Investigating

myalgia in patients taking **statins**

Muscle pain (myalgia) and weakness is experienced by up to 10% of patients taking statins. However, myalgia is commonly experienced by all people at some stage in their life, regardless of statin use. To avoid the unnecessary withdrawal of statin treatment, a systematic approach to the investigation of muscle symptoms in patients taking statins is advised. Routine laboratory monitoring for statin-associated adverse effects is not recommended in asymptomatic patients.

Part one: Safe and effective use of statins

Statins are among the most widely prescribed medicines in New Zealand; in 2013, approximately 500 000 patients were dispensed a prescription for either simvastatin or atorvastatin.[1] Alongside lifestyle modification, statins are the mainstay of lipid management. New Zealand and international guidelines recommend statins for the primary prevention of cardiovascular disease (see: "Guidelines for use of statins", over page.[2, 3, 4] Numerous trials have confirmed that statin treatment is effective in the secondary prevention of cardiovascular events caused by atherosclerosis. Among patients with heart disease who take statins for five years, the number needed to treat (NNT) to prevent one non-fatal myocardial infarction is 39, and the NNT to prevent one death is 83.[5]

Before a patient begins taking statin treatment it is important that causes of dyslipidaemia are considered and managed appropriately, e.g. high saturated fat diet, excessive alcohol consumption, hypothyroidism, diabetes, liver disease, nephrotic syndrome and corticosteroid treatment.[4]

Monitoring lipid profile in patients taking statins

It is recommended that once a patient is initiated on statin treatment that their lipid profile should be monitored every three to six months, until their levels are stable, and then no more than once a year.[4] Measuring lipid levels more frequently may produce misleading results as day-to-day variation can be greater than trends over time.[4]

Low-density lipoprotein bound cholesterol (LDL-C) levels are widely used as an indicator of lipid management in patients taking statins.[6] When given at comparable doses the ability of the various statins to reduce LDL-C is similar.[7] There is no specific target LDL-C in patients with a five-year cardiovascular risk less than 20%; the aim is to achieve a moderate reduction in LDL-C.[4] The intensity of statin treatment is dependent on the patient's cardiovascular risk. A greater reduction in LDL-C from baseline should be expected in patients with a cardiovascular risk greater than 20%.[2]

Monitoring statin safety is not routinely required

Statins are generally considered a safe class of medicine, however, adverse effects are sometimes reported. These adverse effects can be grouped into the "Five Ms":[8]

1. Muscle symptoms, e.g. myalgia and/or weakness
2. Medicine interactions
3. Major organ effects, e.g. hepatic and renal effects
4. Metabolism, i.e. risk of type 2 diabetes
5. Memory, i.e. cognitive adverse effects

Most guidelines suggest taking a baseline measurement of liver function (alanine aminotransferase – ALT) before initiating statin treatment. However, to avoid unnecessary testing, it is suggested by many New Zealand experts that this approach be limited to patients in whom there is reason to suspect liver dysfunction (see over page).

Baseline testing of muscle enzymes (creatine kinase) prior to statin treatment is unnecessary, unless there is a specific reason to do so, e.g. the patient has risk factors (See: Investigating Myalgia, Page 18).

Once treatment has started, monitoring of ALT or creatine kinase is unnecessary unless clinically indicated, i.e. the patient is symptomatic or has specific risk factors.

Guidelines for initiating statins

In the latest update of the New Zealand Cardiovascular Risk Assessment guidelines (2013) it is reinforced that cardiovascular management options should be discussed with patients. It is also recommended that a more graded approach to the intensity of management be taken that reflects the patient's combined cardiovascular risk.

For patients with:[4]

- A five-year cardiovascular risk less than 10% – lifestyle measures are used to manage their cardiovascular health
- A five-year cardiovascular risk of 10 – 20% – a shared decision making approach should be taken when considering the benefits and harms of pharmacological treatment, including statin initiation. Following lifestyle management, patients are recommended to have their lipid profile measured after six to twelve months and their cardiovascular risk recalculated. There is good evidence that statin treatment will lower cardiovascular risk in this patient group with benefit increasing as the patient's cardiovascular risk rises.
- A five-year cardiovascular risk greater than 20%, or with known cardiovascular disease – statin treatment is strongly recommended

The patient's TC:HDL-C (total cholesterol:high-density lipoprotein bound cholesterol) ratio is a powerful marker of cardiovascular risk. In patients with a TC:HDL-C ratio ≥ 8, or a TC ≥ 8 mmol/L lipid-lowering treatment is generally recommended regardless of the patient's combined cardiovascular risk.[4]

Hepatotoxicity with statins

Hepatotoxicity due to statin treatment is highly unusual. Rarely, hepatitis and jaundice are reported in patients taking statins.[9] New Zealand guidelines state that the risk of hepatotoxicity due to statin treatment appears negligible,[6] and routine monitoring of liver function is considered unnecessary.[2, 6]

United States guidelines recommend that a baseline ALT test be performed in patients prior to initiating statin treatment.[2] United Kingdom guidelines also recommend measuring liver enzyme levels within three months of starting statin treatment and at 12 months.[3] However, ALT testing is unlikely to provide useful information unless there is reason to suspect that the patient has liver dysfunction. Elevations in transaminase levels are typically seen in less than 3% of patients taking statins and are not significantly different from rates among patients taking placebo.[8] Furthermore, these elevations often return to normal without patients needing to stop taking statins.[8]

If an ALT test is requested in a patient with suspected liver dysfunction, a markedly elevated level would be considered a risk factor for adverse effects of statins, and the risk versus benefits of statin treatment should be revisited; statins should be used with caution in patients with an ALT greater than three times the upper limit of normal.[9] If the patient does decide to begin statin treatment, a lower dose may be appropriate.[8] Patients with non-alcoholic fatty liver disease will typically display a mild to moderate increase in ALT.[10] Atorvastatin has been found to reduce aminotransferase levels in patients with fatty liver disease. Mildly abnormal LFTs in a patient with non-alcoholic fatty liver disease should not be considered a contraindication for statin treatment.[10]

It is reasonable to monitor hepatic function in patients taking statins with suspected liver dysfunction and an elevated baseline ALT level, or in patients who develop symptoms suggestive of hepatotoxicity, e.g. unexplained fatigue or weakness, loss of appetite, abdominal pain, dark-coloured urine, or yellowing of the skin or sclera.[2]

Best Practice Tip: If a liver function test is requested in the context of statin treatment, request an ALT test only, rather than "LFTs". Further testing of liver function can be performed by the laboratory on the same blood sample if necessary, within a limited time period. Also consider customising your PMS so when requesting investigations, individual liver function tests can be selected rather than "LFTs".

Monitoring for other adverse effects in patients taking statins

Acute kidney injury

The risk of acute kidney injury (AKI) occurring in patients taking statins is slightly increased. It is likely that this is at least in part due to muscle protein entering the blood stream. A large study of over two million patients aged over 40 years who were recently initiated on statins found that the risk of people without chronic kidney disease (CKD) being hospitalised due to AKI was increased by approximately one-third during the first 120 days of high potency (≥ 40 mg daily simvastatin) statin treatment, compared to patients receiving low potency statins.[29] However, the absolute risk of this occurring was small and it was estimated that 1700 patients would have to be treated with high potency statins for four months to cause one additional hospitalisation due to AKI.[29] Interestingly, it was found that patients with CKD who were receiving statin treatment were not at an increased risk of AKI.[29] This unexpected result has caused some researchers to interpret this study with caution. Patients can be advised that the risk of AKI due to statin treatment is exceedingly low. Monitoring of kidney function is a routine part of care in patients at risk of AKI, e.g. older patients or patients taking long-term NSAIDs, however, monitoring kidney function to specifically detect statin-induced renal impairment is not necessary.

For further information see: "Statins and the risk of acute kidney injury", BPJ 52 (Apr, 2013).

Type 2 diabetes

Patients taking statins have an increased risk of developing diabetes that increases according to treatment intensity.[2] For statin treatment described as moderate intensity (simvastatin 20 – 40mg daily), for every 1000 patients approximately one extra patient will develop diabetes per year; in patients taking high-intensity statins there will be approximately three extra cases of diabetes.[2] However, the risk of new-onset diabetes in people taking statins with elevated cardiovascular risk is outweighed by the reduced risk of cardiovascular events in most patients with type 2 diabetes; except for those aged under 40 years, those aged over 75 years and those with low LDL-C for whom treatment decisions should be individualised.[2] In adults with diabetes, some of whom had coronary heart disease, statin treatment is reported to decrease the relative risk of cardiovascular events by 20%.[2] Furthermore, the people who are at most risk of new-onset diabetes are those who are most likely to gain benefit from the use of statins. The patient's HbA_{1c} level from their most recent cardiovascular risk assessment will serve as a baseline for regular monitoring for type 2 diabetes. All patients taking statins should continue to have their HbA_{1c} levels regularly tested each time a cardiovascular risk assessment is performed.[2] If a patient does develop diabetes they can be advised to continue statin treatment and be further encouraged to maintain a healthy lifestyle.[8]

Memory

There is no clear evidence that statins have an adverse effect on memory, despite there being observational data of a link between statins and memory loss and confusion.[8] There are also case reports of cognitive decline in patients taking statins that has resolved with switching or stopping statin treatment.[8] However, two large randomised trials (the Heart Protection Study and the PROSPER study of statin use in older patients) did not detect any significant difference in the rate of cognitive decline in patients taking statins versus placebo.[8] An early meta-analysis of observational studies even suggested that onset of cognitive decline could be delayed with the use of statins, possibly by decreasing the risk of cerebral infarcts.[8] Switching to a different statin, taking a low dose of a statin, or trialling alternate day dosing are possible strategies for treatment in patients with an elevated cardiovascular risk who are concerned about any cognitive effects of statin treatment. Patients can be reassured that if they do experience any cognitive symptoms due to statin use that these are likely to resolve within three to four weeks of stopping treatment.[8]

Part2: Investigating Myalgia

Myalgia is a potential adverse effect of statin treatment

Myalgia, with or without muscle weakness, is the most common adverse effect associated with statin use, and is reported to occur in up to 10% of people prescribed statins.[11] Statins are not necessarily the cause of myalgia in all of these people, however, as myalgia is frequently reported in the general population and can have many aetiologies.

Myalgia may be described as a muscular ache, heaviness, stiffness or cramping sensation; tendon pain and nocturnal leg cramps may also occur.[12] Muscle weakness can also occur without discomfort and may be noticed by patients as an inability to open jars, difficulty snapping their fingers or difficulty getting out of a chair.[12] Statin-associated myalgia is characterised by the symmetrical involvement of large and proximal muscle groups, in particular the legs.[13] Symptoms typically begin within six months of initiating the statin.[13]

When myalgia is associated with muscle inflammation, this is referred to as myositis. Myositis is usually accompanied by an elevation in serum creatine kinase.[12] Rhabdomyolysis occurs when the inflammation is associated with muscle fibre break-down, releasing myoglobin into the bloodstream.[13] The distinction between myositis and rhabdomyolysis is not always clear, however, a broadly accepted criteria for rhabdomyolysis is serum creatine kinase levels more than ten times the upper limit of normal, with evidence of myoglobinaemia.[8, 11, 13] Other definitions of rhabdomyolysis include elevations of creatine kinase greater than 40 times the upper limit of normal, and increased creatine kinase in association with renal failure.[14]

Elevations of creatine kinase are not necessarily diagnostic of a pathological process. Transient elevations can occur in healthy people, e.g. following vigorous exercise. Serious complications of muscle cell damage are more likely to occur in patients with risk factors, such as co-morbid illness, dehydration or pre-existing renal impairment. These complications include acute kidney injury (AKI) and widespread vascular coagulation.[12] Death due to rhabdomyolysis in patients taking statins is extremely rare; more than eight thousand patients would need to take a statin for at least 40 years for one extra death to occur.[15]

A recent study assessing the Effect of Statins On Skeletal Muscle Function and Performance (STOMP) involved giving high dose atorvastatin (80 mg), daily, to over 200 healthy females with no history of statin use, for six months.[16] It was found that the average creatine kinase level in females taking a statin increased by 20.8 U/L, compared to placebo.[16] The normal creatine kinase range is 30 – 180 U/L for females and 60 – 220 U/L for males.[17] Nineteen patients taking atorvastatin reported myalgia, compared to ten taking placebo, but there was no noticeable difference in terms of muscle strength, e.g. hand-grip, elbow flexor and knee extensor strength.[16] A lower incidence of myalgia is reported in clinical trials than is experienced by patients taking statins in clinical practice possibly due to the exclusion from studies of patients with a history of muscle symptoms, or risk factors for the development of myalgia.[8]

The pathophysiology of statin-associated myalgia

Multiple mechanisms are thought to contribute to the development of statin-associated myalgia, and no one mechanism fully explains muscle symptoms associated with statin use:[12]

- Cholesterol plays an important role in maintaining cell membrane function. Disruptions to cholesterol synthesis may affect membrane ion channels and thereby modify muscle membrane excitability. This effect has been observed in some animal models. However, inhibitors of squalene synthase (involved in the final step in cholesterol synthesis) also lower cholesterol, but do not cause muscle damage.
- Mevalonate is a precursor of co-enzyme Q10 (CoQ10 or ubiquinine), as well as being a precursor of cholesterol, and is also an important antioxidant involved in the electron transport chain in mitochondria. Reductions in CoQ10 have been suggested to interfere with cellular respiration and result in muscle toxicity. However, muscle CoQ10 levels do not correlate well with histological changes.[11] There is insufficient evidence to recommend the routine administration of CoQ10 for the prevention of statin-associated myalgia.[18]
- Statins may cause a reduction in other synthetic precursors of cholesterol, which have functional roles in cellular protein physiology
- Programmed cell death (apoptosis) in skeletal muscle may be triggered by statins
- Statins have been shown to decrease muscle strength by altering the movement of calcium within animal muscle cells

Risk factors for statin-associated myalgia

Myalgia is more likely to be experienced in patients taking statins, if they have additional risk factors (Table 1). For example: frail, elderly females; people with co-morbidities such as chronic kidney disease and diabetes; people taking high doses of statins or medicines which interact with statins; and people with a genetic pre-disposition.[13]

Medicine interactions

The risk of patients experiencing myalgia when taking statins metabolised by the cytochrome P-450 (CYP) 3A4 system, e.g. simvastatin and to a lesser extent atorvastatin, is increased if they are taking other medicines that also interact with the CYP 3A4 system, e.g. macrolide antibiotics.[19] A study investigating over 3000 cases of statin-associated rhabdomyolysis found that in more than half of cases, patients were also taking medicines known to affect statin metabolism.[19]

Table 1: Risk factors for statin-associated myalgia, adapted from Ahmad 2014[13]

Patient characteristics	■ Age over 80 years ■ Female ■ Ethnicity: people of African and Caribbean descent are reported to have a substantially increased risk of statin-associated myalgia compared to people of European descent.[12] People of Asian ethnicity have an increased risk of developing adverse effects following treatment with rosuvastatin.[13] It is unknown if there are ethnic differences in the incidence of statin-associated myalgia among Māori and Pacific peoples. ■ Small body size and frailty ■ Excessive physical activity ■ Drinking more than 1 L of grapefruit juice per day ■ Personal or family history of muscle symptoms ■ History of elevated creatine kinase levels ■ Unexplained muscle cramps
Co-morbidities	■ Hypothyroidism ■ Chronic kidney disease ■ Diabetes (type 1 and 2) ■ Alcoholism ■ A history of major surgery or a recent procedure ■ Infections
Medicines	■ High-dose statins, in particular simvastatin ≥ 80 mg, daily.[14] (although this dose is not recommended) ■ Medicines that interact with statins, e.g. macrolides ■ Concurrent use of oral corticosteroids: increases the risk of developing muscle complications by three-fold in females and two-fold in males.[22] ■ Substance use
Genetics	■ Inherited muscle diseases, e.g. McArdle disease, myoadenylate deaminase deficiency and Pompe's disease ■ Polymorphisms in CYP (P450) isoenzymes ■ Polymorphisms in drug transporter genes (see: "Genetic testing for statin-associated myalgia" Page 20)

It may be necessary to temporarily stop simvastatin if patients are required to take the following medicines:[20]

- Erythromycin and clarithromycin
- Azole antifungals, e.g. itraconazole, posaconazole and voriconazole
- Protease inhibitors, e.g. ritonavir, telaprevir, boceprevir
- Gemfibrozil
- Ciclosporin
- Danazol

Atorvastatin should also be avoided, if possible, in patients taking any of the above medicines, but if the combination is required then it should be used with caution and the patient advised to report any muscle symptoms.[20] There have been case reports of rhabdomyolysis occurring in patients taking simvastatin and azithromycin or roxithromycin, however, no clinically significant interactions are known to occur between these antibiotics and atorvastatin.[20]

New Zealand guidelines recommend a maximum daily dose of simvastatin of 20 mg for patients taking amiodarone, verapamil, diltiazem, nicotinic acid > 1 g/day, and amlodipine.[4, 9] The dose of simvastatin should be limited to 10 mg/day if given with bezafibrate.[9] Dose reductions of simvastatin should be considered for patients taking systemic fusidic acid or terbinafine, or colchicine if the patient has renal impairment.[4] Atorvastatin should be used with caution in patients taking these medicines and the patient advised to report any muscle symptoms.[20]

Pravastatin is mainly cleared by the kidneys and is a fully subsidised alternative statin for patients taking medicines that may interfere with the CYP enzyme system. The combination of pravastatin with fibrates is associated with an increased risk of muscle damage.[21]

Rosuvastatin is largely metabolised by another enzyme system (OATp1B1) and therefore has fewer and different interactions than statins metabolised by the CYP 3A4 system, but this statin is unsubsidised in New Zealand.[8]

For further information see: "Simvastatin and atorvastatin: beware of potential CYP3A4 interactions when prescribing other medicines", BPJ 60 (Apr, 2014).

Monitoring and investigating mylagia in patients taking statins

Laboratory monitoring for evidence of muscle damage is not routinely recommended for asymptomatic patients on a stable dose of statins for the treatment of hypercholesterolaemia.[2]

Genetic testing for statin-associated myalgia

Commercial genetic tests are available that can estimate the likelihood of some patients developing statin-associated myalgia. The test detects the presence or absence of a single-nucleotide polymorphism within SLCO1B1 on chromosome 12.[23] The polymorphism has a prevalence of 15% in the general population.[23] The risk of a person developing simvastatin-induced myalgia is increased by four and a half times with one copy of the allele, and by almost 17 times with two copies of the allele.[23] Testing is unsubsidised and has a cost to the patient of approximately NZ$120. This test may be of interest to some younger patients with high cardiovascular risk who are concerned about the possible adverse effects of simvastatin treatment and would like more information before deciding to initiate statin treatment.

Before starting statin treatment

Serum creatine kinase levels should not be routinely measured in patients prior to statin treatment, unless there are risk factors for statin-associated myalgia present (see below).[2] This is because an elevated creatine kinase level in patients without muscle symptoms does not necessarily predict the development of myalgia.[24] Creatine kinase levels up to ten times higher than normal levels have been reported to occur in patients taking statins without symptoms of myalgia.[12]

Before initiating statin treatment patients should be asked about their history of muscle symptoms, such as muscle weakness or fatigue, aching or pain, tenderness, cramps or stiffness, including frequency and duration.[2] The possible adverse effects of statin treatment should be discussed with patients and they should be instructed to report any unexplained muscle symptoms.

For patients who have an increased risk of developing statin-associated mylagia, it is reasonable to take a baseline serum creatine kinase measurement before initiating statin treatment, or alternatively, to have a lower threshold for measuring serum creatine kinase once statin treatment has begun. This includes patients with:[2]

- A personal or family history of statin intolerance
- A personal or family history of muscle disease
- Concurrent medicines that may increase the risk of myalgia
- Risk factors for statin-associated muscle damage, e.g. renal or hepatic impairment

Best Practice Tip: If testing is required, "serum creatine kinase" should be specifically requested on the form along with a note that the purpose of testing is the investigation of myalgia.

Monitoring patients during treatment

Creatine kinase levels should not be routinely monitored in asymptomatic patients taking statins.[2]

If creatine kinase levels are requested, e.g. in patients with risk factors for myalgia, and the patient is asymptomatic, but levels are markedly elevated, withdrawal and rechallenge of statin treatment may be appropriate to determine if the increase is associated with the statin.

If the patient is symptomatic, and creatine kinase levels are found to be elevated, investigate as below.

Investigating myalgia in patients taking statins

Myalgia is commonly reported in clinical trials by patients taking either statins or placebo, therefore it is important to avoid the unnecessary discontinuation of treatment.[8]

Differential diagnosis of myalgia

The characteristics of the patient's pain may help determine the degree of clinical suspicion for statin-associated myalgia:

- Myalgia associated with physical activity is likely to be self-limiting
- Acute onset myalgia with upper respiratory tract symptoms suggests viral infection
- Myalgia with swelling or localised warmth suggests localised inflammation or infection
- Myalgia in a patient with poor sleep quality and stress is suggestive of fibromyalgia syndrome, a common cause of myalgia (see: "Fibromyalgia syndrome: a constellation of symptoms", Page 23)
- Muscle pain and stiffness in the morning suggests polymyalgia rheumatica (see below)
- Slow onset myalgia with long-term symptoms is more suggestive of a chronic condition such as hypothyroidism, hypercalcaemia or severe vitamin D deficiency

Consider the possibility of other causes for the patient's symptoms and investigate as appropriate.[2] In patients who have a consistent history of muscle symptoms prior to starting their statin treatment, it is more likely that the cause of their myalgia is not associated with statin use. Polymyalgia rheumatica should be suspected in patients aged over 60 years who report shoulder and pelvic girdle pain and stiffness in the morning that improves later in the day.[25] An elevated C-reactive protein (CRP) makes a diagnosis of polymyalgia rheumatica more likely.[25] An elevated serum calcium level is suggestive of hyperparathyroidism.

For further information see: "Polymyalgia rheumatica: Look before you leap", BPJ 53 (Jun, 2013).

Red-flags: Symptoms of rhabdomyolysis

Immediately withdraw statin treatment in patients who present with myalgia and any of the following:

- Unexplained brownish-red coloured urine suggestive of myoglobinuria* (often described as "tea brown")
- Decreased urine output
- Fatigue
- Muscle weakness

The myalgia associated with rhabdomyolysis is usually severe and patients are at risk of acute renal insufficiency, which can occur when myoglobin precipitates in the urinary tubules and causes a blockage resulting in acute kidney injury (AKI).

The following tests should be requested if rhabdomyolysis is suspected:[2]

- Serum creatine kinase
- Serum creatinine
- Serum electrolytes, including calcium and phosphate
- Urine dipstick for the presence of haem, which will detect both myoglobin and haemoglobin

There is a relatively low risk of AKI in patients with a serum creatine kinase level less than 15 000 U/L, although AKI may occur with creatine kinase levels as low as 5000 U/L in patients who are older, or who also have sepsis, dehydration or acidosis.[26] If intrinsic renal damage is suspected, the patient should be referred to hospital without delay.

* Myoglobinuria can be confirmed and distinguished from haematuria, if required, by laboratory testing of a random urine sample.[2]

Ask the patient about their adherence to the statin regimen, e.g. have they recently started taking higher doses, and the use of other medicines that may influence statin metabolism. If an obvious cause of the patient's symptoms has not been identified then statin treatment should be withdrawn for at least two weeks while the patient's condition is evaluated further.[13] Recording the patient's subjective baseline score, e.g. muscle pain, on a one to ten scale, before statin treatment is withdrawn, can be a useful way of comparing muscle symptoms over time if a statin rechallenge is tried (see below).

Request a serum creatine kinase test to investigate possible muscle damage and serum creatinine to assess kidney function. However, a normal creatine kinase test does not necessarily exclude the possibility of statin-induced myalgia as biopsy-proven statin-associated muscle damage, in conjunction with muscle weakness, can occur in some patients with normal creatine kinase levels.[13] A symptom-based approach is therefore useful, supported by laboratory test results:[4]

- For patients with muscle pain, but no rise in creatine kinase, a reduction in statin dose or discontinuation of treatment may be required; monitoring of creatine kinase is not necessary.
- For patients with creatine kinase levels between three and ten times the normal level a reduction in statin dose, or discontinuation of treatment is appropriate; the patient's symptoms and creatine kinase levels should be regularly monitored if treatment is continued, e.g. weekly.
- For patients with creatine kinase levels greater than ten times the upper limit of normal, statins should be discontinued immediately

Confirming statins as the cause of myalgia

A rechallenge of the same statin at the original, or lower dose, can be used to indicate if the statin was the cause of the patient's symptoms.[2] Although the sensitivity and specificity of withdrawal and rechallenge is unknown, the STOMP trial found that 4.6% of people receiving placebo experienced myalgia during a controlled withdrawal and rechallenge.[16]

If a causal relationship is found between the patient's symptoms and statin treatment then the original statin should be discontinued.[13] At this point discuss the benefit versus risks of continued statin treatment with the patient. The adverse effects of statin treatment may outweigh the potential benefit of a reduction in cardiovascular risk provided by treatment, e.g. in frail older people. If statin treatment is reintroduced, a low dose of another statin, e.g. pravastatin, can be trialled.[2] Most of the LDL-C lowering benefit of statins occurs at lower doses.[2] The statin dose can be titrated upwards, if appropriate. Alternate day, or even twice weekly, dosing regimens have also been trialled in patients experiencing adverse effects of statin treatment.[12]

Fibromyalgia Syndrome: a constellation of symptoms

Fibromyalgia is a chronic pain syndrome consisting of a constellation of symptoms with no clear pathophysiological explanation. Fibromyalgia is a common cause of myalgia, affecting 2 – 5% of the population.[27]

Fibromyalgia can affect anyone, but occurs most commonly in young to middle-aged females.[27] The cardinal features of fibromyalgia include chronic widespread musculoskeletal pain with tenderness on examination, poor and unrefreshing sleep, fatigue and cognitive effects on short-term memory and concentration.[27] The features of fibromyalgia can therefore provide a challenge when differentiating from statin-induced adverse effects.[27]

The pathophysiology of fibromyalgia is unclear, although it is thought to occur due to long-term psychological or physical stress causing the central nervous system to alter the processing of afferent sensory input.[27] The result of these changes is that normally non-painful stimuli may become amplified and experienced as pain.[27]

The American College of Rheumatology criteria are used to diagnose fibromyalgia which involves recording the patient's pain during the previous week at different locations on their body. Sleep quality and cognitive symptoms are assessed as important features of fibromyalgia as well as the presence of headache, abdominal pain and depression.[27] Fibromyalgia is associated with stress therefore patients should be assessed for psychosocial factors causing emotional distress, muscle tension, pain and other symptoms.

Regular exercise is known to improve pain, fatigue and sleep disturbance in patients with fibromyalgia.[27] A Cochrane review found that aerobic resistance training was of particular benefit.[28] Exercise should be introduced slowly; swimming in a warm pool is a good starting point as the warm water and low resistance relieves symptoms.[27] Yoga, Qi Gong and Tai Chi may also be effective activities.[27]

Management of any psychiatric co-morbidity combined with stress management, e.g. planning and coping strategies, are essential parts of fibromyalgia treatment.[27]

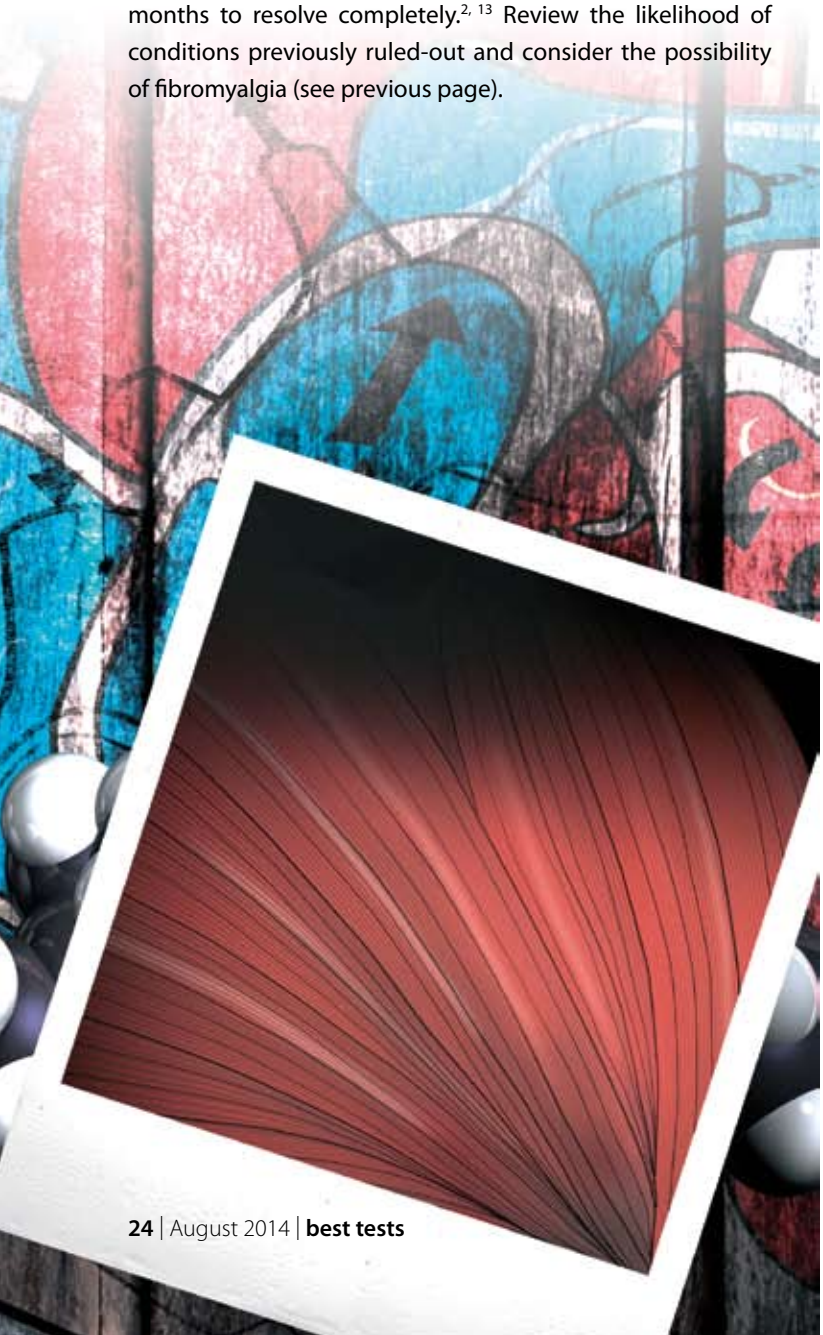
The pharmacological treatment of fibromyalgia is not routinely helpful; currently there are no medicines specifically indicated for the syndrome and patients with fibromyalgia can often experience adverse effects of medicines. Expert opinion is that paracetamol or NSAIDs may provide some relief.[27] Tricyclic antidepressants used off-label may also provide benefit,[27] and can improve sleep quality when taken at low doses. Amitriptyline is the tricyclic antidepressant with the best evidence base for fibromyalgia, e.g. amitriptyline, 10 –30 mg, an hour or two before going to bed.[27] Nortriptyline is also often used. The use of opioids in patients with fibromyalgia is not recommended.[27] Tramadol, however, is reported to provide benefit to some patients with fibromyalgia, via atypical pathways (as opposed to a class effect).[27]

The importance of diet, exercise and avoidance of smoking should be reiterated before considering offering patients alternative lipid-lowering medicines.[2] Expert opinion is that high-risk patients who are intolerant to statin treatment, may benefit from non-statin lipid-lowering medicines, e.g. gemfibrozil or nicotinic acid (see New Zealand Formulary for dosing details).[2] High-risk patients include those with any of the following:[2]

- Atherosclerotic cardiovascular disease
- Diabetes and age 40 – 75 years
- LDL-C ≥ 5.0 mmol/L and an elevated cardiovascular risk

Investigating patients with unresolved symptoms or persistently elevated creatine kinase

If the patient's symptoms or creatine kinase results have not resolved two months after the withdrawal of statin treatment then an alternative diagnosis should be reconsidered, although statin-associated symptoms may take up to three months to resolve completely.[2, 13] Review the likelihood of conditions previously ruled-out and consider the possibility of fibromyalgia (see previous page).



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