Adherence considerations in a person with fibromyalgia

BY ANDREW STAFFORD

Case details

A 47-year-old woman was referred for a Home Medicines Review (HMR) in March 2013. Her medical history included Addison's disease, endometriosis, fibromyalgia (FMS), hypothyroidism and osteopenia. Her current prescribed medications were as follows:

- Amitriptyline 5 mg (1/2 x 10 mg tablet) at night when required for insomnia (used once every three to four months).
- Cortisone acetate 25 mg in the morning and 12.5 mg at night.
- Fludrocortisone 100 microgram in the morning.
- Hydrocortisone 100 mg for injection when required for Addisonian crisis.
- Methylprednisolone aceponate 0.1% ointment applied daily when required.
- Naproxen 275 mg when required for pain associated with endometriosis (purchased over the counter).
- Paracetamol 500 mg when required for headache.
- Thyroxine 50 microgram in the morning.

She had recently moved to the area and no laboratory/pathology results were available prior to undertaking the HMR. Her new general practitioner (GP) requested the HMR as she was unfamiliar with the management of Addison's disease and FMS and wanted to ensure that the patient was managing their medication regimen appropriately.

During the HMR interview, the patient demonstrated a reasonable knowledge of her medical conditions and the role of her medications in managing them. She was very willing to take her medications as prescribed, but described significant issues with remembering whether or not she had taken them. Consequently, she would frequently take doses of thyroxine and cortisone mid-morning if she could not recall having taken them earlier in the morning. She recalled that a GP had once investigated her poor memory via imaging and numerous blood tests, but no apparent cause was identified.

She described her most concerning medical issue as poorly controlled pain due to FMS. Whilst she found that amitriptyline helped with this pain, even very low doses resulted in substantial sedation and grogginess the following day. This case study discusses the considerations that were made in selecting an appropriate management option for pain associated with FMS in this patient.

Dr Andrew Stafford is the Director of the Western Australia Dementia Training Study Centre and a Lecturer at the School of Pharmacy, Curtin University, Western Australia.

LEARNING OBJECTIVES

After reading this article, pharmacists should be able to:

- Describe the signs and symptoms of fibromyalgia
- Evaluate management options for pain associated with fibromyalgia
- Formulate a management plan for patients with pain associated with fibromyalgia.

Competency standards (2010) addressed: 4.2, 6.1, 6.2, 7.1, 7.3

Accreditation number: CAP140101e

This article had been independently researched and peer reviewed.

Clinical assessment and review issues

Overview of FMS

FMS is a condition common in middle-aged adults, particularly women.[1] It is characterised by the gradual onset of widespread musculoskeletal pain that is often described as a deep and burning ache, frequently coexisting with disturbed sleep and fatigue. Symptoms usually stabilise within the first year of onset and remain largely unchanged over time.[1]

The legitimacy of FMS as a medical disorder was questioned for many years by some clinicians due to its seemingly unrelated symptoms and the lack of an identifiable cause.[2] However, it is now recognised as a common, chronic, widespread pain disorder resulting from apparent neurochemical imbalances in the central nervous system. Whilst the aetiology and pathogenesis of FMS remain uncertain, multiple neurophysiological mechanisms appear to be involved, and the disorder is thought to primarily be caused by dysfunctional processing of pain in the central nervous system.[3] This results in a 'central amplification' of pain perception in people with FMS, characterised by phenomena such as allodynia (pain due to a stimulus that is not normally pain- provoking) and hyperalgesia (an increased response to painful stimuli).[2]

A definitive diagnostic laboratory test is yet to be developed for FMS; it is generally diagnosed via criteria that include measures of widespread body pain in addition to coexisting conditions such as fatigue, trouble thinking, depression, abdominal pain and headache.[4] An important consideration in the diagnosis of FMS is that many of the symptoms are similar to a number of rheumatologic and non-rheumatologic disorders (Table 1).[3] It is notable that the patient discussed in this case study also had Addison's disease and hypothyroidism, both of which are differential diagnoses for FMS.[3] Consequently, it was apparent that appropriate management of these conditions would minimise the potential for them to adversely impact upon the severity of her FMS.[5] Conversely, the skeletal effects of excessive doses of cortisone and thyroxine would accelerate her bone mineral density (BMD) loss,[6] so resolving her compliance issues became a high priority in this HMR.

The memory issues described by the patient reviewed in this HMR are not uncommon in people with FMS. It has been reported that cognitive impairment is a common manifestation of FMS, with up to 80% of people with the disorder showing measurable declines in working memory, attention and executive functions.[7] The level of pain associated with FMS may correlate with the degree of memory impairment, with some studies reporting that more severe pain is associated with poorer memory function.[7] Consequently, it is possible that improved pain management in this patient would also potentially alleviate some of her memory issues.

Managing FMS

There is currently no cure for FMS. For most patients, the goals of treatment are to alleviate pain, increase restorative sleep, and improve physical function by reducing associated symptoms.[8] Possibly due to the diversity of symptoms associated with FMS, no single therapy has been found to improve all manifestations of the syndrome. Furthermore, as the condition is heterogeneous in nature, ideal management utilises a patient-tailored multimodal approach that combines non-pharmacologic and pharmacologic treatments.[9]

"FOR MOST PATIENTS, THE GOALS OF TREATMENT ARE TO ALLEVIATE PAIN, INCREASE RESTORATIVE SLEEP, AND IMPROVE PHYSICAL FUNCTION BY REDUCING ASSOCIATED SYMPTOMS."

Non-pharmacological interventions that may benefit patients with FMS, include[8–10]:

- education to improve self-efficacy and coping mechanisms
- exercise (such as aquatic exercises and tai chi; the most studied modalities are aerobic or mixed-type exercises involving aerobic, strength and/or flexibility routines)

Table 1. Differential diagnosis of FMS (Reproduced from Han *et al.*)[3]

Rheumatologic disorders	Non-rheumatologic disorders
• Rheumatoid arthritis	• Lyme disease
• Systemic lupus erythematosus	• Hypothyroidism
• Ankylosing spondylitis	• Infectious diseases
• Polymyalgia rheumatica	• Peripheral neuropathies
• Sjögren's syndrome	• Entrapment syndromes
• Polyarticular osteoarthritis	• Drug-induced myopathy
• Crystal-induced arthritis	• Addison's disease
• Drug-induced lupus	• Hyperparathyroidism
• Inflammatory myositis	• Various neurologic disorders
• Metabolic myopathies	• Cushing's syndrome
	• Mood disorders
	• Sleep disorders
	• Post-traumatic stress disorder
	• Somatisation disorders

- acupuncture, with or without electrical stimulation
- balneotherapy (bathing in water without exercise)
- psychological interventions (for example, cognitive behavioural therapy).

There is no definitive evidence that any of these interventions is superior to the others, and the effect is generally modest.[9] However, they can be valuable adjuncts to pharmacological treatments, particularly education and coping skills.[9]

"IT IS IMPORTANT TO ACKNOWLEDGE THAT MANY OF THE AGENTS USED TO TREAT FMS-ASSOCIATED PAIN MAY EXACERBATE OTHER SYMPTOMS ASSOCIATED WITH THE SYNDROME."

Pharmacological management of FMS generally involves symptom-based treatment. Several classes of agents may be employed, including antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, sedatives, muscle relaxants, hypnotics and anticonvulsants.[3] With regards to pain management, there is no definitive evidence from clinical trials to guide the selection of agent/s. There is greatest evidence for tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), duloxetine and pregabalin.[3] Antidepressants tend to be effective regardless of whether mood disturbance is present. Low doses of TCAs, particularly amitriptyline, are most frequently utilised in the management of FMS, and are effective in treating the sleep disturbances, pain and depressive symptoms associated with the condition.[3] However, these agents are effective for only about 40% of patients, and generally result in greater improvements in sleep quality than pain. Furthermore, they may exacerbate fatigue and cognitive dysfunction,[7] which are important considerations in the patient reviewed in this HMR.

SSRIs and duloxetine have also been reported to reduce pain associated with FMS, and are generally better tolerated than TCAs.[8] Milnacipran (*Joncia*), a SNRI with increased selectivity for noradrenaline than serotonin, is considered to be the most beneficial agent in patients with FMS-associated cognitive dysfunction.[8] However, this agent is not PBS listed in Australia. Of the anticonvulsants, pregabalin is the most studied in FMS.[3] It has been found to reduce pain and improve both sleep and quality of life,[3] although it may cause significant negative effects on cognition.[7]

In terms of NSAIDs and analgesics, ibuprofen and naproxen have been found to be no more effective than placebo in treating pain associated with FMS, although they may augment the effect of TCAs and anticonvulsants.[8] Despite this limited efficacy, the majority of patients with FMS perceive greater pain relief from NSAIDs compared to paracetamol.[8] Opioids are generally not recommended for managing FMS due to limited efficacy and their potential for dependency, although tramadol has been shown to be effective in relieving FMS-associated pain and improving sleep quality.[8]

It is important to acknowledge that many of the agents used to treat FMS-associated pain may exacerbate other symptoms associated with the syndrome.[11] Fatigue may be aggravated by anticonvulsants, antidepressants or opioids; depression may be exacerbated by opioids; gastrointestinal symptoms may be affected by NSAIDs, opioids and antidepressants; and sleep disturbance may be aggravated by opioids and antidepressants.[11] Consequently, it is important to monitor for both efficacy and adverse effects once a drug treatment has been initiated.

As FMS is a chronic condition and conventional treatments are of limited benefit, many patients may use complementary and alternative medicines to manage it.[12] Unfortunately, there is little evidence that complementary medicines are of substantial benefit in treating the symptoms of FMS. Creatine supplementation was recently reported to slightly improve muscle function but not other features of FMS;[13] other trials have investigated St John's Wort, Cat's Claw, Devil's Claw, oral anthocyanidin and topical capsaicin.[12] However, a recent review concluded that there is insufficient evidence for any herbal medicine as a treatment of FMS,[12] and none can be recommended as first line therapy.

Actions and recommendations

In this HMR the patient's primary concern was poorly managed pain associated with FMS. In consideration of the available literature and this patient's poor tolerance of amitriptyline, it was recommended to cease amitriptyline and trial duloxetine. This was based on duloxetine having a lower potential to adversely affect her cognitive function than alternatives such as pregabalin and alternative TCAs.[8] As patients with FMS frequently report considerable sensitivity to pharmacological treatments,[9] a starting dose of 30 mg duloxetine once daily was suggested to reduce the risk of adverse effects.[8] The patient was also encouraged to commence a gentle exercise regimen and was intent upon reviewing behavioural techniques with a psychologist following a discussion of the benefits of these during the HMR interview.

Several recommendations were also made to improve the patient's compliance issues. She was encouraged to first trial a Dosette box to avoid doubling up on doses throughout the day. If this was proved ineffective, it was

recommended to consider two changes to her medication regimen to simplify it:

- moving the thyroxine to a single, possibly supervised, once weekly dose[14]
- changing twice daily cortisone to once daily prednisolone, although there is increasing evidence this may confer a higher risk of long-term adverse metabolic effects compared with cortisone.[15]

A final recommendation about managing this patient's FMS was to consider checking her vitamin D level. This was due to there being some evidence that FMS is a risk factor for hypovitaminosis D, which may negatively impact upon her cognition.[7] Additionally, her coexisting osteopenia was likely to benefit from an adequate level of vitamin D and calcium intake.

OUTCOMES

At the time of writing, the patient had ceased amitriptyline and was taking 30 mg duloxetine twice daily with limited improvement in FMS-associated pain. However, cost was becoming an issue for her as duloxetine is neither licenced nor PBS-subsidised for FMS in Australia (although it is FDA-approved for this indication in the United States).[8] If the cost became prohibitive, her GP intended to switch her to a cheaper SSRI. Whilst she did not believe that her memory had improved, she was using a Dosette box and was confident that she was no longer doubling up on doses of her medications.

This case is an example of the complexities involved in the therapeutic decision-making process undertaken by pharmacists in HMRs. It highlights how a patient's concerns must be addressed within the context of their coexisting conditions, medication regimen, social circumstances and medication-taking behaviour.

References

1. Wierwille L. Fibromyalgia: diagnosing and managing a complex syndrome. J Am Acad Nurse Pract 2012;24:184–92.
2. Clauw DJ, Arnold LM, McCarberg BH. The science of fibromyalgia. Mayo Clin Proc 2011;86:907–11.
3. Han C, Lee SJ, Lee SY, et al. Available therapies and current management of fibromyalgia: focusing on pharmacological agents. Drugs Today 2011;47:539–57.
4. Brummett CM, Clauw DJ. Fibromyalgia: a primer for the anesthesia community. Curr Opin Anesth 2011;24:532–9.
5. Kaganov Y, Gattas N, Rimon D. Fibromyalgia-like syndrome secondary to Addison's disease. J Clin Rheumatol 2000;6:27–9.
6. Rossi S, ed. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook; 2013.
7. Bertolucci PH, de Oliveira FF. Cognitive impairment in fibromyalgia. Curr Pain Headache Rep 2013;17:344.
8. Bellato E, Marini E, Castoldi F, et al. Fibromyalgia syndrome: etiology, pathogenesis, diagnosis, and treatment. Pain Res Treat 2012;2012:426130.
9. Fitzcharles MA, Ste-Marie PA, Pereira JX. Fibromyalgia: evolving concepts over the past 2 decades. CMAJ 2013 [Epub ahead of print].
10. Deare JC, Zheng Z, Xue CC, et al. Acupuncture for treating fibromyalgia. Cochrane Database Syst Rev 2013;5:CD007070.
11. Fitzcharles MA, Ste-Marie PA, Goldenberg DL, et al. 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary. Pain Res Man 2013;18:119–26.
12. Saad M, de Medeiros R. Complementary therapies for fibromyalgia syndrome - a rational approach. Curr Pain Headache Rep 2013;17:354.
13. Alves CR, Santiago BM, Lima FR, et al. Creatine supplementation in fibromyalgia: A double-blind, randomized, placebo-controlled trial. Arthritis Care Res 2013.
14. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: co-sponsored by American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract 2012:1–207.
15. Løvåst K, Husebye E. Replacement therapy for Addison's disease: recent developments. Expert Opin Invest Drugs 2008;17:497–509.

UP TO 1 CPD CREDIT GROUP 2

QUESTIONS

1. Which ONE of the following signs or symptoms is LEAST consistent with fibromyalgia?

a) Allodynia.
b) Gastrointestinal pain.
c) Elevated serum C-reactive protein.
d) Poor memory.

2. Which ONE of the following statements regarding fibromyalgia is the LEAST appropriate?

a) It is most common in middle-aged women.
b) Symptoms usually resolve around a year after onset.
c) Disturbed sleeping patterns is a common manifestation.
d) Associated with inappropriate central pain processing.

3. Which ONE of the following medicines is MOST effective in managing pain associated with fibromyalgia?

a) Amitriptyline.
b) Tramadol.
c) Pregabalin.
d) No medication is definitively more effective than another.

4. A 55 year old man has a medical history of significant depression and hypertension. He is newly diagnosed with fibromyalgia, and describes pain and insomnia as his most concerning symptoms. His current medications are sertraline 100 mg and quinapril 20 mg, both once daily in the morning. His blood pressure is well controlled and his mood is good despite his recent diagnosis.

Which ONE of the following recommendations is the LEAST appropriate for this man at this time?

a) Referral to a psychologist for education about self-efficacy and coping mechanisms.
b) Commence a trial of pregabalin to improve his pain and sleep.
c) Encouragement to commence a gentle exercise program if he leads a sedentary lifestyle.
d) Sertraline should be changed to a low dose of amitriptyline.