check

Independent learning program for GPs

Unit 506 June 2014

Fatigue

RACGP

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Published by

The Royal Australian College of General Practitioners
100 Wellington Parade
East Melbourne, Victoria 3002, Australia
Telephone 03 8699 0414
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www.racgp.org.au

ABN 34 000 223 807
ISSN 0812-9630

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The five domains of general practice

- Communication skills and the patient-doctor relationship
- Applied professional knowledge and skills
- Population health and the context of general practice
- Professional and ethical role
- Organisational and legal dimensions

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ABOUT THIS ACTIVITY

Tiredness or fatigue is a common presentation in general practice. Although a normal part of life, ongoing (chronic) fatigue may be a symptom of a serious undiagnosed illness. Infectious disease, anaemia, undiagnosed endocrine problems, sleep problems, side effects of medication and malignancies may be causes of fatigue.[1] On average, however, investigations have a low rate of identifying underlying disease.[2] The management approach to patients presenting with fatigue is to rule out common organic diseases without over-investigating.[1]

This edition of *check* considers fatigue scenarios of relevance to general practice in Australia, focusing on common causes of fatigue.

LEARNING OUTCOMES

At the end of this activity, participants will be able to:

- outline management options for patients diagnosed with hypothyroidism
- describe investigations used to diagnose iron deficiency anemia and discuss results that require further investigation
- summarise the diagnosis and management of myasthenia gravis
- describe the diagnosis and management of chronic fatigue syndrome/myalgic encephalitis
- list considerations when developing a management plan for a person diagnosed with fibromyalgia.

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GUIDE TO ABBREVIATIONS AND ACRONYMS IN THIS UNIT OF *CHECK*

Ach	acetylcholine
AChR-Ab	acetylcholine receptor antibody
ACR	American College of Rheumatology
CBT	cognitive behaviour therapy
CFS	chronic fatigue syndrome
CSN	central nervous system
EPS	electrophysiological studies
FBE	full blood evaluation
GET	graded exercise therapy
IVIG	intravenous immunoglobulin
LFT	liver function test
MBS	Medicare Benefits Schedule
MCH	mean corpuscular haemoglobin
MCV	mean corpuscular volume
MuSK-Ab	muscle-specific tyrosine kinase antibodies
NICE	National Institute for Health and Care Excellence
NSAID	non-steroidal anti-inflammatory drug
PBM	patient blood management
PBS	Pharmaceutical Benefits Schedule
RDW	red cell distribution width
RNS	repetitive nerve stimulation
SFEMG	single fibre electromyography
SNRI	serotonin and noradrenaline reuptake inhibitor
T3	triiodothyronine
T4	thyroxine
TSH	thyroid stimulating hormone
WPI	widespread pain index

CASE 1

TIFFANY IS TIRED EVERY DAY

Tiffany is a university student aged 24 years. She had glandular fever in her first year at university and since then she tires easily. In the last 6 months she has been tired every day. Activities that she once completed easily now leave her feeling exhausted. She often naps in the afternoon but is unable to fall asleep at night. She struggles to complete assignments and has not been able to keep a part-time job. She does not have much social support as her parents have recently separated. She feels lonely and sometimes angry that this is happening to her. She wants to feel better. On examination her temperature is 36.8°C, her colour is normal and her cardiovascular, respiratory and abdominal examination is normal. She has no skin or joint changes. Her weight is stable.

QUESTION 1

What are possible diagnoses?

QUESTION 2

What investigations, if any, would you arrange for Tiffany?

FURTHER INFORMATION

You get the results back from your investigations and they are all normal. You think that Tiffany may have chronic fatigue syndrome (CFS).

QUESTION 3

Why might you think this is CFS?

FURTHER INFORMATION

Tiffany is not happy with the diagnosis of CFS. She feels that there must be something else wrong with her and seems upset as she leaves.

QUESTION 4

What difficulties might be experienced when discussing a diagnosis of CFS with patients?

QUESTION 5

How can you address a patient's concerns about a diagnosis of CFS?

QUESTION 6

What are the current recommended management options for CFS?

CASE 1 ANSWERS

ANSWER 1

Tiffany's main complaint is of fatigue that has worsened over the past 6 months. Conditions that cause fatigue include depression and anxiety, hypothyroidism, diabetes, anaemia, infection, other endocrine disorders such as Addison's disease, inflammatory bowel disease, and liver or renal disease.[1] Substance misuse should also be excluded.

ANSWER 2

The National Institute for Health and Care Excellence (NICE) UK recommends a number of investigations for fatigue (*Table 1*) in cases where chronic fatigue syndrome is suspected. These investigations screen for known organic causes of fatigue and are intended to exclude serious pathology. Clinical judgement will dictate if additional tests are required to exclude other diagnoses.[1]

Table 1. Recommended investigations for fatigue[1]

Investigations
• Urinanalysis (for protein, blood and glucose)
• Full blood count
• Liver function
• Thyroid function (TSH)
• Erythrocyte sedimentation rate
• C-reactive protein
• Random blood glucose
• Serum creatinine
• Screening blood tests for gluten sensitivity
• Serum calcium
• Creatinine kinase
• Serum ferritin levels (for children and young people only)

ANSWER 3

CFS, also referred to as myalgic encephalomyelitis, is a disabling condition.[2] CFS interferes with activities of daily living, causing debilitating fatigue that can be triggered by minimal activity. Patients have other symptoms, such as cognitive impairment, difficulty in sleeping, muscle and joint pains, lymphanopathy, dizziness or nausea, and sore throat.[1,3] CFS is a diagnosis of exclusion but prompt diagnosis can improve outcomes.

NICE guidelines state that a diagnosis of CFS can be made when other possible causes of excessive fatigue have been excluded and symptoms have persisted for more than 4 months in adults or 3 months in children (for children, the diagnosis should be confirmed by a paediatrician).[1] The peak incidence of CFS occurs at the age of 20–40 years and is more common in women.[4] The average duration is 3–9 years.[2] However, some patients may remain unwell for 20–30 years.[5]

The aetiology of CFS is poorly understood and remains controversial.[1] Suggested aetiologies include viral infection, autoimmune, endocrine, genetic and psychiatric causes, including traumatic life experiences.[6–8] The pathophysiology remains unknown.[9]

ANSWER 4

CFS is a diagnosis that can be associated with negative feelings from patients and stigma from the community.[10] As CFS does not have a clear diagnostic marker and has an uncertain aetiology, it can cause difficulty for GPs, patients and the therapeutic relationship. Research has shown that this uncertainty has lead to scepticism about the legitimacy of CFS as a condition, low confidence in healthcare providers to diagnose and manage CFS, and a lack of empathy, disbelief or negative attitudes towards people with CFS.[11]

ANSWER 5

A patient-centred approach can help to explore the feelings of stigmatisation that occur with a CFS diagnosis.[1,6] It may be helpful to explain that although CFS is a diagnosis of exclusion and it is incompletely understood, there is emerging evidence suggesting there may be a triggering event that can cause chronic fatigue in susceptible patients.[12]

It is important to explain the condition and provide education and hope (eg there is considerable research being done on CFS; most people improve over time; there is a better prognosis in younger people). Referrals to specialists or allied health professionals could be considered. Discuss the possibility of setbacks and relapses, and the need for regular review. In Tiffany's case, you could offer to liase with the university if required. In general, discussing return-to-work issues, support groups and encouraging patients to take rest periods could be helpful.

It is important to tell Tiffany that negative test results do not mean 'there is nothing wrong' and you are not negating her symptoms. For more information on patient-centred approaches and care see Resources for doctors.

ANSWER 6

There is no known pharmacological treatment or cure for CFS.[1] Physical and psychological symptoms of CFS, such as nausea or insomnia, should be managed with usual clinical practice. Cognitive behaviour therapy (CBT) and graded exercise therapy (GET) are the current recommend first-line treatments to improve fatigue and quality of life.[1]

CBT has been found to be effective in reducing the symptoms of fatigue. However, additional studies are required, as most studies have been in small groups and evidence for the comparative effectiveness of CBT alone or in combination with other therapies is currently lacking.[13]

Graded exercise programs have been found to improve levels of fatigue but have minimal impact on depression.[14] There is controversy regarding the role of paced exercise, compared with GET or CBT. The PACE study, a randomised controlled trial of 641 patients, found paced exercise had no effect on patient outcomes, compared with CBT or GET, which were both shown to improve outcomes.[15] However, CFS patient groups support the use of paced exercise as there is patient self-reporting of a worsening of symptoms with CBT and GET but not with pacing.[16]

Pacing is often advised along with other self-management strategies,[17] such as goal-setting and self-advocacy training (education and peer mentoring or support groups, encourage optimism and improvement in quality of life 12 months after intervention).[18] Goal setting can be improved by self-reflection using diaries, creative writing, log books or subjective scales.[19] Self advocacy can be improved by encouraging patients to take an active part in designing their own management plan. Self-advocacy programs consist of group or individual programs that support skills to increase self-reliance and reliance on peer networks in solving problems.

A randomised controlled trial of a self-advocacy program showed improvement in self-reported symptom severity and quality-of-life assessments.[20] The program consisted of an initial group where participants set personal goals for wellness and voted on educational topics that would then be used for discussion in illness management groups. This was supported by one-to-one sessions run by peers with CFS in which participants continued to set and attain goals, and also learn and practise strategies for independent living (eg psychological, financial and nutritional skills).

CFS support groups in Australia have information on current self-help courses and resources (see Resources for patients).

When negotiating a treatment plan for patients with CFS, it is important to be aware that there is a high rate of conventional and complementary medicine use by patients, despite limited evidence of their effectiveness.[21] Patients with CFS are more likely to have seen a complementary or alternative healthcare practitioner rather than a psychologist or physiotherapist in a 6-month time frame.[22]

Certain medications and complementary therapies or supplements were highlighted by the NICE 2007 guidelines as not being useful for treatment of CFS. These include monamine oxidase inhibitors, glucocorticoids (such as hydrocortisone), mineralocorticoids (such as fludrocortisone), dexamphetamine, methylphenidate, thyroxine and antiviral agents.[1] There is insufficient evidence to support the use of complementary therapies or supplements such as vitamin B_{12}, vitamin C, co-enzyme Q10, magnesium, multivitamins or minerals in CFS.[1]

In summary, although CBT and GET have been shown to be effective treatments for CFS, further research into management strategies, including therapies favoured by patients with CFS, is warranted.

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RESOURCES FOR PATIENTS

- Better Health Channel. Chronic Fatigue Syndrome fact sheet. www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Chronic_fatigue_syndrome

RESOURCES FOR DOCTORS

- Arroll M, Aroll B. Chronic fatigue syndrome: A patient-centred approach to management. Aust Fam Physician 2013;42:191–93.

CASE 2

AMY HAS TIREDNESS AND PAIN

Amy is 42 years of age. She presents with a 4-year history of worsening lethargy, generalised body aches, poor-quality sleep and difficulty coping to a point where she has stopped working. She feels that her pain has an aching and burning quality associated with mild intermittent paraesthesia. Amy's initial symptoms, which consisted of shoulder and back pain and significant lethargy, commenced after a severe viral illness. Since then, symptoms have slowly worsened and the pain has become more widespread.

Amy has insulin resistance and her BMI is 32 kg/m^2. She was diagnosed with depression after her divorce 5 years ago, and was previously on venlafaxine.

QUESTION 1

What are the possible causes of Amy's symptoms?

QUESTION 2

What further history and examination would you perform for Amy?

FURTHER INFORMATION

Amy does not have a history suggestive of a connective tissue disease; however, she believes that her hands and feet tend to feel swollen. Amy had a sleep study done 2 years ago, which did not show sleep apnoea. She has noticed multiple chemical sensitivities, including perfume, paint and detergents.

Amy is divorced and currently lives with her two children, aged 8 and 12 years. She feels barely able to cope with the housework and walking her children to school. She has significant stress in her life and her ex-husband's new girlfriend does not get along well with Amy's children. Financial stress has been significant since she ceased working as an office administrator 6 months ago. She stopped working as she found it impossible to perform her regular tasks because of her worsening symptoms. She had been jogging regularly but ceased this activity in the last year because of worsening pain and lethargy.

Her current medications include meloxicam 15 mg daily, paracetamol 2 tablets of 665 mg twice daily or as needed, and oxycontin SR 10 mg twice daily.

Amy seems distressed and anxious, but is not depressed. Physical examination is unremarkable and there is no evidence of joint swelling or lymphadenopathy. Her blood pressure is 130/80 mmHg and she has multiple tender points on formal tender-point examination.

QUESTION 3

What investigations would you request?

FURTHER INFORMATION

The results of Amy's blood investigations are:

- full blood evaluation – within normal limits
- renal and liver function – within normal limits
- erythrocyte sedimentation rate – 5 mm/hr [normal 0–25]
- C-reactive protein – 2 mg/L [normal 0–5]
- thyroid function – within normal limits
- creatine kinase – 105 µg/L [normal 0–190]
- vitamin D (25OHD) level – 60 nmol/L [normal 75–250]
- rheumatoid factor <20 kIU/L [normal 0–20]
- antinuclear antibody – negative.

QUESTION 4

What is the diagnosis?

QUESTION 5

What are the pathophysiological mechanisms involved in fibromyalgia?

QUESTION 6

How is fibromyalgia managed? How would you manage Amy?

CASE 2 ANSWERS

ANSWER 1

Fatigue is a common complaint in general practice, experienced by 5–7% of patients.[1] Chronic, widespread musculoskeletal pain is found in up to 10% of the general community[2] and can coexist with fatigue in many chronic illnesses. Conditions to consider that may be possible causes of Amy's symptoms include infections, metabolic and endocrine problems, sleep apnoea, primary insomnia and rheumatological conditions.[3] The non-specific nature of some of Amy's clinical features means that a broad range of problems need to be considered initially. Many of these conditions, such as infection or rheumatological disease, will have more localising features on history and examination. A combination of widespread musculoskeletal pain and fatigue occurring after a significant physical or psychological stressor, however, should raise the possibility of fibromyalgia.

ANSWER 2

On history taking, a full systems review needs to be undertaken. This should include asking questions about gastrointestinal symptoms, urinary symptoms and bleeding history, including menstrual blood loss. Information regarding the quality and length of sleep, recent infections, joint pains or swelling are essential.[1] A full psychosocial history and enquiries regarding mental health problems, including stressful events and mood, need to be included.[1] Information regarding the use of excessive alcohol, smoking history and illicit drug use is important.

Red flags for underlying serious pathology include older age at new symptom onset, weight loss, night pain, focal pain, fevers and sweats, neurological features and history of malignancy.[3]

A cardiovascular, respiratory, abdominal and neurological examination should be performed. A full rheumatological examination looking for features of inflammatory arthritis or connective tissue disease is important. Other bedside tests, including urine analysis and blood pressure measurement, should be checked.[1]

Any widespread musculoskeletal tenderness should be noted if considering a diagnosis of fibromyalgia.

A formal tender-point count using the 18 standardised tender points[4] is not included in the current fibromyalgia diagnostic criteria published by the American College of Rheumatology (ACR) in 2010.[5] Despite this, the finding of widespread musculoskeletal tenderness is informative in reaching a diagnosis of fibromyalgia.

ANSWER 3

Investigations should include blood tests for a full blood evaluation, renal and liver function, erythrocyte sedimentation rate, C-reactive protein, calcium, magnesium and phosphate, thyroid function, creatinine kinase, vitamin D level, rheumatoid factor and antinuclear antibody.[3]

ANSWER 4

The findings are consistent with fibromyalgia. Fibromyalgia does not cause abnormalities that are detectable on standard blood tests; however, it is important to screen for other potential causes of these generalised symptoms. There are no clinical features or pathology results suggestive of an alternative cause for her symptoms at this time. Amy has a low vitamin D level, which should be corrected with oral supplements; however, it is not low enough to be the major cause of her symptoms.

Fibromyalgia is a common condition affecting approximately 2–4% of the population, predominantly women.[6,7] It has characteristic clinical features of widespread musculoskeletal pain and tenderness, fatigue, poor-quality unrefreshing sleep, cognitive disturbances and high levels of distress. It is classified as a central sensitivity syndrome, often associated with similar sensitivity syndromes, including irritable bowel syndrome, temporomandibular joint disorder, recurrent headache and multiple chemical sensitivities.[8]

Fibromyalgia can be diagnosed and managed in the primary care setting, where the general practitioner is uniquely placed to understand the many different factors influencing the patient's wellbeing.

In 2010 the ACR published preliminary diagnostic criteria for fibromyalgia,[5] which were modified in 2011.[9] The criteria are separated into two components: the Widespread Pain Index (WPI), which assesses the extent of pain over the past week, and the symptom severity score, which takes into account fatigue levels, sleep disturbance, cognitive problems and other sensitivity symptoms. These criteria are evaluated by medical practitioners after asking patients to fill in a simple survey. The nature of the assessment helps to conceptualise the symptoms of fibromyalgia on a central sensitisation continuum.[10]

A patient satisfies diagnostic criteria for fibromyalgia if the following three conditions are met:[5]

- WPI ≥7 and symptom severity score ≥5 or WPI = 3–6 and symptom severity score ≥9
- symptoms present at a similar level for at least 3 months
- absence of other disorder(s) that might account for the pain.

ANSWER 5

Fibromyalgia can be thought of as a 'centralised pain state' and is characterised by pain originating or being amplified by changes in the sensory pathways of the central nervous system (CNS).[10] These changes include sensitisation at the dorsal horn level, augmentation and modification of sensory processing in the higher pain centres and altered descending inhibitory pain modulation pathways.[11,12] The results of this abnormal central pain processing includes heightened sensitivity, allodynia (where normally non-painful stimuli result in pain) and other characteristic features such as fatigue, sleep disorder and cognitive disturbances. The development of changes that lead to the clinical syndrome of fibromyalgia seems to occur in genetically predisposed individuals as a maladaptive response to chronic physical or psychological stress.[13]

ANSWER 6

Management of fibromyalgia needs to be multidisciplinary. A management plan needs to include a combination of patient education, an exercise program, pain management psychology and medications.[14,15] The involvement of the patient in their own management is paramount and the success of treatment often hinges on the extent of patient engagement and ownership of their management plan. Regular reviews are an important part of management. Referral to specialists can be made when required.

The general practitioner is the most appropriate and effective person to assess and coordinate ongoing treatment programs for patients with fibromyalgia.

Chronic disease management Medicare Benefits Schedule (MBS) item numbers can be used when planning treatment for patients with fibromyalgia.

The following items could be considered in a management plan.

Patient education

Good patient education is essential in fibromyalgia management.[16,17] Discussion should cover the clinical features and pathophysiology of fibromyalgia and the need for a multidisciplinary treatment approach. It is important to discuss the fact that although fibromyalgia can be disabling, it is not damaging, inflammatory or degenerative in nature, and that with significant patient engagement and compliance, the prognosis is often good.

Exercise

Aerobic exercise has beneficial effects on physical capacity and helps improve symptoms of fibromyalgia. Strength training may also improve some fibromyalgia symptoms.[18] Any exercise program needs to be initiated gently with small amounts of graded, low-impact aerobic activity 3–5 times per week.[14,19] This can be slowly increased over time within tolerance limits. Hydrotherapy, tai chi, qi gong and yoga may be helpful.[14,20]

Psychology

Cognitive behaviour therapy with relaxation or biofeedback results in significant improvements in pain, mood and disability.[21] This will often be an essential enabling step for a patient to engage with a management program. Information about fibromyalgia support groups might be helpful.

Medications

The only medication currently licensed by the Therapeutic Goods Administration (TGA) for use in fibromyalgia is the serotonin and noradrenalin reuptake inhibitor (SNRI) milnacipran, which currently is not available on the Pharmaceutical Benefits Scheme (PBS).

Other medications that have good evidence for benefit in the management of fibromyalgia include amitriptyline and duloxetine, which prevent the reuptake of serotonin and noradrenaline, and improve the function of descending nociceptive inhibitory control pathways in the CNS,[22,23] and the alpha$_2$ delta ligands, gabapentin and pregabalin.[24,25] Non-steroidal anti-inflammatory agents and paracetamol can be modestly helpful in some patients.[26] There

is insufficient evidence that the use of opioids is beneficial in the management of fibromyalgia[27] and reports of reduced effectiveness of opioids in fibromyalgia pain[28] may relate to hyperactivity in the endogenous opioid system in fibromyalgia.[29] There is some evidence that low-dose naltrexone may be helpful in managing fibromyalgia pain.[30]

Management of comorbid conditions

Associated conditions such as depression, anxiety, restless legs and irritable bowel will need to be assessed and managed as appropriate.

Amy needs to be managed using a multimodal approach, including education, psychological support, initiation of an aerobic exercise plan and medication. The aim would be to wean her off opioid analgesia.

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CASE 3

JANET HAS SEVERE FATIGUE

Janet is an accountant aged 43 years. She has a history of coeliac disease (quiescent on the most recent endoscopy) and depression, for which she remains on a low dose of a selective serotonin reuptake inhibitor and is well managed. Her other medications are calcium and vitamin D for previously diagnosed malabsorption and a family history of osteoporosis.

Over the past 6 months, Janet has experienced severe fatigue. She feels this is negatively affecting her ability to monitor complex financial transactions at work and keep up with her teenage children. Specific questioning reveals additional symptoms, including weight gain of 6 kg, constipation and heavier periods than usual. Her work and home life are often hectic but Janet cannot identify any new psychosocial stressors that could be affecting her life. She hopes to find a cause for her fatigue so that she can 'get on with life'.

QUESTION 1

What is the most likely cause of her fatigue? What differential diagnoses need to be excluded?

QUESTION 2

What investigations should be performed?

QUESTION 3

If all the investigations are normal, what else needs to be considered?

FURTHER INFORMATION

Janet's serum thyroid stimulating hormone (TSH) is markedly elevated at 58 mU/L (reference range 0.4–4.5 mU/L). Mild anaemia (haemoglobin 115 g/dL), mild hyponatraemia (132 mmol/L) and a slightly increased serum creatinine (81 µg/L, compared with 63 µg/L when checked 2 years earlier) are also present. The results of other investigations are within normal limits.

QUESTION 4

Are any other investigations required?

QUESTION 5

What treatment should be commenced? What is the therapeutic target?

QUESTION 6

Are there any circumstances where approach or goals of hypothyroidism treatment need to be altered?

FURTHER INFORMATION

After 3 months, and despite full-dose levothyroxine therapy (including a small dose increase), Janet remains tired. Her periods are less heavy and she has lost 3 kg of excess weight. Her serum TSH has improved but continues to be elevated at 21 mU/L, indicating continued hypothyroidism. Other laboratory abnormalities have returned to baseline.

QUESTION 7

Why isn't the treatment working?

QUESTION 8

What future surveillance, if any, should be performed?

QUESTION 9

Is there any role for T3 in hypothyroidism treatment?

QUESTION 10

When should a specialist endocrinologist or physician's opinion be sought for hypothyroidism?

CASE 3 ANSWERS

ANSWER 1

The combination of fatigue, impaired cognition, weight gain, constipation and menorrhagia suggest hypothyroidism as a likely cause of Janet's fatigue.[1] This is particularly so given her pre-existing autoimmune condition (coeliac disease).[1] Other clinical features of hypothyroidism are outlined in *Table 1*. Recurrent depression is a possible cause of her fatigue but is unlikely because of the absence of specific depressive symptoms. Severe anaemia, which could be a result of iron deficiency from menorrhagia or pernicious anaemia as a second autoimmune condition, is an important differential diagnosis.[1]

A flare-up of coeliac disease is unlikely if Janet is adhering to a gluten-free diet. Symptomatic diabetes mellitus would be expected to be associated with weight loss. Addison's disease (primary adrenal failure) is associated with weight loss and increased skin pigmentation. Heart, liver and renal failure, or nephrotic syndrome could present with weight gain, although pitting oedema and other likely pointers would be expected on history or examination. While Janet is menstruating regularly, pregnancy is easy to exclude and must not be missed. Obstructive sleep apnoea can be screened for on history. Chronic fatigue syndrome is a diagnosis of exclusion.[2]

Table 1: Possible signs and symptoms of hypothyroidism

System	Symptoms	Signs
General	Tiredness Cold intolerance Weight gain Hoarse voice	Mild hypothermia Thyroid findings (goitre or atrophic thyroid with Hashimoto thyroiditis, surgical scar)
Dermatological	Dry skin Alopecia	Dry, coarse skin, occasionally yellow-tinged Cool extremities Myxoedema (puffy face, hands and feet) Alopecia Brittle nails
Neurological	Poor concentration Poor memory Depression Paraesthesia Impaired hearing	Delayed deep tendon reflex relaxation Carpal tunnel syndrome Slow dysarthric speech
Musculoskeletal	Weakness Myalgias Arthralgias	
Cardiorespiratory	Dyspnoea	Bradycardia Diastolic hypertension Pericardial effusion Pleural effusion
Gastrointestinal	Constipation Poor appetite	
Reproductive	Menorrhagia Infertility	

ANSWER 2

Serum TSH is the screening test for primary hypothyroidism.[1] It is the only test for thyroid disease funded by the Medicare Benefits Schedule (MBS) when there is no previous history of thyroid problems.[3]

Additional investigations may be required to exclude differential diagnoses. For example, a full blood evaluation (FBE) will assess for anaemia. Electrolytes and liver function tests will detect increased creatinine resulting from chronic kidney disease, hypoalbuminaemia from chronic disease, liver disease, nephrotic syndrome, hyperglycaemia and hypercalcaemia. Hyponatraemia can be caused by hypothyroidism. Alternatively, hyponatraemia and hyperkalaemia can be associated with Addison's disease, which is rare but important not to miss because treatment of hypothyroidism in the presence of untreated adrenal insufficiency can lead to adrenal crisis.[1] Point-of-care or formal beta-human chorionic gonadotropin will rule out pregnancy.

ANSWER 3

A normal serum TSH finding rules out primary hypothyroidism,[4] which accounts for most cases of hypothyroidism (*Table 2*). However, if the pre-test probability for hypothyroidism is very high, central hypothyroidism (secondary to pituitary or hypothalamic disease) should be considered. In this case, serum free thyroid hormone (free triiodothyronine [T3] and free thyroxine [T4]) levels will be low while serum TSH may be low, normal or minimally above the reference range.[1,4]

Supplementary history and physical examination (if not previously performed) should include alcohol and drug intake (including over-the-counter and alternative therapies), sleep history and assessment for any potential rheumatological (synovitis, rashes) or neurological conditions, including signs of a pituitary tumour and abnormal tendon reflexes. The neck and thyroid should be examined and blood pressure and weight measured.

Screening for other organic disease that could be considered includes C-reactive protein and erythrocyte sedimentation rate.

Table 2: Causes of hypothyroidism

Classification	Cause
Primary	Hashimoto thyroiditis Post-ablative treatment (either radio-iodine or thyroidectomy) Drugs (carbimazole, propylthiouracil, lithium, interferon, amiodarone, rifampicin, tyrosine kinase inhibitors) Subacute thyroiditis (transient) Iodine deficiency (rare in Australia) Excessive iodine intake (kelp, radiocontrast dyes) Neonatal/congenital (TSH receptor blocking antibodies from mother, inborn errors of thyroid hormone synthesis)
Secondary/tertiary	Hypopituitarism Hypothalamic dysfunction
Other	Peripheral resistance to thyroid hormones

ANSWER 4

Other investigations are probably not required in Janet's case. Free T3 and free T4 levels could be assessed but, given Janet's symptoms and markedly elevated TSH, these are likely to be below the reference range and will not change management. The presence of thyroid autoantibody (anti-thyroid peroxidase) levels will confirm the autoimmune nature of thyroid damage (ie Hashimoto thyroiditis). The likelihood of finding elevated levels of autoantibodies is almost certain as Hashimoto thyroiditis is the main cause of spontaneous hypothyroidism in Australia,[5] Janet's hypothyroidism is severe and she already has an autoimmune disorder. Ultrasonography is not indicated unless there are palpable thyroid nodules or cervical lymphadenopathy.[6] There is no role for nuclear thyroid scanning (uptake of pertechtnate will be high) or serum thyroglobulin in this case. Although hypothyroidism causes hypercholesterolaemia,[7] measurement of fasting lipids would only change management if the hypothyroidism were so mild or subclinical that the indication for treatment of hypothyroidism was uncertain. If the clinical and biochemical hypothyroidism had not been so severe (eg a moderately high TSH level identified on screening), a strategy of retesting the serum TSH 2–8 weeks later would be reasonable to ensure the TSH is persistently elevated. Such an approach in Janet's case would simply prolong the hypothyroidism.

The mild anaemia, hyponatraemia and increase in creatinine could be explained by the hypothyroidism. As the abnormalities are mild, further laboratory testing at this stage is not necessary; however, they warrant consideration and follow-up assessment. The anaemia warrants immediate further testing if the mean cell volume is either low (iron deficiency) or high (B_{12} deficiency). Selective serotonin reuptake inhibitors can also induce hyponatraemia[8] but there is no need to cease this medication because the hyponatraemia is mild and likely to be reversed with treatment of hypothyroidism. Supplementary history and physical examination should screen for systemic rheumatological conditions such as systemic lupus erythematosis.[1] A urine dipstick is useful to rule out significant proteinuria or haematuria, which would be present in a coexisting glomerulonephritis. In the absence of the above problems, repeat testing should be performed after commencement of levothyroxine to ensure that the haemoglobin, sodium and creatinine levels have returned to normal with therapy.

ANSWER 5

Levothyroxine should be commenced to relieve symptoms and restore and maintain a euthyroid state.[9] Standard initial replacement doses equate to 1.6 µg/kg of body weight per day, rounded to the nearest 25 µg (ie 100 µg per day for a 60 kg person).[10] For most people being treated for hypothyroidism, the usual dose of thyroxine will be up to 200 µg once daily.[10,11] Full treatment dose could be commenced for Janet and treatment will be life-long.[9,11,13]

Levothyroxine should be taken on an empty stomach,[10,11] preferably 1 hour before breakfast.[12] If this is not possible, 3–4 hours after food is reasonable. The levothyroxine should be stored in the refrigerator, except for in-use blister strips, which may be stored unrefrigerated (<25ºC) and protected from light for up to 2 weeks (or in hot climates, stored in the refrigerator).[11] Two brands of levothyroxine, made by the same manufacturer, are available in Australia and are identical.[14]

Thyroid function tests can be repeated 6–8 weeks after commencing treatment,[10] unless symptoms of over-replacement/hyperthyroidism occur in the meantime. Target levels of serum TSH are not clearly defined but most endocrinologists aim for levels of 1.0–1.9 mU/L (or less commonly <3 mU/L).[15] *Therapeutic Guidelines–Endocrinology* recommend TSH levels of 0.5–2 mU/L, a range that approximates TSH concentration in the general population.[11]

If fine titration of dosing is required or, for convenience of not having too many tablets of different strengths, doses can be alternated or given on defined days (ie 150 µg per day is equivalent to 100 µg on 4 days plus 200 µg on 3 days, or 200 µg on 5 days plus two drug-free days). This flexibility of dosing is possible because of the very long half-life of levothyroxine. In cases of extreme non-adherence, another approach is once weekly dosing (under pharmacist supervision if required).[16]

ANSWER 6

Management of hypothyroidism and treatment goals need to be modified for patients with cardiovascular disease or those aged >60 years. These patients should be commenced on lower than full maintenance doses because of the risk of exacerbating heart disease on levothyroxine commencement.[10] A starting dose of 50 µg per day would be reasonable in most cases. If there is any concern about severe exacerbation of cardiovascular disease, or in the extreme elderly, even lower doses (eg 25 µg per day) could be commenced.[17] Commencement of lower doses is not required following thyroidectomy in euthyroid patients; near or full-dose replacement should be commenced for these patients. Treatment goals are often relaxed with advancing age as the normal TSH range also increases.[15]

For women with pre-existing hypothyroidism, the dose of levothyroxine should be increased by 30–50% on confirmation of pregnancy, because of increased thyroid hormone requirements.[18] The target TSH range is 0.1–2.5 mU/L in the first trimester and 0.1–3.0 mU/L in later pregnancy.[19] It is important to monitor TSH levels regularly during pregnancy, particularly in the first trimester. There is some evidence for treating patients with euthyroid Hashimoto thyroiditis (ie those with thyroid autoantibodies) with low-dose thyroxine (eg 50 µg per day) throughout pregnancy, especially if there is a history of miscarriage. [20]

Serum TSH should not be used to monitor therapy in patients with secondary hypothyroidism due to pituitary or hypothalamic disorders.[1] Serum free T4 should be titrated to a mid–high normal reference range.[21] As with primary adrenal insufficiency, it is important to rule out secondary adrenal deficiency prior to commencement of levothyroxine treatment.

In subclinical hypothyroidism (ie mildly elevated TSH, which is often asymptomatic, with a normal T4) the approach to treatment is controversial.[9] Treatment in more severe disease (ie serum TSH

>10 mU/L) is usually recommended.[9,22] Treatment at lower TSH levels may be justified if progressive deterioration is occurring in the presence of thyroid autoantibodies or as a trial where hypothyroid symptoms may be present.[22] In such cases, lower doses of levothyroxine (eg 25–75 µg daily) than those used for overt hypothyroidism, can be given.[1]

Patients with high-risk, differentiated thyroid cancer (high-risk papillary and follicular cancer) may be treated with higher doses levothyroxine to decrease serum TSH levels to <0.1 mU/L, because of improved survival with this approach.[23]

ANSWER 7

The five most common reasons for treatment failure are:[11]

- inadequate prescribed dose of levothyroxine
- incomplete adherence to medication
- incorrect administration or storage of levothyroxine
- interfering medications
- impaired absorption of levothyroxine.

In Janet's case, interfering medications, in particular, concomitant calcium supplementation, is the prime candidate.[11] If required, the calcium should be spaced as far as possible from levothyroxine. Other medications that can interfere with levothyroxine pharmacokinetics are listed in *Table 3*. Uncontrolled coeliac disease could cause impaired absorption of levothyroxine;[11] this is unlikely given that Janet's coeliac disease has been well controlled but could be assessed clinically and by checking for coeliac antibodies.

If there is continued difficulty in normalising the serum TSH concentration, obtaining Janet's serum free T4 (and free T3) level may be helpful. A high serum TSH but high normal or frankly high serum free T4 is most probably due to non-adherence with administration shortly before the blood test. Rare, organic causes for the inability to normalise serum TSH concentration include interfering (ie heterophile) antibodies and coxisting pituitary tumours secreting TSH.

Table 3: Drugs interfering with levothyroxine pharmacokinetics

Lower absorption	Increased thyroxine requirements
Calcium supplements	Phenytoin
Iron supplements	Phenobarbital
Cholestyramine	Carbamazepine
Aluminium hydroxide	Rifampin
Expresso coffee	Tyrosine kinase inhibitors

ANSWER 8

Once rendered biochemically euthyroid on levothyroxine, the next serum TSH level could be performed after 6 months, provided Janet is asymptomatic. Thereafter, thyroid review and testing could be 12-monthly.[11] Repeat testing for anti-thyroid peroxidase antibodies, if tested initially, are not required. Thyroid imaging is not recommended unless thyroid nodules or lymphadenopathy are detected clinically.[6]

ANSWER 9

Currently, there is no role for T3 in the management of hypothyroidism. Most circulating T3 is formed from deiodination of circulating T4[24] and since the 1970s synthetic levothyroxine has been the treatment of choice for thyroid hormone replacement. While it is true that a subset of patients on appropriate levothyroxine therapy remain symptomatic, the difficulty is that hypothyroid symptoms are often non-specific and are very common in the wider euthyroid population.[25] A 1999 study assessing 33 patients claimed improved mood and neuropsychological function after short-term combination T3/T4 treatment;[23] these results have not been replicated. Further research into potential combination therapies, and whether identifiable patient subgroups might benefit, are ongoing. Oral T3 is not available on the Pharmaceutical Benefits Scheme (PBS) for the treatment of hypothyroidism. Desiccated thyroid hormone products are not registered with the Therapeutic Goods Administration (TGA).

ANSWER 10

GPs can manage most cases of hypothyroidism. The American Thyroid Association and American Association of Clinical Endocrinologists recommend the following groups of patients with hypothyroidism be managed in consultation with an endocrinologist or specialist physician:[1]

- children and infants
- patients in whom it is difficult to render and maintain a euthyroid state
- pregnant women
- women planning conception
- patients with cardiac disease
- patients with a goiter, nodule or other structural changes in the thyroid gland
- patients with other endocrine disease such as adrenal and pituitary disorders
- patients with an unusual constellation of thyroid function test results
- patients with unusual causes of hypothyroidism.

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RESOURCES FOR PATIENTS

- The American Thyroid Association has a large number of patient resources on thyroid disease. www.thyroid.org
- The Hormone Health Network is affiliated with the US Endocrine Society and has a comprehensive range of patient resources on many endocrine disorders. www.hormone.org

RESOURCES FOR DOCTORS

- Thyroid Disease Manager is a free, online, regularly updated textbook with comprehensive coverage of thyroid disease. www.thyroidmanager.org. It is part of a wider endocrinology project called Endotext: www.endotext.org.
- The American Thyroid Association freely provides their treatment guidelines for a range of thyroid disorders, in addition to other thyroid-related resources. www.thyroid.org
- Therapeutic Guidelines remains an excellent Australian medical resource, including the sections on thyroid disease. A subscription is required. www.tg.org.au
- In 2011 the Endocrine Society of Australia produced a position statement on desiccated thyroid or thyroid extract. www.endocrinesociety.org.au

CASE 4

JOHN IS BREATHLESS ON MILD EXERTION

John is an executive aged 58 years. He presents reporting gradual onset of fatigue over the past couple of months. More recently, he has been breathless on mild exertion. He has been well in the past, apart from some sporting injuries and ongoing musculoskeletal pain for which he takes daily non-steroidal anti-inflammatory drugs (NSAIDs). Systematic enquiry elicits no other symptoms. In particular, there has been no change in his bowel habits or the colour of his motions. He follows a vegetarian diet. Physical examination demonstrates conjunctival pallor but no other abnormality.

QUESTION 1

What tests are appropriate at this point?

FURTHER INFORMATION

A full blood evaluation (FBE) shows the following results:

- haemoglobin – 78 g/L (normal 135–175)
- mean corpuscular volume (MCV) – 70 fL (normal 80–100)
- mean corpuscular haemoglobin (MCH) – 16.8 pg (normal 27–33)
- blood film comment: hypochromic
- red cell distribution width (RDW) – 18% (normal 12–15)
- white cell count and platelet count – normal.

QUESTION 2

What type of anaemia is this likely to be and what further blood tests are indicated?

FURTHER INFORMATION

Iron studies are requested and show the following results:

- serum ferritin – 9 µg/L (normal 30–300 µg/L)
- serum iron – 4 µmol/L (normal 5–30 µmol/L)
- total iron-binding capacity – 90 µmol/L (normal 46–70 nmol/L)
- transferrin saturation – 5% (normal 10–40%).

QUESTION 3

What do these results indicate?

FURTHER INFORMATION

John has not eaten meat for 20 years.

QUESTION 4

Is it reasonable to accept that the iron deficiency is a result of a long-term vegetarian diet? What further investigations, if any, should be undertaken at this point?

QUESTION 5

Could John's daily use of NSAIDs have a bearing on this presentation?

QUESTION 6

What conditions can be associated with malabsorption resulting in this type of anaemia?

FURTHER INFORMATION

Colonoscopy reveals a carcinoma at the caecal pole and biopsies confirm adenocarcinoma. John is referred to a surgeon for right hemicolectomy. Surgery is scheduled in 2 weeks. He is still very fatigued.

QUESTION 7

What is the best way of dealing with John's anaemia, to improve his fitness for surgery and quality of life?

CASE 4 ANSWERS

ANSWER 1

John's fatigue and conjunctival pallor suggest anaemia so a FBE is an appropriate first-line test.[1] His vegetarian diet places him at risk of iron deficiency anaemia, so iron studies are warranted regardless of the FBE results, as iron deficiency without anaemia can cause fatigue and decreased physical performance.

ANSWER 2

This is a hypochromic microcytic anaemia. Although this type of blood film can be associated with the anaemia of chronic disease/inflammation, or thalassaemia[2] and sideroblastic anaemia,[3] the most likely cause of this blood picture is iron deficiency. It is appropriate to order iron studies as the next line of investigation.

ANSWER 3

These results confirm that the anaemia is indeed due to iron deficiency. In particular, the low serum ferritin is indicative of low iron stores.[1] No other condition leads to reduced ferritin levels.[1]

Serum iron is not a reliable indicator of iron deficiency.[4] Total iron binding capacity is elevated in iron deficiency and iron saturation is decreased. The amount of stainable iron in the bone marrow is decreased, but a bone marrow biopsy is rarely needed to make the diagnosis. Occasionally, ferritin levels can be falsely elevated as it is an acute-phase reactant in inflammation, chronic liver disease and malignancy.[4] Markers such as C-reactive protein may help identify coexisting inflammation.[5]

ANSWER 4

More than 10% of the world population is iron deficient.[5] Causes include poor intake of dietary iron, heavy menstrual loss, loss associated with childbirth and breastfeeding, and chronic parasitic infection.[1] Vegetarians are more likely to be iron deficient than people who eat meat.[1] However, in Australia, an otherwise healthy vegetarian man should be investigated to exclude gastrointestinal pathology causing iron deficiency and this should take the form of endoscopy and colonoscopy.[5] Poor oral intake is not an adequate explanation.[1] Faecal occult blood testing is a screening test that is appropriate only for asymptomatic people and not in the presence of gastrointestinal symptoms, rectal bleeding or iron deficiency anaemia, as further investigation will be required, even if the faecal occult blood test is negative.[6]

If endoscopy and colonoscopy do not provide a diagnosis, John should have a small bowel capsule study to exclude small bowel pathology,[5] including benign and malignant small bowel tumours, angiodysplasia, Crohn's disease and, on occasion, small bowel strictures related to NSAID use. A small bowel capsule study is appropriate only in a patient who has already had the more common causes of blood loss ruled out by an endoscopy and colonoscopy.

A Medicare rebate for the capsule study is not available unless endoscopy and colonoscopy have been performed. There was a time constraint attached but this has been removed.

It should be remembered that regular blood donation can, over years, lead to iron deficiency; however, assessment for other causes is still required.[7]

ANSWER 5

John reports daily use of NSAIDs, which can be associated with gastric ulceration, erosions and chronic gastric blood loss.[1] It can also cause small bowel ulceration and strictures, which may not cause any pain but can present as anaemia from chronic blood loss. Therefore, chronic use of NSAIDs is a possible reason for the anaemia[1] but further investigation is required.

ANSWER 6

Malabsorption is a cause of iron deficiency but it can occur in coeliac disease[1] and in achlorhydria.[1]

Coeliac disease affects about 1% of the Australian population.[8] Iron is absorbed in the upper small intestine and is best absorbed in an acidic environment.[1] Coeliac disease affects the proximal small intestine, so iron deficiency is a common presentation with or without gastrointestinal symptoms. Therefore, it is appropriate to perform coeliac serology or, alternatively, a small intestine biopsy at the time of endoscopy, when investigating iron deficiency.[7] About one-third of the Australian population has at least one coeliac gene so a positive gene test is not helpful in making a diagnosis. However, a negative gene test can be helpful in the setting of an equivocal small intestine biopsy, ruling out coeliac disease.

Achlorhydria occurs in atrophic gastritis,[1] which is associated with pernicious anaemia, and can also occur with *Helicobacter pylori* gastritis. Achlorhydia has also been described as arising from long-term use of proton-pump inhibitors.[9]

Some people who have had bariatric surgery may fail to absorb iron.

It is important to note that a significant percentage of people who have an abnormality on gastroscopy, when investigated for iron deficiency, have colonic pathology, including cancer.[1] Therefore it is not appropriate to limit investigation to the upper gastrointestinal tract.[7]

Malignancy at any site in the gastrointestinal tract, reflux oesophagitis, oesophageal varices and angiodysplasia can lead to iron deficiency through chronic blood loss.[1] Benign gastric and duodenal ulcers bleed acutely, resulting in anaemia but not iron deficiency. An old axiom states that 'ulcers gush, cancers ooze' and it is the slow ooze that results in iron deficiency anaemia. Iron deficiency is common in inflammatory bowel disease,[1] but it would be unusual, although not impossible, for there to be no gastrointestinal symptoms.

Premenopausal women may have iron deficiency anaemia as a result of gynaecological blood loss and increased requirements associated with pregnancy, particularly coupled with poor oral iron intake.[1] Gastrointestinal investigations may not be appropriate in all cases, but coeliac disease should be excluded and endoscopy and colonoscopy considered if there is clinical doubt, gastrointestinal symptoms or failure to respond to an appropriate period of oral iron supplementation. Current British guidelines recommend oesophageal gastroduodenoscopy for premenopausal women with iron deficiency anaemia and upper gastrointestinal symptoms, to check for possible upper gastrointestinal cancer.[7]

ANSWER 7

Investigation and management of iron deficiency are parallel strands of care. Iron therapy should be initiated while assessment of the cause is being undertaken.

For most patients the best first-line option for the treatment of iron deficiency is oral iron supplementation. Blood transfusion is not usually appropriate unless an immediate increase in oxygen delivery is required, such as when the patient is experiencing end organ compromise (eg angina or cardiac failure) or iron deficiency anaemia is complicated by serious, acute ongoing bleeding.[9] In Australia, oral iron preparations take the form of ferrous salts (sulphate, gluconate and fumarate) and include tablets and liquid preparations. The usual recommended dose of oral iron for the treatment of iron deficiency anaemia in adults is 100–200 mg of elemental iron daily in 2–3 divided doses.[5] When given at equivalent elemental iron doses, different oral iron salts have similar efficacy and tolerability.[5] Less potent oral therapy may not cause side effects but may not correct the iron deficiency. Iron in multivitamins is insufficient. John should be warned that bowel motions will become black and that oral iron can cause side effects, particularly constipation, diarrhoea and nausea.[10] Haemoglobin levels usually rise by 1–2 g/L daily or 20 g/L over 3–4 weeks.[10]

Taking iron supplements on an empty stomach, although generally advised, is associated with an increased rate of gastrointestinal side effects.[11] Compliance may be improved by suggesting the patient take the supplement with food.[11] Coffee,[11] tea,[11]calcium supplements,[11] antacids and some medications, for example quinolones (eg ciprofloxacin),[4] can impair iron absorption.

For patients with John's degree of iron deficiency, it is necessary to emphasise that they may require daily therapy for 3–6 months after haemoglobin levels have returned to normal to replenish stores.[4,8] For John, this is complicated by his impending surgery, which will be associated with further iron loss, and an infusion of iron may be more appropriate. The new National Patient Blood Management (PBM) Guidelines[12] support the use of intravenous iron when there is a short time before non-deferrable surgery to minimse the risk of red cell transfusion, which is associated with an increased risk of morbidity, mortality and length of stay. The important role of the GP in PBM has recently been highlighted. Many hospitals are now implementing programs to improve management of pre-operative anaemia, including timely access to intravenous iron when needed. An iron infusion is also useful if oral iron causes unacceptable side effects, if compliance is poor, if there is malabsorption with ongoing iron losses exceeding absorptive capacity, and where there is a clinical need for rapid iron supply to help prevent transfusion/decompensation.[10,11]

Intramuscular injections of iron are not adequately absorbed, stain the skin with a greyish discolouration and occasionally cause palpable masses. There is also a possible association with sarcoma. Its use, therefore, is discouraged unless other approaches cannot be practically delivered (eg when parenteral iron is indicated in remote settings).

Iron dextran is associated with a significant risk of anaphylaxis (approximately 0.61%) and is no longer used.

Two parenteral forms of iron are available in Australia on authority script: iron polymaltose and iron sucrose. The latter has PBS approval only for patients with chronic kidney disease on erythropoietin who have had a systemic reaction to polymaltose. The rate of anaphylaxis associated with these preparations is low (<0.1%); however, about one-quarter of patients report influenza-like symptoms for about 2 days after the infusion. Ferric carboxymaltose is an alternative parenteral preparation and can be given more quickly but it is not on the Pharmaceutical Benefits Schedule (PBS) in Australia.[13] Some hospital drug committees have approved the use of ferric carboxymaltose (eg for day patients) as it allows a large dose of iron to be given over 15 minutes.

Lastly, a discussion about diet and non-haem sources of iron would be useful in John's case.

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RESOURCES FOR PATIENTS

- Gastroenterological Society of Australia – Iron deficiency. www.gesa.org.au/consumer.asp?id=84
- BloodSafe patient resources www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+programs/blood+products+and+programs/bloodsafe/bloodsafe+information+for+consumers/iron+therapy
- Australian Red Cross Blood Service – Iron Deficiency Anaemia. http://mytransfusion.com.au/node/iron-deficiency-anaemia

RESOURCES FOR DOCTORS

- National Blood Authority Patient Blood Management guidelines. www.blood.gov.au/pbm-guidelines
- BloodSafe eLearning Iron Deficiency Anaemia (IDA) module. www.bloodsafelearning.org.au/node/56
- BloodSafe eLearning Australia Iron Deficiency Anaemia app. www.bloodsafelearning.org.au/node/71Diagnosis and management of iron deficiency anaemia. www.mja.com.au/journal/2010/193/9/diagnosis-and-management-iron-deficiency-anaemia-clinical-updateGuidelines for the Management of Iron Deficiency Anaemia. www.bsg.org.uk/clinical-guidelines/small-bowel-nutrition/guidelines-for-the-management-of-iron-deficiency-anaemia.html
- Patient blood management The GP's guide. www.racgp.org.au/download/Documents/AFP/2013/May/201305minck.pdf
- Australian Red Cross Blood Service – patient blood management and anaemia management guidelines. www.transfusion.com.au
- Oral iron dosing chart for clinicians. www.sahealth.sa.gov.au/wps/wcm/connect/81d0f6804f7202a8b7aef774733d1f2b/OralIronDosingTreatmentAnaemia-BloodSafe-Oct2011.pdf?MOD=AJPERES&CACHEID=81d0f6804f7202a8b7aef774733d1f2b

CASE 5

LISA'S FATIGUE AND MUSCLE WEAKNESS

Lisa is 33 years of age and she presents with fatigue and muscle weakness, which have been present since the birth of her first child 7 years ago. Lisa says the weakness mainly affects her lower limbs and that she waddles when she walks. People often comment, 'Are you limping?'. Recently, she has noticed that she has difficulty holding her hairdryer when she dries her hair. Her bowels are often loose and she has stomach pains after eating.

Over the past 7 years Lisa has seen several GPs and been referred to two different neurologists. She has had many investigations but no diagnosis has been made.

Lisa looks well and has a normal colour but has mild bilateral ptosis.

You notice that Lisa sat forward during the history taking, resting her elbow on the desk and supported her chin in her cupped left hand.

No abnormality is found on further examination. Her gait is normal and there is no detectable muscle weakness.

QUESTION 1

What is the possible diagnosis?

QUESTION 2

What else should be considered in the differential diagnosis?

QUESTION 3

What would you do next?

FURTHER INFORMATION

Lisa's test results were all normal and the acetylcholine (ACh) receptor antibody (AChR-Ab) test was negative.

At Lisa's next visit you confirm mild bilateral ptosis and note that she is very quickly fatigued when holding her upper limbs in an elevated position.

You discuss the negative AChR-Ab results with her and then refer her back to the neurologist.

QUESTION 4

Does the negative serology exclude myasthenia gravis?

FURTHER INFORMATION

The neurologist ordered a muscle-specific tyrosine kinase antibody (MuSK-Ab) test and this was negative.

QUESTION 5

Are there any other investigations that would confirm myasthenia gravis in Lisa's case?

FURTHER INFORMATION

Lisa was referred for electrophysiological studies (EPS) and her single fibre electromyography (SFEMG) test result was positive.

QUESTION 6

What treatment is available for Lisa?

CASE 5 ANSWERS

ANSWER 1

Lisa presents with muscle weakness that affects her eyes and limbs. This should raise the suspicion of myasthenia gravis, which is the most common disorder of neuromuscular transmission.[1] Myasthenia gravis is an autoimmune disorder in which the ACh receptors or associated receptor proteins in the postsynaptic membrane are attacked by antibodies.[2] T-lymphocytes are also involved in the pathogenesis of myasthenia gravis.[2] Most patients with myasthenia gravis have an abnormality, either hyperplasia or thymoma, in their thymus gland.

The disease is characterised by symptoms that are often transient early in its presentation. Symptoms may remit completely for days or weeks but gradually worsen and become more persistent.

Myasthenia gravis is an uncommon disorder; it has an annual incidence of 10–20 new cases per million people[3,4] and a prevalence of 150–200 per million.[5,6] The prevalence of myasthenia gravis has been increasing over the past five decades and this increase is attributed to better recognition of the condition, an ageing population and the longer life span of affected patients.[7]

Myasthenia gravis occurs at any age but there tends to be a bimodal distribution to the age of onset with an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decade (male predominance).[7]

Lisa's symptoms have fluctuated and affect a combination of muscle groups, which is characteristic of the condition.

ANSWER 2

As Lisa's fatigue has already been thoroughly assessed and investigated at multiple consultations and with tests involving all systems, the differential diagnosis is restricted to diseases with neurological or neuromuscular pathology. These potentially include:[8]

- thyroid eye disease (this may mimic myasthenia gravis)
- motor neuron disease
- drugs (eg penicillamine and statins have been implicated in causing a myasthenia presentation)
- thymic disease (eg thymic hyperplasia, thymoma and, rarely, thymic carcinoma)
- paraneoplasia associated with extrathymic tumours (eg small cell lung cancer and Hodgkin lymphoma)
- autoimmune disorders
- botulism, which has a rapid course and is therefore excluded.

ANSWER 3

You review Lisa and exclude all of the differential diagnoses listed above on the basis of her history and your examination findings. You confirm the presence of her ocular and limb symptoms and then discuss her situation with her most recent neurologist, who recommends testing for AChR-Ab.

You order further blood tests, including a full blood evaluation (FBE), liver function tests (LFTs), thyroid stimulating hormone (TSH), thyroid antibodies, C-reactive protein, iron studies and the test for AChR-Ab, which the neurologist recommended.

ANSWER 4

The negative ACh serology results do not exclude myasthenia gravis. It is estimated that 6–12% of patients with myasthenia gravis have negative antibody serology for both AChR-Ab and MusSK-Ab.[1] Such patients are often referred to as having seronegative myasthenia gravis and there is a suggestion that these patients may have better outcomes following treatment.[11] Seropositive myasthenia gravis occurs in 88–94% of cases.[1] Tests are for the presence of AChR-Ab and MuSK-Ab. AChR-Ab are present in 80–90% of patients with generalised myasthenia gravis[9,10] and in 40–55% of those with ocular myasthenia.[9]

ANSWER 5

Historically, the icepack test and edrophonium (tensilon) test have been used. In the ice pack test, a bag (or surgical glove) is filled with ice and placed on the closed lid for 2 minutes. The ice is then removed and the extent of ptosis is immediately assessed. The sensitivity seems to be about 80% in those with prominent ptosis. The predictive value of the test has not yet been established. This test can be used in patients with ptosis, particularly those

in whom the tensilon test is considered too risky. It is not helpful for those with extraocular muscle weakness. As it is based on the physiological principle of improving neuromuscular transmission at lower muscle temperatures, the eyelid muscles are the most easily cooled by the application of ice.[12,13]

Edrophonium chloride is an acetylcholinesterase inhibitor with a rapid onset (30–45 seconds) and short duration of action (5–10 minutes). It prolongs the presence of ACh in the neuromuscular junction and results in an immediate increase in muscle strength in many of the affected muscles. The edrophonium test should be used only in those patients with obvious ptosis or ophthalmoparesis, in whom improvement after infusion of the drug can easily be observed. The difficulty in quantifying strength independently of volition in other muscle groups makes the interpretation of the response to edrophonium too unreliable. The sensitivity of this test is in the range of 80–90% but it is associated with many false-negative and false-positive results.[9,14] Some patients with clearly established myasthenia gravis may have an equivocal or no response to edrophonium. A positive test is not specific for myasthenia gravis, as it can also occur in other conditions, such as motor neuron disease, brainstem tumors and compressive cranial neuropathies, which can present in a similar fashion.

The icepack and edrophonium tests are sensitive and easy to perform but there are concerns about high rates of false-positives with these techniques. Confirmation of a diagnosis by these tests alone is unwise.

EPS is the most important supplement to serological studies and may be used to confirm a myasthenia gravis diagnosis.[1] The two EPS tests are the repetitive nerve stimulation (RNS) and single fibre electromyography (SFEMG). The latter test is the more sensitive and is positive in >95% of those with generalised myasthenia gravis and in 85–95 % of those with ocular presentations.

ANSWER 6

In the past, myasthenia gravis was a disabling and often fatal condition, whereas today it is managed more effectively. The therapeutic approach is highly individualised and complicated and is best managed by the treating neurologist with the assistance of the GP. Variables such as the age of the patient and the severity and progression of the disease will influence treatment decisions.[15–18]

Table 1 summarises the four basic therapies used to treat myasthenia gravis. Medications used may include pyridostigmine (first-line treatment), neostigmine, prednisone, azathioprine and cyclosporine.[19,20] Other agents (ie rituximab, monthly pulse cyclophosphamide and tacrolimus) may be used in some circumstances (eg refractory myasthenia gravis).[21] Most people with myasthenia gravis will require some form of immunotherapy during the course of their illness and some people may require immunotherapy indefinitely.[21]

Table 1: Treatment options for myasthenia gravis[18–22]

Treatment option	Comments
Symptomatic treatments Acetylcholinesterase inhibitors (anticholinesterase medications)	Some patients may require no additional therapies.
Chronic immunomodulating treatments Glucocorticoids and other immunosuppressive drugs	Anticholinesterase medications may be used to reduce the dose of immunosuppressive drugs and minimise their side effects.
Rapid immunomodulating treatments Plasmapheresis and intravenous immune globulin	These agents work quickly but have a short duration of therapy. They are reserved for use in specific circumstances (eg myasthenic crisis, pre-operatively before thymectomy, when initiating slower-acting immunotherapies or as an adjuvant to other medications in patients with refractory myasthenia gravis).
Surgical treatment Thymectomy	It usually takes years for the benefits of surgery to become apparent.

CONCLUSION

Lisa was commenced on pyridostigmine, which provided a dramatic, immediate benefit. Unfortunately, this was not sustained and after 12 months she required the addition of prednisolone. Azathioprine was added later in an attempt to reduce the dose of prednisolone.

Lisa eventually had a thymectomy but, unfortunately, did not obtain any definite benefit from the procedure so she remained on pyridostigmine, prednisolone and azathioprine

In cases of myasthenia gravis, the GP is the first point of contact. Disease often evolves over time and the diagnosis may take time to emerge, causing confusion for the patient, GP and specialists along the way. In the management of such cases, there is a need to revisit the symptoms and review what could be missing.

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RESOURCES FOR PATIENTS

- Better Health Channel. Myasthenia Gravis. Fact sheet. www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Myasthenia_gravis?open

Fatigue

In order to qualify for 6 Category 2 points for the QI&CPD activity associated with this unit:

- read and complete the unit of *check* in hard copy or online at the *gplearning* website at http://gplearning.racgp.org.au
- log into the *gplearning* website at http://gplearning.racgp.org.au and answer the following 10 multiple choice questions (MCQs) online
- complete the online evaluation.

If you are not an RACGP member, please contact the *gplearning* helpdesk on 1800 284 789 to register in the first instance. You will be provided with a username and password that will enable you access to the test.

The expected time to complete this activity is 3 hours.

Do not send answers to the MCQs into the *check* office. This activity can only be completed online at http://gplearning.racgp.org.au

If you have any queries or technical issues accessing the test online, please contact the *gplearning* helpdesk on 1800 284 789.

FOR A FULL LIST OF ABBREVIATIONS AND ACRONYMS USED IN THESE QUESTIONS PLEASE GO TO PAGE 3.
FOR EACH QUESTION BELOW SELECT ONE OPTION ONLY.

QUESTION 1

For patients presenting with symptoms suggestive of thyroid disease, which one of the following options CORRECTLY outlines investigations required for a diagnosis of primary hypothyroidism?

A. Serum TSH

B. Serum TSH and T4

C. Serum TSH and T3

D. Serum TSH, T4 and T3

E. Serum TSH, T4 and T3 and thyroid ultrasound

QUESTION 2

The management of hypothyroidism and therapeutic treatment goals may need to be altered for certain patients depending on age and other factors. Which of the following statements regarding changes in management and goals is CORRECT?

A. Pregnant women with hypothyroidism and a history of miscarriage should cease levothyroxine treatment.

B. People with cardiovascular disease or those aged >60 years should be started on lower levels of levothyroxine.

C. Women with hypothyroidism who become pregnant do not require any change in their thyroid medication.

D. More strict treatment goals apply with advancing age.

E. None of the above is correct.

QUESTION 3

Cartier, aged 48 years, presents with a 2.5-year history of ongoing tiredness, generalised aches and pains and difficulty sleeping. She receives antidepressant therapy for depression that was diagnosed 1 year ago. She retired recently, as she could not cope with working part time. Examination reveals extensive musculoskeletal tenderness. Which of the following most CORRECTLY describes appropriate investigations for Cartier?

A. Full blood evaluation (FBE), erythrocyte sedimentation rate

B. Renal, liver and thyroid function tests

C. Vitamin D, calcium, magnesium and phosphate levels

D. Answers A, B and C

E. Answers A and B

QUESTION 4

A fibromyalgia management plan should include a combination of patient education, an exercise program, pain management, psychology and medications. Which of the following statements most CORRECTLY describes medications for fibromyalgia?

A. Amitriptyline is not useful for the management of fibromyalgia.

B. Paracetamol is not a useful adjunct therapy in fibromyalgia.

C. Milnacipran is the only medication licensed for use in fibromyalgia.

D. Duloxetine is not useful for management of fibromyalgia.

E. Non-steroidal anti-inflammatory agents are of no benefit in fibromylagia.

QUESTION 5

William is 19 years of age and presents complaining of increasing weakness and tiredness, which commenced about 1 year ago. Questioning reveals he also experiences occasional dizziness. He became a vegetarian several years ago. Examination reveals conjunctival pallor. Which of the following statements is CORRECT?

A. William should be investigated for fibromyalgia.

B. William may have iron deficiency anaemia and a FBE and iron studies are suitable first-line tests.

C. William may have a thyroid problem and a thyroid function test is a suitable first-line test.

D. William's vegetarian diet does not place him at increased risk of iron deficiency anaemia.

E. William should have an endoscopy and colonoscopy as first-line tests.

QUESTION 6

Which of the following statements regarding iron deficiency anaemia is CORRECT?

A. Serum iron is a reliable indicator of iron deficiency.

B. Hypochromic microcytic anaemia is not associated with thalassemia.

C. Reduced ferritin levels have been associated with various blood dyscrasias.

D. Hypochromic microcytic anaemia may be associated with anaemia of chronic disease.

E. Iron supplements must be taken on an empty stomach.

QUESTION 7

Which of the following options most CORRECTLY outlines investigations for fatigue recommended by guidelines where chronic fatigue syndrome is suspected?

A. FBE, erythrocyte sedimentation rate, C-reactive protein, serum ferritin

B. FBE, C-reactive protein, serum ferritin

C. FBE, erythrocyte sedimentation rate, serum ferritin (children and young people only)

D. Answers A and B

E. Answer B only

QUESTION 8

Julianne is an optometry student aged 20 years and has a history of viral infections and fatigue. She has put her university studies on hold, as she was not able to cope with the daily commute and the workload required by her course. She was recently diagnosed with chronic fatigue syndrome (CFS)/myalgic encephalomyelititis. Which of the following statements regarding her diagnosis and potential management is the most CORRECT?

A. Most diagnoses of CFS occur in people aged 20–40 years.

B. Guidelines state that a diagnosis of CFS can be made in an adult when other possible causes of excessive fatigue have been excluded and symptoms have persisted for more than 3 months.

C. A trial of complementary therapies and supplements (eg vitamin B_{12}, vitamin C, co-enzyme Q10, magnesium, multivitamins or minerals) is warranted, as these agents improve symptoms.

D. Medications such as monamine oxidase inhibitors, glucocorticoids (such as hydrocortisone), mineralocorticoids (such as fludrocortisone), dexamphetamine, methylphenidate, thyroxine and antiviral agents may be useful for people with CFS.

E. The only medication that has been approved for use in people with CFS is milnacipran.

QUESTION 9

Myasthenia gravis is a rare condition but the GP most often is the first point of contact for patients. Which of the following statements is CORRECT?

A. Myasthenia gravis occurs mainly in people aged >70 years.

B. Negative AChR-Ab serology excludes a diagnosis of myasthenia gravis.

C. Negative MuSK-Ab serology excludes a diagnosis of myasthenia gravis.

D. Most people with myasthenia gravis have an abnormality with their thyroid gland.

E. The prevalence of myasthenia gravis has risen in recent decades due to better recognition of the condition, an ageing population and the longer life span of affected patients.

QUESTION 10

Pria is 39 years of age and was recently diagnosed with myasthenia gravis following a 5-year history of increasing fatigue and muscle weakness of her eyes and limbs, eventually resulting in minor ptosis of her right eye and pronounced ptosis in her left eye. Which of the following is CORRECT with regards to current treatment options for myasthenia gravis?

A. There are no known pharmacological treatment options for myasthenia gravis.

B. The benefits of thyroid surgery for myasthenia gravis may take years to become apparent.

C. Plasmapherisis is of no benefit for people with myasthenia gravis.

D. Most people with myasthenia gravis will require immunotherapy indefinitely.

E. Management of myasthenia gravis is highly individualised and complicated and should be managed by a neurologist with GP assistance.

check

Independent learning program for GPs