectious Diseases
Peter MacCallum Cancer Centre
Melbourne

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Introduction

Surgical antimicrobial prophylaxis refers to the use of antibiotics for the prevention of surgical site infections,[1] and does not include preoperative decolonisation or treatment of established infections. It is the most common indication for antimicrobial use in Australian hospitals. However, 40% of prescriptions were found to be inappropriate in the 2015 National Antimicrobial Prescribing Survey, which analysed 22 021 prescriptions from 281 hospitals.[2] Inappropriate use, such as extended duration of surgical prophylaxis (e.g. 5 days of cefalexin at discharge), contributes to the overall burden of antibiotic use in the community and exposes patients to adverse reactions and *Clostridium difficile* infections.

Optimal prescribing in surgical prophylaxis is ideally concordant with the Therapeutic Guidelines: Antibiotic[3] or local guidelines (as endorsed by the Antimicrobial Stewardship Clinical Care Standard).[4] Prescribing of prophylaxis occurs in acute and primary care. However, current data on the extent of prescribing in primary care are lacking.

Antimicrobial stewardship

Antimicrobial stewardship is defined as 'coordinated actions designed to promote and increase the appropriate use of antimicrobials',[2] and is considered an important strategy for the conservation of the effectiveness of antibiotics. Since 2011, it has been one of the compulsory criteria for hospital accreditation.[5] Appropriate surgical antimicrobial prophylaxis prescribing is part of the national Antimicrobial Stewardship Clinical Care Standard, which was released in 2014.[4] This standard was developed for hospital and general practice prescribers and patients. Monitoring antimicrobial use and resistance is a requirement of the National Safety and Quality Health Service Standards.[6]

Significant improvement in prescribing practices (potentially attributable to antimicrobial stewardship programs) in hospitals has been observed by auditing tools such as the National Antimicrobial Prescribing Survey.[2] Despite identifying surgical antimicrobial prophylaxis prescriptions as a key area of concern, the 2015 Survey found a decline in the proportion of surgical prophylaxis prescriptions extending greater than 24 hours.[2] Further improvements are still required to meet the best-practice target of less than 5%.[2]

The 2016 Surgical National Antimicrobial Prescribing Survey solely focuses on surgical prophylaxis prescribing.[7] Its results highlight ongoing concerns regarding inappropriate procedural and post-procedural prescribing (43.4% and 46.5% respectively) in Australian hospitals. Procedural prophylaxis was defined as any antimicrobial prescribed immediately before or during the surgery, while post-procedural prescribing refers to antimicrobials given after the procedure. Where guidelines were available, 41% of procedural and 62% of post-procedural prophylaxis was non-concordant with guidelines (see Table).[7]

Appropriate surgical antimicrobial prophylaxis

The key elements of appropriate surgical antimicrobial prophylaxis prescribing include the correct indication, antimicrobial, drug dose, route, timing of administration and duration.

Table **2016 Surgical National Antimicrobial Prescribing Survey results**

Key assessments	Procedural prophylaxis*	Post-procedural prophylaxis
Overall inappropriateness of prescribed antimicrobials	43.4%† (1384/3189)	46.5%‡ (1032/2218)
Prescribed antimicrobials non-compliant with guidelines (where guidelines were available)	41%† (1211/2954)	62%‡ (894/1442)
Surgical episodes where antimicrobial prophylaxis was prescribed but not indicated	10.6% (281/2641)	40.3% (503/1248)

* antimicrobials prescribed immediately before or during the surgical procedure
† procedural antimicrobials measured in doses
‡ post-procedural antimicrobials measured in prescriptions (or courses)
Source: Reference 7

Right indication

All surgical procedures carry a risk of infection. However, the benefit of prescribing prophylaxis must be balanced against the potential risks of antimicrobial use, including allergic reactions, antibiotic-associated *C. difficile* and antibiotic resistance.

The 2016 Surgical National Antimicrobial Prescribing Survey found procedural antimicrobial prophylaxis was prescribed but not indicated in 10% of surgical procedures, and post-procedural prophylaxis was prescribed but not indicated in 40% of procedures (see Table).[7]

Prophylaxis is not indicated for clean non-prosthetic-associated procedures as defined by international guidelines.[3,8,9] It is more likely to be indicated for procedures where:

- the incidence of surgical site infections tends to be high, for example, colorectal surgery
- the consequences of infection are significant, for example, surgery with implanted material such as arthroplasty and cardiac valve surgery.

Overall, there is insufficient evidence to support surgical prophylaxis for minor procedures, and prophylaxis in general practice is usually not warranted.[3,9-11] If a patient has an associated infection (e.g. ingrown toenail, or abscess with cellulitis), an appropriate course of antibiotics should be given but this would not be considered prophylaxis. Key practice points for prescribing appropriate surgical antimicrobial prophylaxis in primary care are listed in the Box.

For dental procedures, guidelines recommend that antimicrobial prophylaxis may be appropriate for surgery in immunocompromised patients, and for surgical removal of a bone-impacted tooth or periapical surgery in a patient with a history of recurrent infections.[3,8,12]

Box **Best-practice surgical antimicrobial prophylaxis in general practice**

- Do not prescribe surgical antimicrobial prophylaxis without an appropriate indication
- Avoid topical antimicrobials for surgical procedures
- Use the eTG for specific information regarding optimal drug, dose, route and timing[3]
- Query long-term use of post-procedural antibiotics with the initial prescriber or surgical team
- Avoid prescribing ongoing supply of topical and oral antimicrobials without a clear indication from the initial prescriber
- Monitor for surgical complications such as superficial, deep and organ space infections, and discuss with the surgeon or treating hospital

The presence of catheters or surgical drains is not an appropriate indication for prolonging surgical prophylaxis.[13] This use is not supported by current evidence and may increase the risk of adverse events associated with antimicrobial use.[8]

Right antimicrobial

The choice of antimicrobial is ultimately influenced by the surgical procedure and associated risk factors. It should provide coverage of the expected microbiological flora at the incision site.[14] This is further influenced by multiple patient-specific risk factors including:

- pre-existing infection
- recent antimicrobial use
- known colonisation with a resistant organism
- prolonged hospitalisation
- prostheses
- weight[15-17]

- renal function
- allergy status
- comorbidities
- immunosuppression.

For the majority of procedures, a first-generation cephalosporin, such as cefazolin, remains the preferred antimicrobial for prophylaxis.[3,14,18] Uptake of this recommendation was shown across current Australian practice in the 2016 Surgical National Antimicrobial Prescribing Survey, with cefazolin being the most commonly prescribed antimicrobial for procedural (69%) and post-procedural prophylaxis (57%). However, 50% of the post-procedural cefazolin prescribing was deemed inappropriate.[7]

Right dose

When indicated, a single defined dose of antibiotic(s), for example, 2 g intravenous cefazolin, is sufficient for most procedures.[3,14] This dose may be influenced by patient-related risk factors such as age, renal function and weight.[15-17]

Right route of administration

Parenteral administration (intravenous or intramuscular) is the preferred route for surgical antimicrobial prophylaxis. However, there are exceptions, including intracameral use for ophthalmic procedures,[3,19] oral antibiotics for transurethral resections of the prostate[3] and surgical terminations of pregnancy,[3,20] and oral amoxicillin before certain dental procedures for endocarditis prophylaxis.[3,12,21]

Within the acute setting, the 2016 Surgical National Antimicrobial Prescribing Survey identified intravenous administration as the most common route for procedural (94.2%) and post-procedural antimicrobials (64.5%). Oral administration accounted for 20.4% of post-procedural antimicrobials, however only 18.4% of oral administrations were deemed appropriate.[7]

Topical prophylaxis

Overall, there are conflicting data regarding the benefits of topical antimicrobial prophylaxis,[22] and it is currently not indicated for most wounds, especially those resulting from clean procedures. The most recently updated Centers for Disease Control and Prevention guidelines for the prevention of surgical site infections also advise against the application of topical prophylaxis.[8] Despite insufficient evidence, antibiotic ointments and creams are frequently used for topical prophylaxis.[23]

Antimicrobial prophylaxis should not be used as a stopgap for inadequate infection prevention measures. Similarly, topical prophylaxis should not be a substitute for good surgical closure technique and dressing management, particularly in cases where wounds are hard to seal and dress.

The most recent Cochrane review proposes that topical prophylaxis 'probably' prevents surgical site infections when compared to antiseptics or no topical antibiotic use.[24] However, when comparing topical antibiotics to no topical antibiotic use, the number needed to treat for one additional beneficial outcome was 50. It is important to note that this Cochrane review of trials from 1967 to 2014 found a considerably high risk of bias. The authors could not draw conclusions regarding the influence of topical antibiotics on antibiotic resistance and wound healing.

An earlier review on topical prophylaxis in dermatological procedures concluded that there was no significant difference between topical antimicrobials and petrolatum or paraffin for postsurgical wound infections.[25] An Australian study found that topical chloramphenicol for high-risk suture wounds produced only a moderate absolute reduction in infection rate that was statistically but not clinically significant.[26] An earlier Australian randomised controlled trial including 1801 surgical wounds found no significant benefit from mupirocin or paraffin ointments before occlusive dressings when compared to no ointment use.[27]

Antimicrobial resistance

High use of topical prophylaxis may increase the risk of antimicrobial resistance. A New Zealand study has correlated increasing use of topical fusidic acid with a rapid clonal expansion of fusidic acid-resistant *Staphylococcus aureus*.[28]

Topical mupirocin is commonly indicated for decolonisation of methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA). Increased use has been associated with 'emergence of resistance through enhanced selective pressure and cross-transmission'.[29] A Korean drug utilisation review found an increase in mupirocin consumption correlated with increases of low- and high-level mupirocin resistance in MRSA infections.[30]

Unrestricted use of mupirocin, in particular for wounds and pressure sores, is strongly associated with increased resistance.[29] Fortunately, in Australia, mupirocin is a Schedule 4 prescription-only medicine so both GPs and hospital prescribers have a significant role in reducing its inappropriate use.

Right timing of administration

Appropriate surgical prophylaxis achieves antimicrobial serum and tissue concentrations that exceed the minimum inhibitory concentration for the most probable organisms at the surgical site during the procedure.[14] Appropriate timing of antimicrobial administration is crucial to prevent effective surgical site infection.

Incorrect timing of prophylaxis before or during a procedure was the most common factor in inappropriate prescribing in the 2016 Surgical National Antimicrobial Prescribing Survey (45.7%).[7]

Most guidelines, including Therapeutic Guidelines: Antibiotic, recommend that preoperative intravenous antibiotics be given within 60 minutes of incision.[3,8,14,31-34] More recently, the World Health Organization recommended administration within 120 minutes of incision.[35] For caesarean sections, evidence supports antimicrobial prophylaxis before cord clamping rather than afterwards.[36,37]

Right duration

A single preoperative dose is adequate for the majority of procedures. Post-procedural doses of intravenous antibiotics (up to 24 hours) are only required in defined circumstances, such as some cardiac and vascular surgeries, and lower limb amputation.[38-40]

The 2016 Surgical National Antimicrobial Prescribing Survey found that incorrect duration was the most common factor in inappropriate post-procedural antimicrobial prescribing (73.7%).[7] Prophylaxis should not extend beyond 24 hours, regardless of the surgical procedure. Intravenous and oral antibiotic prophylaxis offer no benefit beyond this period.[3]

Post-procedural antimicrobials may be initiated in the acute setting but can be reviewed and re-assessed during follow-up with the GP. It is essential that the surgical team clearly communicates with the GP about post-procedural antimicrobial use (usually in the discharge summary).

A recent retrospective cohort study included 1488 patients who received at least 24 hours of parenteral or oral antibiotic therapy. The study identified 20% (n=298) of these patients experienced at least one antibiotic-associated adverse event, and 20% (n=56) of those adverse events were associated with non-clinically indicated antibiotic regimens.[41] The authors stated for every 10 additional days of antibiotic therapy, there was a 3% increased risk of adverse events.[41]

Conclusion

It is important that all prescribers conserve the usefulness of available antibiotics through the practice of appropriate antimicrobial prescribing. GPs and surgeons play a role in reducing inappropriate surgical antimicrobial prophylaxis by only prescribing prophylaxis when indicated.

Further research into surgical antimicrobial prophylaxis prescribing is warranted to tailor future antimicrobial stewardship interventions for these targeted areas and to ensure that there are appropriate guidelines tailored for general practice that are available at the point of care. ≺

Conflict of interest: none declared

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DENTAL NOTE

Antimicrobial prophylaxis for dental surgery

Paul Sambrook
Chair
Dental Therapeutics Committee
Australian Dental Association
Sydney

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Antibiotic prophylaxis for most dental and oral surgical procedures is not needed, especially if the patient is fit and has no cardiac conditions. There is no evidence that it prevents postoperative infection.[1]

There are no studies that show a benefit from prophylactic antibiotics in patients undergoing routine dentoalveolar procedures. Procedures such as removal of teeth including third molars, biopsy of tissues within the mouth, scaling and cleaning, and even placement of dental implants, do not usually require prophylaxis. Antibiotic prophylaxis is considered if there is a risk of infective endocarditis.

Practitioners must distinguish between prophylactic and therapeutic antibiotics. The management of established infection requires an adequate course of an antibiotic, which is effective against the most likely organism. If indicated, prophylaxis is often a single high dose. It is inappropriate to prescribe a so-called 'prophylaxis regimen' for more than five days, to give antibiotics 'just in case', or to use them when a procedure has become more complicated than expected.

Dental practitioners can refer to Therapeutic Guidelines: Oral and Dental, and Therapeutic Guidelines: Antibiotic.[2] The patient's medical practitioner can also be consulted.

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ARTICLE

Clozapine in primary care

SUMMARY

Clozapine is the most effective antipsychotic, but is reserved for people with schizophrenia who have not adequately responded to two other antipsychotics. It has a high adverse event burden and requires close monitoring.

Whether prescribed by the hospital specialist or the GP, the GP will often be responsible for the monitoring of adverse effects and overall health of patients taking clozapine. All health professionals managing these patients must register with a clozapine monitoring service.

Serious adverse effects include neutropenia, agranulocytosis and myocarditis. Monitoring helps to prevent fatal outcomes.

Changes to the dose of clozapine, especially treatment interruptions, should be discussed with the patient's psychiatrist.

Karl Winckel
Senior pharmacist
Princess Alexandra Hospital

Conjoint lecturer
Pharmacy

University of Queensland

Dan Siskind
Psychiatrist
Metro South Addiction and Mental Health Services
Brisbane

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Introduction

Schizophrenia is defined as being treatment resistant if it leads to at least moderate impairment in functioning, and fails to respond to an adequate trial (six weeks with >80% adherence) of two or more antipsychotic drugs at a dose equivalent to at least 600 mg chlorpromazine daily.[1] As many as one-third of patients with schizophrenia experience treatment resistance.

Clozapine is the most effective antipsychotic for reducing positive symptoms and hospitalisations among people with treatment-resistant schizophrenia.[2-4] It should be used in combination with psychosocial therapies such as cognitive behavioural therapy (CBT) for psychosis, illness self-management training, and family support and education.

Clozapine was introduced in the 1960s but was withdrawn in the 1970s because it caused agranulocytosis. As better drugs for treatment-resistant schizophrenia did not emerge, clozapine was reintroduced with a strict scheme for neutrophil monitoring. Since clozapine was reintroduced in Australia in 1993, its use has steadily increased.[5]

Neutrophil monitoring has been so effective at minimising deaths due to agranulocytosis that in 2015 the US Food and Drug Administration recommended weakening the neutrophil cut-off for cessation of treatment to 1 x 10^9/L (currently 1.5 x 10^9/L in Australia, with increased monitoring below 2 x 10^9/L). There have been calls to adopt these relaxed requirements in other countries.[6] However, this should not lead to health professionals underestimating the importance of monitoring and managing adverse effects.

Regulations

Clozapine is usually first prescribed by a psychiatrist according to a treatment protocol. Some Australian states have allowed shared-care prescribing arrangements with GPs, but from 1 July 2015 GPs became eligible to prescribe maintenance clozapine without needing to be affiliated with a hospital.[3] At the same time community pharmacies became eligible to dispense clozapine under the Pharmaceutical Benefits Scheme (PBS).[3]

Clozapine is listed as a section 100 'highly specialised' drug on the PBS.[7] Although GPs not affiliated with a hospital may prescribe maintenance clozapine under section 100, a review at least every six months by a specialist is prudent. Formal GP shared-care arrangements may offer less fragmented care.[8]

Treatment centres, individual patients, prescribers and pharmacists must also be registered with a clozapine patient monitoring system. Each brand of clozapine has its own monitoring service. There is usually a clozapine coordinator associated with each mental health service who links the hospital, GP, pharmacist, and the patient.

Adverse effects and monitoring

Clozapine is contraindicated in patients with bone marrow disorders and severe hepatic or renal impairment. Adverse effects can affect many systems (Table 1) so regular monitoring is required (Table 2), particularly at the start of treatment. The prescribing doctor should ensure that all members of the team are clear about who is responsible for monitoring the patient.

Blood

The risk of neutropenia and agranulocytosis is greatest in the first four months of therapy. Patients must have weekly full blood counts for the first 18 weeks of treatment and four-weekly full blood counts thereafter. These stringent monitoring requirements have significantly reduced the risk of death for these rare but serious adverse events.

Cardiovascular

Patients with schizophrenia suffer from higher rates of cardiovascular disease than the general population. This is often aggravated by a higher use of tobacco, poor diet, obesity, a sedentary lifestyle and the use of clozapine itself.[9] Assessment of absolute cardiovascular risk with ongoing monitoring and risk reduction is required. Resources around monitoring[10] and intervening[11] for cardiometabolic health are available.

Table 1 **Management of adverse effects of clozapine**

Adverse effect	Frequency in patients	Usual time course	Management
Neutropenia/ agranulocytosis	Approximately 2.7% (neutropenia)	First 18 weeks	Cease clozapine and send to hospital
Myocarditis	Widely variable but may be anywhere up to 1%	First 4 weeks	Cease clozapine and send to hospital
Cardiomyopathy	Estimated to be between 1 in 1000 and 1 in 5000	Any time, but more likely with longer treatment durations	Seek cardiologist diagnosis Seek cardiologist and psychiatrist advice before cessation
Tachycardia	Approximately 25%	First 4 weeks	Monitor for signs/symptoms of myocarditis
Fever	Varied	Varies depending on cause	Urgent full blood count Troponin if within the first 4 weeks of treatment
Seizures	0.9–29% depending on dose, patient, seizure subtype	Any time	Seek specialist advice Check clozapine dose and concentration, reducing where possible Ask about any recent attempts to quit smoking Consider adding valproate or lamotrigine
Constipation	15–60%	Any time	Potentially life threatening Treat and prevent aggressively Stool softeners, stimulants or osmotic laxatives may be used first-line
Sedation	10–58%	Any time, but more common in first few months	Adjust time of doses Review other sedative drugs
Hypersalivation	Up to 30%	Any time, but more common in first few months	First-line – non-pharmacological options Second-line – sublingual anticholinergics
Postural hypotension	Approximately 10%	First 4 weeks	First-line – ensure adequate fluid intake and advise patient to sit up or stand slowly Second-line – low-dose fludrocortisone (starting dose 100 micrograms daily)
Weight gain	1 in 5 patients will gain >10% of their body weight (average weight gain is 8 kg)	First year	Advise on diet and exercise Seek allied health input Consider metformin controlled-release 1000 mg daily
Dyspepsia/gastro-oesophageal reflux disease	Approximately 20%	First 6 weeks	Consider proton pump inhibitor
Nocturnal enuresis	Approximately 20%	Any time	Reduce caffeine and fluids late at night (ensure adequate fluids during the day) Consider desmopressin nasal spray 10–20 micrograms intranasally at night

Chest pain, myocarditis and cardiomyopathy

Chest pain requires careful consideration. Simple causes of chest pain such as gastro-oesophageal reflux disease are common in patients taking clozapine, however myocardial infarction, myocarditis and cardiomyopathy should be considered as differential diagnoses.

Myocarditis typically occurs in the first three weeks of therapy while cardiomyopathy occurs later in treatment (median nine months).[12,13] Although rare (between 1 in 1000 and 1 in 5000) in short-term studies, in one retrospective Australian study of patients treated with clozapine and followed for 11 years, the incidence of cardiomyopathy was 4.65% (6/129).[13]

Ceasing clozapine may have catastrophic consequences for some patients and care should be taken not to diagnose myocarditis without clinical investigations.[14,15] A same-day review by an emergency department or cardiologist for ECG, troponin, chest X-ray and possible echocardiogram may be required. Myocarditis or cardiomyopathy should be confirmed by a cardiologist to avoid unnecessary cessation of clozapine.

Tachycardia

Tachycardia is common especially during the first four weeks of clozapine therapy. It is usually benign.[12,13]

Postural hypotension

Postural hypotension is common. Regular adequate fluid intake should be advocated, although specific advice to avoid sugary drinks is important. General advice around getting up slowly and leg muscle flexing is appropriate. Alcohol may worsen postural hypotension and the patient's intake should be assessed. In rare cases fludrocortisone may be required.[12]

Gastrointestinal

Nausea is a common and dose-related adverse effect of clozapine.[12] Dyspepsia and reflux may be treated with proton pump inhibitors. Although variations in clozapine concentrations have been reported with omeprazole,[16-18] all proton pump inhibitors are generally considered to be safe to use in patients taking clozapine.

Constipation

The prevalence of constipation is up to 60%.[19] Severe untreated constipation may cause a fatal bowel obstruction.[20-22] Red flag signs and symptoms include abdominal pain, distension, vomiting, overflow diarrhoea, absent bowel sounds and signs or symptoms of sepsis.[12]

Concomitant drugs with significant anticholinergic effects such as oxybutynin, and amitriptyline should be avoided when possible. Preventative aperients should be started at the first sign of constipation. A regular intake of sugar-free fluid should be recommended to all patients especially those prescribed increased dietary fibre. Regular exercise is also recommended. When intestinal obstruction has been excluded, a stimulant and softener combination such as docusate with senna may be used.[12] The literature suggests that stimulant laxatives such as senna are not harmful to the colon, although this does not include studies of patients taking clozapine.[23,24]

Metabolic

After starting treatment a weight gain of over 10 kg is common and may continue for a year or longer. Half of the patients taking clozapine will develop metabolic syndrome and type 2 diabetes.[12] Dietary modification and exercise may have significant positive effects on weight if patients can adhere to these regimens.

Metformin is an underused, evidence-based intervention for weight loss that is both safe and effective in patients without glucose intolerance or diabetes.[9] On average there is a 3.1 kg weight loss,[12] but metformin may cause a vitamin B_{12} deficiency so B_{12} concentrations should be checked.

Dsylipidaemia and hyperglycaemia may occur with or without weight gain.[12] Metformin is the recommended first-line treatment for hyperglycaemia.[12] Patients with dyslipidaemia should be treated in the same way as other patients. Statins should be used for patients who meet the clinical criteria for their prescription.

Fever

Fever, cold and flu-like symptoms due to viral upper respiratory tract infections are common in the community, including in patients taking clozapine. In most cases these symptoms do not require adjustment of therapy. However, because these signs and symptoms may indicate myocarditis or secondary infections due to neutropenia, these conditions should be ruled out. Urgent full blood counts should be ordered.

Sedation

Sedation is a common and troubling adverse effect. Many patients sleep 10–12 hours per night. While shifting doses to night-time may reduce afternoon sedation, it can increase morning tiredness. The dosing schedule should be negotiated with patients. Treatment augmentation with drugs such as aripiprazole may help to reduce the required clozapine dose. This can reduce sedation, but should not be prescribed without consultation with a psychiatrist.[12]

Table 2 **Monitoring during clozapine treatment**

Test	Frequency	Reason	What to do if abnormal	Comments
Weight/ BMI/waist circumference	Each GP visit	Clozapine may cause ongoing and profound weight gain	Give lifestyle advice Refer to allied health Consider metformin	Metformin is an underused option to reduce weight gain with clozapine
Temperature	Daily for first 3 weeks, then advise patient to monitor	May indicate myocarditis (if early in therapy) or infection secondary to neutropenia	Screen for myocarditis if in the first 4 weeks of therapy Check full blood count	Raised temperature may occur in the first few weeks of treatment
Pulse/blood pressure	Daily if possible for first 3 weeks then at each GP visit thereafter	Tachycardia is common with clozapine, especially on initiation. However, tachycardia may indicate myocarditis. Initial hypotension may occur, but long-term hypertension may occur as a consequence of weight gain	If there is tachycardia in first 4 weeks, screen for myocarditis Beta blockers may be used where clinically indicated Hypotension may respond to dividing the clozapine dose	Long-term tachycardia is a risk factor for cardiomyopathy
Bowel motions/ constipation	Each GP visit	Deaths have occurred due to clozapine-induced faecal impaction/ bowel obstruction	Stool softeners, stimulants, or osmotic laxatives may be used first-line	Treat aggressively and early
Cardiovascular risk assessment	6-monthly	Clozapine increases cardiovascular risk	Treat as appropriate	–
Fasting glucose	6-monthly	Clozapine may cause hyperglycaemia	Advise on diet and exercise Start metformin	–
White blood cell count	Every week for 18 weeks then 4-weekly	Clozapine may cause neutropenia/ agranulocytosis	Discuss with clozapine monitoring service and psychiatrist	If neutrophils below 1.5 x 10^9/L, cease clozapine If between 1.5 and 2 x 10^9/L, increase frequency of monitoring
Lipids	6-monthly	Clozapine may cause dyslipidaemia	Advise on diet Start statins for raised low-density lipoprotein Advise on alcohol reduction for raised triglycerides	–
Clozapine concentration	6-monthly and extra measurements if quitting smoking or starting interacting drugs	Tobacco and other drugs may have interactions Low concentrations may indicate non-compliance Concentrations >600 micrograms/L may increase seizure risk and >1000 micrograms/L are considered high risk for seizures	Discuss with psychiatrist before adjusting dose	Measure trough concentration
Troponin	Weekly for first 4 weeks	May help to identify myocarditis	Screen for myocarditis if in first 4 weeks of therapy Consult with psychiatrist before cessation	The diagnosis of myocarditis requires more evidence than a positive troponin
C-reactive protein	Weekly for first 4 weeks	May help to identify myocarditis	Screen for myocarditis if in first 4 weeks of therapy	–
Echocardiogram	Baseline and then annually	May identify cardiomyopathy	Refer to cardiologist and consult with psychiatrist before cessation	–
ECG	6–12 monthly (more frequently during initiation)	There are ECG changes in both myocarditis and cardiomyopathy but ECG will also show QTc prolongation and consequent risk of ventricular arrhythmias	Refer to cardiology	ECGs are less useful than echocardiograms at identifying cardiomyopathy and do not replace need for regular echocardiograms

Hypersalivation

Hypersalivation, particularly while sleeping, is a troublesome adverse effect that may embarrass and stigmatise patients. Sucking sugar-free lozenges may help to remind patients to swallow saliva. Absorbent pillow slips and placing a towel over the pillow at night may also help. Sublingual anticholinergic drugs have also been used to some effect. Drugs that have been tried include:[12]

- atropine eye drops either used sublingually directly or as a mouthwash (2 drops in 10 mL water)
- hyoscine hydrobromide tablets 300 micrograms sucked or chewed up to three times a day (systemic absorption is possible and may potentially cause or aggravate tachycardia, constipation or confusion)
- ipratropium metered dose inhaler 1–2 sprays up to three times a day sublingually.

Seizures

Clozapine has been associated with seizures with a cumulative one-year risk of approximately 2.9–5%.[25,26] Seizures include a wide variety of epileptic activity and not just generalised tonic-clonic seizures.

The risk is increased in patients with serum clozapine concentrations greater than 1000 nanograms/mL.[12,25-28] Reducing the intake of alcohol may reduce the risk.

Immediate referral to an emergency department is indicated for patients who have a seizure while taking clozapine. Clozapine concentrations, testing for illicit drugs, brain imaging and a neurology review may be required. An accurate diagnosis of seizures is essential before considering stopping clozapine. It may be in the best interests of the patient to continue taking clozapine with the addition of an antiepileptic drug such as sodium valproate or lamotrigine.[12,27,28] The patient's psychiatrist should be consulted before any changes.

Nocturnal enuresis

Nocturnal enuresis affects up to one in five patients.[29] Non-drug treatments are first-line and include:

- bladder training (physiotherapists may help with this)
- reducing caffeine intake
- reducing night-time fluids (but not total daily fluid intake)
- planned night-time wakening to urinate.

Continence pads and sheet protectors may be used if these methods are ineffective. In resistant cases desmopressin nasal spray (10–20 micrograms at night) may be used under specialist advice, although it is not listed on the PBS for this indication, and hyponatraemia may result.[12,30]

Smoking and other cytochrome P450 inducers and inhibitors

Brief interventions to encourage smoking cessation are appropriate in patients taking clozapine and GPs are in an ideal position to facilitate these. However, clozapine metabolism is accelerated by the non-nicotine components of tobacco which induce cytochrome P450 (CYP) 1A2 enzymes. Smoking cessation is therefore likely to significantly increase clozapine concentrations. Careful monitoring of clozapine concentrations is required during attempts to quit, and any planned change in dose should occur in consultation with a psychiatrist.[12,31,32] Nicotine patches do not affect clozapine metabolism.

Carbamazepine is a CYP1A2 inducer and fluvoxamine is a CYP1A2 inhibitor so they are not advised in patients taking clozapine. Carbamazepine also should be avoided with clozapine therapy due to the additive risk of neutropenia. Drugs metabolised by CYP2D6 such as fluoxetine can increase clozapine levels so should not be prescribed to patients taking clozapine.

Strategies to improve adherence

Multifaceted interventions to improve adherence may include dose administration aids (e.g. Webster-pak), phone alarms, and direct monitoring of medication-taking by carers. Clozapine coordinators and case managers can help identify non-government organisations that may offer a monitoring service. Individual or group education from clozapine coordinators and pharmacists is also recommended.

Treatment interruptions

Abrupt withdrawal of clozapine should be avoided as it may cause cholinergic rebound and acute psychosis.

Treatment interruptions for more than 48 hours, for example because of non-adherence, require an increase in the frequency of blood tests to weekly (if patients are having monthly blood tests). If the treatment interruption lasts more than 72 hours, re-titration of the clozapine dose is required. Failure to re-titrate causes an unacceptably high risk of seizures, severe hypotension, and coma.[12] The patient's regular clozapine monitoring service and psychiatrist should be contacted.

Therapeutic drug monitoring

Clozapine concentrations are measured in trough samples and most studies show that the threshold for response is 350–600 micrograms/L.[12] Concentrations of the main metabolite, norclozapine, are routinely reported with clozapine concentrations, but its importance for therapeutic efficacy is uncertain.

SELF-TEST QUESTIONS

True or false?

3. Dry mouth is a common adverse effect of clozapine.

4. The dose of clozapine may need to be reduced if the patient stops smoking.

Answers on page 247

Shared care

GPs are well placed to provide ongoing care for people taking clozapine. Essential components of GP shared-care programs include agreed monitoring protocols, and agreed prescribing responsibilities for prophylaxis and treatment of any clozapine-related adverse effects. Close communication between clozapine coordinators, GPs and patients is essential for monitoring and management of patients' adverse effects and for ensuring that the patients are attending their GPs.

Conclusion

Clozapine is a highly effective drug for treatment-resistant schizophrenia, however careful monitoring for, and accurate diagnosis of, clozapine-related adverse effects is essential. Therapeutic interventions to treat adverse effects are underused yet may significantly improve the quality of life of patients. Good communication between specialists, GPs and pharmacists is essential for the safe use of clozapine.

Conflict of interest: none declared

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FEATURE

Top 10 drugs 2016–17

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Tables 1–3 show the top 10 drugs for the year July 2016 – June 2017. The figures are based on PBS and RPBS prescriptions from the date of supply. This year's figures include prescriptions under the co-payment (non-subsidised).

The capture of below co-payment data probably explains why drugs such as amoxicillin, which were previously absent, now appear in the top 10 drugs by prescription count. Drugs for hepatitis C continue to dominate the top 10 most expensive drugs.

Table 1 **Top 10 drugs by DDD/1000 pop/day**

	Drug	DDD/1000 pop/day *
1.	atorvastatin	69.34
2.	rosuvastatin	50.14
3.	perindopril	49.23
4.	amlodipine	43.72
5.	irbesartan	34.02
6.	candesartan	32.51
7.	telmisartan	29.59
8.	esomeprazole	29.54
9.	ramipril	28.20
10.	metformin	23.61

Table 2 **Top 10 drugs by prescription counts**

	Drug	Prescriptions
1.	atorvastatin	10 354 080
2.	rosuvastatin	10 239 733
3.	esomeprazole	9 284 540
4.	pantoprazole	6 737 757
5.	perindopril	6 184 545
6.	cefalexin	5 473 562
7.	amoxicillin	5 445 791
8.	metformin	4 941 822
9.	amoxicillin and clavulanic acid	4 908 573
10.	irbesartan	4 076 242

Table 3 **Top 10 drugs by cost to government (does not include rebates)**

	Drug	Cost to government	DDD/1000 pop/day *	Prescriptions
1.	ledipasvir and sofosbuvir †	$969 208 772	‡	43 139
2.	sofosbuvir	$927 284 256	1.70	47 160
3.	daclatasvir	$347 075 507	1.64	44 178
4.	adalimumab	$320 626 014	35.15	207 325
5.	aflibercept	$261 241 529	‡	203 140
6.	ranibizumab	$213 069 118	‡	169 657
7.	trastuzumab	$160 173 513	‡	52 733
8.	pregabalin	$159 616 588	32.76	3 796 237
9.	denosumab	$152 044 886	36.24	534 918
10.	etanercept	$146 737 356	12.09	97 266

* DDD/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people in every thousand Australians are taking the standard dose of a drug every day. DDD includes use in combination products. The calculation is based on ABS 3101.0 – Australian Demographic Statistics for December 2016 (as at March 2017).

† DDDs in combination products are accounted for in constituent drugs

‡ The World Health Organization has not allocated a DDD for this drug

DDD defined daily dose

PBS Pharmaceutical Benefits Scheme

RPBS Repatriation Pharmaceutical Benefits Scheme

Source: Department of Health, November 2017. © Commonwealth of Australia

FEATURE

Medicines Australia Code of Conduct: breaches 2016–17

Keywords
Medicines Australia, codes of conduct

Aust Prescr 2017;40:238
https://doi.org.au/10.18773/austprescr.2017.072

The Medicines Australia Code of Conduct guides the promotion of prescription products by pharmaceutical companies.[1] Each year Medicines Australia publishes a report, from its Code of Conduct Committee, which details all the complaints that have been received about advertising and other promotional activities.

In 2016–17 only five complaints were dealt with by the Code of Conduct Committee and in the April–June 2017 quarter there were no complaints at all.

The Table shows the one complaint where at least one breach was identified, and more details can be found in the full report.[2] The complaints were dealt with under the current (18th) edition of the Code of Conduct.[1]

Table **Breaches of the Code of Conduct July 2016 – June 2017**

Company	Brand (generic) name	Material or activity	Sanction
Sanofi Genzyme	Aubagio and Lemtrada (teriflunomide and alemtuzumab)	Misleading advertising	$50 000 fine, material withdrawn

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BOOK REVIEW

Pharmaceutical Calculations. 5th ed.

Teixeira MG, Zatz JL
Hoboken, New Jersey: John Wiley & Sons; 2017.
536 pages

This new edition has been updated and has new content, yet it retains a practical approach to pharmaceutical calculations. It follows a skill-building approach starting at basic mathematical concepts. Each chapter sets the scene with learning objectives and then systematically works through relevant content.

As the reader moves through the book and builds knowledge and confidence, mathematical concepts and calculations become increasingly complex. Those who wish to revise a specific area can go to that section through the comprehensive table of contents or from the index.

For students and those new to pharmaceutical calculations, this book comprehensively covers the range of calculations required. Although presented from an American context (with some American drug names), the majority of the calculations use metric measures. There is a chapter covering systems of measurement used internationally.

Complex calculations covering electrolytes, injectable medicines, total parenteral nutrition, intravenous flow rates and novel dose forms (e.g. lollipops) are also included. Each concept is introduced and worked examples are given. The reader is then led through additional practice questions and each chapter culminates in a list of practice problems. Answers and fully worked solutions are provided for all questions and problems.

This book would be a useful addition for pharmacists working in compounding pharmacies, as well as pharmacy students and interns preparing for their exams. It would also be a good resource for prescribers who use different compounded dose forms, such as total parenteral nutrition, who may require additional information about dosage calculation.

Greg Kyle
Professor of Pharmacy
Queensland University of Technology
Brisbane

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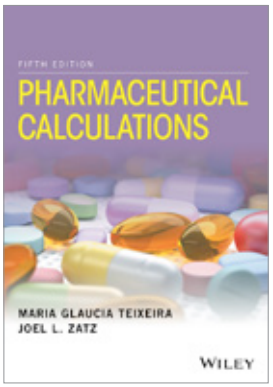

NEW DRUGS

New drugs

Aust Prescr 2017;40:240–1
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First published 31 October 2017

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Daratumumab

Approved indication: multiple myeloma

Darzalex (Janssen-Cilag)
vials containing 100 mg in 5 mL or 400 mg in 20 mL concentrate

Multiple myeloma is a malignant proliferation of plasma cells. They produce monoclonal paraproteins (M proteins). The proliferation in the bone marrow causes skeletal damage and the paraproteins can cause kidney failure. Advances in therapy such as bone marrow transplants and drugs such as bortezomib and lenalidomide have improved the prognosis, but most patients eventually relapse. This has led to a search for new targets for drug therapy. One of these targets is the CD38 glycoprotein which is found on myeloma cells. Daratumumab is a monoclonal antibody that binds to CD38 and leads to the death of the cells.

The drug is diluted and given as an intravenous infusion. The half-life increases with repeated and increasing doses and it takes many weeks to reach a steady-state serum concentration. The drug is cleared in a similar way to other antibodies. Liver and renal disease have no significant effects on the pharmacokinetics of daratumumab. The molecule may interfere with some laboratory investigations, such as the Coombs test.

The clinical trials of daratumumab have involved patients who had been previously treated for multiple myeloma. Efficacy was assessed according to the criteria of the International Myeloma Working Group.

The approval of daratumumab monotherapy appears to be based on two open-label, uncontrolled, phase II trials.[1,2] There was a total of 148 patients in the pooled analysis of these trials.[3] The patients had received a median of five previous treatments and most of them had disease that was refractory to immunomodulatory drugs and proteasome inhibitors, such as bortezomib. After a median treatment duration of 3.4 months, the overall response rate was 31.1%, including four patients with a complete response. The median duration of the response was 7.6 months with a median overall survival of 20.1 months.[1] Based on the results of these studies, the recommended regimen for monotherapy is a weekly infusion for eight weeks, followed by every two weeks, until 24 weeks, then monthly until the disease progresses.

This regimen was used in a phase III, open-label, randomised controlled trial, which studied daratumumab in combination with lenalidomide and dexamethasone in 286 patients who had received at least one previous treatment. Their outcomes were compared with those of 283 patients who were treated with lenalidomide and dexamethasone. The overall response rate for those taking daratumumab was 92.9% compared with 76.4% in the control group. There was a complete response in 43.1% of the daratumumab group and 19.2% of the control group. When the results were reported, the median progression-free survival had not been reached with the daratumumab combination, but was 18.4 months with lenalidomide and dexamethasone.[4]

Daratumumab has also been studied in combination with bortezomib and dexamethasone. In this phase III, open-label, randomised controlled trial, daratumumab was given every three weeks, rather than fortnightly, from weeks 10–24 of the regimen. The patients had all received at least one previous treatment for myeloma. In the 251 patients randomised to receive the combination, the overall response rate was 82.9% compared with 63.2% in the 247 patients who received bortezomib and dexamethasone. The respective complete response rates were 19.2% and 9.0%. The median progression-free survival was not reached with the combination, but was 7.2 months in the control group.[5]

As the CD38 glycoprotein is also found on haemopoietic cells, daratumumab's effects are not limited to cancer cells. It is very common for patients to develop anaemia, neutropenia and thrombocytopenia, so the full blood count must be monitored during treatment.

Approximately half of the patients in the trials had infusion-related reactions, so pre-medication is required. Corticosteroids are also recommended for two days after the infusion to reduce the risk of delayed reactions.

In the studies of monotherapy only 4.1% of the patients discontinued daratumumab because of adverse events. The most frequent adverse effects were fatigue, nausea and anaemia.[3]

Adverse events which were more frequent when daratumumab was added to lenalidomide and dexamethasone included neutropenia, diarrhoea and cough. Discontinuations due to adverse events were slightly less frequent than

in the control group (6.7% vs 7.8%).[4] There was a similar result when daratumumab was given with bortezomib and dexamethasone (7.4% vs 9.3%). In that trial, the combination caused more haematological adverse events than the control group and it was also associated with a higher rate of peripheral neuropathy.[5]

Daratumumab improves the response to treatment, particularly when used in combination with lenalidomide (see Table). However, its effect on longer term survival needs further study. While combination therapy is currently limited to patients who have relapsed after at least one other therapy, and monotherapy is restricted to those who have had at least three therapies, the optimum approach to treatment needs to be studied. Trials are underway to assess the role of daratumumab earlier in the disease.

T T manufacturer provided additional useful information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.

Table **Efficacy of daratumumab in multiple myeloma**

Trial	Treatment	Number of patients	Median duration of follow-up (months)	Overall response rate	Proportion of patients without disease progression at 12 months	Overall survival at 12 months
GEN501[1]	Monotherapy	42 (16 mg/kg group)	10.2	36%	65% (of 15 responders)	77%
SIRIUS[2]	Monotherapy	106	9.3	29.2%	–	64.8%
POLLUX[4]	Daratumumab, lenalidomide and dexamethasone	286	13.5	92.9%	83.2%	92.1%
	Lenalidomide and dexamethasone	283		76.4%	60.1%	86.8%
CASTOR[5]	Daratumumab, bortezomib and dexamethasone	251	7.4	82.9%	60.7%	–
	Bortezomib and dexamethasone	247		63.2%	26.9%	–

NEW DRUGS

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https://doi.org/10.18773/austprescr.2017.070
First published 3 October 2017

Lenvatinib

Approved indication: thyroid cancer, renal cell cancer

Lenvima (Eisai)

4 mg, 10 mg capsules

Australian Medicines Handbook section 14.2.4

In order to grow, cancers develop new blood vessels. This neovascularisation is the target of anticancer drugs such as the tyrosine kinase inhibitors.[1] Lenvatinib is a tyrosine kinase inhibitor which acts on a range of receptors including those for vascular endothelial growth factor and fibroblast growth factor. This action decreases the proliferation of endothelial cells.

Lenvatinib is well absorbed. Food does not affect the extent of absorption, but slows the rate. The drug is mainly metabolised by cytochrome P450 (CYP) 3A4. Although inducers or inhibitors of this enzyme will alter the concentrations of lenvatinib, no dose adjustments are recommended. The terminal half-life is 28 hours with metabolites appearing in the faeces and urine. A reduced starting dose is recommended for patients with severe hepatic or renal impairment.

Lenvatinib mesilate has been studied in a variety of solid tumours. Its initial approval is for progressive differentiated thyroid cancer that is refractory to radioactive iodine. Lenvatinib, in combination with everolimus, is also approved for advanced renal cancer that has not responded to therapy aimed at vascular endothelial growth factor.

The main trial in thyroid cancer randomised 261 patients to take daily doses of lenvatinib and 131 to take placebo. The median follow-up in the study was 17.1 months for the lenvatinib group and 17.4 months for the placebo group. Imaging revealed a 64.8% response rate with lenvatinib compared with 1.5% for placebo. The cancer progressed in 35.6% of the patients taking lenvatinib and 83.2% of those taking placebo. This led to a significant difference in progression-free survival – 18.3 months with lenvatinib and 3.6 months with placebo.[2]

The approval for lenvatinib in renal cell carcinoma appears to be based on an open-label phase II trial in 153 patients. These patients had advanced or metastatic disease and had previously been treated with a drug, such as sunitinib, aimed at vascular endothelial growth factor. They were randomised to take lenvatinib, everolimus or both drugs once daily and their radiographic response was assessed every eight weeks. The median duration of treatment was 7.4 months with lenvatinib, 4.1 months with everolimus and 7.6 months with the combination. The respective response rates were 27%, 6% and 43%. The median progression-free survival was significantly longer with the combination than with everolimus alone (14.6 months vs 5.5 months). Patients treated with lenvatinib alone also had a longer progression-free survival (7.4 months) than those taking everolimus.[3]

As tyrosine kinase inhibitors affect endothelial cells, they cause adverse effects such as thrombosis, bleeding and hypertension.[1] In the study of thyroid cancer, 68% of the patients taking lenvatinib developed hypertension compared with 9% of the placebo group.[2] In both trials frequent adverse events in patients taking lenvatinib included diarrhoea, fatigue, reduced appetite, nausea and vomiting. These were all more frequent than reported in patients taking everolimus or placebo.[2,3]

Adverse events led to the discontinuation of treatment in 14% of the patients taking lenvatinib for thyroid cancer.[2] In the study of renal cancer, 25% of the patients taking lenvatinib and 24% of those taking it with everolimus stopped treatment because of adverse events, compared with 12% taking everolimus alone.[3] Some adverse events, such as cerebral haemorrhage and pulmonary embolism, were fatal.[2,3]

Many patients will need to have their treatment reduced or interrupted because of toxicity. Patients with renal impairment are more prone to serious adverse effects. Lenvatinib may cause cardiac dysfunction and, as it can prolong the QT interval, the ECG should be regularly monitored. Monthly monitoring of thyroid function is recommended because lenvatinib can cause hypothyroidism. In the trial of renal cancer more than 35% of the patients taking lenvatinib developed hypothyroidism.[3] Liver function has to be frequently monitored because of the risk of hepatotoxicity. Other serious adverse effects include gastrointestinal fistula and perforation and proteinuria. Treatment should be permanently stopped if the patient develops nephrotic syndrome.

At present there is more published evidence about lenvatinib in thyroid cancer than in renal cancer. Further research will be needed to find out if overall survival improves. When the trial in thyroid cancer was published, there was no significant difference in overall survival between lenvatinib and placebo.[2] In the phase II trial in renal cancer, there were initially no significant differences in overall survival between the treatments. A later post hoc analysis found a significant difference between lenvatinib plus everolimus and everolimus alone (median 25.5 months vs 15.4 months). However, there was no significant difference between the combination and lenvatinib alone (median overall survival 19.1 months).[3]

Sorafenib is another tyrosine kinase inhibitor which improves progression-free survival in thyroid cancers refractory to radioactive iodine.[4] A systematic review has indirectly compared sorafenib and lenvatinib. It found that lenvatinib had more effect on progression-free survival, but there were not enough data to show a difference in overall survival.[5]

Patients considering treatment with lenvatinib need to be aware of the current uncertainty about its effect on survival. While this may be resolved with more research, it is inevitable that almost every patient will suffer adverse effects during treatment with lenvatinib.[2,3]

T T T Manufacturer provided the clinical evaluation

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

NEW DRUGS

Aust Prescr 2017;40:244–5
https://doi.org/10.18773/austprescr.2017.078
First published 23 October 2017

Milnacipran hydrochloride

Approved indication: fibromyalgia
Joncia (Pierre Fabre Medicament)
25 mg, 50 mg and 100 mg capsules

Fibromyalgia is a chronic painful condition. It can reduce quality of life and is frequently associated with other symptoms such as fatigue, poor sleep and depressed mood. The non-drug management of fibromyalgia is important, but there is some evidence to support the use of drugs such as amitriptyline and duloxetine.

Like duloxetine, milnacipran inhibits the reuptake of noradrenaline and serotonin, but it has not been marketed as an antidepressant. Altering the neurotransmitters may inhibit pain signals, but the exact mechanism of action of milnacipran in fibromyalgia is unknown.

There have been several studies of milnacipran in fibromyalgia. Five of these were included in a systematic review. These trials involved 4138 patients, mostly female, randomised to take placebo or up to 200 mg milnacipran daily. In the analysis, 41% of patients obtained some pain relief (at least 30%) with milnacipran 100 mg daily, however 30% of the placebo group had the same outcome.[1] These response rates were not increased with a dose of 200 mg daily. Some of the trials used an endpoint which combined 30% pain relief with the patients' impressions of improvement. This composite endpoint was achieved by 27% of the patients taking milnacipran 100 mg and 25% of those taking 200 mg. The placebo response was 16–18%.[1]

Although fibromyalgia is a chronic disease, most of the studies in the review were short-term. The longest had a duration of 27 weeks. It randomised 888 patients and found that there was a statistically significant difference between milnacipran and placebo for several outcomes including pain, fatigue and function.[2]

Some of the studies had extension phases. In one of these, 198 patients who had completed three months of treatment could continue for a year. The 270 patients who had taken placebo were randomised to take milnacipran 100 mg, 150 mg or 200 mg. After a year the response rate ranged from 27.5% to 35.9%. There were improvements in pain, fatigue and sleep.[3]

In the systematic review, adverse events occurred in 86–87% of the milnacipran groups and 78% of the placebo group. Adverse events which were significantly more frequent with milnacipran included nausea, vomiting, constipation, dizziness, hot flushes, hypertension, palpitations and tachycardia.[1] Pulse and blood pressure should be measured before and during treatment. Although there were few men in the studies, 23.9% developed dysuria and 8.7% reported testicular pain. Milnacipran is not recommended in pregnancy and is contraindicated during lactation.

Antidepressants, tramadol and St John's wort are contraindicated. Other drugs which may interact with milnacipran include lithium, parenteral digoxin, oral anticoagulants and the serotonin agonists ('triptans') used in the treatment of migraine.

A dose reduction may be needed in renal disease as milnacipran is mainly excreted in the urine. It has a half-life of about eight hours so twice-daily doses are recommended. The dose should be gradually titrated to 50 mg twice a day. This can be increased to 100 mg twice a day, but if there is no response after 12 weeks, treatment should stop. The drug should be gradually withdrawn over at least two weeks.

Another systematic review has analysed the trial data for milnacipran in comparison to amitriptyline and duloxetine. Although there were methodological problems, amitriptyline was superior for improving pain, fatigue and sleep. Milnacipran was superior to duloxetine for fatigue, but inferior for pain and sleep.[4]

A difficulty in assessing the effectiveness of milnacipran is that many patients dropped out of the trials. In the systematic review 34% of the patients taking milnacipran 100 mg dropped out, mainly because of adverse events, compared with 30% of the placebo group.[1] How the data from these patients are handled influences the efficacy results. In the 27-week trial 42% of the patients discontinued treatment. Depending on the analysis used, the response rates to milnacipran 100 mg could be 33.3% or 18.3%. The lower value is not statistically different from placebo.[2] It is also uncertain how much benefit milnacipran has beyond a possible effect on depression. In the clinical trials approximately 30% of the patients had a history of depression. In 2009 the evidence of efficacy was insufficient for milnacipran to gain marketing approval in Europe.

Only a minority of patients will benefit from milnacipran. Approximately nine need to be treated for one patient to get a 30% reduction in pain. However, for every seven patients treated with 200 mg, or 14 treated with 100 mg, one will have to stop milnacipran because of adverse events.[1]

T manufacturer provided the AusPAR

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The Transparency score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

NEW DRUGS

Aust Prescr 2017;40:246–7
https://doi.org/10.18773/austprescr.2017.071
First published 3 October 2017

Nepafenac

Approved indication: cataract surgery

Ilevro (Novartis)
Bottles containing 3 mg/mL eye drops suspension
Australian Medicines Handbook section 11.3.4

Nepafenac is a non-steroidal anti-inflammatory drug indicated for the prevention and treatment of inflammation and pain associated with cataract surgery. After administration, nepafenac penetrates the cornea and is rapidly metabolised to amfenac by hydrolases. Nepafenac and amfenac work by potently inhibiting COX-1 and COX-2 enzymes.

One drop a day should be administered the day before surgery, on the day of surgery and then for 14 days after surgery. An extra dose should be given 30–120 minutes before surgery.

In a phase 3 trial of over 2000 patients, nepafenac 0.3% eye drops were significantly better than vehicle eye drops at reducing inflammation in patients who had undergone cataract surgery (see Table). After 14 days of post-surgical treatment, inflammation had resolved in 68.4% of patients receiving nepafenac 0.3% compared with 34% receiving vehicle drops. Resolution of inflammation was defined as a score of zero for aqueous cells and flare, which were detected using slitlamp biomicroscopy. A secondary endpoint was the percentage of patients who were pain-free at day 14. Of those given nepafenac 0.3%, 91% were pain free compared with 49.7% in the corresponding vehicle group.[1]

Patients with a history of ocular surgery, inflammatory eye disease or infection, uncontrolled glaucoma or diabetic retinopathy were excluded from the trial. Other anti-inflammatory drugs, except low-dose aspirin, were not allowed during the trial.

The most common reason for patients discontinuing the trial was treatment failure. This occurred in 2.9% of patients receiving nepafenac 0.3% and 32.7% of those receiving the corresponding vehicle eye drops. Overall, 12.4% of patients had an adverse event. The most common events with nepafenac 0.3% were headache (2.7%, 22/817) and increase in intraocular pressure (1%, 8/817).[1] Treatment-emergent events with nepafenac included one case of eye pain and one case of hypersensitivity.

Nepafenac is contraindicated in people who have hypersensitivity (asthma, urticaria, acute rhinitis) to non-steroidal anti-inflammatory drugs including aspirin. Soft contact lenses should not be used with these eye drops as preservative in the solution may be absorbed by the lenses.

Punctate keratitis was reported in 3% of patients with diabetes following prolonged exposure to nepafenac (>2 months). Post-marketing experience suggests that patients with complicated ocular surgeries or repeat surgery in a short time period, corneal denervation, corneal epithelial defects, diabetes, dry eye syndrome or rheumatoid arthritis may be at risk of serious corneal adverse reactions with topical non-steroidal anti-inflammatory drugs.

Patients should be advised to avoid sunlight while using nepafenac eye drops. Concomitant topical steroids with nepafenac should be used with caution as both drugs can delay healing, particularly in those at risk of corneal adverse reactions.

There are no safety data on nepafenac in pregnant women and it is not recommended during pregnancy or lactation. However, as systemic exposure is negligible after eye drops are administered, the risk of toxicity to the fetus or breastfeeding infant is likely to be low.

Table **Efficacy of nepafenac eye drops for pain and inflammation after cataract surgery**

Parameter*	Daily eye drops†			
	nepafenac 0.3%*	vehicle	nepafenac 0.1%*	vehicle
Ocular inflammation % cured‡	68.4% (552/807)	34% (67/197)	70% (568/811)	35.6% (73/205)
Ocular pain % cured	91% (734/807)	49.7% (98/197)	90.9% (737/811)	56.1% (115/205)

* Efficacy outcomes were measured at day 14 after surgery in the intent-to-treat population.
† One eye drop a day (for nepafenac 0.3%), or one drop three times a day (for nepafenac 0.1%), was given in the conjunctival sac starting the day before surgery and for 14 days after surgery. An extra dose was given 30–120 minutes before surgery.
‡ A cure was defined as a score of zero for aqueous cells and flare detected using slitlamp biomicroscopy.
Source: Reference 1

Nepafenac 0.3% eye drops were significantly better at resolving inflammation and pain after cataract surgery than vehicle eye drops. As there were no comparative studies, it is unclear if this product will be more effective than other non-steroidal anti-inflammatory eye drops. However, patients may prefer nepafenac as it only needs to be administered once a day whereas diclofenac and ketolorac need to be taken several times a day.

T manufacturer provided the AusPAR

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

REFERENCE

1. Modi SS, Lehmann RP, Walters TR, Fong R, Christie WC, Roel L, et al. Once-daily nepafenac ophthalmic suspension 0.3% to prevent and treat ocular inflammation and pain after cataract surgery: phase 3 study. J Cataract Refract Surg 2014;40:203-11. http://dx.doi.org/10.1016/j.jcrs.2013.07.042

A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 True
3 False 4 True

EDITORIAL OFFICE

For general correspondence such as Letters to the Editor, contact the Editor.

Postal The Editor
Australian Prescriber
PO Box 104
DEAKIN WEST 2600

Telephone (02) 6202 3100

Fax (02) 6282 6855

Email info@australianprescriber.com

Website nps.org.au/australianprescriber

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