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Drug induced muscle disorders

By John Smithson

Learning objectives

After reading this article you should be able to:

- Define and differentiate between the terms myalgia, myositis, myopathy and rhabdomyolysis
- List the common drugs involved in causing muscle disorders
- Describe the mechanistic action by which the most common myotoxic drugs cause their respective dysfunction
- Recognise risk factors for the different drug induced muscle disorders
- Modify the risk for drug induced muscle disorders and manage symptoms if present

Competencies addressed: 3.1.2, 3.2.2, 4.2.2, 4.2.3

Drug induced musculoskeletal disorders can potentially affect the spectrum of anatomical structures including bone, connective tissue and the musculature. Skeletal muscles represent a significant proportion of the body's mass, receive a large fraction of blood supply, and are metabolically highly active. This tissue therefore has significant exposure to circulating drugs, which has the potential to cause drug induced disorders ranging from trivial myalgias and asymptomatic elevations in creatine kinase through to life threatening rhabdomyolysis with myoglobin induced renal failure.[1] Accepted definitions of muscle related side effects may differ slightly from study to study, though the following definitions are a commonly accepted consensus[2, 3] and are used throughout this article.

Myalgia (muscle pain) is characterised by diffuse muscle pain, tenderness and cramps with the presence or absence of muscle weakness. Myalgia is not accompanied by elevations in creatine kinase. While the presentation may be mild, symptoms such as muscle cramps and aches or non-specific muscle pain may be a precursor to more serious musculoskeletal conditions such as rhabdomyolysis.[4]

Myositis is the inflammation of voluntary muscle fibres and has muscle symptoms similar to myalgia but is accompanied by an elevation in serum creatine kinase (CK). The two main sources of creatine kinase are myocardium (relatively small contributor) and skeletal muscle which accounts for around 94% of creatine kinase.[5] The presence of this marker for muscle damage may result from exercise, physical muscle trauma, inherited or acquired diseases or extrinsic drug causes.

Myopathy is a general term referring to any disease of muscles and is sometimes used interchangeably with myositis. Myopathies can be acquired or inherited and can occur at birth or in later life. There is a strong correlation between many drugs and myopathy. Features of drug induced myopathy are polymorphous and include:[3,6]

- Fatigue
- Generalised muscle pain
- Muscle tenderness
- Muscle weakness
- Significantly elevated serum creatine kinase (CK) > 10 x upper limit of normal (ULN)
- Nocturnal cramping
- Tendon pain.

The symptoms of myopathy tend to be worse at night and are aggravated by exercise. Myopathy should be considered when serum CK levels are more than 10 x ULN, or in patients with increases in serum CK (less than 10 x ULN) accompanied by symptoms of myalgia. Muscle biopsy is non-specific but may reveal muscle fibre inflammation, atrophy and in some cases necrosis and regeneration. Muscle biopsy may be useful where CK remains elevated post drug withdrawal.

'Needle myopathy' is a focal myopathy due to traumatic necrosis, haematoma formation or low grade infections resulting from intramuscular injections. Chronic focal myopathy can occur after repeated injections at the same site caused by needle trauma, pH of the injected solution or the inherent myotoxicity of the drug injected.[4]

Rhabdomyolysis usually appears as an acute event; however it may have an insidious onset over a period of weeks. Pain (not a prominent feature in up to 50% of cases), muscle weakness, muscle swelling, myoglobinuria (presenting as tea or cola coloured urine, elevated serum and urine myoglobin levels) and a marked elevation in serum CK (between 10 and 100 x ULN) are the hallmarks of the syndrome. Secondary renal failure may follow myoglobinuria and results from the release of intracellular contents (enzymes and myoglobin) from damaged myocytes into the

John Smithson is a Lecturer, Discipline of Pharmacy, School of Pharmacy and Molecular Sciences, James Cook University.

Table 1. Common drugs that may cause myalgia or myopathy[4, 7]

Class	Family	Examples
Antibiotics	Quinolones	ciprofloxacin, norfloxacin, ofloxacin
	Miscellaneous	cotrimoxazole, isoniazid, minocycline, pipercillin-tazobactam
Anti-neoplastic agents and related compounds	Anti-metabolites	cladribine, cytarabine, methotrexate
	Miscellaneous	docetaxel, paclitaxel, letrozole, leuprorelin, procarbazine, vincristine,
Anti-ulcer agents	Histamine H_2 receptors antagonists and proton pump inhibitors	cimetidine, ranitidine, nizatidine pantoprazole
Antiviral agents	Antiretroviral agents	indinavir, lamivudine, ritonavir, saquinavir, stavudine, zidovudine
	Other	gancyclovir
Corticosteroids		fluorinated steroids such as dexamethasone, betamethasone and triamcinolone, but may be any steroid taken by injection, inhalation or oral ingestion
Cytokines		
Bisphosphonates		alendronate, ibandronate, pamidronate, risedronate
Lipid-lowering drugs	Fibrates	fenofibrate, gemfibrozil, nicotinic acid
	Statins	atorvastatin, fluvastatin, pravastatin, simvastatin
Antifungal agents		amphotericin B, terbinafine
Antithyroid drugs		carbimazole, propylthiouracil,
Immunosuppressants		cyclosporine, uromonab-CD3, mycophenolate mofetil, tacrolimus
Cardiovascular agents		amiodarone, beta-blockers, bumetanide, captopril, diuretics, enalapril, eprosartan, lercanidipine, methyldopa
Miscellaneous		baclofen, chloroquine, colchicine, ethanol, iloprost, isotretinoin, ivermectin, infliximab, mebeverin, mefloquine, metoclopramide, montelukast, nafarelin, naltrexone, penicillamine, phenytoin, salmeterol, sildenafil, somatropin, suxamethonium, tacrine, tianeptine, triazolam.

Table adapted from Lee A, ed. Adverse Drug Reactions. 2nd ed. Great Britain: Pharmaceutical Press; 2009;296, & Bannwarth B. Drug-induced myopathies. Expert Opinion on Drug Safety. 2002;1(1):69.

Table 2. – Broad classification of drug induced myalgia and example drugs

Classification and example mechanism	Example drugs and toxins
Necrotising myopathies – reduced essential co-enzyme production, myocyte membrane changes and increased oxidation	HMG CoA-reductase inhibitors (statins), fibrates, nicotinic acid
Corticosteroid myopathy – disruption of RNA synthesis	Fluorinated steroids such as dexamethasone and triamcinolone
Mitochondrial myopathies – inhibition of mitochondrial DNA polymerase	Zidovudine
Lysosomal storage myopathy – increased lysosomal activity degrading muscle fibres	Hydroxychloroquine, amiodarone
Antimicrotubular myopathy – accumulation of lysosomes and autophagic vacuoles	Colchicine, vincristine
Hypokalaemic myopathy – disruption of water and electrolyte homeostasis	Diuretics, oral contraceptives
Inflammatory myopathies – activation of immune system, resembles autoimmune disease	D-penicillamine and interferon-α

Adapted from Sieb JP, Gillessen T. Iatrogenic and toxic myopathies. Muscle & Nerve. 2003;27(2):142-56.

circulation which are toxic to the kidney (and other organs). Other sequelae of rhabdomyolysis include hyperkalaemia, hypocalcaemia, disseminated intravascular coagulation, cardiomyopathy, respiratory failure and severe metabolic acidosis.[4] The management of rhabdomyolysis requires discontinuation of the causative agent, and supportive therapy including intravenous fluids, correction of electrolyte abnormalities and alkalinisation of the urine.[4] Patients generally recover completely if the syndrome is recognised early and treated appropriately.[6]

Recognising drug induced muscle disease

A high degree of clinical suspicion in patients presenting with muscle pain offers pharmacists the opportunity to identify extrinsic drug causes. Early recognition and appropriate management often prevents a severe outcome with complete resolution commonly following. The relationship between the muscle disorder and a drug is suggested by several clinical features:[4, 7]

- Lack of pre-existing muscular symptoms
- Presence of a reasonable temporal relationship between the start of treatment or change of dose and the appearance of symptoms
- Lack of any other cause for the myopathy
- Partial or compete resolution of symptoms after the drug is withdrawn.

Additionally, there are a number of patient factors that increase the risk of drug induced myotoxicity. They include:

- Advanced age (> 70 years)
- The administration of a single or multiple myotoxic drugs
- High doses of myotoxic drugs
- Female gender
- Thyroid disease
- Existing hepatic or renal disease
- Surgery (perioperative period)
- Existence of metabolic muscle disease
- Genetic polymorphisms.

Studies into genetic risk factors associated with lipid-lowering drug-induced myopathies by Vladutiu *et al.* (2006), found four prominent biochemical abnormalities on muscle biopsy findings of patients with statin induced myalgia. CPT (carnitine palmitoyltransferase) II deficiency and CoQ10 (coenzyme Q10) deficiency were the most frequent abnormalities observed. Respiratory (cellular) chain defects and carnitine abnormalities are the remaining common biochemical abnormalities. Patients with these metabolic muscle conditions were found to be over-represented in patient populations with statin induced myopathy. A higher percentage of individuals with multiple abnormalities had serum CK levels >10 x ULN.[8]

CoQ10 deficiency is the most common muscle defect. It is an essential cofactor in mitochondrial (cellular) respiration in the electron transport chain.

CPT II deficiency is a mitochondrial abnormality most likely acquired due to exposure to statins rather than genetic inheritance. CPT II is located in the mitochondrial membrane where it facilitates the transport of long-chain fatty acids into the mitochondrion.[8]

Myotoxic drugs. Numerous drugs cause myotoxic effects by various mechanisms making it unrealistic to discuss them all. Table 1 lists drugs that are known to be myotoxic in some individuals. The primary cause is direct toxicity and this is often (but not always) dose-related. Secondary causes include electrolyte disturbances, increased or excessive energy requirements or insufficient nutrient supply. Muscle damage may be generalised when drugs are taken orally, or local for those drugs injected via intramuscular route.[9] Some drugs cause these effects more frequently than others. Corticosteroid and cholesterol lowering agent myopathies are probably the most common cause of drug related muscle pain. Other drugs worthy of mention include zidovudine, colchicine, amiodarone, cyclosporin, D-penicillamine and valproic acid. Table 1.2 briefly outlines the most common classifications of drug induced myalgia.

Common myotoxic drugs and their presentation

Corticosteroid induced myalgia. Chronic use of oral corticosteroids can cause proximal muscle weakness and atrophy of the lower limbs and is probably the most common cause of toxic muscle disease. The course is often slow and mild and is often associated with other chronic systemic side effects of corticosteroids.[10] Inhaled steroids or doses ≥ 10 mg of prednisolone (or equivalent) daily for more than 30 days have been observed to be myotoxic.[9] A second, more severe form of corticosteroid induced myopathy presents as acute severe weakness that usually affects critically ill patients in ICU. The fluorinated corticosteroids such as dexamethasone, betamethasone and triamcinolone have a higher propensity to induce myopathy compared with non-fluorinated corticosteroids.[4,10]

Table 3. Factors that increase risk for corticosteroid induced myalgia

Risk factors for steroid induced myalgia
• Fluorinated steroids such as dexamethasone, betamethasone and triamcinolone
• Accumulative dose
• Concomitant use of other myotoxic drugs
• Electrolyte disturbances (manifesting as muscle weakness)
• Sepsis or multi-organ failure.

The commonly accepted cause of corticosteroid myotoxicity is disruption of RNA synthesis, leading to type-2 muscle fibre atrophy and muscle necrosis. Another possible mechanism

identified is the induction of breakdown of muscle proteins by calpain (a calcium-activated protease) and anti-ubiquitin antibodies.[10] Table 3 outlines the risk factors for corticosteroid induced myalgia.

Cholesterol Lowering Agents Myopathy (CLAM). Lipid-lowering agents such as fibrates, nicotinic acid derivatives and statins are associated with myopathy, and while they are generally well tolerated and safe,[11] the large volume of prescriptions for these agents make myalgia or myopathy an observable event. The reported incidence in patients using all lipid-lowering therapy varies. The occurrence rate of myalgia among statin users varies between randomised controlled trials which suggest a rate of 1.5 to three percent and prospective clinical studies which suggest rates between 10-13%.[3, 12] By 2007, the Therapeutic Goods Administration had received 5,846 adverse reaction reports implicating a statin, of which one-third described a muscle disorder previously defined.[13] In two large trials involving simvastatin, the *Scandinavian Simvastatin Survival Study* (4S) trial and the *Heart Protection Study* of cholesterol lowering with Simvastatin (HPS) trial rates of myotoxicity in the simvastatin group were similar to that of the placebo group (< 0.1%) (it should be noted this trial excluded patients with high risk factors). In the ExPRESS (The examination of probands and relatives in statin studies with familial hypercholesterolemia) trial the observed rate of drug related myalgia was 8.9% and no cases of myopathy were reported.[14]

A small retrospective study by Hansen, *et al.*[15] found the mean duration of therapy before onset of symptoms was 6.3 months and the mean duration of myalgia after stopping statin therapy was 2.3 months. The conclusion drawn was that muscle symptoms that develop in a patient who has been taking statins for several years are unlikely to have been caused by these drugs and symptoms will largely resolve on withdrawal of the drug.[6,15]

The use of combined lipid-lowering drugs increases the risk of myopathy and results in a more severe clinical presentation, very occasionally leading to rhabdomyolysis.[16] Studies reported by Saleh and Seidman (2003) report CLAM takes place in 0.5% patients taking one lipid lowering therapy and up to 5% of patients taking combination lipid lowering therapy. The Adverse Drug Reaction Advisory Committee (ADRAC) received 91 reports of rhabdomyolysis with simvastatin and 26 with atorvastatin by 2004. An Australian analysis of PBS data by Ronaldson, *et al.* found the incidence of rhabdomyolysis at 2.1 cases per 1,000,000 prescriptions for simvastatin and 1.3 per 1,000,000 prescriptions for atorvastatin.[17] These numbers indicate rhabdomyolysis occurs very rarely. The risk of rhabdomyolysis is increased with advanced age, statin dose ≥ 40mg daily, concurrent cyclosporine, gemfibrozil and diltiazem administration and diabetes.[18] Fibrates inhibit phase 2 glucuronidation reaction in statin metabolism as well as being inherently myotoxic themselves.[19] At times when recalcitrant or very high cholesterol levels dictate the use of combination statin/fibrate therapy, fenofibrate may be a more suitable alternative to gemfibrozil due to its lower tendency toward pharmacokinetic interactions with statins.[11,20]

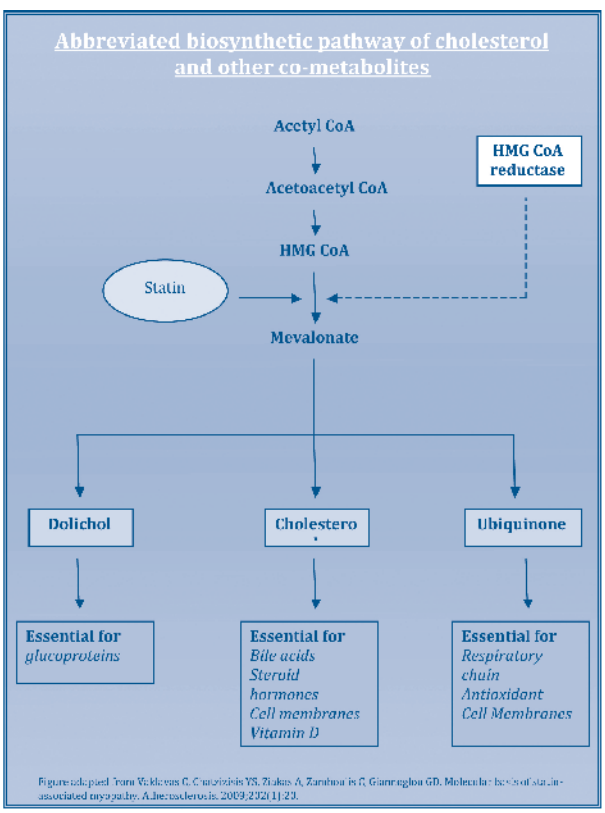
The mechanism of CLAM is not well understood but is attributed to the reduced synthesis of mevalonate which is a precursor to a number of important components of the cell membrane, as well as being a precursor molecule for steroid hormones, vitamin D and bile acids. Endogenous cholesterol biosynthesis occurs in the endoplasmic reticulum and cytosol and is shown in *Figure 1.* The mechanism by which statins induce muscle disorders is a result of one or a combination of the following;[2,3,10]

- An increase in the fluidity of the myocyte membrane due to changes in cholesterol.
- Impaired synthesis of compounds in the cholesterol pathway, particularly of heme A and CoQ10 synthesis resulting in mitochondrial dysfunction, reduced energy and eventual cell death.
- Increased activity of caritine palmityl transferase leading to caritine and fatty acid deficiency and damage to muscle fibres.

Risk factors for statin induced myopathy

The two main independent risk factors for statin induced myopathy are dose (or increased bioavailability) and lipophilicity of the statin. The greater the lipophilicity of a statin, the greater penetration into muscle tissue, which

Figure 1. The biosynthetic pathway of cholesterol and other co-metabolites



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explains in part their myotoxic effects. This suggests the use of a hydrophilic agent in patients with pre-existing muscle disease may be prudent.[3] However myopathy has been reported with largely hydrophilic statins such as pravastatin, demonstrating that lipophilicity is not the sole factor in predicting myotoxic potential. This is explained by the observation that while poor lipophilicity limits passive diffusion into myocytes, it also dictates a low hepatic extraction ratio, and in the case of pravastatin, results in a mean expected plasma concentration up to 10 times higher than the more lipophilic statins.[2,21] Table 4 lists the lipophilicity of commonly used statins.

Table 4. Lipophilicity of statins

Lipophilic agents	Hydrophilic agents
simvastatin (most lipophilic agent)	pravastatin
atorvastatin	rosuvastatin
	fluvastatin

Any factor that increases the serum concentration or bioavailability (for example drug interactions decreasing metabolism or clearance or changes in drug transport proteins) has the potential to increase the risk of myopathy.[3] Table 5 outlines some patient and statin characteristics that increase the risk of statin induced myopathy and Table 6 outlines some drugs that increase the bioavailability of commonly used statins.

Table 5. Factors that increase the risk of statin-induced myopathy[2–4,12,14]

Patient characteristics	Statin properties
Increasing age (>70–80 years)	High statin dose
Female gender	Increasing lipophilicity
Renal insufficiency	High bioavailability
Hypothyroidism	Limited protein binding
Excessive consumption of grapefruit or cranberry juice	
Concomitant medications	
Diabetes or other multisystem disease	
Hepatobiliary dysfunction	
Low body mass index	
Vigorous exercise	
Excessive alcohol consumption	
Major surgery or trauma.	
Increasing lipophilicity	
High bioavailability	
Limited protein binding	

Table 6. Examples of common drugs that inhibit the CYP450 pathway or independently cause myositis[3,12]

Drugs that inhibit CYP3A4 (metabolic pathway for simvastatin and atorvastatin)	Drugs that inhibit CYP2C9 (metabolic pathway for fluvastatin and rosuvastatin)
macrolide antibiotics	warfarin
azole antifungals	amiodarone
HIV protease inhibitors	cimetidine
fluoxetine	trimethoprim/ sulfamethoxazole fluoxetine
verapamil	fluvoxamine
warfarin	isoniazid
grapefruit juice	metronidazole
fibrates	zafirlukast
	itraconazole
	ketoconazole

Current NHFA/CSANZ* guidelines recommend baseline creatine kinase levels be taken before starting lipid lowering therapy, and if symptoms such as muscle weakness or pain are reported, compared against a second level. Routing serial monitoring is not recommended, although it may be appropriate in those on multiple medicines known to cause myalgia or inhibit CYP450 3A4, patients with advanced age or with kidney dysfunction.[11]

Management of statin induced myopathy

If a patient displays symptoms of myopathy, conditions unrelated to statin therapy should be ruled out, and CK level should be assessed. A CK level > 10 x ULN is a predictor of rhabdomyolysis and these patients should be investigated for elevated urine myoglobin levels, deteriorating renal function and thyroid function. Their statin therapy should be ceased immediately, and the benefits of continued lipid lowering therapy should be weighed against the risks of further myotoxicity. These patients may sometimes be recommenced on a lower dose, or prescribed lower-risk alternative therapy after symptom resolution. For patients whose CK is elevated < 10 x ULN, the dose may be continued at the same or lower dose providing muscle symptoms are tolerable. If intolerable, the drug should be ceased, and the patient observed until symptoms resolve and CK returns to normal. They may then be recommenced on the same drug, at a lower dose, which is often uneventful.[19]

Conditions unrelated to statin therapy[3]

- Bursitis
- Myofascial pain
- Muscle strain
- Osteoarthritis
- Radiculopathy
- Tendinitis.

Key points for pharmacists managing statin induced myopathy[3]

- Slightly increased creatine kinase is common in the general population.
- Myopathy that develops after a patient has taken statins for several years is unlikely to be caused by these drugs
- Thyroid stimulating hormone should be checked in patients on statins who develop a myopathy because hypothyroidism is a common cause of hypercholesterolaemia and raised creatine kinase
- If muscle-related symptoms or raised creatine kinase concentrations persist after statin therapy is stopped, further specialist investigation and intervention is required
- Drugs that inhibit CYP3A4 increase the risk of statin induced myopathy
- Combination statin and fibrate therapy increases myopathy risk
- Monitoring for serum CK is not routinely indicated but patients should have CK levels taken at commencement of statin therapy.

Small scale research has demonstrated positive results for the use of CoQ10 supplementation as a treatment for statin induced myopathy; however there remains insufficient evidence for routine use of CoQ10 supplementation in patients taking statins. It is thought certain subgroups of patients susceptible to statin induced myopathy may benefit, and these patients may be candidates for CoQ10 supplementation.[2]

Other drug causes of myopathy

A mitochondrial myopathy caused by **zidovudine** occurs in patients with human immunodeficiency virus (HIV). Zidovudine myopathy resembles HIV-associated myopathy, with patients presenting with myalgia, fatigue and limb-girdle weakness which is sometimes associated with either normal or moderately elevated CK levels.[7] It has a reported incidence of between 2 and 17 % of patients dependant on duration of therapy.[10] The myopathy results from a mitochondrial dysfunction as a result of inhibition of mitochondrial DNA polymerase (zidovudine acts as a false substrate for viral reverse transcriptase but also for mitochondrial DNA polymerase). The myopathy is both reversible and dose related.[9] It is treated by ceasing zidovudine and corticosteroid therapy if myositis is present.[10]

Chloroquine and hydroxychloroquine myopathies are most likely induced by increased lysosomal activity within the myocyte and present as a painless, insidious weakness beginning in the proximal leg muscles and later the arms and face. It was

far more common with chloroquine (no longer available in Australia), than with hydroxychloroquine, the later infrequently occurring as a result of hydroxychloroquine intoxication, albeit with reduced symptoms compared to chloroquine.[9]

Colchicine myopathy may develop as a result of its affect on cellular mitosis after long term use at normal doses or as a result of toxicity secondary to organ failure. It presents most often in patients between the age of 50 and 70 years with mild chronic renal insufficiency,[10] with symptoms of subacute proximal weakness, and generally in the absence of pain or other symptoms of colchicine toxicity. CK is sometimes moderately elevated.[23] Patients on long-term colchicine therapy should be monitored for this effect.[9]

Penicillamine may cause inflammatory muscle disease as a result of an immune reaction which may occur in up to 1% of patients.[7, 10] Myositis induced by penicillamine may occur at any time in the course of therapy and may also occur at low doses. Corticosteroid therapy is sometimes required to induce remission from this side effect which can take between six weeks and six months to be complete.[7,9]

Antipsychotic drug therapies that have more potent 5-HT2A effect over dopamine D2 produce a more marked increase in CK than the dopamine D2 neuroleptics. CK levels may increase in up to 10% of patients treated with clozapine, risperidone, olanzapine or haloperidol.[9]

Drug induced causes should be considered in all patients presenting with muscle disorders. Observation of factors and drugs that may predispose a patient to drug induced muscle disorders should give enough clinical clues to decide if referral for further investigation is warranted. If drug induced muscle disease is detected early, potentially catastrophic outcomes for patients can be avoided.

**NHFA/CSANZ – National Heart Foundation of Australia / Cardiac Society of Australia and New Zealand*

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Questions

(A score of 4 out of 5 attracts one credit point.)

1. Which of the following statements about myopathy is **INCORRECT**?

a. Symptoms of myopathy include muscle tenderness and weakness, fatigue. They may be worse at night and aggravated by exercise.
b. Myopathy is not associated with significant elevations of creatine kinase.
c. Risk for drug induced muscle myopathy is increased in the elderly, females and those with thyroid disease.
d. Fibrates, corticosteroids and statins are implicated in myopathy.
e. None of the above.

2. Which of the following statements about statin induced myopathy and rhabdomyolysis is/are **TRUE**?

a. Statins have a greater chance of inducing myopathy when therapy has been taken for many years.
b. While the risk of CLAM is relatively small, pharmacists should have a high degree of clinical suspicion in patients taking statins and presenting with muscle complaints.
c. The risk of myopathy is increased for the lipophilic statins such as simvastatin and atorvastatin.
d. Statin induced myopathy is not linked to dose, and occurs irrespective of statin dose.
e. (b) and (c) only.

3. Corticosteroid induced myopathy has been associated with which of the following?

a. High accumulative dose of corticosteroid.
b. Fluorinated steroids such as dexamethasone.
c. Both inhaled and oral doses of corticosteroids.
d. Long duration of corticosteroid therapy.
e. All of the above.

4. Which of the following factors is generally **NOT** indicative of a muscle disorder being drug-induced?

a. Temporal relationship between the start of treatment or change in dose and the appearance of symptoms.
b. Lack of pre-existing muscle conditions.
c. Symptom onset within 2 years of initiation of drug therapy.
d. Partial or complete resolution after drug withdrawal.
e. Lack of any other cause of the myopathy.

5. Which of the following increases susceptibility to drug induced muscle disease?

a. High doses of drugs known to cause elevations in CK.
b. Advanced age.
c. Concomitant administration of corticosteroids and colchicines.
d. Concomitant hepatic failure and atorvastatin.
e. All of the above.