
Abstract
The most common drugs currently in use that may cause myopathies were reviewed using the Medline database (U.S. National Library of Medicine, Bethesda, Maryland). Our review included results from epidemiologic and database surveys, clinical trials, and case reports. The clinical spectrum is wide, and presentations range from asymptomatic elevations in serum creatine phosphokinase levels to severe life-threatening rhabdomyolysis. Management of suspected drug-induced myopathy should include immediate discontinuation of the offending agent, as well as supportive care when needed. Earlier diagnosis and drug discontinuation raises the likelihood of resolution and recovery.

Many drugs can cause myopathies, either predictably or as an intermittent phenomenon. Clinically, drug-induced myopathies range from benign processes that cause asymptomatic elevations in serum creatine phosphokinase (CK) levels (asymptomatic hyper-CK-emia) to mild-to-severe myalgias, cramps, exercise intolerance, or various degrees of muscle weakness. Severe cases may result in rhabdomyolysis, with myoglobinuria that can result in renal failure and even death (Table 1). Diagnosing drug-induced myopathy can be challenging, particularly as individual drugs may have different clinical presentations in different patients. Clinicians turning to the literature will frequently encounter confusion, in part, because the terminology used to describe muscle toxicity has been both evolving and, in some cases, imprecise. In this article, we examine commonly-used drugs that may induce myopathies and review their clinical syndromes, diagnosis, and treatment. We particularly focus on newer agents that have been recently described. Potential mechanisms for myopathies associated with specific drugs are summarized.

Materials and Methods
A Medline (U.S. National Library of Medicine, Bethesda, Maryland) search was performed of all English-language published studies from 1980 to 2008 describing drug-induced myopathies; keywords employed are listed in Table 2. Additional references needed to provide background information were also collected. All articles were evaluated for significance and relevance. Those articles found to contain redundant information were excluded.

The Medline search identified 264 articles of potential relevance. Of these, 162 were appropriate to our objective and were included in this review, including case series and reports, clinical trials, and reviews. For purposes of presentation, drug-inducing myopathies have been separated into discrete categories, including: rheumatologic and immunosuppressive, anti-infectious, cardiovascular, gastrointestinal, neurologic, and anti-neoplastic drugs. Drugs that alter electrolyte concentrations and drugs of abuse are also discussed. Finally, myopathic phenomena that may occur in patients in the intensive care setting are considered.

Results
Rheumatologic and Immunosuppressive Drugs
Corticosteroids
The most common drug-induced myopathies seen by rheumatologists are probably caused by corticosteroids. Although the use of high-dose intravenous corticosteroids can result in
Acute generalized weakness (acute quadriplegic myopathy, see below), the typical corticosteroid myopathy is characterized by the insidious onset of proximal muscle weakness with normal serum CK levels. Respiratory muscles can be affected as well; their involvement mimics therapy-resistant asthma. Corticosteroid myopathy most typically develops with chronic use of high doses (equivalent of 30 mg of prednisone or more a day) but can occur with lower doses or within a few weeks. Although a necrotizing myopathy has been reported, it is extremely rare. Risks of developing steroid myopathy increase with cumulative dose or duration, as well as multiple doses per day. Corticosteroid myopathy is more common among females than males, and is increased with the use of fluorinated agents (triamcinolone, betamethasone, and dexamethasone). An alternate-day dosing schedule reduces the risk of occurrence.

An EMG is normal and of little help in the diagnosis of steroid-induced myopathy. Muscle histology appears normal or shows nonspecific type 2 (fast-twitch glycolytic type 2B) fiber atrophy. Histochemical staining with oil red O may reveal increased lipid in type 1 fibers, and electron microscopy may show mild mitochondrial abnormalities. How corticosteroids induce myopathy is unclear. Hypotheses proposed include a catabolic effect on protein synthesis, increased protein degradation, altered carbohydrate or mitochondrial metabolism, or reduced sarcolemmal excitability. Furthermore, corticosteroid-induced hypokalemia may also be a factor.

Treatment of corticosteroid myopathy involves discontinuation of the offending agent or reduction to a physiologic dose in those with presumed adrenal suppression. Exercise programs may also be beneficial. Recovery may be observed within 24 hours in some cases, but may take more time, particularly if the usage has been chronic. A diagnostic dilemma occurs when a patient with an inflammatory muscle disease (e.g., polymyositis) is treated with corticosteroids, seems to improve, and then regresses again. If this scenario is accompanied by rising serum CK values, EMG abnormalities, or edema on magnetic resonance imaging (MRI) of the affected muscles, then the myositis is probably flaring. However, the only way to definitively evaluate the problem is to either increase or decrease the corticosteroid dose and assess the clinical response. If the patient improves with a decrease in dosage, the diagnosis was likely steroid myopathy. The clinician must also be aware that overly rapid withdrawal of chronically used steroids may itself lead to weakness and fatigue, in part, as a consequence of hypoadrenalism.

**Colchicine**

Colchicine use is associated with a variety of neuromuscular complications, including generalized myopathy, painful neuromyopathy, rhabdomyolysis, and, rarely, clinical and electrophysiologic myotonia. These complications may occur after months of therapy or be of rapid onset. Concomitant use of diuretics and the presence of chronic kidney disease, or either, increases the risk of myopathy, whereas concomitant use of an HMG CoA reductase in-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Drugs that Can Cause Rhabdomyolysis</th>
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<td>Direct toxic effects</td>
<td>Colchicine</td>
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<td>Cyclosporine</td>
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<td></td>
<td>Succinylcholine</td>
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<td></td>
<td>Tacrolimus</td>
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<td></td>
<td>Toluene (inhaled)</td>
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<td>Metabolic effects</td>
<td>Alcohol</td>
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<td></td>
<td>Aspirin</td>
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<td></td>
<td>5-Azacytidine</td>
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<td></td>
<td>Azathioprine</td>
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<td></td>
<td>Cyclophosphamide</td>
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<td></td>
<td>Fibric acid derivatives (fibrates)</td>
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<td>Heroin</td>
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<td></td>
<td>HMG CoA reductase inhibitors (statins)</td>
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<td></td>
<td>Hypokalemic agents (see Table 3)</td>
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<td></td>
<td>Methadone</td>
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<td>Mitoxantrone</td>
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<td>Ritanovir</td>
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<td></td>
<td>Tenofovir</td>
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<td></td>
<td>Valproic acid</td>
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<tr>
<td>Exercise, agitation, or seizures</td>
<td>Amphetamines</td>
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<td></td>
<td>Cocaine</td>
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<td></td>
<td>Neurollepetic agents</td>
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<td></td>
<td>Phencyclidine</td>
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<td>Ischemia</td>
<td>Cocaine</td>
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hibitor (statin) or cyclosporine increases the likelihood of rhabdomyolysis.19-22

In colchicine myopathy, serum CK levels are typically elevated (at times in the absence of symptoms), ranging from minimal increase to 100-times the upper limit of normal. EMG may show neuropathic changes in distal muscles, as well as generalized myopathic changes. Nerve conduction studies reveal prolonged motor and sensory latencies distally.23 A vacuolar myopathy is observed on muscle histology. The vacuoles are autophagic and stain strongly for acid phosphatase.23 Colchicine myopathy is believed to result from an inhibition of tubulin polymerization into microtubules, as well as alteration in the expression of dopaminergic receptors.24 Colchicine “bodies” (clumps of chromatin in the nuclei of hepatocytes) have been seen on electron microscopy.25 Findings of axonal neuropathy are typically present on nerve biopsy. Complete recovery of nerve and muscle function commonly occurs once the colchicine is discontinued. Although pain usually resolves within 3 weeks, full recovery may take up to 6 months.

Hydroxychloroquine and Chloroquine
These quinoline derivatives can cause similar reversible myopathies, although the chloroquine myopathy is generally more severe.26-28 Quinoline (also known as 1-azanaphthalen) myopathies are painless and slowly progressive, with proximal muscle weakness that tends to be more severe in the lower extremities. An associated neuropathy is found in some cases, and cardiomyopathy has been reported. Symptoms can develop after 6 months to 10 years of treatment.29 In addition, chloroquine can cause a myasthenia-like syndrome or myotonia.26,30 Muscle involvement in response to these drugs, particularly chloroquine, may be more common than usually presumed and as high as 20%.31,32 Serum CK values are usually elevated. EMG shows myopathic changes of increased insertional activity, with positive waves, fibrillations, and voluntary motor unit action potentials (MUAPs) that are polyphasic, with decreased amplitude and short duration.26 Acid phosphatase staining vacuoles are present on muscle histology. Electron microscopy reveals that the vacuoles contain concentric lamellar debris and curvilinear bodies. In cases of clinical myopathy, an anatomical-pathological tissue study, including an ultrastructural study, is mandatory to confirm the diagnosis.31

The mechanism of hydroxychloroquine and chloroquine myopathy is thought to relate to their amphiphilic nature. The presence of both hydrophobic and hydrophilic regions allows them to localize to and interact with anionic phospholipids in organelles and membranes. The drug-lipid complexes are resistant to lysosomal enzyme digestion and lead to the formation of autophagic vacuoles. Large autophagic vacuoles may not be visible on biopsy unless the patient has been treated with the drug for at least 6 months.32,33 Furthermore, in an experimental chloroquine myopathy model, the administration of 50 mg/kg/day of chloroquine to rats for 8 weeks produced myopathy characterized by accumulation of similar autophagic vacuoles.34

<table>
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<tr>
<th>Table 2</th>
<th>Keyword Terms Used in Search of Drug-induced Myopathies*</th>
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<tbody>
<tr>
<td>Adverse-Drug-Reaction</td>
<td>Itraconazole</td>
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<td>Alcohol</td>
<td>Ketoconazole</td>
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<td>Amiodarone</td>
<td>Leuprolide</td>
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<tr>
<td>Amphetamines</td>
<td>Macrolides</td>
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<tr>
<td>Azathioprine</td>
<td>Metabolic-Myopathies</td>
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<tr>
<td>Cardiomyopathy</td>
<td>Myopathy</td>
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<tr>
<td>Chloroquine</td>
<td>Muscle</td>
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<td>Cocaine</td>
<td>Myalgias</td>
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<tr>
<td>Colchicine</td>
<td>Myoglobinuria</td>
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<td>Corticosteroids</td>
<td>Niacin</td>
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<td>Cramps</td>
<td>Phenytoin</td>
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<td>Creatine-Phosphokinase</td>
<td>Procainamide</td>
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<td>Cyclophosphamide</td>
<td>Quinolones</td>
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<td>Cytochrome-P450</td>
<td>Renal-Failure</td>
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<td>Cyclosporine</td>
<td>Rhabdomyolysis</td>
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<td>Drug-Induced</td>
<td>Rifampin</td>
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<td>Electromyography (EMG)</td>
<td>Statin</td>
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<td>Fibrate</td>
<td>Tacrolimus</td>
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<tr>
<td>Heroin</td>
<td>Toxicity</td>
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<tr>
<td>Highly-Active-Antiretroviral-Therapy</td>
<td>Valproic-Acid</td>
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<tr>
<td>HIV</td>
<td>Vincristine</td>
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<tr>
<td>Hydroxychloroquine</td>
<td>Ubiquinone</td>
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<tr>
<td>Hypokalemia</td>
<td>Zidovudine</td>
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<tr>
<td>Imatinib-Mesylate</td>
<td>Weakness.</td>
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*List is not exhaustive for study
After stopping treatment with these agents, most patients improved favorably, some over periods of up to 6 months. Animal studies showed that administration of cysteine proteinase inhibitor, EST (epoxysuccinylleucylamido-3-methylbutane ethyl ester), may improve chloroquine myopathy. Hydroxychloroquine may also induce ciliary body muscle dysfunction, leading to impairment of visual accommodation. This problem presents early, after initiation of the agent, and typically resolves with continued use.

Cyclosporine and Tacrolimus
Cyclosporine and tacrolimus may cause generalized myalgias, cramps, and proximal muscle weakness. These symptoms usually follow after several months of use, and resolve with lowering of the dose or discontinuing the medication. Some patients taking these agents develop rhabdomyolysis. This severe complication is more likely if the patient is also taking either a lipid-lowering agent (statin or fibrate) or colchicine. Serum CK levels are elevated. EMG changes include fibrillation potentials, sharp positive waves, and myotonic potentials. Type 2 fibers atrophy, and vacuoles and necrosis may be seen with muscle histology. It is theorized that these agents destabilize lipophilic muscle membranes. It is important to keep in mind that the complications of these drugs are important, since it was reported recently that these agents have a role in the treatment of inflammatory muscle diseases, such as dermatomyositis and inclusion body myositis.

Other Rheumatologic Agents
Up to 1.4% of patients taking D-penicillamine develop polymyositis or dermatomyositis. Azathioprine has been linked very rarely to rhabdomyolysis. Myokymia, or arrhythmic rippling of muscles (see later), is an unusual side effect of gold salt therapy. According to a single case report, aspirin may also cause rhabdomyolysis. Oral bisphosphonates may rarely induce severe muscle pain. Antimicrobial drugs
Ketoconazole and itraconazole use can cause myopathy or rhabdomyolysis when used with a statin. Rifampin may cause a severe proximal myopathy with normal serum CK levels, normal EMG, and type 2 fibers atrophy on biopsy. Myalgias can occur, associated with tendinopathy and arthralgia, with the use of fluoroquinolones. These agents can also trigger malignant hyperthermia. In rare cases, nalidixic acid can cause myopathy characterized by proximal muscle weakness. It develops shortly after initiation of drug treatment and resolves after withdrawal of the agent.

Anti-Infectious Drugs
Lipid-Lowering Agents
The most common drug-induced myopathies encountered today are caused by lipid-lowering agents, including 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), fibric acid derivatives (fibrates), and niacin. Ezetimibe may also cause myopathy in individual cases. Although the risk of developing myotoxicity from one of these agents is low for the individual patient, the large number of patients taking these agents renders this a common problem. In many clinical trials, statin-induced myopathy has been defined as muscle pain, tenderness, and weakness, with elevated serum CK levels greater than 10-times the upper limit of normal. According to this definition, the incidence of myopathy in patients treated with statins is 11 per 100,000 person-year. The incidence of rhabdomyolysis is 3.4 per 100,000 person-year. This number is 10-times greater when fibrates are used in combination with statins. Clinical data shows that the incidence is higher with lovastatin, simvastatin, and atorvastatin, which are metabolized by cytochrome P450 (see below), compared to pravastatin and fluvastatin. In vitro data suggests that the rank order of cytotoxicity is pravastatin as least toxic, followed by rosuvastatin, pitavastatin, lovastatin, atorvastatin, and fluvastatin.
simvastatin, and cerivastatin as the most cytotoxic statin.\textsuperscript{70}

Clinically, some patients develop myopathic symptoms with statin exposure, despite normal CK levels, while others have persistently elevated CK levels without muscle symptoms.\textsuperscript{71-73} Interestingly, in some studies, isolated CK elevations (less than 10-times the upper limit of normal) occur with similar frequency on the placebo- and statin-treated arms.\textsuperscript{80} Symptoms of statin-induced myopathy include any combination of myalgias, muscle tenderness, or weakness. Patients describe an aching or cramping sensation in their muscles, particularly those of the proximal limbs and the trunk.\textsuperscript{74} Nocturnal leg cramps and tendon pain may be prominent features.\textsuperscript{75,76} Statin-attributed tendinopathy is rare, considering the huge number of statin prescriptions. Recent work characterized tendon manifestations in 96 statin-treated patients; 65\% of the patients exhibited tendinitis, while 35\% had tendon rupture.\textsuperscript{77} Tendinopathy more often occurred within the first year after statin initiation. Tendon manifestations were related to atorvastatin, simvastatin, pravastatin, fluvastatin, and rosuvastatin. In this work, as well as in other reported cases, rechallenge produced tendinopathy.\textsuperscript{78,79} Repair of an injured tendon requires degradation and remodeling of the extracellular matrix through matrix metalloproteinases (MMPs). Statins inhibit MMPs, and it is, therefore, hypothesized that these drugs may increase the risk of tendon rupture by altering MMP activity.\textsuperscript{78,79}

Although muscle weakness in statin-associated myopathy is usually proximal, distal muscles can occasionally be involved.\textsuperscript{71} Vigorous exercise is poorly tolerated by many statin users and can aggravate statin-induced myotoxicity.\textsuperscript{80,81} Myopathy due to lipid-lowering agents can develop at any time, but the average time to onset is about six months. The mean duration for symptoms to resolve after discontinuing the therapy is two months.\textsuperscript{72} Although muscle symptoms generally resolve after cessation of statin therapy, they may persist.\textsuperscript{80,81} In some patients, such persistent symptoms may be related to previously unrecognized neuromuscular disorders, including inflammatory myopathies\textsuperscript{81-83}; hypothyroidism\textsuperscript{84}; metabolic myopathies (myophosphorylase deficiency, acid maltase deficiency, and mitochondrial myopathy)\textsuperscript{80,85,86}; myotonic dystrophy\textsuperscript{87}; spinal muscular atrophy\textsuperscript{85}; or susceptibility to malignant hyperthermia.\textsuperscript{87} Statin-associated myopathy can be distinguished from polymyalgia rheumatica, since the erythrocyte sedimentation rate is not elevated in the former. The most severe form of myotoxicity in patients taking statins is rhabdomyolysis, which may result in acute renal failure, disseminated intravascular coagulation, and death.\textsuperscript{88,89} There is no specific imaging study to support the diagnosis. A recent case report described the findings on 18FDG-PET [F-18-fluoro-2-deoxy-D-glucose positron emission tomography] imaging in a patient with statin-induced rhabdomyolysis. There was intense patchy tracer uptake in the skeletal muscles, particularly in the upper extremities, around the pelvic girdle, and in intercostal muscles.\textsuperscript{90} It is unclear whether there is tracer uptake in patients with less severe statin-induced myopathy.

Muscle tissue from patients with lipid-lowering drug-associated myopathy is often normal by light microscopy.\textsuperscript{91} However, biopsies may show changes indicative of mitochondrial dysfunction, including ragged red fibers, and fibers with absent cytochrome C oxidase activity by immunohistochemistry.\textsuperscript{92} Lipid-filled vacuoles\textsuperscript{71,92} and fibers atrophy may also be seen.\textsuperscript{80}

The risk of myotoxicity due to lipid-lowering agents is determined primarily by factors that lead to higher drug levels in the blood or tissues. These include drug dose, propensity for drug-to-drug interactions, or renal and hepatic dysfunction.\textsuperscript{73,93-98} Myotoxicity is more common when two classes of lipid-lowering drugs are administered simultaneously. Gemfibrozil impairs statin elimination through inhibition of statin glucuronidation, whereas fenofibrate does not have that effect.\textsuperscript{96} The concomitant use of niacin with a statin is rarely associated with rhabdomyolysis.\textsuperscript{97}

Most statins are metabolized primarily by the hepatic microsomal cytochrome (CY) P-450 system. Exceptions include pravastatin, which is metabolized in the hepatic cytosol, and rosuvastatin, excreted largely in its parent form. Co-administration of a statin and another drug that is metabolized by the same CYP-450 isozyme can lead to a clinically significant drug-to-drug interaction. In addition, drugs that are CYP-3A4 substrates also increase the risk of statin-induced myotoxicity. These include cyclosporine, erythromycin and other macrolide antibiotics, azole antifungals, diltiazem (and other nondihydropyridine calcium channel blockers), ritonavir (and other protease inhibitors), nefazodone, and grapefruit juice. Fluvastatin is a CYP-2C9 substrate, and its hepatic metabolism can be impaired by coadministration of other CYP-2C9 substrates, such as diclofenac, warfarin, and tolbutamide.

The mechanisms that may contribute to the myotoxicities of lipid-lowering agents are not completely understood. Most of the mechanisms proposed involve membrane alterations or mitochondrial abnormalities. Inhibition of HMG-CoA reductase may impair synthesis of transfer RNAs, glycoproteins, the electron transport chain proteins heme A, and ubiquinone (coenzyme Q10), as well as small G-proteins involved in cell signaling and attenuation of apoptosis.\textsuperscript{99} Levels of ubiquinone are modestly decreased in the affected muscle in some patients.\textsuperscript{80,100} An important work suggested that the muscle-specific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity.\textsuperscript{101} Respiratory chain and citrate synthase enzyme activities are decreased, and some patients have abnormalities in muscle carnitine levels.\textsuperscript{80,102} Cardiopulmonary exercise testing may show decreased anaerobic thresholds and increased fasting respiratory exchange ratios (RER), compared to normal volunteers.\textsuperscript{80} Rippling muscle disease is a rare disorder involving muscle contractions, which
produces a visible rippling affect. A report that simvastatin can trigger rippling muscle disease suggests statins may have muscle side effects other than those traditionally reported. 80 Thyroid function tests and genetic tests for the most common metabolic myopathies (myophosphorylase, carnitine palmitoyltransferase II, and myoadenylate), may identify individuals at higher risk of developing myotoxicity from lipid-lowering agents. 80

If a patient taking a lipid-lowering drug develops intolerable muscle symptoms or a marked CK elevation, the drug should be discontinued. Hospitalization is required for significant rhabdomyolysis. For less severe symptoms or for CK elevations that are under 10-times the upper limit of normal, management recommendations vary. 80, 104 One can continue the agent with close monitoring of the patient’s symptoms and CK levels, or lower the dose. Another option is to discontinue the drug until the symptoms resolve, and then either reinstitute the drug at the same or a lower dose, or switch to a different statin or class of lipid-lowering drug therapy. Ubiquinone (coenzyme Q10) supplementation may be helpful in some, but not all, cases. 106 Recently, the SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) collaborative group carried out a genomewide association study in order to identify markers of statin-associate myopathy. They found a strong association of myopathy with single-nucleotide polymorphism located within the SLCO1B1 gene. This gene encodes anion-transporting protein that has been shown to regulate hepatic uptake of statins. 107

Antiarrhythmic Agents
The adrenergic blocker labetalol may be associated with either acute or insidious onset of myalgias or proximal muscle weakness. 108 Serum CK levels are elevated, and muscle histology may be unremarkable or demonstrate necrotic and regenerating fibers.

Amiodarone can cause significant proximal and distal muscle weakness that tends to be more severe in the lower extremities. Distal sensory loss, tremor, and ataxia can also develop. 109 These toxicities are rare but occur more commonly in patients with chronic kidney disease. Serum CK levels are increased in amiodarone myopathy. EMG reveals fibrillation potentials, positive sharp waves, and early recruitment of myopathic MUAP in proximal muscles. In contrast, changes in distal muscles include polyphasic MUAP of large amplitude and long duration, with decreased recruitment when neuropathy is present. 110 Neuropsychiologic testing reveals decreased amplitudes of CMAP (compound motor action potential) and SNAP (sensory nerve action potential) in the lower extremities. Autophagic vacuoles containing myeloid inclusions and debris are found on histology and electron microscopy. Amiodarone-induced myopathy gradually resolves after therapy is discontinued. However, amiodarone treatment can also lead to myopathy by causing hypothyroidism. The latter would respond to thyroid replacement therapy. Caution is required when amiodarone is administered along with statins. 111

Procainamide treatment can be accompanied by myalgias and proximal muscle weakness. 111-113 These symptoms usually develop in the context of the drug-induced lupus syndrome. Serum CK levels are increased and EMG changes are consistent with an inflammatory myopathy. Muscle histology of procainamide toxicity resembles that of idiopathic inflammatory myopathy. This includes necrotic fibers and perivascular inflammation. Thus, procainamide myopathy should be suspected in cases of idiopathic inflammatory myopathy when history suggests treatment with this agent.

Gastrointestinal Drugs
Omeprazole use is rarely associated with a neuromyopathy that mainly affects the lower extremities. Features include proximal muscle weakness, myalgias, paresthesias, and sensory loss in a stocking distribution. 113 Levels of serum CK are increased. EMG and nerve conduction studies are consistent with an axonal sensorimotor neuropathy. Type 2 fiber atrophy is the typical histologic alteration. Patients taking cimetidine may rarely experience myalgias, cramps, myokymia, or weakness. A few reports have linked the use of cimetidine or ranitidine to polymyositis. 114, 115 Interferon-α is used in the management of viral hepatitis. Whether this agent causes myalgias and fatigue is not clear, as these are common complaints in patients with hepatitis B and hepatitis C. Interferon-α, however, can cause autoimmune disorders, including myositis and myasthenia gravis. 116, 117

Neurological Drugs
Myalgias and weakness may accompany hypersensitivity reactions to phenytoin and are characterized by fever, rash, and lymphadenopathy. 118, 119 Serum CK levels are elevated. Muscle histology reveals degenerating and regenerating fibers. Patients improve with discontinuation of the drug and may also benefit from corticosteroids. The anti-seizure medication valproic acid can induce a limb-girdle weakness with myopathic EMG changes by causing carnitine deficiency. 120 Valproic acid also has been recognized to trigger myopathic symptoms and rhabdomyolysis in individuals with lipid storage disorders or carnitine palmitoyltransferase deficiency. 121, 122 The use of the levodopa to treat Parkinson’s disease has been associated with myositis. 123

Anti-Neoplastic Drugs
Although the most common toxic effect of vincristine is a peripheral axonal neuropathy, proximal muscle weakness and myalgias can also occur. 123 Nerve conduction and EMG studies reveal neuropathic changes. The primary abnormality on muscle histology and histochemistry is denervation atrophy, but areas of segmental necrosis occasionally can be seen. Vincristine toxicity is ascribed to the drug’s primary mechanism of action, specifically, disruption of microtu-
bule polymerization, resulting in alterations of lysosomal function.

The kinase inhibitor imatinib mesylate, used to treat chronic myelogenous leukemia, causes myalgias in up to 50% of patients. There is one report of polymyositis developing in a patient receiving this drug. The myositis resolved after imatinib discontinuation and a course of corticosteroids. The investigators speculated that this was the result of an autoimmune response, since circulating antibodies directed against CML28 were found in the patient. CML28 is a component of a multiprotein complex, also known as an exosome, involved in RNA processing. Curiously, antibodies directed against this antigen and other exosome proteins (PM-Scl 100 and PM-Scl 70) are found in many patients with idiopathic inflammatory myopathies. Cardiotoxicity and dermatomyositis-like disease were reported as well.

An inflammatory myopathy has been attributed to the use of leuprolide acetate in the treatment of prostate cancer. Rare cases of rhabdomyolysis have been reported in patients taking 5-azacytidine, cytarabine, and the combination of cyclophosphamide and mitoxantrone.

### Drugs That Change Electrolyte Concentrations

Most drug-induced myopathies are due to direct effects on cellular structures or alterations in muscle fiber metabolism. However, use of a variety of drugs may be associated with myalgias, cramps, or weakness, resulting from effects they have on the concentrations of sodium, potassium, calcium, magnesium, or phosphorous. Normal muscle contraction and relaxation are energy-dependent processes that require the activities of a sodium-potassium ATPase on the sarclemma (a calcium-dependent ATPase in the sarcoplasmic reticulum) and a magnesium-dependent ATPase in the sarcoplasm. Accordingly, any drug that raises or lowers the concentration of these electrolytes can interfere with the orderly function of the tissue, causing myopathy. Clinically, this form of myopathy is most commonly caused by drugs that induce hypokalemia (Table 3). Muscle histology may show vacuoles in hypokalemic myopathy, regardless of the offending drug. Severe electrolyte imbalance also may cause rhabdomyolysis.

#### Table 3  Drugs That Can Cause Hypokalemia

<table>
<thead>
<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>Alcohol</td>
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<tr>
<td>Amphotericin B</td>
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<td>Cisplatin</td>
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<td>Corticosteroids</td>
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<tr>
<td>Diuretics</td>
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<tr>
<td>Glycyrrhizic acid (licorice)</td>
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<tr>
<td>Laxatives</td>
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<tr>
<td>Lithium</td>
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<tr>
<td>Mineralocorticoids</td>
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<tr>
<td>Parenteral nutrition</td>
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<tr>
<td>Theophylline</td>
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<td>Toluene (inhaled)</td>
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### Addictive Or Illicit Drugs

Excessive use of alcohol, narcotics, or illicit drugs can cause muscle injury by several mechanisms: direct toxic injury to the muscle fibers, ischemia from vasoconstriction, compression injury that occurs during coma, or inflammatory reactions to substances (drug or contaminant) injected intramuscularly.

#### Alcohol

Alcoholic myopathies may be classified into several types, although the different forms may coexist or overlap. These conditions include: 1) acute necrotizing myopathy, 2) acute hypokalemic myopathy, and 3) chronic alcoholic myopathy. Alcohol use can also be associated with asymptomatic hyper-CK-emia. Recovery may occur if the offending agent is discontinued and the patient receives appropriate supportive care and nutrition.

Acute necrotizing myopathy is typically seen in chronic alcohol users after consuming large quantities in a short period of time (binge drinking). Such individuals develop acute muscle pain with swelling and tenderness. Serum CK levels are markedly elevated and myoglobinuria can precipitate renal failure. Extensive fiber necrosis, intracellular edema, and tubular aggregates are seen on muscle histology. In contrast, patients with alcohol-induced hypokalemic myopathy develop painless, generalized weakness (sometimes flaccid paralysis). There is no cramping or muscle tenderness on exam. Serum CK levels are elevated and serum potassium levels may be less than 2.0 mEq/L. As with other hypokalemic states, vacuoles are seen on biopsy.

Chronic alcoholic myopathy causes weakness with a proximal distribution of insidious onset or generalized muscle wasting, but no complaints of myalgias. The patients themselves may be unaware of any weakness. Serum CK levels are variable; typically, they are mildly elevated and return to normal with abstinence. Although degenerating and regenerating fibers may be observed on muscle histology, fiber atrophy, especially of type 2B fibers, is the more common finding.

#### Illicit Drugs

Cocaine, amphetaamines, phencyclidine, marijuana, and heroin can all cause muscle damage, via either vasoconstrictive ischemia; compression injuries that occur with coma, agitation, and seizures; or direct toxic effects. Frequently, these present as acute syndromes with rhabdomyolysis (see below). However, cocaine use can also lead to asymptomatic hyper-CK-emia that persists for 1 to 2 months after use. Local necrosis or focal myositis may result from the intramuscular injection of these substances or foreign materials used to “cut” the agents. Toluene is a component of some substances that are inhaled (“huffed”). Its abuse can lead to profound generalized weakness and coma, associated with elevated serum CK levels, hypokalemia, hypophosphatemia, and hypocalcemia, and a profound metabolic acidosis.
Possible Drug-Related Myopathies in the Intensive Care Unit

A number of acute muscle disorders may be seen in patients on intensive care units, with some ascribable in whole or part to medications.

Acute Quadriplegic Myopathy

The first case of acute quadriplegic myopathy was described, in 1977, in a mechanically ventilated patient with status asthmaticus, who received neuromuscular blockade and high doses of intravenous corticosteroids. Subsequently, the terms “critical care illness myopathy,” “acute illness myopathy,” and “myopathies associated with thick filament (myosin) loss” have also been applied to this syndrome. It is often seen with coexisting critical care polyneuropathy. Organ transplant patients who have received high-dose corticosteroids may be at increased risk. Although most patients who have developed this syndrome have received high doses of intravenous corticosteroids with or without neuromuscular blocking agents, it has also been reported in patients with sepsis or multi-organ failure who had received neither agent.

In acute quadriplegic myopathy, generalized muscle weakness, typically, develops over several days. Ophthalmoplegia is rarely associated. The diagnosis should be suspected in candidate patients who cannot be weaned from a ventilator support. Sensory examination is normal, but deep tendon reflexes are diminished or absent. Serum CK values are modestly elevated in about half the patients, and EMGs are abnormal. Nerve conduction studies in patients with acute quadriplegic myopathy reveal a dramatic decrease in compound muscle action potential amplitude in the setting of normal sensory potentials. EMG has demonstrated diffuse fibrillation, short duration, polyphasic, and often low amplitude motor unit potentials, which recruited in a myopathic fashion. Affected muscles are also electrically inexcitable. Changes in muscle histology include type 2 fiber atrophy, generalized atrophy, and necrosis. Diminished myosin filaments are observed on electron microscopy or with histochemical staining. This change is attributed to the increased expression of calpain, a calcium-activated protease.

Treatment involves discontinuing the corticosteroids and neuromuscular blocking agents, if possible, and resolving the underlying condition. Physical therapy is useful in preventing contractures. Although acute quadriplegic myopathy is associated with a 30% mortality rate, those that recover gradually regain strength over a period of several months.

Malignant Hyperthermia

Malignant hyperthermia is characterized by high fever with intense muscle rigidity and myoglobinuria, and it is often associated with cardiac arrhythmias. The vast majority of cases occur in patients after receiving either depolarizing muscle relaxants, such as succinylcholine, or inhaled anesthetics, such as halothane. Caffeine, tricyclic antidepressants, monamine-oxidase inhibitors, and fluoroquinolones, as well as exercise and stress, have been reported to trigger attacks. Individuals with a muscular dystrophy may have a greater risk of developing this condition. Malignant hyperthermia occurs in 0.0005% to 0.5% of patients who receive anesthesia. Over half of the individuals who developed malignant hyperthermia had previously undergone anesthesia without a problem.

Serum CK levels may be initially normal or mildly elevated in asymptomatic, susceptible individuals, but rise dramatically during attacks. Myoglobinuria, hyperkalemia, and lactic acidosis all develop. Malignant hyperthermia has an autosomal dominant inheritance and can result from several different mutations, including mutations in the genes for the ryanodine receptor, the dihydropyridine-sensitive L-type voltage-dependent calcium channel gene, and the calcium channel subunit CACNA 2. These mutations allow excessive calcium release from the sarcoplasmic reticulum into the sarcoplasm, resulting in intense muscle contraction. Why this release is provoked by certain medications is unknown.

Summary and Conclusions

The clinical spectrum of drug-induced myopathies is wide and ranges from asymptomatic elevations in serum CK levels to severe rhabdomyolysis. While some drugs commonly cause muscle problems, virtually any medication may cause muscle symptoms on a rare or idiopathic basis. Biopsy and EMG results may vary, ranging from normal to severe disruption, and, in addition, may not always correlate perfectly well with the degree of symptomatology. In most cases, the pathophysiology of the affected muscle is poorly understood, but can range from atrophic to frankly inflammatory. Overall, our understanding of muscle disease, whether drug-induced or otherwise, is clearly in its infancy. Nonetheless, the frequency with which muscle symptoms or pathology may occur makes it important for clinicians to be aware of potential myopathy resulting from pharmacologic therapies. Although no review can be exhaustive, we have attempted to address the most commonly used agents associated with muscle disease.

Careful monitoring of rheumatic and other conditions is important when prescribing therapies with potential for muscle toxicity. A drug-induced myopathy should be suspected when no other recognizable cause of myopathy is available and when there is no history of muscle symptoms prior to initiating the therapy. Although in many cases the myopathy will be seen to occur shortly after starting the agent, in some cases, a myopathy may develop chronically or come on acutely after long-term use of a particular therapy. When a drug-related myopathy is suspected, the possible offending agent should be withdrawn or reduced if at all possible. Subsidence of symptoms or pathology, or both, upon discontinuation of the agent supports a diagnosis of drug-induced myopathy.
presumed drug-induced myopathies experience persistence of difficulties even after the agent is discontinued. Nonetheless, early diagnosis and drug discontinuation improves the chances of a rapid and complete resolution.

Disclosure Statement
None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References


