Patient Profile for Washington, D. C.

General Information

ID:	dc1234232
Prescriber:	Vu, John N M.D.
Name:	Washington, D. C.
Address:	100 Gaylord Resort Rd
City:	Baltimore
State:	MD
Zip:	0987
Country:	USA
Phone:	703.703.7703

Current Conditions

- allergic rhinitis
- angina
- asthma
- cardiopulmonary bypass
- edema
- fatigue
- females
- gout
- hypercholesterolemia
- hypertension
- hypothyroidism
- insomnia
- muscle cramps
- orthostatic hypotension
- peripheral neuropathy
- renal impairment
- skin abrasion
- skin inflammation
- stroke prophylaxis
- urticaria
- vertigo
- xerophthalmia

Current Allergies

No allergies noted

Current Medications

• Medication		
• Amlodipine	Dosage: 5mg	Sig: tab 1 daily
• Atorvastatin	Dosage: 40 mg	Sig: tab 1 at night
• Bumex®	Dosage: 2mg	Sig: tab 1 daily
• Clonazepam	Dosage: 1 mg	Sig: at bedtime
• Clonidine	Dosage: 0.1 mg	Sig: tab 1 twice a day
• Colchicine	Dosage: 0.3mg (Colcrys)	Sig: tab 1 daily
• Hydralazine	Dosage: 50mg	Sig: tab 1 four times a day
• Hydrocortisone; Neomycin		Sig: apply daily at night
• Levothyroxine	Dosage: 150 mcg	Sig: tab 1 daily
• Aspirin	Dosage: 81 mg	Sig: one tablet daily
• Metoprolol	Dosage: 50mg	Sig: tab 1 twice a day
• Nitrostat®	Dosage: 0.4mg	Sig: under tongue as needed for chest pain
• Plavix®	Dosage: 75mg	Sig: tab 1 daily
• Prednisone	Dosage: 5mg	Sig: 2.5mg AM & PM
• Restasis™	Dosage: 0.05%	Sig: drop 1 in each eye twice a day
• Singulair®	Dosage: 10mg	Sig: tab 1 daily
• Symbicort	Dosage: 160/4.5	Sig: 2 puffs twice a day
• Triamcinolone	Dosage: 0.10%	Sig: apply daily at night
• Ventolin® HFA	Sig: puffs 2 every 4 hours as needed for severe episodes	

Dosing Parameters

Gender:	Female
Birthdate:	4/19/1945
Weight:	80 kgs
Height:	160.02 cm
Ideal Body Weight:	55.05 kgs
Body Surface Area:	1.89 m²
Serum Creatinine:	2.08 mg/dL
Creatinine Clearance:	22.81 mL/min

Notes

Title: Initial Interview & Assessment
Date: 08/06/2012

This 74 year old white female presents with a multitude of problems. She complains of pain throughout her body, leg muscles and back muscles cramp and keep her awake at night, has a rash that covers her body that the corticosteroids are not helping, has large bruise spots on her legs, arms and over other parts of her body, has no energy and is depressed and anxious about her current condition. She is afraid of pain medications and refuses to take any. She explains that most of her problems started after her double bypass surgery about a year ago and the addition of all the new drugs. She had never had asthma until the surgery and since then the dizziness makes it where she can't walk without a walker. My observation of the patient shows very pale skin color, skin rashes that in some places she has scratched until bleeding occurs, numerous evidence of capillary fragility and she continued to doze off throughout the interview. Although we were able to finish our interview and assess her depression and anxiety, she dozed off 17

times during the session. Her depression score consistent with the Short Geriatric Depression Scale was 9 indicating a degree of anxiety and depression that needed to be treated. Review of her laboratory results showed a Serum Creatine of 2.08mg/DL which calculated to a 20cc/min renal clearance and constant elevated BUN levels making many of the drugs currently ordered contraindicated in this patient. She has an HGB of 10g/dL, HCT 31.9 and RDW 15.5 which have deteriorated down since her surgery from HGB 11.2, HCT 34.5 and RDW 13.4 which are strong indications of Aplastic Anemia due to the suppression of bone marrow production by the Allopurinol, clopidogrel, and colchicine. The colchicine and clopidogrel will be discontinued. Additionally the compromised renal clearance is probably due to these drugs and is surely due to the use of Statin therapy . Renal clearance will not allow for any statin therapy and the reduction in clearance makes some of the myelosuppression acting drug linger in the body, exacerbating this condition. Although the allopurinol will have to continue because of the history of severe gout the other drugs can be removed or replaced. The need for five different antihypertensive drugs is outside of accepted parameters and use of a beta blocker in this patient is causing the asthma and insomnia requiring more drugs to resolve the drug induced adverse events. Stopping the Beta Blocker Metoprolol should stop the need for the respiratory drugs, the benzodiazepine for sleep and reduce some of the myalgia. Additionally the need for the Singulair for the rhinitis should be resolved with stopping the beta blocker. Changing the patient to a benzothiazepine calcium channel blocker (diltiazem CD 24 hour release) is very geriatric friendly and should support her hypertensive needs alone. Starting the patient at 120mg twice a day of the 24 hour time release Diltiazem CD given in 12 hour increments will increase the activity under the curve, providing more protection and reducing adverse events. The Metoprolol, Clonidine, Hydralazine, Amlodipine will all be tapered to discontinue. The use of a 24 hour acting Loop Diuretic (torsemide) will allow for a 50% dose reduction of the Loop (Bumex) and spare more Potassium and Calcium as well as not allowing for the rebound antidiuretic effects seen with 2 hour short acting Loops. Torsemide will allow for more uric acid to clear which prevents additional gout problems. The prednisone compromises several systems in the patient's immune system and in conjunction with an immunosuppressant (cyclosporine Restasis drops) places the patient at very high risk for infection. Additionally use of prednisone in an anemic patient is not recommended. Restasis oph drops should never be used in the older patient. Due to the already compromised immune systems consistent with age, the addition of an immunosuppressant to the eyes, the most exposed part of the body to foreign bodies and viral and bacterial infections, is not good medicine. Older patients have a greater incidence of shingles (herpes Zoster) and to have any type of immunosuppression especially in the eyes could cause serious complications and possible blindness if the shingles are in or around the eyes. The use of (ketotifen) will better support the dry eyes with less risk and more comfort. The last TSH shows 20.38mlu/L but I think this is where the levothyroxine was initiated at 100mcg daily. Now the dose of the levothyroxine is 150mcg daily based on another TSH on a later date of 0.96 mIU/L. In an effort to treat the depression and anxiety and improve sleep, use of Venlafaxine ER will be initiated at bedtime and reevaluated in 6 months for continued use. This drug will also help with the neuropathy and

muscle cramps which will probably go away by stopping the Statin therapy. Each drug will be discussed in detail further in this report. But before any changes are implemented other than stopping the clopidrogrel, colchicine, prednisone, Lipitor this patient needs some IV Iron immediately to replenish the iron stores and stimulate the bone marrow to start to work. Use of Venofer (Iron Sucrose) is recommended until the Ferritin level is above 50 and the HGB is 12 or above.

Additionally for the physician's analysis and support of each statement made in this report, there are eight (8) pages of references to substantiate all findings and recommendations.

Step # 1: Drug Therapy Evaluation & Recommendations

Venofer - Iron sucrose is a safe drug to increase iron stores fast. Additional sample tests are not necessary and the Iron can be infused at once. Dosing in small increments reduces any problems and allows for stopping the iron supplementation when just enough is reached. Start the Venofer 100mg IV using 50cc Normal Saline and infuse over a 20 minute period every other day checking the HGB and Ferritin levels after each 3 doses for a maxium of HGB = 12 and Ferritin level of 50-60.

Step # 2: Drug Therapy Evaluation & Recommendations

Date: 08/06/2012

Review of the drug therapy currently prescribed resulted in the following problem areas:

Allopurinol - an excellent drug to prevent the manufacture of Uric Acid and dosing should be increased to 200mg daily and evaluate for further titrations. Although this drug suppresses the bone marrow stopping the other offending drugs should allow the use of the Allopurinol.

Clonazepam - use of benzodiazepine drugs in the older adult is not recommended. Exacerbation of respiratory problems is a high risk as well as falls, which the patient has serious problems with at this time. Palpitations , chest pain (unspecified), edema, and orthostatic hypotension were reported in patients receiving clonazepam in clinical trials.

Singulair - since this therapy will not be needed after stopping the beta blocker and because of some rare adverse events associated with Singulair and reduction of corticosteroids stopping the Singulair is necessary. Caution is advised when oral corticosteroid withdrawal or a reduction in corticosteroid dose is being considered in patients taking montelukast. Although a causal relationship has not been established; in rare cases, reduction in oral corticosteroid dose in patients taking montelukast has resulted in Churg-Strauss syndrome, a systemic eosinophilic vasculitis. Symptoms may include eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy.

Levothyroxine - continued use of the levothyroxine is recommended. We need to get a baseline TSH as we start removing these drugs.

Aspirin - use of 81mg dose aspirin needs to be changed to a full strength 325mg dose. Studies show that about 40% of the female population is not protected with the 81mg dose. Taking the full strength Enteric Coated 325mg is recommended along with 3600mg of Fish Oil daily to provide optimum antiplatelet inhibition for this patient at the lowest risk. Although the Aspirin may have some aplastic anemia warnings they are very rare and should not affect this patient. The use of fish oil is two fold in elevating the effective level of antiplatelet inhibition as well as help lower triglycerides helping the control of lipids.

Nitrostat - nitroglycerine tablets are excellent for onset attacks of Angina. Continue this drug as needed.

Colchicine - Colchicine should be used cautiously in geriatric or debilitated patients because of susceptibility to cumulative toxicity. The risk of neuromuscular toxicity and rhabdomyolysis is increased in elderly patients with or without concomitant renal or hepatic dysfunction. Chronic and/or excessive administration of colchicine is associated with bone marrow suppression. Pancytopenia, thrombocytopenia, leukopenia, neutropenia, agranulocytosis, aplastic anemia, and disseminated intravascular coagulation (DIC) have been reported. Myelosuppression is generally a later stage of colchicine toxicity occurring after the development of GI adverse events and concurrent with multi-organ damage. Here are reasons to suspect kidney damage consistent with the constant use of Colchicine and Statin (Lipitor) therapy.

Amlodipine - a good dihydropyridine calcium channel blocker that is hepatically metabolized but has a very long half life which causes a compounding of dosing leading to edema and other adverse events. This is an excellent antihypertensive for younger adults. The half life is extended in the older adult to about 50 hours causing the activity under the curve (AUC) to increase 40 to 60%. The benzothiazipine calcium channel blockers have shorter half lives and AUC can be controlled with the time release dosage form.

Metoprolol - beta blocker use is not recommended in the older patient. Beta blocker use is definitely not recommended in patients with a history of lung disease. The beta blocker is probably responsible for all the asthma problems and these problems will resolve themselves with the removal of the beta blocker. Additionally the beta blocker exacerbates problems with insomnia, and sleep disorders as well as rhinitis and muscle cramp problems. Patients with preexisting bronchospastic disease are at greater risk. Rhinitis has also been reported as an adverse event. Hypersensitivity reactions manifested by laryngospasm and respiratory distress have been reported with other beta-blockers and should therefore be considered potential adverse reactions to metoprolol.

Ventolin HFA - Albuterol use may not be needed after stopping the Metoprolol dosing

Symbicort Inhaler - Formoterol and corticosteroids therapy may not be needed after stopping the beta blocker. Geriatric patients may be more sensitive to the effects of beta-agonists, especially tremor and tachycardia. Although not clearly established, airway responsiveness to beta-agonist medications may change with age. In addition, elderly patients may be at increased risk for bone mineral density loss that is associated with long-term use of budesonide; formoterol

therapy. Stopping both the Ventolin and Symbicort and using a rescue inhaler Combivent may support the patient's needs.

Hydrocortisone cream - the need for these creams may go away as the anemia problems improve.

Triamcinolone cream - this cream may not be needed in a few months after resolving the anemia problems.

Atorvastatin - Lipitor risks are greater than the benefits received in the geriatric patient. With an NNT number of 168 and a risk of Diabetes and Memory loss of 10% the odds for success with the Lipitor is not acceptable. Atorvastatin may be contraindicated or temporarily withheld in conditions that can cause decreased renal perfusion since renal failure is possible if atorvastatin-induced *myopathy* and *rhabdomyolysis* occurs. Predisposing conditions for renal failure secondary to *rhabdomyolysis* include hypotension, sepsis or severe acute infection, severe/uncontrolled endocrine disease, acute electrolyte imbalance, uncontrolled seizure disorder, major surgery, and trauma. Alternative treatments such as Vitamin B12, Folic Acid and Vitamin B6 which may lower the homocystine levels which will then lower the lipids levels is safe and usually works in the older population. Although the patient LDL is over 200, Statin use places patient at greater risk of organ failure and cannot be considered. You only have the Vitamin Bs, exercise and diet to work with in this patient.

Bumetanide - a very short acting LOOP diuretic is not recommended in this patient. Due to the rebound antidiuretic actions in the 22 plus hours after the half life of 1 to 1.5 hours makes use unnecessary. Because the body will rebound with more fluid, the dosing continues to have to be raised to meet the fluid volume of the patient. Use of a 24 hour half life Loop will allow for maximum diuretic effects with no rebound antidiuretic effects.

Clopidogrel - this antplatelet inhibitor is probably the major factor in the Aplastic Anemia problems in this patient. Hematological effects that have been reported during post-marketing use of clopidogrel include: agranulocytosis, aplastic anemia, and pancytopenia. Renal adverse events reported during post-marketing surveillance of clopidogrel include glomerulonephritis and increased creatinine concentrations.

Prednisone - long term use of corticosteroids in the older patient is not recommended. Recorded problems with anemia and bone deterioration along with no apparent reason for use on this patient make a trial taper and discontinue a trial to pursue.

Hydralazine - an excellent antihypertensive drug is not recommended in this patient. Geriatric patients are more sensitive to the orthostatic hypotensive effects of hydralazine, and are also more likely to have age-associated renal impairment. Initiation of a reduced dosage, or beginning at the lower end of the adult dosage range is prudent for these patients. Changing to a single dose drug therapy for hypertension will reduce risk of adverse events.

Clonidine - alpha blockers in patient with renal impairment is not recommended. Orthostatic hypotension is a very high adverse event seen with the use of this drug. Alpha blockers also can exacerbate depression in the older patient.

Restasis - the use of an immunosuppressant in a geriatric patient whose immune system is more compromised is putting the patient at very high risk for serious adverse events. The eye is subject to more exposure to all kinds of virus and bacteria and all particles throughout the day. Studies show that the cyclosporine drops are only about 15% effective and are uncomfortable to use This makes continuation of use not recommended. Th use of ketotifen fumarate 0.025% oph. drops twice a day will support the needs of the patient's dry eyes with less risk and discomfort.

Drug Therapy Management

STOP the following:

Stop: Allopurinol 100mg
Stop: Clonazepam 1mg (follow taper instructions listed with Venlafaxine orders)
Stop: Singulair 10mg
Stop: Aspirin 81mg
Stop: Colchicine 0.3mg
Stop: Amlodipine 5mg
Stop: Metoprolol 50mg (follow taper instructions listed with Diltiazem CD)
Stop: Ventolin HFA
Stop: Symbicort Inhaler
Stop: Atrovastatin 40mg
Stop: Bumetanide 1mg
Stop: Clopidogrel 75mg
Stop: Prednisone 2.5mg daily x 7 days and STOP completely
Stop: Hydralazine 50mg
Stop: Clonidine 0.1mg
Stop: Restasis 0.05%

New Drug Therapy

Start or continue the following:
Levothyroxine 150mcg daily
Nitrostat 0.4mg under the tongue as needed for chest pain
Hydrocortisone Cream apply daily at night x 30 days and STOP
Triamcinolone Cream apply daily at night x 30 days and STOP
Diltiazem CD 120mg cap 1 twice a day
Taper to Discontinue Metoprolol 50mg daily x 4 doses then 50mg every other day x 4 doses and STOP
Venlafaxine ER 37.5mg at bedtime x 5 days, then 75mg at bedtime x 5 days then 150mg at bedtime thereafter
Taper to Discontinue Clonazepam 1mg every other night x 8 doses and STOP
Aspirin 325mg EC daily
Fish Oil 1200mg take one capsule three times a day
Vitamin B12 SUBLINGUAL 2500mcg tab 1 dissolve under the tongue each morning
Folic Acid 800mcg daily
Vitamin B6 200mg daily
Allopurinol 200mg daily
Ketotifen Fumarate 0.025% 1 drop in each eye AM and PM
Torsemide 5mg tab 1 daily
Combivent Inhaler puffs 2 every 4 hours as needed for rescue
Tramadol 50mg + Tylenol 325mg every four hours as needed for pain

Remember that it will take time to see all the changes that the new drug therapy will produce. After completing the titration processes that are required, we should see big improvements relating to the complaints recorded. The additional vitamin supplements should also make you feel better after 30 days or so. Further titration of the diltiazem dosing may be needed until we reach your dose. Continue to keep your blood pressure and pulse log. This is very important. I want you to call me each week and share with me your blood pressure log. Any adjustments in the drug dosing can be discussed at any time but call me at least weekly. Stopping all these

medications should make you feel much better and let you get back to your old activities. The tramadol 50mg I listed will work well for aches and pains and you don't have to worry about taking them. I know you feel better from the Iron injections so it will make your progress forward easier and quicker.

It is very important that we stay in touch. With this in mind I would like for you to call me if you experience any problems anytime and at least weekly to share your blood pressure and pulse values with me. These follow up calls are included in your initial fee and no further charges are placed on you until after our January visit. Please call in December and make an appointment for some time in January.

Let me remind you that this drug therapy regimen is thoroughly thought out and should be followed in its entirety. Choosing only bits and pieces of it may keep us from reaching our mutual goal of improvement in your quality of life and health. I am as close as your phone, so if problems occur please call me. *I look forward to seeing you for a follow-up visit around the end of January or the first of February but would like a progress report weekly by phone until we have all your medication dosages adjusted for you.*

Additionally a computerized analysis of the patient's current drug therapy accompanies this report with attached references for all areas of drug therapy.

Drug Interactions

Amlodipine and Bumetanide (Bumex®)
⚠Severity: Moderate

Amlodipine can have additive hypotensive effects with other antihypertensive agents [5825] including alpha-blockers, other calcium-channel blockers, vasodilators, and diuretics. This additive effect can be desirable, but the patient should be monitored carefully and the dosage should be adjusted based on clinical response. The concomitant use of dihydropyridine calcium-channel blockers and beta-blockers can reduce angina and improve exercise tolerance. When these drugs are given together, however, hypotension and impaired cardiac performance can occur, especially in patients with left ventricular dysfunction, cardiac arrhythmias, or aortic stenosis.

Concomitant use of metolazone with a loop diuretic can cause severe electrolyte loss.[6135] Metolazone should only be used in combination with bumetanide in patients who are refractory to loop diuretics alone. Close monitoring of serum electrolytes and cardiac function is advised. In patients with creatinine clearances > 30 ml/min, the combination of a loop diuretic with a thiazide diuretic may also lead to profound fluid and electrolyte loss. Thus, bumetanide should be used very cautiously in combination with either metolazone or thiazide diuretics. Conversely, potassium-sparing diuretics (amiloride, spironolactone, and triamterene) can counteract bumetanide-induced hypokalemia.[5351] In addition, amiloride and triamterene may counteract the magnesium wasting actions of loop diuretics. Finally, bumetanide may lead to additive hypotension if used in combination with any other antihypertensive agents.[5351] Hyponatremia or hypovolemia predisposes patients to acute hypotensive episodes following initiation of ACE inhibitor therapy. ACE inhibitors and loop diuretics are routinely administered together, however, in the treatment of heart failure. If an ACE inhibitor is to be administered to a patient receiving bumetanide, initial doses should be conservative.

Amlodipine and Clonidine

Severity: Moderate

Amlodipine can have additive hypotensive effects with other antihypertensive agents [5825] including alpha-blockers, other calcium-channel blockers, vasodilators, and diuretics. This additive effect can be desirable, but the patient should be monitored carefully and the dosage should be adjusted based on clinical response. The concomitant use of dihydropyridine calcium-channel blockers and beta-blockers can reduce angina and improve exercise tolerance. When these drugs are given together, however, hypotension and impaired cardiac performance can occur, especially in patients with left ventricular dysfunction, cardiac arrhythmias, or aortic stenosis.

Clonidine can produce bradycardia and should be used cautiously in patients who are receiving other drugs that lower the heart rate such as amiodarone, beta-blockers, cardiac glycosides, diltiazem, guanethidine, or verapamil.[5017] Complete AV block resulting in a nodal rhythm has been reported during combination therapy of clonidine with verapamil. Also, concomitant use of clonidine with beta-blockers, diltiazem, guanethidine, verapamil or opiate agonists can cause additive hypotension. Beta-blockers should not be substituted for clonidine when modifications are made in a patient's antihypertensive regimen because beta-blocker administration during clonidine withdrawal can augment clonidine withdrawal which may lead to a hypertensive crisis.[5017] If a beta-blocker is to be substituted for clonidine, clonidine should be gradually tapered and the beta-blocker should be gradually increased over several days to avoid the possibility of rebound hypertension; administration of beta-blockers during withdrawal of clonidine can precipitate severe increases in blood pressure as a result of unopposed alpha stimulation.[5017] It is possible to administer clonidine and beta-blockers concurrently without sequelae, although hypotensive effects can be additive. The concomitant administration of clonidine with diuretics or other antihypertensive agents can result in additive hypotensive effects.[5017] This interaction can be therapeutically advantageous, but dosages must be adjusted accordingly.

Amlodipine and Hydralazine

Severity: Moderate

Amlodipine can have additive hypotensive effects with other antihypertensive agents [5825] including alpha-blockers, other calcium-channel blockers, vasodilators, and diuretics. This additive effect can be desirable, but the patient should be monitored carefully and the dosage should be adjusted based on clinical response. The concomitant use of dihydropyridine calcium-channel blockers and beta-blockers can reduce angina and improve exercise tolerance. When these drugs are given together, however, hypotension and impaired cardiac performance can occur, especially in patients with left ventricular dysfunction, cardiac arrhythmias, or aortic stenosis.

The concomitant administration of hydralazine with diuretics, other antihypertensive agents, or vasodilators can result in additive hypotensive effects.[6035] This interaction can be therapeutically advantageous, but dosages must be adjusted accordingly. Marked hypotensive episodes can result from concomitant administration of diazoxide and hydralazine.[6278] Hydralazine should not be administered within 6 hours of administration of IV diazoxide.[6278]

Amlodipine and Metoprolol

Severity: Moderate

Amlodipine can have additive hypotensive effects with other antihypertensive agents [5825] including alpha-blockers, other calcium-channel blockers, vasodilators, and diuretics. This additive effect can be desirable, but the patient should be monitored carefully and the dosage should be adjusted based on clinical response. The concomitant use of dihydropyridine calcium-channel blockers and beta-blockers can reduce angina and improve exercise tolerance. When these drugs are given together, however, hypotension and impaired cardiac performance can occur, especially in patients with left ventricular dysfunction, cardiac arrhythmias, or aortic stenosis.

Metoprolol is an antihypertensive agent, so its effects are additive with other antihypertensive agents.[6714] This interaction is often used advantageously in treating hypertension; however, lower doses of each agent may be necessary. Hypotension can be potentiated when beta-blockers are co-administered with dihydropyridine-type calcium-channel blockers, most notably rapid-release nifedipine. Nicardipine been reported to increase plasma concentrations and oral bioavailability of certain beta-blockers (e.g., metoprolol, propranolol). It is prudent to avoid using beta-blockers with guanethidine, reserpine, or other rauwolfia alkaloids that have a high incidence of orthostatic hypotension due to catecholamine depletion, since beta-blockers will interfere with reflex tachycardia, worsening the orthostasis.[5269]

Amlodipine and Cyclosporine (Restasis™)
Severity: Moderate

Amlodipine is a CYP3A4 substrate [4718]. Theoretically, CYP3A4 inhibitors, such as cyclosporine [4718], may increase the plasma concentration of amlodipine via CYP3A4 inhibition [5825]; this effect might lead to hypotension in some individuals. Caution should be used when cyclosporine is coadministered with amlodipine; therapeutic response should be monitored.

Diltiazem, nicardipine, and verapamil may inhibit cyclosporine CYP3A4-mediated metabolism, which may result in increased cyclosporine blood concentrations.[5936] Diltiazem, nicardipine, and verapamil also inhibit P-glycoprotein, which may lead to increased absorption of cyclosporine. Diltiazem has been documented to reduce cyclosporine dosage by approximately 30-50% in organ transplant patients without reports of severe adverse effects; this strategy has been investigated to reduce cyclosporine economic costs.[3697] In addition, diltiazem has been shown to protect the kidney from the vasoconstrictive effects of cyclosporine. Vigilant serum cyclosporine serum concentration monitoring is warranted if used with either diltiazem, nicardipine, or verapamil. A reduced dosage of cyclosporine may be necessary. Other calcium-channel blockers, such as amlodipine, isradipine, and nitrendipine have been shown to have minimal effects on cyclosporine blood concentrations.

Amlodipine and Ethanol
Severity: Moderate

Ethanol interacts with antihypertensive agents by potentiating their hypotensive effect.[5944]

Atorvastatin and Colchicine
Severity: Moderate

Case reports exist describing the development of myotoxicity (i.e., muscle pain and weakness, rhabdomyolysis) with the concurrent administration of colchicine and HMG-CoA reductase inhibitors (Statins).[11130] [11131] [11132] [11133] [11134] [11135] [11136] [11137] [11138] Statins involved in the reported cases include simvastatin, atorvastatin, fluvastatin, lovastatin, and pravastatin. The pharmacokinetic and/or pharmacodynamic mechanism of this interaction is not clear; however, both colchicine and statins are associated with the development of myotoxicity and concurrent use may increase the risk of myotoxicity. Patients receiving these agents concurrently should be monitored for myotoxicity.

Atorvastatin and Cyclosporine (Restasis™)
Severity: High

While the manufacturer's product literature warns of using immunosuppressives with atorvastatin, this warning is based mainly on the interaction with cyclosporine and may not apply to all immunosuppressives.[5460] The risk of developing myopathy during therapy with HMG-CoA reductase inhibitors is increased if they are administered concomitantly with cyclosporine.[5460] Atorvastatin is a substrate for OATP1B1 transporter, and cyclosporine is an inhibitor of this transporter. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an 8.7-fold increase in atorvastatin AUC.

Significant elevations of HMG-CoA reductase inhibitor plasma concentrations may occur if administered concomitantly with cyclosporine. The interaction does not appear to be mediated solely by an effect on CYP enzymes. Cyclosporine may reduce transport of a HMG-CoA reductase inhibitor to the liver, which would increase the drug's plasma concentration. Elevated concentrations of the HMG-CoA reductase inhibitor may increase the risk of myositis and rhabdomyolysis. For example, coadministration of rosuvastatin with cyclosporine in heart transplant patients resulted in an 11-fold elevation of the Cmax and a 7-fold elevation of the AUC of rosuvastatin as compared with historical data from normal volunteers. Reduced clearance of lovastatin and myositis development has been observed when used concomitantly with cyclosporine.[5936] When administered in combination with immunosuppressive therapy including cyclosporine, the incidence of lovastatin-induced myopathy rises to 30%. Although the systemic exposure of all HMG-CoA reductase inhibitors (Statins) may be increased by cyclosporine, pravastatin may be less effected since pravastatin undergoes both CYP metabolism and renal elimination of unchanged and conjugated parent drug. If an HMG-CoA reductase inhibitor must be used concurrently with cyclosporine, low initial doses of the HMG-CoA reductase inhibitor are advisable; selected HMG-CoA reductase inhibitors require dosage adjustments (see Dosage for individual agents) and limit maximum dosages if cyclosporine is used concomitantly. Although cyclosporine pharmacokinetic parameters do not appear to be affected by concurrent use of a HMG-CoA inhibitor, careful monitoring of cyclosporine serum concentrations during concurrent use is advisable. Since compounds in red yeast

rice claim to have HMG-CoA reductase inhibitor activity, red yeast rice should not be used in combination with cyclosporine.[5911] [5335]

Atorvastatin and Clopidogrel (Plavix®)
Severity: Low

Atorvastatin has been reported to attenuate the antiplatelet activity of clopidogrel potentially by inhibiting CYP3A4 metabolism to its active metabolite;[5163] [5477] however, conflicting data exists.[5398] The clinical significance of this theoretical interaction is not known. Patients should be monitored for therapeutic effectiveness when clopidogrel is administered with atorvastatin or other HMG CoA reductase inhibitors metabolized by the CYP 3A4 isozyme (i.e., lovastatin, simvastatin, and cerivastatin).

Atorvastatin has been reported to attenuate the antiplatelet activity of clopidogrel potentially by inhibiting CYP3A4 metabolism to its active metabolite;[5163] [5477] however, conflicting data exists.[5398] The clinical significance of this theoretical interaction is not known. Patients should be monitored for therapeutic effectiveness when clopidogrel is administered with atorvastatin or other HMG Co-A reductase inhibitors metabolized by the CYP 3A4 isozyme (i.e., lovastatin, simvastatin, and cerivastatin).

Atorvastatin and food
Severity: High

Food-drug interactions with atorvastatin include grapefruit juice. Grapefruit juice contains a compound that inhibits the CYP3A4 isozyme in the gut wall.[4718] [5506] Studies have reported that coadministration with grapefruit juice increases the peak serum concentrations and the AUC of lovastatin,[5335] and may have a similar effect on the serum concentrations of simvastatin [4718] [5506], atorvastatin [4718] [5506], and cerivastatin [5506], all of which are CYP3A4 substrates. Grapefruit juice should be avoided in patients taking agents to avoid the potential for drug accumulation and toxicity (i.e., myopathy and rhabdomyolysis).

Atorvastatin and grapefruit juice
Severity: High

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Bumetanide (Bumex®) **and Albuterol** (Ventolin® HFA)
Severity: Moderate

Hypokalemia and/or ECG changes associated with loop diuretics can be acutely worsened by beta-agonists. Hypokalemia due to beta-agonists appears to be dose-related. Caution is advised when loop or thiazide diuretics are coadministered with high doses of beta-agonists; potassium levels may need to be monitored.

Non-potassium sparing diuretics, such as loop diuretics and thiazide diuretics may potentiate hypokalemia and ECG changes seen with beta-agonists such as albuterol.[5262] Hypokalemia due to beta-agonists appears to be dose-related. Caution is advised when loop or thiazide diuretics are coadministered with high doses of beta-agonists; potassium levels may need to be monitored.[5262]

Bumetanide (Bumex®) **and Aspirin, ASA** (Low Dose Adult Aspirin)
Severity: Moderate

Salicylates can increase the risk of renal toxicity in patients receiving diuretics because salicylates inhibit renal prostaglandin synthesis, which can lead to fluid retention and increased peripheral vascular resistance.

The efficacy of selected antihypertensive agents needs to be carefully assessed during aspirin usage. During antihypertensive therapy with beta-blockers, high concentrations of vasodilatory prostaglandins are produced in response to reflex-mediated pressor mechanisms (e.g., sympathetic tone). Concurrent use of beta-blockers with aspirin may result in loss of antihypertensive activity due to inhibition of renal prostaglandins and thus, salt and water retention and decreased renal blood flow.[5717] Aspirin can increase the risk of renal insufficiency in patients receiving diuretics, secondary to the effects of aspirin on renal blood flow. Aspirin inhibits renal prostaglandin production, which causes salt and water retention and decreased renal blood flow. Thus, the effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin.[5717] Aspirin may decrease the hyperuricemic effect of thiazide diuretics (e.g., hydrochlorothiazide) or loop diuretics like furosemide. Concomitant use of aspirin and potassium-sparing diuretics, such as triamterene or spironolactone, may cause hyperkalemia.[5717] The hyponatremic and hypotensive effects of angiotensin-converting enzyme (ACE) inhibitors may be diminished by concurrent use of aspirin; the inhibition of cyclooxygenase by aspirin prevents the formation of vasodilatory prostaglandins.[5717] Furthermore, reduced

renal blood flow is expected from the decreased pressure gradient created in the glomeruli when aspirin is used with an ACE inhibitor.[5718] Low-dose aspirin (e.g., 81 mg/day) may be less likely to attenuate the antihypertensive or cardioprotective effects of ACE inhibitors; however, the dose-related effect is controversial.[6439] The established benefits of using low-dose aspirin in combination with an ACE inhibitor in patients with ischemic heart disease and left ventricular dysfunction generally outweigh concerns, especially with appropriate renal function and serum potassium monitoring.[5718] [6060] [6439] Monitor the patient's blood pressure, renal function, and clinical status for the desired responses and adjust therapy accordingly.

Bumetanide (Bumex®) **and Clonidine**
Severity: Moderate

Concomitant use of metolazone with a loop diuretic can cause severe electrolyte loss.[6135] Metolazone should only be used in combination with bumetanide in patients who are refractory to loop diuretics alone. Close monitoring of serum electrolytes and cardiac function is advised. In patients with creatinine clearances > 30 ml/min, the combination of a loop diuretic with a thiazide diuretic may also lead to profound fluid and electrolyte loss. Thus, bumetanide should be used very cautiously in combination with either metolazone or thiazide diuretics. Conversely, potassium-sparing diuretics (amiloride, spironolactone, and triamterene) can counteract bumetanide-induced hypokalemia.[5351] In addition, amiloride and triamterene may counteract the magnesium wasting actions of loop diuretics. Finally, bumetanide may lead to additive hypotension if used in combination with any other antihypertensive agents.[5351] Hyponatremia or hypovolemia predisposes patients to acute hypotensive episodes following initiation of ACE inhibitor therapy. ACE inhibitors and loop diuretics are routinely administered together, however, in the treatment of heart failure. If an ACE inhibitor is to be administered to a patient receiving bumetanide, initial doses should be conservative.

Clonidine can produce bradycardia and should be used cautiously in patients who are receiving other drugs that lower the heart rate such as amiodarone, beta-blockers, cardiac glycosides, diltiazem, guanethidine, or verapamil.[5017] Complete AV block resulting in a nodal rhythm has been reported during combination therapy of clonidine with verapamil. Also, concomitant use of clonidine with beta-blockers, diltiazem, guanethidine, verapamil or opiate agonists can cause additive hypotension. Beta-blockers should not be substituted for clonidine when modifications are made in a patient's antihypertensive regimen because beta-blocker administration during clonidine withdrawal can augment clonidine withdrawal which may lead to a hypertensive crisis.[5017] If a beta-blocker is to be substituted for clonidine, clonidine should be gradually tapered and the beta-blocker should be gradually increased over several days to avoid the possibility of rebound hypertension; administration of beta-blockers during withdrawal of clonidine can precipitate severe increases in blood pressure as a result of unopposed alpha stimulation.[5017] It is possible to administer clonidine and beta-blockers concurrently without sequelae, although hypotensive effects can be additive. The concomitant administration of clonidine with diuretics or other antihypertensive agents can result in additive hypotensive effects.[5017] This interaction can be therapeutically advantageous, but dosages must be adjusted accordingly.

Bumetanide (Bumex®) **and Hydralazine**
Severity: Moderate

Concomitant use of metolazone with a loop diuretic can cause severe electrolyte loss.[6135] Metolazone should only be used in combination with bumetanide in patients who are refractory to loop diuretics alone. Close monitoring of serum electrolytes and cardiac function is advised. In patients with creatinine clearances > 30 ml/min, the combination of a loop diuretic with a thiazide diuretic may also lead to profound fluid and electrolyte loss. Thus, bumetanide should be used very cautiously in combination with either metolazone or thiazide diuretics. Conversely, potassium-sparing diuretics (amiloride, spironolactone, and triamterene) can counteract bumetanide-induced hypokalemia.[5351] In addition, amiloride and triamterene may counteract the magnesium wasting actions of loop diuretics. Finally, bumetanide may lead to additive hypotension if used in combination with any other antihypertensive agents.[5351] Hyponatremia or hypovolemia predisposes patients to acute hypotensive episodes following initiation of ACE inhibitor therapy. ACE inhibitors and loop diuretics are routinely administered together, however, in the treatment of heart failure. If an ACE inhibitor is to be administered to a patient receiving bumetanide, initial doses should be conservative.

The concomitant administration of hydralazine with diuretics, other antihypertensive agents, or vasodilators can result in additive hypotensive effects.[6035] This interaction can be therapeutically advantageous, but dosages must be adjusted accordingly. Marked hypotensive episodes can result from concomitant administration of diazoxide and hydralazine.[6278] Hydralazine should not be administered within 6 hours of administration of IV diazoxide.[6278]

Bumetanide (Bumex®) **and Hydrocortisone** (found in Hydrocortisone; Neomycin)
Severity: Moderate

Fludrocortisone and glucocorticoids with mineralocorticoid activity (e.g., cortisone, hydrocortisone) can cause sodium retention and hypokalemia. Additive hypokalemia may occur when loop diuretics are coadministered with other corticosteroids or corticotropin, ACTH. Concomitant administration of bumetanide with any of these agents can lead to significant hypokalemia and/or hypomagnesemia.[3085] [5351] While it is possible to use loop diuretics with these agents safely, close monitoring of serum potassium and serum magnesium should occur in these patients.

The potassium-wasting effects of corticosteroid therapy [6762] can be exacerbated by concomitant administration of other potassium-depleting drugs including diuretics. Serum potassium levels should be monitored in patients receiving these drugs concomitantly.[3085]

Bumetanide (Bumex®) **and Metoprolol**
⚠Severity: Moderate

Concomitant use of metolazone with a loop diuretic can cause severe electrolyte loss.[6135] Metolazone should only be used in combination with bumetanide in patients who are refractory to loop diuretics alone. Close monitoring of serum electrolytes and cardiac function is advised. In patients with creatinine clearances > 30 ml/min, the combination of a loop diuretic with a thiazide diuretic may also lead to profound fluid and electrolyte loss. Thus, bumetanide should be used very cautiously in combination with either metolazone or thiazide diuretics. Conversely, potassium-sparing diuretics (amiloride, spironolactone, and triamterene) can counteract bumetanide-induced hypokalemia.[5351] In addition, amiloride and triamterene may counteract the magnesium wasting actions of loop diuretics. Finally, bumetanide may lead to additive hypotension if used in combination with any other antihypertensive agents.[5351] Hyponatremia or hypovolemia predisposes patients to acute hypotensive episodes following initiation of ACE inhibitor therapy. ACE inhibitors and loop diuretics are routinely administered together, however, in the treatment of heart failure. If an ACE inhibitor is to be administered to a patient receiving bumetanide, initial doses should be conservative.

Metoprolol is an antihypertensive agent, so its effects are additive with other antihypertensive agents.[6714] This interaction is often used advantageously in treating hypertension; however, lower doses of each agent may be necessary. Hypotension can be potentiated when beta-blockers are co-administered with dihydropyridine-type calcium-channel blockers, most notably rapid-release nifedipine. Nicardipine been reported to increase plasma concentrations and oral bioavailability of certain beta-blockers (e.g., metoprolol, propranolol). It is prudent to avoid using beta-blockers with guanethidine, reserpine, or other rauwolfia alkaloids that have a high incidence of orthostatic hypotension due to catecholamine depletion, since beta-blockers will interfere with reflex tachycardia, worsening the orthostasis.[5269]

Bumetanide (Bumex®) **and Neomycin** (found in Hydrocortisone; Neomycin)
⚠Severity: Moderate

The oral use of neomycin is rarely associated with ototoxicity or nephrotoxicity due to low systemic absorption under most circumstances; the risk is highest with the parenteral systemic use of aminoglycosides. The risk of ototoxicity or nephrotoxicity secondary to aminoglycosides may be increased by the addition of concomitant therapies with similar side effects, including loop diuretics. Ototoxicity from furosemide or other loop diuretics, while uncommon, can be a transient or permanent side effect of significance. Ototoxicity is best documented with the loop diuretics ethacrynic acid [5138] and furosemide [5159], but may also occur with either bumetanide or torsemide. The exact mechanism by which furosemide or other loop diuretics produce ototoxicity is unknown. Usually, reports indicate that furosemide ototoxicity is associated with rapid injection, severe renal impairment, higher than recommended dosages or infusion rates, or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid, or other ototoxic drugs.[51] [52] [5159] Additionally, loop diuretics may cause volume depletion and allow for the concentration of aminoglycosides within the nephron; concurrent therapy has been considered a risk-factor for aminoglycoside-induced nephrotoxicity.[4921] Some experts, based on data from controlled trials, do not consider administration of furosemide a major risk for aminoglycoside-induced auditory or nephro-toxicity.[5180] However, caution is advised and risk should be determined individually. If loop diuretics and aminoglycosides are used together, it would be prudent to monitor renal function parameters, serum electrolytes, and serum aminoglycoside concentrations during therapy. Audiologic monitoring may be advisable during high dose therapy or therapy of long duration, when hearing loss is suspected, or in selected risk groups (e.g., neonates).

The risk of ototoxicity or nephrotoxicity secondary to aminoglycosides may be increased by the addition of concomitant therapies with similar side effects, including loop diuretics. Ototoxicity from furosemide or other loop diuretics, while uncommon, can be a transient or permanent side effect of significance. Ototoxicity is best documented with the loop diuretics ethacrynic acid [5138] and furosemide [5159], but may also occur with either bumetanide [5351] or torsemide. The exact mechanism by which furosemide or other loop diuretics produce ototoxicity is unknown. Usually, reports indicate that furosemide ototoxicity is associated with rapid injection, severe renal impairment, higher than recommended dosages or infusion rates, or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid, or other ototoxic drugs.[51] [52] [5159] Additionally, loop diuretics may cause volume depletion and allow for the concentration of aminoglycosides within the nephron; concurrent therapy has been considered a risk-factor for aminoglycoside-induced nephrotoxicity.[4921] Some experts, based on data from controlled trials, do not consider administration of furosemide a major risk for aminoglycoside-induced auditory or nephro-toxicity.[5180] However, caution is advised and risk should be determined individually. If loop diuretics and aminoglycosides are used together, it would be prudent to monitor renal function parameters, serum electrolytes, and serum aminoglycoside concentrations during therapy. Audiologic monitoring may be advisable during high dose therapy or therapy of long duration, when hearing loss is suspected, or in selected risk groups (e.g., neonates).

Bumetanide (Bumex®) **and Prednisone**
⚠Severity: Moderate

Fludrocortisone and glucocorticoids with mineralocorticoid activity (e.g., cortisone, hydrocortisone) can cause sodium retention and hypokalemia. Additive hypokalemia may occur when loop diuretics are coadministered with other corticosteroids or corticotropin, ACTH. Concomitant administration of bumetanide with any of these agents can lead to significant hypokalemia and/or hypomagnesemia.[3085] [5351] While it is possible to use loop diuretics with these agents safely, close monitoring of serum potassium and serum magnesium should occur in these patients.

The potassium-wasting effects of corticosteroid therapy [6524] may be exacerbated by concomitant administration of other potassium depleting drugs including diuretics and amphotericin B. Serum potassium levels should be monitored in patients receiving these drugs concomitantly.

Bumetanide (Bumex®) **and Triamcinolone**
⚠Severity: Moderate

Fludrocortisone and glucocorticoids with mineralocorticoid activity (e.g., cortisone, hydrocortisone) can cause sodium retention and hypokalemia. Additive hypokalemia may occur when loop diuretics are coadministered with other corticosteroids or corticotropin, ACTH. Concomitant administration of bumetanide with any of these agents can lead to significant hypokalemia and/or hypomagnesemia.[3085] [5351] While it is possible to use loop diuretics with these agents safely, close monitoring of serum potassium and serum magnesium should occur in these patients.

The potassium-wasting effects of corticosteroid therapy can be exacerbated by concomitant administration of other potassium-depleting drugs such as diuretics and amphotericin B. Serum potassium levels should be monitored in patients receiving these drugs concomitantly.[3085]

Bumetanide (Bumex®) **and Budesonide; Formoterol** (Symbicort)
⚠Severity: Moderate

Hypokalemia and/or ECG changes associated with loop diuretics can be acutely worsened by beta-agonists. Hypokalemia due to beta-agonists appears to be dose-related. Caution is advised when loop or thiazide diuretics are coadministered with high doses of beta-agonists; potassium levels may need to be monitored.

Fludrocortisone and glucocorticoids with mineralocorticoid activity (e.g., cortisone, hydrocortisone) can cause sodium retention and hypokalemia. Additive hypokalemia may occur when loop diuretics are coadministered with other corticosteroids or corticotropin, ACTH. Concomitant administration of bumetanide with any of these agents can lead to significant hypokalemia and/or hypomagnesemia.[3085] [5351] While it is possible to use loop diuretics with these agents safely, close monitoring of serum potassium and serum magnesium should occur in these patients.

Non-potassium sparing diuretics, such as loop diuretics and thiazide diuretics, may potentiate hypokalemia and ECG changes seen with beta-agonists such as formoterol.[5038] Hypokalemia appears to be a dose-related effect with formoterol.[5038] One dose escalating study noted no differences in potassium levels between a 12 mcg dose of formoterol and placebo, however, significant changes were noted with a 24, 48, and 96 mcg dose.[3098] Caution is advised when loop or thiazide diuretics are coadministered with higher doses of budesonide; formoterol [9798]; potassium concentrations may need to be monitored.

Bumetanide (Bumex®) **and Ethanol**
⚠Severity: Moderate

Ethanol, since it also possesses diuretic properties, should be taken in small quantities in patients receiving loop diuretics. The diuretic properties may be additive, leading to dehydration in some patients. In addition, ethanol has hypotensive properties [5944] which can enhance the antihypertensive effects of diuretics.

Clonazepam and Ethanol
⚠Severity: High

Concomitant administration of clonazepam with other CNS-depressant drugs [7168], including barbiturates, buprenorphine, butorphanol, dronabinol, THC [7185], entacapone [5769], ethanol [7198], sedating H_1-blockers, general anesthetics [6892], nabilone [9044], nalbuphine [6778], opiate agonists, pentazocine, phenothiazines, pregabalin [7523], tolcapone, tramadol, tricyclic antidepressants, or other anxiolytics, sedatives, and hypnotics, can potentiate the CNS effects (i.e., increased sedation or respiratory depression) of either agent.[5174] Additionally, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of zolpidem and other CNS depressants than with zolpidem alone.[6473]

Clonidine and Clonazepam
⚠Severity: Moderate

Clonidine has CNS depressive effects [5017] and can potentiate the actions of other CNS depressants including barbiturates, benzodiazepines, ethanol [6341], general anesthetics, opiate agonists [2086] [2087], and sedatives. Epidural clonidine may prolong the duration of action of local anesthetics,[2084] [2088] [2090] including both sensory and motor blockade.

Clonidine and Hydralazine
⚠Severity: Moderate

Clonidine can produce bradycardia and should be used cautiously in patients who are receiving other drugs that lower the heart rate such as amiodarone, beta-blockers, cardiac glycosides, diltiazem, guanethidine, or verapamil.[5017] Complete AV block resulting in a nodal rhythm has been reported during combination therapy of clonidine with verapamil. Also, concomitant use of clonidine with beta-blockers, diltiazem, guanethidine, verapamil or opiate agonists can cause additive hypotension. Beta-blockers should not be substituted for clonidine when modifications are made in a patient's antihypertensive regimen because beta-blocker administration during clonidine withdrawal can augment clonidine withdrawal which may lead to a hypertensive crisis.[5017] If a beta-blocker is to be substituted for clonidine, clonidine should be gradually tapered and the beta-blocker should be gradually increased over several days to avoid the possibility of rebound hypertension; administration of beta-blockers during withdrawal of clonidine can precipitate severe increases in blood pressure as a result of unopposed alpha stimulation.[5017] It is possible to administer clonidine and beta-blockers concurrently without sequelae, although hypotensive effects can be additive. The concomitant administration of clonidine with diuretics or other antihypertensive agents can result in additive hypotensive effects.[5017] This interaction can be therapeutically advantageous, but dosages must be adjusted accordingly.

The concomitant administration of hydralazine with diuretics, other antihypertensive agents, or vasodilators can result in additive hypotensive effects.[6035] This interaction can be therapeutically advantageous, but dosages must be adjusted accordingly. Marked hypotensive episodes can result from concomitant administration of diazoxide and hydralazine.[6278] Hydralazine should not be administered within 6 hours of administration of IV diazoxide.[6278]

Clonidine and Metoprolol
⚠Severity: High

Care must be taken when abruptly stopping clonidine to avoid the possibility of rebound hypertension, which can be augmented in patients currently receiving or simultaneously beginning therapy with metoprolol or another beta-blocker.[5017] Administration of beta-blockers during withdrawal of clonidine can precipitate severe blood pressure increases as a result of unopposed alpha stimulation. If metoprolol is to be substituted for clonidine, clonidine should be gradually discontinued; metoprolol can be initiated several days after clonidine has been stopped. It is possible to administer clonidine and metoprolol concurrently without sequelae, although hypotensive effects will be additive.

Clonidine can produce bradycardia and should be used cautiously in patients who are receiving other drugs that lower the heart rate such as amiodarone, beta-blockers, cardiac glycosides, diltiazem, guanethidine, or verapamil.[5017] Complete AV block resulting in a nodal rhythm has been reported during combination therapy of clonidine with verapamil. Also, concomitant use of clonidine with beta-blockers, diltiazem, guanethidine, verapamil or opiate agonists can cause additive hypotension. Beta-blockers should not be substituted for clonidine when modifications are made in a patient's antihypertensive regimen because beta-blocker administration during clonidine withdrawal can augment clonidine withdrawal which may lead to a hypertensive crisis.[5017] If a beta-blocker is to be substituted for clonidine, clonidine should be gradually tapered and the beta-blocker should be gradually increased over several days to avoid the possibility of rebound hypertension; administration of beta-blockers during withdrawal of clonidine can precipitate severe increases in blood pressure as a result of unopposed alpha stimulation.[5017] It is possible to administer clonidine and beta-blockers concurrently without sequelae, although hypotensive effects can be additive. The concomitant administration of clonidine with diuretics or other antihypertensive agents can result in additive hypotensive effects.[5017] This interaction can be therapeutically advantageous, but dosages must be adjusted accordingly.

Metoprolol is an antihypertensive agent, so its effects are additive with other antihypertensive agents.[6714] This interaction is often used advantageously in treating hypertension; however, lower doses of each agent may be necessary. Hypotension can be potentiated when beta-blockers are co-administered with dihydropyridine-type calcium-channel blockers, most notably rapid-release nifedipine. Nicardipine been reported to increase plasma concentrations and oral bioavailability of certain beta-blockers (e.g., metoprolol, propranolol). It is prudent to avoid using beta-blockers with guanethidine, reserpine, or other rauwolfia alkaloids that have a high incidence of orthostatic hypotension due to catecholamine depletion, since beta-blockers will interfere with reflex tachycardia, worsening the orthostasis.[5269]

Clonidine and Cyclosporine (Restasis™)
⚠Severity: Low

Several interactions occur between clonidine and cyclosporine. Cyclosporine can cause constriction of preglomerular arterioles. Clonidine can inhibit cyclosporine-induced glomerular vasoconstriction and has been shown to offset cyclosporine-induced

nephrotoxicity.[256] Clonidine may adversely affect cyclosporine pharmacokinetics; limited data suggest that cyclosporine concentrations increase - dramatically, in some cases - when clonidine is added. Until more data are available, clinicians should use clonidine cautiously in patients stabilized on cyclosporine.

Clonidine and Ethanol
⚠Severity: Moderate

Clonidine has CNS depressive effects [5017] and can potentiate the actions of other CNS depressants including barbiturates, benzodiazepines, ethanol [6341], general anesthetics, opiate agonists [2086] [2087], and sedatives. Epidural clonidine may prolong the duration of action of local anesthetics,[2084] [2088] [2090] including both sensory and motor blockade.

Colchicine and Cyclosporine (Restasis™)
⚠Severity: High

A single case report is noted of cyclosporine nephrotoxicity occurring after the addition of colchicine. Cyclosporine concentrations increased and renal function worsened 2 days after the addition of colchicine. The mechanism appears to be reduced cyclosporine metabolism via p-glycoprotein and CYP3A4 inhibition by colchicine; colchicine increases cyclosporine concentrations.[5936] Cyclosporine toxicity (i.e., renal and/or hepatic dysfunction, cholestasis, paresthesias, myopathy) may occur. Although cyclosporine can cause hyperuricemia [36], it would be prudent to avoid the use of colchicine in patients receiving cyclosporine.[5134] [5936] In addition, the risk for colchicine toxicity is higher in patients with renal dysfunction.[66] [70] [5134] [7151]

Although data are limited, both azotemia and neurotoxicity have been reported when colchicine was added to a regimen containing cyclosporine. Potentiation of renal dysfunction may occur with concomitant colchicine and cyclosporine usage. Also, colchicine increases cyclosporine serum concentrations.[5936] Avoidance of colchicine use in patients receiving cyclosporine may be advisable.[5134]

Colchicine and Ethanol
⚠Severity: Moderate

Colchicine may increase the sensitivity to CNS depressants like ethanol. In animals, colchicine depresses the respiratory center. Too much colchicine can cause respiratory arrest.[8783] Ethanol ingestion also increases the risk of adverse gastrointestinal effects developing in patients receiving colchicine, and it also can increase serum urate concentrations, diminishing the antigout effects of the drug.[7152] Advise patients to avoid alcohol.

Hydralazine and Metoprolol
⚠Severity: Moderate

The concomitant administration of hydralazine with diuretics, other antihypertensive agents, or vasodilators can result in additive hypotensive effects.[6035] This interaction can be therapeutically advantageous, but dosages must be adjusted accordingly. Marked hypotensive episodes can result from concomitant administration of diazoxide and hydralazine.[6278] Hydralazine should not be administered within 6 hours of administration of IV diazoxide.[6278]

Metoprolol is an antihypertensive agent, so its effects are additive with other antihypertensive agents.[6714] This interaction is often used advantageously in treating hypertension; however, lower doses of each agent may be necessary. Hypotension can be potentiated when beta-blockers are co-administered with dihydropyridine-type calcium-channel blockers, most notably rapid-release nifedipine. Nicardipine been reported to increase plasma concentrations and oral bioavailability of certain beta-blockers (e.g., metoprolol, propranolol). It is prudent to avoid using beta-blockers with guanethidine, reserpine, or other rauwolfia alkaloids that have a high incidence of orthostatic hypotension due to catecholamine depletion, since beta-blockers will interfere with reflex tachycardia, worsening the orthostasis.[5269]

Hydralazine and Ethanol
⚠Severity: Moderate

Ethanol interacts with antihypertensive agents by potentiating their hypotensive effect.[5944]

Hydralazine and Nitroglycerin (Nitrostat®)
⚠Severity: Moderate

A study of 28 patients with heart failure indicated that concomitant administration of oral hydralazine prevented the development of tolerance to continuous nitroglycerin infusions.[1096]

Nitroglycerin can cause hypotension.[6124] This action may be additive with other agents that can cause hypotension such as antihypertensive agents or other peripheral vasodilators.[6124] Other agents that may also cause hypotension include diuretics; antidepressants; phenothiazines; some antiarrhythmics, such as quinidine or procainamide; benzodiazepines; or opiate agonists. Patients should be monitored more closely for hypotension if nitroglycerin is used concurrently with any of these drugs.

Hydrocortisone (found in Hydrocortisone; Neomycin) **and Aspirin, ASA** (Low Dose Adult Aspirin)
Severity: Moderate

Salicylates or NSAIDs should be used cautiously in patients receiving corticosteroids. While there is controversy regarding the ulcerogenic potential of corticosteroids alone, concomitant administration of corticosteroids with aspirin may increase the GI toxicity of aspirin and other non-acetylated salicylates. Withdrawal of corticosteroids can result in increased plasma concentrations of salicylate and possible toxicity. Concomitant use of corticosteroids may increase the risk of adverse GI events due to NSAIDs.[1162] Although some patients may need to be given corticosteroids and NSAIDs concomitantly, which can be done successfully for short periods of time without sequelae, prolonged coadministration should be avoided.

Corticosteroids enhance the renal clearance of salicylates. Thus, cessation of corticosteroid use may lead to salicylism.[5232] Dose adjustments may be necessary in patients receiving both corticosteroids and aspirin. Also, concomitant administration of corticosteroids with aspirin may increase the GI toxicity of aspirin. Combinations of aspirin with corticosteroids may be just as likely as combinations of nonsalicylate NSAIDs with corticosteroids to cause gastric mucosal injury.[1163]

Hydrocortisone (found in Hydrocortisone; Neomycin) **and Cyclosporine** (Restasis™)
Severity: Low

Because systemically administered corticosteroids exhibit immunosuppressive effects when given in high doses and/or for extended periods [7714], additive effects may be seen with other immunosuppressives or antineoplastic agents. While therapy is designed to take advantage of this effect, patients may be predisposed to over-immunosuppression resulting in an increased risk for the development of severe infections.[7714] Close clinical monitoring is advised with concurrent use; in the presence of serious infections, continuation of the corticosteroid or immunosuppressive agent may be necessary but should be accompanied by appropriate antimicrobial therapies as indicated.

Several interactions have been documented when cyclosporine and corticosteroids are used concomitantly. Cyclosporine can decrease the clearance of prednisolone. Conversely, methylprednisolone has been reported to increase the serum concentrations of cyclosporine. Seizures have been reported in adults and children receiving cyclosporine and high-dose methylprednisolone therapy.[5936] A budesonide dose reduction should be considered, as plasma concentrations of orally administered budesonide may increase during coadministration with CYP3A4 inhibitors; toxicity may occur, particularly excessive HPA-axis suppression. Theoretically, CYP3A4 inhibition may be clinically significant for inhaled forms of budesonide, including budesonide nasal spray.[8629]

Hydrocortisone (found in Hydrocortisone; Neomycin) **and Prednisone**
Severity: Low

Glucocorticoids may interact with cholinesterase inhibitors, including ambenonium, neostigmine, and pyridostigmine, occasionally causing severe muscle weakness in patients with myasthenia gravis.[6762] [7895] Glucocorticoids are occasionally used therapeutically, however, in the treatment of some patients with myasthenia gravis.[7896] In such patients it is recommended that corticosteroid therapy be initiated at low dosages (i.e., 10-25 mg/day of prednisone or equivalent) and with close clinical monitoring. The dosage should be increased gradually as tolerated, with continued careful monitoring of the patient's clinical status.[7895] [7896]

Systemic corticosteroids increase blood glucose levels [4751]; a potential pharmacodynamic interaction exists between corticosteroids and all antidiabetic agents. Diabetic patients who are administered systemic corticosteroid therapy may require an adjustment in the dosing of the antidiabetic agent. Blood lactate concentrations and the lactate to pyruvate ratio increased when metformin was coadministered with corticosteroids (e.g., hydrocortisone). Elevated lactic acid concentrations are associated with an increased risk of lactic acidosis, so patients on metformin concurrently with systemic steroids should be monitored closely.

Because systemically administered corticosteroids exhibit immunosuppressive effects when given in high doses and/or for extended periods [7714], additive effects may be seen with other immunosuppressives or antineoplastic agents. While therapy is designed to take advantage of this effect, patients may be predisposed to over-immunosuppression resulting in an increased risk for the development of severe infections.[7714] Close clinical monitoring is advised with concurrent use; in the presence of serious infections, continuation of the corticosteroid or immunosuppressive agent may be necessary but should be accompanied by appropriate antimicrobial therapies as indicated.

Neomycin (found in Hydrocortisone; Neomycin) **and Aspirin, ASA** (Low Dose Adult Aspirin)
Severity: Low

Other aminoglycosides, amphotericin B, cidofovir [5118], carboplatin, cisplatin [5123], cyclosporine [5132][5133][5134], foscarnet [5106], ganciclovir [5173], pamidronate [7799], salicylates, tacrolimus, methoxyflurane, parenteral vancomycin [5198], and zoledronic acid [6318] should be used cautiously with systemic neomycin because they can increase the risk of nephrotoxicity or ototoxicity.[5062][5063][5068][2305]

Due to the inhibition of renal prostaglandins by salicylates, concurrent use of salicylates and other nephrotoxic agents may lead to additive nephrotoxicity. Also, the plasma salicylic acid concentration is increased by conditions that reduce the glomerular filtration rate or tubular secretion.[7823] Salicylates should be given with caution to patients taking aminoglycosides, amphotericin B, systemic bacitracin, cisplatin, cyclosporine, foscarnet, or parenteral vancomycin. Monitor renal function carefully during concurrent therapy.

Neomycin (found in Hydrocortisone; Neomycin) **and Cyclosporine** (Restasis™)
Severity: Low

Other aminoglycosides, amphotericin B, cidofovir [5118], carboplatin, cisplatin [5123], cyclosporine [5132][5133][5134], foscarnet [5106], ganciclovir [5173], pamidronate [7799], salicylates, tacrolimus, methoxyflurane, parenteral vancomycin [5198], and zoledronic acid [6318] should be used cautiously with systemic neomycin because they can increase the risk of nephrotoxicity or ototoxicity.[5062][5063][5068][2305]

Cyclosporine should be used cautiously with nephrotoxic drugs, as cyclosporine itself can cause structural kidney damage.[5134] Additive nephrotoxicity can occur if cyclosporine is administered with other nephrotoxic drugs such as amphotericin B [5936], acyclovir, adefovir [5516], aminoglycosides (i.e., amikacin, gentamicin, kanamycin, streptomycin, and tobramycin) [5132] [5133] [5134], systemic bacitracin, cisplatin [5123], foscarnet [5106], cimetidine [5936], systemic polymyxin B [5177], ganciclovir [5173], pamidronate [7799], zoledronic acid [6318], and vancomycin [5936]. Because the systemic absorption of neomycin and oral paromomycin is minimal, the risk of nephrotoxicity or ototoxicity is expected to be low, but combined use should still be approached with caution. Use of cyclosporine can aggravate the nephrotoxicity and electrolyte loss seen with cisplatin if given concurrently or shortly after cisplatin therapy.[5123] Systemic polymyxin B should not be used concurrently or sequentially with other drugs that have the potential for nephrotoxicity or neurotoxicity.[5177] Monitor renal function and fluid status carefully during cyclosporine usage.

Levothyroxine and Hydrocortisone (found in Hydrocortisone; Neomycin)
Severity: Low

The metabolism of corticosteroids and corticotropin (ACTH) are increased in patients with hyperthyroidism and decreased in patients with hypothyroidism. Additionally, short-term administration of large corticosteroid doses (i.e., dexamethasone) may decrease serum T3 concentrations by 30%, and long-term corticosteroid therapy may result in decreased thyroid binding globulin production, causing slightly decreased T3 and T4 concentrations.[5178] Therefore, caution should be taken when initiating, changing or discontinuing thyroid agents.

Levothyroxine and Metoprolol
Severity: Low

Because thyroid hormones cause cardiac stimulation including increased heart rate and increased contractility [5178], the effects of beta-blockers may be reduced by thyroid hormones. The reduction of effects may be especially evident when a patient goes from a hypothyroid to a euthyroid state or when excessive amounts of thyroid hormone is given to the patient. In addition, because liothyronine (T3) has more pronounced cardiovascular side effects when compared to levothyroxine (T4), the effects on beta-blockers may be more common in patients treated with liothyronine.[6268]

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Levothyroxine and Prednisone
Severity: Low

The metabolism of corticosteroids and corticotropin (ACTH) are increased in patients with hyperthyroidism and decreased in patients with hypothyroidism. Additionally, short-term administration of large corticosteroid doses (i.e., dexamethasone) may decrease serum T3 concentrations by 30%, and long-term corticosteroid therapy may result in decreased thyroid binding globulin production, causing slightly decreased T3 and T4 concentrations.[5178] Therefore, caution should be taken when initiating, changing or discontinuing thyroid agents.

The metabolism of corticosteroids is increased in hyperthyroidism and decreased in hypothyroidism.[6524] Dosage adjustments may be necessary when initiating, changing or discontinuing thyroid hormones or antithyroid agents.

Levothyroxine and Triamcinolone
Severity: Low

The metabolism of corticosteroids and corticotropin (ACTH) are increased in patients with hyperthyroidism and decreased in patients with hypothyroidism. Additionally, short-term administration of large corticosteroid doses (i.e., dexamethasone) may decrease serum T3 concentrations by 30%, and long-term corticosteroid therapy may result in decreased thyroid binding globulin production, causing slightly decreased T3 and T4 concentrations.[5178] Therefore, caution should be taken when initiating, changing or discontinuing thyroid agents.

Levothyroxine and Budesonide; Formoterol (Symbicort)
Severity: Low

The metabolism of corticosteroids and corticotropin (ACTH) are increased in patients with hyperthyroidism and decreased in patients with hypothyroidism. Additionally, short-term administration of large corticosteroid doses (i.e., dexamethasone) may decrease serum T3 concentrations by 30%, and long-term corticosteroid therapy may result in decreased thyroid binding globulin production, causing slightly decreased T3 and T4 concentrations.[5178] Therefore, caution should be taken when initiating, changing or discontinuing thyroid agents.

Based on the cardiovascular stimulatory effects of sympathomimetic drugs like budesonide; formoterol [6289], the concomitant use of other sympathomimetics and thyroid hormones can enhance the effects on the cardiovascular system.[9798] Patients with coronary artery disease have an increased risk of coronary insufficiency from either agent. Combined use of these agents may further increase this risk.

Levothyroxine and Cyclosporine (Restasis™)
Severity: Moderate

Serum trough cyclosporine concentrations appear to be reduced by concurrent oral cyclosporine and levothyroxine use. Among 10 patients who took Neoral® capsules twice daily for at least a year and oral levothyroxine 100 mcg daily for at least 3 months, the trough serum cyclosporine concentration was significantly lower as compared with values from 30 patients who only took cyclosporine. The mechanism of the interaction may be decreased oral cyclosporine absorption due to P-glycoprotein induction by levothyroxine.[9504] Cyclosporine is a substrate of P-glycoprotein, and levothyroxine appears to be an inducer of P-glycoprotein.[4718] [9508] In patients who take oral cyclosporine, carefully monitor cyclosporine concentrations with levothyroxine initiation or discontinuation.

Levothyroxine and food
Severity: Very High. This drug combination should be avoided.

Certain foods and enteral feedings can inhibit the absorption of thyroid hormones.[5178] To minimize the risk of an interaction, thyroid hormones should be administered on an empty stomach at least 30-60 minutes prior to food or enteral feedings. Foods that may decrease thyroid hormone absorption include soybean flour and soy-based infant formulas or enteral feedings, as well as high fiber diets, cottonseed meal and walnuts. In addition to decreasing the absorption of thyroid hormones, limited data indicate that soy containing foods and supplements may also influence thyroid physiology. Concentrated soy isoflavones (e.g., genistein and daidzein) may interfere with thyroid peroxidase catalyzed iodination of thyroglobulin, resulting in a decreased production of thyroid hormones and an increased secretion of TSH endogenously.[3045] More studies are required to assess the exact mechanism of this interaction. Caution should be used in administering soy isoflavone supplements concurrently with thyroid hormones.[5178]

Levothyroxine and enteral feedings
Severity: Very High. This drug combination should be avoided.

Certain foods and enteral feedings can inhibit the absorption of thyroid hormones.[5178] To minimize the risk of an interaction, thyroid hormones should be administered on an empty stomach at least 30-60 minutes prior to food or enteral feedings. Foods that may decrease thyroid hormone absorption include soybean flour and soy-based infant formulas or enteral feedings, as well as high fiber diets, cottonseed meal and walnuts. In addition to decreasing the absorption of thyroid hormones, limited data indicate that soy containing foods and supplements may also influence thyroid physiology. Concentrated soy isoflavones (e.g., genistein and daidzein) may interfere with thyroid peroxidase catalyzed iodination of thyroglobulin, resulting in a decreased production of thyroid hormones and an increased secretion of TSH endogenously.[3045] More studies are required to assess the exact mechanism of this interaction. Caution should be used in administering soy isoflavone supplements concurrently with thyroid hormones.[5178]

Aspirin, ASA (Low Dose Adult Aspirin) **and Cyclosporine** (Restasis™)

Severity: Low

Due to the inhibition of renal prostaglandins by salicylates, concurrent use of salicylates and other nephrotoxic agents may lead to additive nephrotoxicity. Also, the plasma salicylic acid concentration is increased by conditions that reduce the glomerular filtration rate or tubular secretion.[7823] Salicylates should be given with caution to patients taking aminoglycosides, amphotericin B, systemic bacitracin, cisplatin, cyclosporine, foscarnet, or parenteral vancomycin. Monitor renal function carefully during concurrent therapy.

Due to aspirin's effect on platelet aggregation and GI mucosa, aspirin should be used cautiously in patients with thrombocytopenia following treatment with antineoplastic agents due to an increased risk of bleeding.[5717] In general, because certain antineoplastic agents can cause clinically significant thrombocytopenia, they may increase the risk of aspirin-associated bleeding (i.e. GI bleeding, inhibited platelet aggregation, and prolonged bleeding time). Also, aspirin may mask signs of infection such as fever and pain in patients following treatment with antineoplastic agents or immunosuppressives.[6859] Aspirin, ASA should be used with caution in patients receiving immunosuppressive therapy. Although usually seen with large salicylate doses, aspirin may displace mercaptopurine, 6-MP from secondary binding sites, resulting in bone marrow toxicities and blood dyscrasias.[5232] Special consideration should be given to myelosuppressed patients prior to receiving aspirin.

Nonsteroidal antiinflammatory drugs (NSAIDs) may mask fever, pain, swelling and other signs and symptoms of an infection; use NSAIDs with caution in patients receiving immunosuppressants such as cyclosporine.[5046] Significant interactions may occur between cyclosporine and NSAIDs.[5134] Clinical status and serum creatinine and potassium concentrations should be closely monitored when cyclosporine is given with salicylates or other nonsteroidal antiinflammatory drugs (NSAIDs).[5134] Renal dysfunction associated with cyclosporine may be potentiated by concurrent usage of diclofenac, naproxen, or sulindac.[5936] Potentiation of renal dysfunction may especially occur in a dehydrated patient. Although concomitant administration of diclofenac does not affect cyclosporine blood concentrations, a doubling of diclofenac blood concentrations and occasional reports of reversible decreases in renal function have been noted. Consequently, the dose of diclofenac should be in the lower end of the therapeutic range.[5936] The mechanism of the interaction may be inhibition of diclofenac metabolism, as diclofenac is a substrate for and cyclosporine an inhibitor of CYP3A4.[4718] Increased tear production was not seen in patients receiving ophthalmic NSAIDs or using punctual plugs concurrently with cyclosporine ophthalmic emulsion.

Aspirin, ASA (Low Dose Adult Aspirin) **and Metoprolol**
Severity: Moderate

The efficacy of selected antihypertensive agents needs to be carefully assessed during aspirin usage. During antihypertensive therapy with beta-blockers, high concentrations of vasodilatory prostaglandins are produced in response to reflex-mediated pressor mechanisms (e.g., sympathetic tone). Concurrent use of beta-blockers with aspirin may result in loss of antihypertensive activity due to inhibition of renal prostaglandins and thus, salt and water retention and decreased renal blood flow.[5717] Aspirin can increase the risk of renal insufficiency in patients receiving diuretics, secondary to the effects of aspirin on renal blood flow. Aspirin inhibits renal prostaglandin production, which causes salt and water retention and decreased renal blood flow. Thus, the effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin.[5717] Aspirin may decrease the hyperuricemic effect of thiazide diuretics (e.g., hydrochlorothiazide) or loop diuretics like furosemide. Concomitant use of aspirin and potassium-sparing diuretics, such as triamterene or spironolactone, may cause hyperkalemia.[5717] The hyponatremic and hypotensive effects of angiotensin-converting enzyme (ACE) inhibitors may be diminished by concurrent use of aspirin; the inhibition of cyclooxygenase by aspirin prevents the formation of vasodilatory prostaglandins.[5717] Furthermore, reduced renal blood flow is expected from the decreased pressure gradient created in the glomeruli when aspirin is used with an ACE inhibitor.[5718] Low-dose aspirin (e.g., 81 mg/day) may be less likely to attenuate the antihypertensive or cardioprotective effects of ACE inhibitors; however, the dose-related effect is controversial.[6439] The established benefits of using low-dose aspirin in combination with an ACE inhibitor in patients with ischemic heart disease and left ventricular dysfunction generally outweigh concerns, especially with appropriate renal function and serum potassium monitoring.[5718] [6060] [6439] Monitor the patient's blood pressure, renal function, and clinical status for the desired responses and adjust therapy accordingly.

During antihypertensive therapy with beta-blockers, high concentrations of vasodilatory prostaglandins are produced in response to reflex-mediated pressor mechanisms (e.g., sympathetic tone). Concurrent use of beta-blockers with aspirin and other salicylates may result in loss of antihypertensive activity due to inhibition of renal prostaglandins and thus, salt and water retention and decreased renal blood flow.[5717]

Aspirin, ASA (Low Dose Adult Aspirin) **and Prednisone**
Severity: Moderate

Corticosteroids enhance the renal clearance of salicylates. Thus, cessation of corticosteroid use may lead to salicylism.[5232] Dose adjustments may be necessary in patients receiving both corticosteroids and aspirin. Also, concomitant administration of corticosteroids with aspirin may increase the GI toxicity of aspirin. Combinations of aspirin with corticosteroids may be just as likely as combinations of nonsalicylate NSAIDs with corticosteroids to cause gastric mucosal injury.[1163]

Due to aspirin's effect on platelet aggregation and GI mucosa, aspirin should be used cautiously in patients with thrombocytopenia following treatment with antineoplastic agents due to an increased risk of bleeding.[5717] In general, because certain antineoplastic agents can cause clinically significant thrombocytopenia, they may increase the risk of aspirin-associated bleeding (i.e. GI bleeding, inhibited platelet aggregation, and prolonged bleeding time). Also, aspirin may mask signs of infection such as fever and pain in patients following treatment with antineoplastic agents or immunosuppressives.[6859] Aspirin, ASA should be used with caution in patients receiving immunosuppressive therapy. Although usually seen with large salicylate doses, aspirin may displace mercaptopurine, 6-MP from secondary binding sites, resulting in bone marrow toxicities and blood dyscrasias.[5232] Special consideration should be given to myelosuppressed patients prior to receiving aspirin.

Salicylates or NSAIDs should be used cautiously in patients receiving corticosteroids. While there is controversy regarding the ulcerogenic potential of corticosteroids alone, concomitant administration of corticosteroids with aspirin may increase the GI toxicity of aspirin and other non-acetylated salicylates. Withdrawal of corticosteroids can result in increased plasma concentrations of salicylate and possible toxicity. Concomitant use of corticosteroids may increase the risk of adverse GI events due to NSAIDs.[1162] Although some patients may need to be given corticosteroids and NSAIDs concomitantly, which can be done successfully for short periods of time without sequelae, prolonged coadministration should be avoided.

Aspirin, ASA (Low Dose Adult Aspirin) **and Triamcinolone**
⚠Severity: Moderate

Corticosteroids enhance the renal clearance of salicylates. Thus, cessation of corticosteroid use may lead to salicylism.[5232] Dose adjustments may be necessary in patients receiving both corticosteroids and aspirin. Also, concomitant administration of corticosteroids with aspirin may increase the GI toxicity of aspirin. Combinations of aspirin with corticosteroids may be just as likely as combinations of nonsalicylate NSAIDs with corticosteroids to cause gastric mucosal injury.[1163]

Salicylates or NSAIDs should be used cautiously in patients receiving corticosteroids. While there is controversy regarding the ulcerogenic potential of corticosteroids alone, concomitant administration of corticosteroids with aspirin may increase the GI toxicity of aspirin and other non-acetylated salicylates. Withdrawal of corticosteroids can result in increased plasma concentrations of salicylate and possible toxicity. Concomitant use of corticosteroids may increase the risk of adverse GI events due to NSAIDs.[1162] Although some patients may need to be given corticosteroids and NSAIDs concomitantly, which can be done successfully for short periods of time without sequelae, prolonged coadministration should be avoided.

Aspirin, ASA (Low Dose Adult Aspirin) **and Clopidogrel** (Plavix®)
⚠Severity: High

Use caution in combining aspirin therapy with other platelet inhibitors due to the potential for additive effects; patients should be monitored for an increased risk of bleeding when aspirin is combined with other platelet inhibitors. Some combinations are therapeutic. For example, the results of the CHARISMA trial, a study that enrolled > 15,000 patients and randomized patients to either clopidogrel plus low-dose aspirin or low-dose aspirin alone, indicate that combination antiplatelet therapy, in patients with established cardiovascular disease, significantly reduces the risk of recurrent myocardial infarction, stroke, or cardiovascular death by 12.5% when compared to aspirin therapy alone (n= 12,153; p=0.046). However, in patients without established cardiovascular disease, combination antiplatelet therapy is associated with a nonsignificant trend towards an increased risk of adverse outcomes (n=3284; 20% increased relative risk for combination therapy, p=0.22). Specifically, in this subgroup of patients, there is an increase in cardiovascular mortality as well as a nonsignificant increase in bleeding. The risk of bleeding is not increased with the use of combination therapy in those patients with established cardiovascular disease.[8833] Until more data are available, it may be prudent to avoid using clopidogrel and aspirin combination therapy in patients that do not have established cardiovascular disease. Also, aspirin should not be used in combination with ticlopidine for > 30 days, as safety and efficacy have not been established.

Theoretically feverfew, Tanacetum parthenium may enhance the effects of the platelet inhibitors (including aspirin, ASA) via inhibition of platelet aggregation or via antithrombotic activity.[2913] [2914] [2915] Feverfew also inhibits the secretion of various substances (e.g., arachidonic acid, and serotonin) from the platelet.[1797] In theory, concurrent use may increase the risk of bleeding. Clinical interactions have not yet been reported; however, avoidance of the use of feverfew during antiplatelet therapy seems prudent.[5314]

Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other drugs that affect hemostasis such as platelet inhibitors.[5164] Ticlopidine and clopidogrel inhibit platelets via the same mechanism [5165] [5166]; combination therapy would therefore be illogical. Because clopidogrel and cilostazol cause platelet inhibition through different mechanisms [5165] [5167], clinical evaluation may reveal that the combined use of these two drugs is both safe and effective; currently such evidence is lacking and combination therapy should be used with caution, if at all, as the magnitude of increased risk of bleeding is unknown. The manufacturers of cilostazol have indicated that studies are planned to determine the pharmacodynamic effects of clopidogrel and cilostazol combination therapy. Dipyridamole and clopidogrel also cause platelet inhibition via different mechanisms [5168]; however, their combined use has not been formally evaluated in clinical trials. The increased risk of bleeding is not known at this time and combined use should be avoided until data supporting safety and efficacy are known.

Concomitant administration of clopidogrel and aspirin (500 mg twice daily for 1 day) did not significantly increase bleeding time prolongation induced by clopidogrel. However, clopidogrel does potentiate the effect of aspirin on collagen-induced platelet aggregation.[5165] In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and clopidogrel has not been shown to be more effective than clopidogrel alone; however, the incidence of major bleeding (i.e., bleeding that was substantially disabling, intraocular, or required >= 2 units of transfused blood) is more common with combination therapy. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia [5170], an additional risk factor for bleeding. The CHARISMA trial, a study that enrolled > 15,000 patients with established or at risk for cardiovascular disease, randomized patients to either clopidogrel plus low-dose aspirin or low-dose aspirin alone. The findings from this trial indicate that combination antiplatelet therapy does not reduce the risk of MI, stroke, or CV death; furthermore, combination therapy is associated with an increased risk of moderate bleeding (rate of 2.1% in the combination therapy group vs. 1.3% in the placebo group, p<0.001), but not severe bleeding. Data from a subgroup analysis of patients with established cardiovascular disease, which should be interpreted with caution, indicate that combination antiplatelet therapy reduces the relative risk of recurrent myocardial infarction, stroke, or cardiovascular death by 12.5% when compared to aspirin therapy alone (n=12,153; p=0.046). However, in patients without established cardiovascular disease, but who have risk factors for cardiovascular disease including diabetes mellitus, hypertension, or hypercholesterolemia, combination antiplatelet therapy is not associated with a difference in clinical outcomes and may be associated with an increase in cardiovascular death.[8833] More data are needed to determine the role of combination antiplatelet therapy in patients with established cardiovascular disease; however, it may be prudent to avoid using clopidogrel and aspirin combination therapy in patients that do not have established cardiovascular disease. Regardless of the indication, patients receiving both aspirin and clopidogrel should be monitored for an increased risk of bleeding.

Aspirin, ASA (Low Dose Adult Aspirin) **and Budesonide; Formoterol** (Symbicort)
Severity: Moderate

Corticosteroids enhance the renal clearance of salicylates. Thus, cessation of corticosteroid use may lead to salicylism.[5232] Dose adjustments may be necessary in patients receiving both corticosteroids and aspirin. Also, concomitant administration of corticosteroids with aspirin may increase the GI toxicity of aspirin. Combinations of aspirin with corticosteroids may be just as likely as combinations of nonsalicylate NSAIDs with corticosteroids to cause gastric mucosal injury.[1163]

Aspirin, ASA (Low Dose Adult Aspirin) **and Ethanol**
Severity: High

Ethanol can cause an increased risk of gastric irritation and GI mucosal bleeding when given with aspirin, as both ethanol and aspirin are mucosal irritants and aspirin decreases platelet aggregation. Patients that consume 3 or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.[5717] Administration of aspirin should be limited or avoided altogether in patients with alcoholism or who consume ethanol regularly. Chronic alcoholism is often associated with hypoprothrombinemia, which increases the risk of aspirin-induced bleeding.

Concomitant ingestion of ethanol with NSAIDs or salicylates, especially aspirin, ASA, increases the risk of developing gastric irritation and GI mucosal bleeding.[7181] Ethanol and salicylates are mucosal irritants and NSAIDs and aspirin decrease platelet aggregation. Routine ingestion of ethanol and aspirin or NSAIDs can cause significant GI bleeding, which may or may not be overt. Even occasional concomitant use of NSAIDs or salicylates and ethanol should be avoided. Chronic alcoholism is often associated with hypoprothrombinemia and this condition increases the risk of salicylate-induced bleeding. Patients should be warned regarding for potential increased risk of GI bleeding if alcohol-containing beverages are taken concurrently with salicylates or NSAIDs.

Metoprolol and Ethanol
Severity: Moderate

Acute alcohol consumption lowers blood pressure; ethanol may interact with antihypertensive agents by potentiating their hypotensive effect.[5944]

Nitroglycerin (Nitrostat®) **and Amlodipine**
Severity: Moderate

In vitro studies have not shown any effect of amlodipine on the protein binding of digoxin, phenytoin, warfarin and indomethacin.[5825] Coadministration of amlodipine with digoxin did not affect serum digoxin concentrations or digoxin renal clearance in normal volunteers.[5825] Prothrombin time is not altered when amlodipine is given to patients receiving warfarin therapy.[5825] Concurrent administration of amlodipine did not alter the pharmacokinetics of atorvastatin (80 mg/day) or ethanol.[5825] Coadministration of cimetidine or aluminum hydroxide; magnesium hydroxide with amlodipine did not change the pharmacokinetics of amlodipine.[5825] In clinical trials, amlodipine has been safely administered with warfarin, digoxin, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, antibiotics, oral hypoglycemic agents, thiazide diuretics, and beta-adrenergic blocking agents.[5825]

Nitroglycerin can cause hypotension.[6124] This action may be additive with other agents that can cause hypotension such as antihypertensive agents or other peripheral vasodilators.[6124] Other agents that may also cause hypotension include diuretics; antidepressants; phenothiazines; some antiarrhythmics, such as quinidine or procainamide; benzodiazepines; or opiate agonists. Patients should be monitored more closely for hypotension if nitroglycerin is used concurrently with any of these drugs.

Nitroglycerin (Nitrostat®) **and Bumetanide** (Bumex®)
Severity: Moderate

Nitroglycerin can cause hypotension.[6124] This action may be additive with other agents that can cause hypotension such as antihypertensive agents or other peripheral vasodilators.[6124] Other agents that may also cause hypotension include diuretics; antidepressants; phenothiazines; some antiarrhythmics, such as quinidine or procainamide; benzodiazepines; or opiate agonists. Patients should be monitored more closely for hypotension if nitroglycerin is used concurrently with any of these drugs.

Nitroglycerin (Nitrostat®) **and Clonazepam**
Severity: Low

Nitroglycerin can cause hypotension.[6124] This action may be additive with other agents that can cause hypotension such as antihypertensive agents or other peripheral vasodilators.[6124] Other agents that may also cause hypotension include diuretics; antidepressants; phenothiazines; some antiarrhythmics, such as quinidine or procainamide; benzodiazepines; or opiate agonists. Patients should be monitored more closely for hypotension if nitroglycerin is used concurrently with any of these drugs.

Nitroglycerin (Nitrostat®) **and Clonidine**
Severity: Moderate

Nitroglycerin can cause hypotension.[6124] This action may be additive with other agents that can cause hypotension such as antihypertensive agents or other peripheral vasodilators.[6124] Other agents that may also cause hypotension include diuretics; antidepressants; phenothiazines; some antiarrhythmics, such as quinidine or procainamide; benzodiazepines; or opiate agonists. Patients should be monitored more closely for hypotension if nitroglycerin is used concurrently with any of these drugs.

Nitroglycerin (Nitrostat®) **and Metoprolol**
Severity: Moderate

Nitroglycerin can cause hypotension.[6124] This action may be additive with other agents that can cause hypotension such as antihypertensive agents or other peripheral vasodilators.[6124] Other agents that may also cause hypotension include diuretics; antidepressants; phenothiazines; some antiarrhythmics, such as quinidine or procainamide; benzodiazepines; or opiate agonists. Patients should be monitored more closely for hypotension if nitroglycerin is used concurrently with any of these drugs.

Nitroglycerin (Nitrostat®) **and Ethanol**
Severity: High

Although it has not been demonstrated clinically, the combination of ethanol [5944] and nitroglycerin [6124] could theoretically produce additive vasodilation, possibly leading to cardiovascular collapse. Unless the physician is aware of the patient's ethanol use, this cardiovascular collapse may be incorrectly attributed to coronary insufficiency or occlusion. Patients receiving nitroglycerin should be advised to use ethanol with caution.[6124] Clinicians should note that many intravenous preparations of nitroglycerin contain ethanol.

Prednisone and Cyclosporine (Restasis™)
Severity: Low

Ranitidine may potentiate renal dysfunction associated with cyclosporine.[5134] As determined by a retrospective review, a cardiac allograft recipient taking ranitidine, cyclosporine, and prednisone developed renal failure requiring dialysis. Both the blood urea nitrogen and serum creatinine concentrations returned to pretreatment concentrations within 2 weeks of ranitidine discontinuation.[10990] However, a prospective evaluation did not find an effect of ranitidine on renal function. Among 9 patients with a renal allograft taking cyclosporine and prednisone, the mean inulin clearance, creatinine clearance, and serum creatinine concentrations were similar during receipt of ranitidine 150 mg PO twice daily and 2 weeks after ranitidine discontinuation. Plasma cyclosporine concentrations with or without ranitidine were also similar.[10989] Cautious use of ranitidine and cyclosporine is warranted; cyclosporine can cause nephrotoxicity (see Adverse Reactions), and ranitidine is substantially excreted by the kidney. The risk of toxic reactions to ranitidine may be greater in patients with impaired renal function; ranitidine dose reduction is needed for renal impairment (see ranitidine monograph).

Because systemically administered corticosteroids exhibit immunosuppressive effects when given in high doses and/or for extended periods [7714], additive effects may be seen with other immunosuppressives or antineoplastic agents. While therapy is designed to

take advantage of this effect, patients may be predisposed to over-immunosuppression resulting in an increased risk for the development of severe infections.[7714] Close clinical monitoring is advised with concurrent use; in the presence of serious infections, continuation of the corticosteroid or immunosuppressive agent may be necessary but should be accompanied by appropriate antimicrobial therapies as indicated.

Several interactions have been documented when cyclosporine and corticosteroids are used concomitantly. Cyclosporine can decrease the clearance of prednisolone. Conversely, methylprednisolone has been reported to increase the serum concentrations of cyclosporine. Seizures have been reported in adults and children receiving cyclosporine and high-dose methylprednisolone therapy.[5936] A budesonide dose reduction should be considered, as plasma concentrations of orally administered budesonide may increase during coadministration with CYP3A4 inhibitors; toxicity may occur, particularly excessive HPA-axis suppression. Theoretically, CYP3A4 inhibition may be clinically significant for inhaled forms of budesonide, including budesonide nasal spray.[8629]

Do not administer cyclosporine with other immunosuppressives with the exception of adrenal corticosteroids.[5936] For example, cyclosporine should not be used in patients undergoing radiation therapy, such as PUVA or UVB.[5936] Because cyclosporine is an immunosuppressant, additive affects may be seen with other immunosuppressives or antineoplastic agents. While therapy is designed to take advantage of this effect, patients may be predisposed to over-immunosuppression resulting in an increased risk for the development of severe infections, malignancies including lymphoma and leukemia, myelodysplastic syndromes, and lymphoproliferative disorders. The risk is related to the intensity and duration of immunosuppression rather than the specific agents.

Cyclosporine (Restasis™) **and Triamcinolone**
⚠Severity: Moderate

Several interactions have been documented when cyclosporine and corticosteroids are used concomitantly. Cyclosporine can decrease the clearance of prednisolone. Conversely, methylprednisolone has been reported to increase the serum concentrations of cyclosporine. Seizures have been reported in adults and children receiving cyclosporine and high-dose methylprednisolone therapy.[5936] A budesonide dose reduction should be considered, as plasma concentrations of orally administered budesonide may increase during coadministration with CYP3A4 inhibitors; toxicity may occur, particularly excessive HPA-axis suppression. Theoretically, CYP3A4 inhibition may be clinically significant for inhaled forms of budesonide, including budesonide nasal spray.[8629]

Because systemically administered corticosteroids exhibit immunosuppressive effects when given in high doses and/or for extended periods [7714], additive effects may be seen with other immunosuppressives or antineoplastic agents. While therapy is designed to take advantage of this effect, patients may be predisposed to over-immunosuppression resulting in an increased risk for the development of severe infections.[7714] Close clinical monitoring is advised with concurrent use; in the presence of serious infections, continuation of the corticosteroid or immunosuppressive agent may be necessary but should be accompanied by appropriate antimicrobial therapies as indicated.

Cyclosporine (Restasis™) **and Budesonide; Formoterol** (Symbicort)
⚠Severity: Moderate

Due to CYP3A inhibition, ketoconazole may enhance the cortisol suppression associated with budesonide administered via inhalation.[5006] [6865] Use caution when budesonide; formoterol is coadministered with drugs that inhibit CYP3A enzymes.[9798] Toxicity may occur, particularly excessive HPA-axis suppression. Inhibition of CYP3A4 may be clinically significant for inhaled forms of budesonide.[8629] Other drugs known to inhibit CYP3A enzymes include aprepitant [7438], clarithromycin [4964], cyclosporine [4718], danazol [4718], delavirdine [5206] [5492], diltiazem [6192], erythromycin [4978], fluconazole [5405], fluoxetine [5738] [5928], fluvoxamine [5635], indinavir [5462], isoniazid, INH [4930], itraconazole [5005], mibefradil [6556], nefazodone [5414], nelfinavir [5572], nicardipine [4718], norfloxacin [6866], quinidine [4976], ritonavir [5044], saquinavir [5192], troleandomycin [4718], verapamil [4718], voriconazole [4882] [6646], and zafirlukast [4948]. Additionally, both macrolide antibiotics (i.e., clarithromycin, erythromycin) listed above are known to prolong the QT interval and should be used with caution in combination with budesonide; formoterol. Although formoterol is metabolized by several CYP450 isoenzymes, the potential for drug interactions is limited due to extremely low plasma levels of budesonide; formoterol after inhalation.

Several interactions have been documented when cyclosporine and corticosteroids are used concomitantly. Cyclosporine can decrease the clearance of prednisolone. Conversely, methylprednisolone has been reported to increase the serum concentrations of cyclosporine. Seizures have been reported in adults and children receiving cyclosporine and high-dose methylprednisolone therapy.[5936] A budesonide dose reduction should be considered, as plasma concentrations of orally administered budesonide may increase during coadministration with CYP3A4 inhibitors; toxicity may occur, particularly excessive HPA-axis suppression. Theoretically, CYP3A4 inhibition may be clinically significant for inhaled forms of budesonide, including budesonide nasal spray.[8629]

Cyclosporine (Restasis™) **and Ethanol**
⚠Severity: High

Although the effects probably do not involve the ethanol content of red wine, in vitro data suggest that red wine may interact with cytochrome P450 and/or P-glycoprotein. In one small cross-over study when compared with water, 12 oz. of red wine (a merlot) increased the oral clearance of cyclosporine (Non-modified) by 50%. The peak concentration and AUC were also significantly affected (decreased 38% and 30%, respectively). The elimination half-life of cyclosporine was not affected, suggesting that red wine decreased cyclosporine absorption. In vitro, the solubility of cyclosporine (Non-modified) in red wine appeared less than in water. It should be noted that these results may not extrapolate to cyclosporine (Modified) formulations.[3669]

Cyclosporine (Restasis™) **and food**
⚠Severity: High

The oral bioavailability of cyclosporine (Non-modified) is highly variable and food interactions are possible. Administration with high-fat content meals increases both cyclosporine (Non-modified) bioavailability and cyclosporine clearance; however, the AUC does not change significantly. Cyclosporine (Non-modified) appears to be more significantly affected by a high-fat meal than cyclosporine (Modified).[1567] In general, food will decrease the absorption of cyclosporine (Modified). It is important to take cyclosporine consistently with or without food to ensure uniform cyclosporine concentrations.[5936]

Cyclosporine (Restasis™) **and grapefruit juice**
⚠Severity: High

Grapefruit juice inhibits the enterocyte CYP3A4 isoenzyme and increases cyclosporine serum concentrations. Thus, grapefruit and grapefruit juice consumption by patients receiving cyclosporine should be avoided.[5936] Grapefruit juice contains compounds that can inhibit P-450 isozymes and the p-glycoproteins lining the intestinal wall. Administration of either formulation of cyclosporine with grapefruit juice significantly increased cyclosporine concentrations and AUC compared to administration with either orange juice or water. Separating dose of grapefruit juice from cyclosporine may not eliminate the interaction completely, as the inhibitory effect of grapefruit juice can last for several hours. Patients stabilized on cyclosporine should avoid large changes (i.e., either increases or decreases) in their daily intake of grapefruit juice. Do not mix cyclosporine oral solution with grapefruit juice.

Budesonide; Formoterol (Symbicort) **and Albuterol** (Ventolin® HFA)
⚠Severity: High

Systemic corticosteroids increase blood glucose concentrations [4751]; a potential pharmacodynamic interaction exists between corticosteroids and all antidiabetic agents. Doses of the related beta-2 adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.[9798] Additionally, a report of an elderly patient receiving high dose budesonide (2 mg/day) administered by metered dose inhaler developed increased glycosuria during weeks 1-6 of therapy. An increase in HbA1c to 8.2% at the end of week 5 followed by a fall to 7.4% at the end of week 15 occurred. With a gradual reduction of the budesonide dose, the patients diabetic control returned and no deterioration of asthmas control was observed.[9799] Although the dose of budesonide used in this report is well above the recommended dose of budesonide from this combination product, patients receiving antidiabetic agents and budesonide; formoterol may require an adjustment in the dosing of the antidiabetic agent.

If asthma symptoms occur between budesonide; formoterol controller doses, short-acting beta-2 agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5038] When beginning treatment with budesonide; formoterol, patients who have been taking inhaled, short-acting beta-2 agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta-2 agonist use is a signal of deteriorating asthma. Due to the pharmacology of formoterol [5038], the concomitant use of formoterol with other long-acting beta-agonists (e.g., salmeterol-containing products [5197]) is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should be used when budesonide; formoterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects based on the pharmacology of formoterol.[9798]

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta-2 agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5197] [5262] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta-2 agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta-2 agonist use is a signal of deteriorating asthma. Due to the pharmacology of albuterol [5262], the concomitant use of albuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when albuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5262]

Corticosteroids [3085] may aggravate the potential hypokalemic effects seen with beta-agonists.[5197] Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with corticosteroid therapy.

Budesonide; Formoterol (Symbicort) **and Metoprolol**
Severity: High

Formoterol and beta-blockers are pharmacologic opposites, and will counteract each other when given concomitantly.[5038] Beta-blockers may also lead to severe bronchospasm in asthmatic patients.[5038] Concurrent use of beta-blockers and budesonide; formoterol should be avoided. However, if no acceptable alternative exists, a cardioselective beta-blocker (examples: atenolol, metoprolol) may be used with caution.[9798]

Budesonide; Formoterol (Symbicort) **and grapefruit juice**
Severity: High

Grapefruit juice is an inhibitor of gut mucosal CYP3A4a and roughly doubles the bioavailability of oral budesonide [6865]; however, administration with orally inhaled budesonide; formoterol is not expected to cause significant changes in absorption.

Triamcinolone and Prednisone
Severity: Low

Glucocorticoids may interact with cholinesterase inhibitors, including ambenonium, neostigmine, and pyridostigmine, occasionally causing severe muscle weakness in patients with myasthenia gravis.[6524] [6763] [6776] [7895] Glucocorticoids are occasionally used therapeutically, however, in the treatment of some patients with myasthenia gravis.[7896] In such patients it is recommended that corticosteroid therapy be initiated at low dosages (i.e., 10-25 mg/day of prednisone or equivalent) and with close clinical monitoring. The dosage should be increased gradually as tolerated, with continued careful monitoring of the patient's clinical status.[7895] [7896]

Because systemically administered corticosteroids exhibit immunosuppressive effects when given in high doses and/or for extended periods [7714], additive effects may be seen with other immunosuppressives or antineoplastic agents. While therapy is designed to take advantage of this effect, patients may be predisposed to over-immunosuppression resulting in an increased risk for the development of severe infections.[7714] Close clinical monitoring is advised with concurrent use; in the presence of serious infections, continuation of the corticosteroid or immunosuppressive agent may be necessary but should be accompanied by appropriate antimicrobial therapies as indicated.

Albuterol (Ventolin® HFA) **and Hydrocortisone** (found in Hydrocortisone; Neomycin)
Severity: Moderate

Corticosteroids [3085] may aggravate the potential hypokalemic effects seen with beta-agonists.[5197] Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with corticosteroid therapy.

Albuterol (Ventolin® HFA) **and Levothyroxine**
Severity: Moderate

Based on the cardiovascular stimulatory effects of sympathomimetic drugs,[6289] the concomitant use of sympathomimetics and thyroid hormones can enhance the effects on the cardiovascular system. Patients with coronary artery disease have an increased risk of coronary insufficiency from either agent. Combined use of these agents may further increase this risk.

Albuterol (Ventolin® HFA) **and Metoprolol**
Severity: High

Albuterol and beta-blockers are pharmacologic opposites, and will counteract each other when given concomitantly.[5262] Beta-blockers may also lead to severe bronchospasm in asthmatic patients. Concurrent use of beta-blockers and albuterol should be avoided.[5262] However, if no acceptable alternative exists, a cardioselective beta-blocker (i.e., atenolol, metoprolol) may be used with caution.[5262]

Albuterol (Ventolin® HFA) **and Prednisone**
Severity: Moderate

Corticosteroids [3085] may aggravate the potential hypokalemic effects seen with beta-agonists.[5197] Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with corticosteroid therapy.

Albuterol (Ventolin® HFA) **and Triamcinolone**

Severity: Moderate

Corticosteroids [3085] may aggravate the potential hypokalemic effects seen with beta-agonists.[5197] Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with corticosteroid therapy.

Albuterol (Ventolin® HFA) **and Caffeine**
Severity: Moderate

Concomitant use of drugs and herbals such as cocaine, caffeine, guarana, green tea, and other sympathomimetics (such as oral decongestants or ephedra, ma huang) with beta-agonists might result in additive CNS stimulation (e.g., tremor, insomnia) or cardiovascular effects (e.g., increased blood pressure and heart rate).

Adverse Reactions

• abdominal pain (Amlodipine | Low Dose Adult Aspirin | Bumex® | Clonazepam | Clonidine | Colchicine | Restasis™ | Metoprolol | Prednisone | Triamcinolone | Atorvastatin | Plavix® | Singulair® | Symbicort)
• acne vulgaris (Prednisone | Triamcinolone)
• acneiform rash (Restasis™ | Triamcinolone)
• acute generalized exanthematous pustulosis (AGEP) (Low Dose Adult Aspirin)
• acute respiratory distress syndrome (ARDS) (Restasis™)
• adrenocortical insufficiency (Prednisone | Triamcinolone | Symbicort)
• agitation (Singulair®)
• agranulocytosis (Low Dose Adult Aspirin | Colchicine | Hydralazine | Metoprolol | Plavix®)
• alopecia (Colchicine | Restasis™ | Levothyroxine | Metoprolol | Atorvastatin)
• amenorrhea (Levothyroxine | Prednisone | Triamcinolone)
• amnesia (Clonazepam | Metoprolol)
• anaphylactoid reactions (Ventolin® HFA | Low Dose Adult Aspirin | Restasis™ | Triamcinolone | Atorvastatin | Plavix® | Singulair® | Symbicort)
• angina (Ventolin® HFA | Amlodipine | Hydralazine | Levothyroxine | Prednisone | Symbicort)
• angioedema (Ventolin® HFA | Amlodipine | Low Dose Adult Aspirin | Colchicine | Prednisone | Triamcinolone | Atorvastatin | Plavix® | Singulair® | Symbicort)
• anorexia (Amlodipine | Bumex® | Colchicine | Restasis™ | Hydralazine | Levothyroxine | Prednisone | Triamcinolone)
• anuria (Colchicine)
• anxiety (Ventolin® HFA | Clonazepam | Clonidine | Levothyroxine | Prednisone | Triamcinolone | Singulair®)
• aplastic anemia (Low Dose Adult Aspirin | Colchicine | Plavix®)
• appetite stimulation (Prednisone | Triamcinolone)
• arachnoiditis (Triamcinolone)
• arrhythmia exacerbation (Ventolin® HFA | Symbicort)
• arthralgia (Bumex® | Restasis™ | Hydralazine | Metoprolol | Prednisone | Triamcinolone | Atorvastatin | Singulair® | Symbicort)
• arthropathy (Triamcinolone)
• asthenia (Amlodipine | Clonidine | Hydralazine | Atorvastatin | Singulair®)
• ataxia (Clonazepam | Restasis™)
• atopic dermatitis (Singulair®)
• atrial fibrillation (Levothyroxine)
• atrial tachycardia (Symbicort)
• AV block (Metoprolol)
• avascular necrosis (Prednisone | Triamcinolone)
• azotemia (Low Dose Adult Aspirin | Bumex® | Restasis™)
• back pain (Atorvastatin | Symbicort)
• bleeding (Low Dose Adult Aspirin | Plavix® | Singulair®)
• blurred vision (Amlodipine | Clonazepam | Restasis™ | Metoprolol)
• bone fractures (Prednisone | Triamcinolone)
• bradycardia (Amlodipine | Clonazepam | Clonidine | Metoprolol)
• bronchospasm (Ventolin® HFA | Low Dose Adult Aspirin | Restasis™ | Metoprolol | Triamcinolone | Plavix® | Symbicort)
• bullous rash (Atorvastatin)
• candidiasis (Triamcinolone | Symbicort)
• cataracts (Prednisone | Triamcinolone | Symbicort)
• chest pain (unspecified) (Metoprolol)
• chills (Hydralazine | Atorvastatin)
• cholestasis (Atorvastatin)
• Churg-Strauss syndrome (Singulair®)

- cirrhosis (Atorvastatin)
- colitis (Plavix®)
- coma (Restasis™)
- confusion (Low Dose Adult Aspirin | Clonazepam | Clonidine | Restasis™ | Metoprolol | Plavix®)
- conjunctival hyperemia (Restasis™)
- constipation (Amlodipine | Low Dose Adult Aspirin | Clonazepam | Clonidine | Hydralazine | Metoprolol | Prednisone | Triamcinolone | Atorvastatin)
- contact dermatitis (Clonidine | Triamcinolone)
- cough (Ventolin® HFA | Triamcinolone | Singulair® | Symbicort)
- Cushing's syndrome (Prednisone | Triamcinolone)
- cyanosis (Nitrostat®)
- dehydration (Low Dose Adult Aspirin)
- delirium (Restasis™)
- depression (Clonazepam | Restasis™ | Metoprolol | Prednisone | Triamcinolone)
- diabetes mellitus (Metoprolol | Prednisone | Triamcinolone)
- diaphoresis (Ventolin® HFA | Low Dose Adult Aspirin | Clonidine | Levothyroxine | Nitrostat® | Prednisone | Triamcinolone)
- diarrhea (Amlodipine | Low Dose Adult Aspirin | Bumex® | Colchicine | Restasis™ | Hydralazine | Levothyroxine | Metoprolol | Prednisone | Triamcinolone | Atorvastatin | Plavix® | Singulair® | Symbicort)
- diplopia (Clonazepam)
- disseminated intravascular coagulation (DIC) (Low Dose Adult Aspirin)
- dizziness (Ventolin® HFA | Amlodipine | Low Dose Adult Aspirin | Bumex® | Clonazepam | Clonidine | Restasis™ | Hydralazine | Metoprolol | Singulair® | Symbicort)
- drowsiness (Ventolin® HFA | Amlodipine | Low Dose Adult Aspirin | Clonazepam | Clonidine | Hydralazine | Metoprolol | Atorvastatin | Singulair®)
- dysarthria (Clonazepam | Restasis™ | Atorvastatin)
- dysgeusia (Triamcinolone)
- dysmenorrhea (Prednisone | Triamcinolone)
- dyspepsia (Ventolin® HFA | Low Dose Adult Aspirin | Bumex® | Restasis™ | Atorvastatin | Plavix® | Singulair® | Symbicort)
- dysphagia (Amlodipine | Low Dose Adult Aspirin | Levothyroxine | Atorvastatin)
- dysphonia (Triamcinolone)
- dysphoria (Symbicort)
- dyspnea (Clonidine | Restasis™ | Metoprolol | Atorvastatin)
- dysuria (Clonidine)
- ecchymosis (Prednisone | Triamcinolone)
- edema (Amlodipine | Hydralazine | Prednisone | Triamcinolone | Atorvastatin | Singulair®)
- EEG changes (Prednisone | Triamcinolone)
- ejaculation dysfunction (Clonidine)
- elevated hepatic enzymes (Amlodipine | Low Dose Adult Aspirin | Restasis™ | Metoprolol | Triamcinolone | Atorvastatin | Plavix® | Singulair®)
- emotional lability (Prednisone | Triamcinolone)
- encephalopathy (Low Dose Adult Aspirin | Bumex® | Restasis™)
- endophthalmitis (Triamcinolone)
- eosinophilia (Atorvastatin | Singulair®)
- epiphora (Restasis™)
- epistaxis (Ventolin® HFA | Amlodipine | Triamcinolone | Singulair®)
- erythema (Clonidine | Hydralazine | Prednisone | Triamcinolone | Atorvastatin)
- erythema multiforme (Amlodipine | Atorvastatin | Plavix®)
- erythema nodosum (Low Dose Adult Aspirin | Singulair®)
- esophageal stricture (Low Dose Adult Aspirin)
- esophageal ulceration (Low Dose Adult Aspirin | Prednisone | Triamcinolone)
- esophagitis (Low Dose Adult Aspirin | Triamcinolone)
- euphoria (Clonazepam | Prednisone | Triamcinolone)
- excitability (Ventolin® HFA)
- exfoliative dermatitis (Metoprolol | Prednisone | Triamcinolone)
- exophthalmos (Prednisone | Triamcinolone)
- fatigue (Amlodipine | Bumex® | Clonazepam | Clonidine | Restasis™ | Metoprolol | Atorvastatin)
- fever (Low Dose Adult Aspirin | Restasis™ | Hydralazine | Levothyroxine | Prednisone | Triamcinolone | Atorvastatin | Plavix® | Singulair® | Symbicort)
- flatulence (Amlodipine | Restasis™ | Metoprolol | Atorvastatin)
- fluid retention (Hydralazine | Prednisone | Triamcinolone)
- flushing (Ventolin® HFA | Amlodipine | Clonazepam | Restasis™ | Nitrostat® | Triamcinolone | Atorvastatin)
- folliculitis (Restasis™ | Triamcinolone)

- foreign body sensation (Restasis™)
- gastritis (Low Dose Adult Aspirin | Prednisone | Triamcinolone | Plavix® | Singulair®)
- GI bleeding (Low Dose Adult Aspirin | Triamcinolone | Plavix®)
- GI perforation (Low Dose Adult Aspirin | Triamcinolone)
- gingival hyperplasia (Amlodipine | Restasis™)
- gingivitis (Restasis™)
- glomerulonephritis (Hydralazine | Plavix®)
- glossitis (Prednisone | Triamcinolone)
- growth inhibition (Prednisone | Triamcinolone | Symbicort)
- gynecomastia (Amlodipine | Restasis™)
- hallucinations (Low Dose Adult Aspirin | Restasis™ | Metoprolol | Plavix® | Singulair®)
- headache (Ventolin® HFA | Amlodipine | Low Dose Adult Aspirin | Bumex® | Clonazepam | Clonidine | Restasis™ | Hydralazine | Levothyroxine | Metoprolol | Nitrostat® | Prednisone | Triamcinolone | Atorvastatin | Singulair® | Symbicort)
- hearing loss (Low Dose Adult Aspirin | Bumex®)
- heart failure (Levothyroxine | Metoprolol | Prednisone | Triamcinolone)
- heat intolerance (Levothyroxine)
- hematuria (Colchicine)
- hemolytic anemia (Low Dose Adult Aspirin | Atorvastatin)
- hemolytic-uremic syndrome (Restasis™)
- hemorrhoids (Low Dose Adult Aspirin)
- hepatic failure (Atorvastatin | Plavix®)
- hepatic necrosis (Low Dose Adult Aspirin | Atorvastatin)
- hepatitis (Amlodipine | Low Dose Adult Aspirin | Metoprolol | Atorvastatin | Plavix® | Singulair®)
- hepatomegaly (Triamcinolone)
- hirsutism (Restasis™ | Prednisone | Triamcinolone)
- hoarseness (Ventolin® HFA | Triamcinolone)
- hostility (Ventolin® HFA | Clonazepam)
- hyperbilirubinemia (Low Dose Adult Aspirin | Restasis™)
- hypercholesterolemia (Restasis™ | Prednisone | Triamcinolone)
- hyperglycemia (Ventolin® HFA | Low Dose Adult Aspirin | Bumex® | Restasis™ | Metoprolol | Prednisone | Triamcinolone | Symbicort)
- hyperkalemia (Restasis™)
- hyperkinesis (Ventolin® HFA)
- hyperlipidemia (Restasis™)
- hypernatremia (Low Dose Adult Aspirin | Prednisone | Triamcinolone)
- hyperprolactinemia (Restasis™)
- hyperreflexia (Clonazepam)
- hypersalivation (Clonazepam)
- hypertension (Ventolin® HFA | Restasis™ | Prednisone | Triamcinolone | Symbicort)
- hypertensive crisis (Symbicort)
- hyperthyroidism (Levothyroxine)
- hypertrichosis (Restasis™ | Triamcinolone)
- hypertriglyceridemia (Restasis™ | Metoprolol)
- hyperuricemia (Low Dose Adult Aspirin | Bumex® | Restasis™)
- hyperventilation (Low Dose Adult Aspirin)
- hypocalcemia (Bumex® | Prednisone | Triamcinolone)
- hypochloremia (Bumex®)
- hypoesthesia (Singulair®)
- hypoglycemia (Low Dose Adult Aspirin | Metoprolol)
- hypokalemia (Ventolin® HFA | Low Dose Adult Aspirin | Bumex® | Prednisone | Triamcinolone | Symbicort)
- hypomagnesemia (Bumex® | Restasis™)
- hyponatremia (Bumex®)
- hypophosphatemia (Bumex®)
- hypoprothrombinemia (Low Dose Adult Aspirin)
- hypotension (Ventolin® HFA | Amlodipine | Bumex® | Clonazepam | Clonidine | Hydralazine | Metoprolol | Nitrostat® | Prednisone | Triamcinolone | Plavix® | Symbicort)
- hypothalamic-pituitary-adrenal (HPA) suppression (Prednisone | Triamcinolone | Symbicort)
- hypothyroidism (Colchicine)
- hypovolemia (Bumex®)
- ileus (Colchicine)
- immunosuppression (Prednisone | Triamcinolone)
- impaired cognition (Restasis™ | Hydralazine)

- impaired wound healing (Prednisone | Triamcinolone)
- impotence (erectile dysfunction) (Bumex® | Clonidine | Metoprolol)
- increased intracranial pressure (Prednisone | Triamcinolone)
- infection (Restasis™ | Prednisone | Triamcinolone | Atorvastatin | Singulair® | Symbicort)
- infertility (Restasis™)
- influenza (Symbicort)
- injection site reaction (Colchicine | Triamcinolone)
- insomnia (Ventolin® HFA | Restasis™ | Levothyroxine | Metoprolol | Prednisone | Triamcinolone | Singulair®)
- interstitial nephritis (Low Dose Adult Aspirin | Bumex®)
- intracranial bleeding (Low Dose Adult Aspirin | Plavix®)
- irritability (Ventolin® HFA | Levothyroxine | Singulair®)
- jaundice (Amlodipine | Low Dose Adult Aspirin | Metoprolol | Atorvastatin)
- laryngeal edema (Low Dose Adult Aspirin)
- laryngitis (Singulair®)
- lethargy (Prednisone | Triamcinolone)
- leukocytosis (Low Dose Adult Aspirin | Triamcinolone)
- leukopenia (Amlodipine | Low Dose Adult Aspirin | Bumex® | Colchicine | Restasis™ | Hydralazine | Atorvastatin)
- libido decrease (Clonazepam | Clonidine | Metoprolol)
- lupus-like symptoms (Hydralazine | Atorvastatin)
- lymphadenopathy (Hydralazine)
- maculopapular rash (Ventolin® HFA | Low Dose Adult Aspirin | Plavix® | Singulair®)
- malaise (Atorvastatin)
- mania (Clonazepam)
- melena (Low Dose Adult Aspirin)
- meningitis (Triamcinolone)
- menstrual irregularity (Restasis™ | Levothyroxine | Prednisone | Triamcinolone)
- metabolic acidosis (Low Dose Adult Aspirin | Restasis™)
- metabolic alkalosis (Bumex® | Prednisone | Triamcinolone)
- methemoglobinemia (Nitrostat®)
- migraine (Symbicort)
- miliaria (Triamcinolone)
- muscle cramps (Ventolin® HFA | Singulair® | Symbicort)
- muscle paralysis (Atorvastatin)
- musculoskeletal pain (Bumex® | Metoprolol)
- myalgia (Restasis™ | Hydralazine | Prednisone | Triamcinolone | Atorvastatin | Plavix® | Singulair® | Symbicort)
- myasthenia (Atorvastatin)
- myocardial infarction (Prednisone)
- myoglobinuria (Atorvastatin)
- myopathy (Colchicine | Prednisone | Triamcinolone | Atorvastatin)
- myopia (Singulair®)
- nasal congestion (Singulair® | Symbicort)
- nasal dryness (Triamcinolone)
- nasal irritation (Triamcinolone)
- nasal septum perforation (Triamcinolone)
- nausea/vomiting (Ventolin® HFA | Amlodipine | Low Dose Adult Aspirin | Bumex® | Clonazepam | Clonidine | Colchicine | Restasis™ | Hydralazine | Levothyroxine | Metoprolol | Nitrostat® | Prednisone | Triamcinolone | Atorvastatin | Singulair® | Symbicort)
- neuritis (Colchicine | Triamcinolone)
- neutropenia (Colchicine | Plavix®)
- nightmares (Ventolin® HFA | Clonazepam)
- ocular discharge (Restasis™)
- ocular hemorrhage (Triamcinolone | Plavix®)
- ocular hypertension (Prednisone | Triamcinolone | Symbicort)
- ocular inflammation (Triamcinolone)
- ocular irritation (Restasis™)
- ocular pain (Restasis™)
- ocular pruritus (Restasis™)
- odynophagia (Low Dose Adult Aspirin)
- oliguria (Bumex®)
- optic neuritis (Prednisone | Triamcinolone)
- orthostatic hypotension (Amlodipine | Bumex® | Clonidine | Hydralazine | Nitrostat®)
- osteoporosis (Prednisone | Triamcinolone | Symbicort)

• palpitations (Ventolin® HFA | Amlodipine | Clonidine | Hydralazine | Levothyroxine | Metoprolol | Nitrostat® | Prednisone | Triamcinolone | Singulair® | Symbicort)
• pancreatitis (Amlodipine | Prednisone | Triamcinolone | Atorvastatin | Plavix® | Singulair®)
• pancytopenia (Low Dose Adult Aspirin | Colchicine | Plavix®)
• papilledema (Restasis™ | Prednisone | Triamcinolone)
• paresis (Triamcinolone)
• paresthesias (Amlodipine | Restasis™ | Hydralazine | Triamcinolone | Singulair®)
• peptic ulcer (Low Dose Adult Aspirin | Prednisone | Triamcinolone | Plavix®)
• pericarditis (Hydralazine)
• peripheral edema (Amlodipine | Hydralazine | Levothyroxine | Metoprolol | Atorvastatin)
• peripheral neuropathy (Colchicine | Restasis™ | Hydralazine | Prednisone | Triamcinolone | Atorvastatin)
• peripheral vasoconstriction (Metoprolol)
• peripheral vasodilation (Ventolin® HFA | Amlodipine | Hydralazine)
• petechiae (Prednisone | Triamcinolone)
• pharyngitis (Restasis™ | Atorvastatin | Singulair® | Symbicort)
• phlebitis (Prednisone | Triamcinolone)
• photosensitivity (Metoprolol | Atorvastatin)
• physiological dependence (Clonazepam | Prednisone)
• platelet dysfunction (Low Dose Adult Aspirin | Plavix®)
• pneumonitis (Plavix®)
• polyuria (Bumex®)
• prolonged bleeding time (Low Dose Adult Aspirin | Plavix®)
• proteinuria (Colchicine | Hydralazine)
• pruritus (Bumex® | Clonidine | Hydralazine | Metoprolol | Triamcinolone | Atorvastatin | Plavix® | Singulair®)
• pseudotumor cerebri (Levothyroxine | Prednisone)
• psoriasis (Metoprolol)
• psychological dependence (Clonazepam)
• psychosis (Metoprolol | Prednisone | Triamcinolone)
• pulmonary edema (Low Dose Adult Aspirin | Restasis™)
• purpura (Low Dose Adult Aspirin | Colchicine | Atorvastatin | Plavix®)
• pyrosis (heartburn) (Metoprolol)
• QT prolongation (Ventolin® HFA | Symbicort)
• rash (unspecified) (Bumex® | Clonazepam | Restasis™ | Hydralazine | Levothyroxine | Metoprolol | Nitrostat® | Triamcinolone | Atorvastatin | Plavix® | Singulair® | Symbicort)
• renal failure (unspecified) (Low Dose Adult Aspirin | Bumex®)
• renal papillary necrosis (Low Dose Adult Aspirin)
• renal tubular necrosis (Low Dose Adult Aspirin | Restasis™)
• renal tubular obstruction (Atorvastatin)
• respiratory depression (Low Dose Adult Aspirin)
• restlessness (Ventolin® HFA | Clonazepam | Prednisone | Triamcinolone | Singulair®)
• retinal detachment (Triamcinolone)
• retinal hemorrhage (Plavix®)
• retinopathy (Prednisone | Triamcinolone)
• retroperitoneal bleeding (Plavix®)
• Reye's syndrome (Low Dose Adult Aspirin)
• rhabdomyolysis (Atorvastatin)
• rhinitis (Low Dose Adult Aspirin | Restasis™ | Metoprolol | Singulair® | Symbicort)
• secondary malignancy (Restasis™)
• seizures (Low Dose Adult Aspirin | Restasis™ | Prednisone | Triamcinolone | Singulair®)
• serum sickness (Plavix®)
• sinus tachycardia (Ventolin® HFA | Amlodipine | Clonidine | Restasis™ | Hydralazine | Levothyroxine | Nitrostat® | Prednisone | Triamcinolone | Symbicort)
• sinusitis (Restasis™ | Atorvastatin | Singulair® | Symbicort)
• skin atrophy (Prednisone | Triamcinolone)
• skin hyperpigmentation (Clonidine | Metoprolol | Triamcinolone)
• skin hypopigmentation (Triamcinolone)
• skin irritation (Triamcinolone)
• skin necrosis (Colchicine)
• skin ulcer (Restasis™ | Triamcinolone)
• sodium retention (Prednisone | Triamcinolone)
• spermatogenesis inhibition (Restasis™)
• Stevens-Johnson syndrome (Low Dose Adult Aspirin | Atorvastatin | Plavix®)

• stomatitis (Restasis™ | Prednisone | Triamcinolone | Plavix®)
• striae (Prednisone | Triamcinolone)
• stroke (Prednisone)
• ST-T wave changes (Ventolin® HFA)
• suicidal ideation (Singulair®)
• syncope (Ventolin® HFA | Amlodipine | Bumex® | Clonazepam | Metoprolol | Nitrostat®)
• telangiectasia (Triamcinolone)
• tendon rupture (Triamcinolone)
• teratogenesis (Clonazepam)
• throat irritation (Ventolin® HFA)
• thrombocytopenia (Amlodipine | Low Dose Adult Aspirin | Bumex® | Colchicine | Metoprolol | Triamcinolone | Atorvastatin)
• thromboembolism (Prednisone | Triamcinolone)
• thrombosis (Prednisone | Triamcinolone)
• thrombotic thrombocytopenic purpura (TTP) (Restasis™ | Plavix®)
• tinnitus (Low Dose Adult Aspirin | Bumex® | Metoprolol)
• tissue necrosis (Colchicine)
• tolerance (Clonazepam | Nitrostat® | Triamcinolone)
• toxic epidermal necrolysis (Low Dose Adult Aspirin | Atorvastatin | Plavix®)
• tremor (Ventolin® HFA | Amlodipine | Clonazepam | Restasis™ | Levothyroxine | Singulair® | Symbicort)
• urinary incontinence (Prednisone | Triamcinolone)
• urinary retention (Ventolin® HFA | Clonidine)
• urinary urgency (Prednisone | Triamcinolone)
• urticaria (Ventolin® HFA | Low Dose Adult Aspirin | Bumex® | Clonazepam | Colchicine | Hydralazine | Levothyroxine | Metoprolol | Prednisone | Triamcinolone | Atorvastatin | Singulair® | Symbicort)
• vasculitis (Hydralazine | Atorvastatin | Plavix® | Singulair®)
• ventricular tachycardia (Symbicort)
• vertigo (Amlodipine | Bumex® | Clonazepam | Prednisone | Triamcinolone)
• visual impairment (Low Dose Adult Aspirin | Restasis™ | Prednisone | Triamcinolone)
• weakness (Bumex® | Hydralazine | Nitrostat® | Prednisone | Triamcinolone | Atorvastatin)
• weight gain (Prednisone | Triamcinolone)
• weight loss (Levothyroxine | Prednisone | Triamcinolone | Singulair®)
• wheezing (Low Dose Adult Aspirin | Restasis™ | Metoprolol | Triamcinolone)
• withdrawal (Clonazepam | Clonidine | Prednisone | Triamcinolone)
• xerosis (Metoprolol | Triamcinolone)
• xerostomia (Ventolin® HFA | Bumex® | Clonidine | Nitrostat® | Triamcinolone)

Precautions

Precaution: Atorvastatin in females
Atorvastatin has been classified as a *pregnancy* category X drug by the FDA and is contraindicated for use during *pregnancy*, because of the potential effects of HMG-CoA reductase inhibitors on cholesterol pathways and the potential for fetal harm. Cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Treatment should be immediately discontinued as soon as pregnancy is recognized. Other HMG-CoA reductase inhibitors have been shown to cause malformations of vertebrae and ribs in fetal rats when given in high doses. In a prospective review of about 100 pregnancies in women exposed to simvastatin or another structurally related HMG-CoA reductase inhibitor, the incidence of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed what would be expected in the general population.[1525] However, atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. If the patient becomes pregnant while taking this drug, atorvastatin should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus. Atorvastatin should only be administered to females of child-bearing potential, including adolescents at least 1 year post-menarche, when such patients are highly unlikely to conceive and have been informed of the potential hazards. Females should be counseled regarding appropriate methods of contraception while on therapy.

Precaution: Atorvastatin in renal impairment
Other HMG-CoA reductase inhibitors have been associated with toxicity to the skeletal muscle system. Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values > 10 times upper limit of normal (ULN), should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Any evidence of myalgia, muscle weakness, or elevated CPK values may indicate myopathy, particularly if symptoms include fever or malaise. Clinicians should note that *rhabdomyolysis* and renal failure have been associated with HMG-CoA reductase inhibitor therapy. The risk of developing myopathy appears to be increased when HMG-CoA reductase inhibitors are used in combination with other drugs (see Drug Interactions). Atorvastatin should be discontinued immediately in any patient who develops myopathy or

elevations in CPK. In addition, atorvastatin may be contraindicated in conditions that can cause decreased renal perfusion because renal failure is possible if atorvastatin-induced rhabdomyolysis occurs. Predisposing conditions include renal disease or renal impairment, hypotension, acute infection, endocrine disease, electrolyte imbalance, uncontrolled seizure disorder, major surgery, and trauma. Atorvastatin should be used with caution in organ transplant patients receiving immunosuppressant therapy such as cyclosporine because of an increased risk of rhabdomyolysis and renal failure (see Drug Interactions). Renal disease has no influence on atorvastatin plasma concentrations or LDL cholesterol reductions; dosage adjustments are not needed in patients with renal impairment.

Precaution: Bumex® in gout
Since loop diuretics can reduce the clearance of uric acid, patients with gout or hyperuricemia can have exacerbations of their disease.

Precaution: Bumex® in orthostatic hypotension
Patients with pre-existing hypovolemia or hypotension should have their condition corrected before bumetanide is initiated. Orthostatic hypotension may occur during treatment with loop diuretics.[9371] Excessive hypotension can result in syncope. The antihypertensive effects of diuretics may be enhanced in patients predisposed for orthostatic hypotension, including the post-sympathectomy patient. Greater sensitivity to the hypotensive and diuretic effects of bumetanide is possible in elderly patients.

Precaution: Bumex® in renal impairment
Bumetanide can cause dehydration. Patients should be careful monitored; dosage adjustments may be necessary. Because of this, bumetanide is contraindicated in any patient with *anuria*. Bumetanide should be used with caution in patients with severe renal disease such as severe renal impairment or renal failure. Bumetanide-induced hypovolemia can precipitate oliguria and azotemia in these patients. Although bumetanide can be used to induce diuresis in renal insufficiency, any marked increase in blood urea nitrogen or serum creatinine, or the development of oliguria during therapy of patients with progressive renal disease, is an indication for discontinuation of treatment with bumetanide. Renal failure may reduce drug clearance and warrant the use of higher doses with extended dosing intervals. Bumetanide may be less effective in patients with renal failure and higher doses may be required. Delayed excretion of bumetanide in patients with renal failure may increase the risk of toxicity (e.g., ototoxicity).

Precaution: Clonazepam in females
Clonazepam is classified as FDA pregnancy category D. Females of childbearing potential should discuss options with their prescriber or health care professional prior to beginning treatment with clonazepam. The possibility that a woman of child-bearing potential may be pregnant at the time of institution of therapy should be considered and/or ruled out. In general, the use of clonazepam in pregnant epileptic women should be considered only when the clinical situation outweighs any potential risk to the fetus. In the treatment of panic disorder, alternative treatments should be considered. Pregnant rabbits were given clonazepam doses lower or similar to maximum human doses during the period of organogenesis. Cleft palate, open eyelid, fused sternebrae and limb defects were observed in a low, non-dose related incidence in exposed litters from all dosage groups. No maternal or embryo-fetal anomalies were noted in mice and rats receiving 4 and 20 times the maximum recommended human dose. There may also be non-teratogenic risks associated with benzodiazepines during the perinatal period, including neonatal flaccidity, respiratory suppression, feeding difficulties, and hypothermia in infants born to mothers who received benzodiazepines late in pregnancy. In women with epilepsy, abrupt withdrawal of clonazepam may result in life-threatening status epilepticus. Additionally, even mild seizures may pose hazards to the developing fetus. If a woman becomes pregnant while taking clonazepam, she should be counseled regarding the potential risks to the fetus. Clonazepam has not been studied for use in obstetrical procedures or obstetric delivery, including cesarean section; however, other benzodiazepines have been associated with perinatal complications.

Precaution: Clonazepam in renal impairment
Clonazepam should be administered cautiously to patients with renal impairment or renal failure; in general, initial dose selection should be in the lower range and dosage titration should proceed cautiously. Assess renal function during prolonged therapy and adjust dosage as clinically indicated.

Precaution: Clonidine in females
The manufacturer does not recommend the use of epidural clonidine as an analgesic during labor and delivery, post-partum, or peri-operative analgesia due to the risks of hemodynamic instability, especially hypotension and bradycardia. However, potential benefits of clonidine may outweigh the possible risks in a rare obstetrical, post-partum, or perioperative patient. Several trials examining the efficacy, safety, or dosing of epidural clonidine in obstetrics have been reported. In a study comparing epidural clonidine combined with bupivacaine and bupivacaine alone for analgesia during labor, there was no difference in maternal blood pressure decreases and apgar scores at 1 and 5 minutes between the two groups. The duration of labor was prolonged in patients receiving clonidine.[2090] Females and lower weight patients may be more susceptible to the hypotensive effects of epidural clonidine.

Precaution: Clonidine in renal impairment
Clonidine has been used safely in patients with renal disease. Clonidine is 45% renally excreted and drug concentrations may accumulate in renal failure. Therefore, the manufacturer recommends careful monitoring and dosage adjustment (no specific guidelines) based on the degree of renal impairment in patients with renal disease. In clinical practice, dosage adjustments are usually not clinically needed in patients with renal failure or renal disease, and the dosage of clonidine is titrated to achieve clinical goals.

Elderly patients should be treated with caution because they are more likely to have decreased renal function and are more susceptible to the hypotensive and sedative effects of clonidine; dosage reduction may be considered.

Precaution: Clonidine in skin abrasion
Absorption of clonidine can be increased in areas of skin irritation or skin abrasion, so placement of the patches in these areas should be avoided.

Precaution: Colchicine in renal impairment
Colchicine is contraindicated in patients with severe cardiac disease, hepatic disease, or renal disease, and in patients with combined hepatic and renal disease because these patient populations are at risk for developing cumulative toxicity. [7677] Colchicine should be used with caution in patients exhibiting early manifestations of these disorders. Patients with renal impairment or elevated plasma levels of colchicine due to renal disease can develop a myoneuropathy characterized by proximal weakness and elevated serum creatine kinase (see Adverse Reactions). Although this reaction has been reported in patients receiving colchicine for several years [70], caution should be used when prescribing colchicine to patients with renal insufficiency. Colchicine is eliminated primarily through biliary pathways; therefore, patients with hepatic disease should be monitored closely during treatment with this agent. Consider alterative therapies in patients with extrahepatic biliary obstruction. The risk of colchicine toxicity may be higher with intravenous therapy than with oral therapy, and is not recommended intravenously in patients with hepatic disease.

Precaution: Hydralazine in angina
Hydralazine has been implicated in causing angina and myocardial infarction secondary to reflex sympathetic nervous system stimulation (i.e., reflex tachycardia); hydralazine, therefore, should be used with extreme caution in patients with coronary artery disease as reflex tachycardia increases myocardial oxygen demand and can aggravate angina and ischemia and precipitate acute myocardial infarction. Hydralazine should be used cautiously in patients with an aortic aneurysm. Because hydralazine can cause sodium and fluid retention, its use is generally not recommended in patients with congestive heart failure, although it has been used in patients with intractable left ventricular dysfunction. However, when used with isosorbide dinitrate, this 2-drug combination is considered to be an appropriate alternative to patients who cannot tolerate standard heart failure therapy, mainly angiotensin converting enzyme (ACE) inhibitors. Furthermore, combination therapy of isosorbide dinitrate and hydralazine, in conjunction with standard therapy, has been shown to improve mortality, rate of first hospitalizations, and quality of life in black patients; a fixed-dose combination of isosorbide dinitrate and hydralazine (BiDil®) is FDA-approved for the treatment of heart failure in black patients.

Precaution: Hydralazine in renal impairment
The dosage of hydralazine should be modified in patients with renal failure or severe renal impairment with a CrCl < 10 ml/min (see dosage). Elderly patients are more sensitive to the orthostatic hypotensive effects of hydralazine, and are also more likely to have age-associated renal impairment. Initiation of a reduced dosage, or beginning at the lower end of the adult dosage range (see adult dosage) is prudent.

Precaution: Hydrocortisone; Neomycin in asthma
Some commercially available formulations of hydrocortisone may contain sulfites. Sulfites may cause allergic reactions in some people. They should be used with caution in patients with known sulfite hypersensitivity. Patients with asthma are more likely to experience this sensitivity reaction than non-asthmatic patients.

Precaution: Hydrocortisone; Neomycin in hypertension
Systemic corticosteroids can cause edema and weight gain. Use with caution in patients with congestive heart failure or hypertension as this can cause an exacerbation of their condition.

Precaution: Hydrocortisone; Neomycin in hypothyroidism
Systemic corticosteroids should be used with extreme caution in patients with psychosis, emotional instability, renal disease, and seizure disorder because the drugs can exacerbate these conditions. Patients with hepatic disease, such as cirrhosis, or hypothyroidism can have an exaggerated response to systemic corticosteroids. Use systemic corticosteroids with caution in these patients.

Precaution: Hydrocortisone; Neomycin in skin abrasion
Systemic corticosteroids can aggravate Cushing's syndrome and should be avoided in patients with *Cushing's syndrome*. Prolonged administration of pharmacological doses of systemic corticosteroids or topical preparations (resulting in systemic absorption) may result in hypothalamic-pituitary-adrenal (HPA) suppression and/or manifestations of Cushing's syndrome in some patients. Acute adrenal insufficiency and even death may occur following abrupt discontinuation of prolonged systemic therapy. In addition, a withdrawal syndrome unrelated to adrenocortical insufficiency may occur following sudden discontinuation of corticosteroid therapy. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels (see Adverse Reactions). Withdrawal from prolonged systemic corticosteroid therapy should be gradual. HPA suppression can last for up to 12 months following cessation of systemic therapy. Recovery of HPA axis function is generally prompt and complete upon discontinuation of the topical corticosteroid. HPA-suppressed patients may need supplemental corticosteroid treatment during periods of physiologic stress, such as surgical procedures, acute blood loss, or infection, even after the corticosteroid has been discontinued.

Conditions that increase systemic absorption of topical corticosteroids include use over large surface areas, prolonged use, use in areas where the epidermal barrier is disrupted (i.e., skin abrasion), and the use of an occlusive dressing. Patients receiving large doses of hydrocortisone applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression and/or manifestations of Cushing's syndrome. If these effects are noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid.

Precaution: Hydrocortisone; Neomycin in renal impairment
Neomycin is an aminoglycoside and is absorbed systemically after oral administration; toxic reactions may occur. Patients receiving aminoglycosides should be closely monitored for ototoxicity and nephrotoxicity (see Adverse Reactions). Aminoglycosides are associated with major toxic effects on the auditory and vestibular branches of the eighth nerve and renal tubules. Ototoxicity is manifest by bilateral auditory toxicity which often is permanent and, sometimes, by vestibular ototoxicity. High-frequency hearing loss usually occurs before there is noticeable clinical hearing loss; clinical symptoms may not be present to warn of developing cochlear damage. Vertigo may occur and may indicate vestibular injury. Other neurotoxic manifestations may include numbness, skin tingling, muscle twitching, and seizures. The risk of hearing loss increases with the degree of exposure to either high peak or high trough serum concentrations and continues to progress after stopping the drug. Use aminoglycosides with caution in patients with pre-existing hearing impairment, especially eighth-cranial-nerve impairment. In patients with renal impairment or renal disease and, in those with normal renal function who receive high doses or prolonged therapy, the risks of severe ototoxic and nephrotoxic adverse reactions are sharply increased. Nephrotoxicity can manifest as decreased creatinine clearance, the presence of cells or casts, oliguria, proteinuria, decreased urine specific gravity, or evidence of increasing nitrogen retention (increasing BUN, NPN, or serum creatinine). Renal and eighth nerve function should be closely monitored during aminoglycoside therapy. Evidence of ototoxicity or nephrotoxicity requires dosage adjustment or discontinuance of therapy. In rare cases, ototoxicity and nephrotoxicity may not be evident until soon after completion of therapy. Aminoglycoside-induced ototoxicity is usually irreversible, however, nephrotoxicity usually is reversible. Avoid concurrent and/or sequential coadministration of aminoglycosides with other drugs that are potentially nephrotoxic and/or neurotoxic because toxicity may be additive. Neonates (age < 1 month), the elderly (age > 65 years), and patients with dehydration are at increased risk of developing toxicity. Aminoglycosides should not be given concomitantly with potent diuretics since certain diuretics by themselves may cause ototoxicity. Also, intravenous diuretics may alter aminoglycoside concentrations in serum and tissue and thereby enhance aminoglycoside toxicity.

Precaution: Levothyroxine in angina
Levothyroxine is contraindicated in patients with an *acute myocardial infarction* that is not associated with hypothyroidism; small amounts of levothyroxine may be used only if the MI is complicated or caused by hypothyroidism. Thyroid agents are cardiostimulatory and should be used with great caution in patients with angina pectoris or other preexisting cardiac disease, including uncontrolled hypertension, cardiac arrhythmias, coronary artery disease, or a previous myocardial infarction; do not use levothyroxine therapy in patients with heart disease and nontoxic diffuse goiter or nodular thyroid disease if the serum TSH concentration is suppressed. Many authorities recommend lower initial dosages and slower titration of thyroid hormones in patients with heart disease (see Dosage). If adverse cardiac symptoms develop or worsen, reduce or withhold levothyroxine and cautiously restart at a lower dose. Over-treatment with thyroid hormones may cause cardiac stimulation and lead to increased heart rate, cardiac wall thickening and increased cardiac contractility, which may precipitate angina or cardiac arrhythmias. Concomitant administration of levothyroxine with sympathomimetic agents in patients with coronary artery disease may precipitate coronary insufficiency and associated symptoms. Patients with coronary artery disease who are receiving thyroid hormones may be at a higher risk for developing arrhythmias, particularly during surgery.

Precaution: Levothyroxine in hypertension
Levothyroxine is contraindicated in patients with an *acute myocardial infarction* that is not associated with hypothyroidism; small amounts of levothyroxine may be used only if the MI is complicated or caused by hypothyroidism. Thyroid agents are cardiostimulatory and should be used with great caution in patients with angina pectoris or other preexisting cardiac disease, including uncontrolled hypertension, cardiac arrhythmias, coronary artery disease, or a previous myocardial infarction; do not use levothyroxine therapy in patients with heart disease and nontoxic diffuse goiter or nodular thyroid disease if the serum TSH concentration is suppressed. Many authorities recommend lower initial dosages and slower titration of thyroid hormones in patients with heart disease (see Dosage). If adverse cardiac symptoms develop or worsen, reduce or withhold levothyroxine and cautiously restart at a lower dose. Over-treatment with thyroid hormones may cause cardiac stimulation and lead to increased heart rate, cardiac wall thickening and increased cardiac contractility, which may precipitate angina or cardiac arrhythmias. Concomitant administration of levothyroxine with sympathomimetic agents in patients with coronary artery disease may precipitate coronary insufficiency and associated symptoms. Patients with coronary artery disease who are receiving thyroid hormones may be at a higher risk for developing arrhythmias, particularly during surgery.

Precaution: Low Dose Adult Aspirin in asthma
Patients with a *tartrazine dye hypersensitivity* or *salicylate hypersensitivity* should avoid aspirin. The risk of cross-sensitivity with other nonsteroidal antiinflammatory drugs is significantly greater with aspirin than other salicylates; avoid use in patients with a known NSAID hypersensitivity. Patients with *nasal polyps* or with allergic reactions (e.g. *urticaria*) to aspirin are at risk of developing bronchoconstriction or anaphylaxis and should not receive aspirin. Patients with asthma are at risk of developing severe and

potentially fatal exacerbations of asthma after taking aspirin. Aspirin should be avoided in asthmatics with a history of aspirin-induced *acute bronchospasm*.

Precaution: Low Dose Adult Aspirin in gout
In patients with gout, salicylates may increase serum uric acid levels, resulting in hyperuricemia, and interfere with the efficacy of uricosuric agents.

Precaution: Low Dose Adult Aspirin in hypertension
Sodium-restricted patients or patients with hypovolemic states (e.g., ascites, dehydration, heart failure, hypertension, or hypovolemia) may be more susceptible to adverse renal effects of salicylate therapy. Buffered aspirin contains a high sodium content. In patients with carditis, high doses of salicylates may precipitate congestive heart failure or pulmonary edema.

Precaution: Low Dose Adult Aspirin in renal impairment
Salicylates should be used with caution in patients with renal impairment and with extreme caution, if at all, in patients with advanced, chronic renal failure since salicylic acid and its metabolites are excreted in the urine. In addition, these patients may be at increased risk of developing salicylate-induced nephrotoxicity. In a case-controlled study of patients with early renal failure, the regular use of aspirin (without acetaminophen) was associated with a risk of chronic renal failure that was 2.5-times as high as that for non-aspirin users.[4064] The risk increased significantly with increasing cumulative lifetime dose and increasing average dose during periods of regular use; duration of therapy was not associated with increased risk. When aspirin was given regularly in analgesic doses (> 500 g per year during periods of regular use) the odds ratio for chronic renal failure was 3.5 (95% confidence interval 1.4 to 8). Low-dose aspirin use for cardiovascular prophylaxis was not significantly associated with the development of renal failure. In this study, it appears that pre-existing renal disease or systemic disease is a required precursor to the development of analgesic-induced renal failure; patients without preexisting renal disease who used analgesics had only a small risk of developing end-stage renal disease. Renal function should be monitored periodically in patients receiving prolonged or high-dose salicylate therapy. Salicylates should be used cautiously in patients with renal disease or systemic lupus erythematosus (SLE) due to the risk of decreased glomerular filtration rate in these patients.

Precaution: Low Dose Adult Aspirin in urticaria
Patients with a *tartrazine dye hypersensitivity* or *salicylate hypersensitivity* should avoid aspirin. The risk of cross-sensitivity with other nonsteroidal antiinflammatory drugs is significantly greater with aspirin than other salicylates; avoid use in patients with a known NSAID hypersensitivity. Patients with *nasal polyps* or with allergic reactions (e.g. *urticaria*) to aspirin are at risk of developing bronchoconstriction or anaphylaxis and should not receive aspirin. Patients with asthma are at risk of developing severe and potentially fatal exacerbations of asthma after taking aspirin. Aspirin should be avoided in asthmatics with a history of aspirin-induced *acute bronchospasm*.

Precaution: Metoprolol in asthma
Although beta-1-selective beta-blockers such as metoprolol are preferred over nonselective agents in patients with asthma or other pulmonary disease (e.g., chronic obstructive pulmonary disease (COPD), emphysema, bronchitis) in which *acute bronchospasm* would put them at risk, all beta-blockers should nevertheless be used with caution in these patients, particularly with high-dose therapy.

Precaution: Nitrostat® in orthostatic hypotension
Nitroglycerin should not be given to patients with uncorrected hypovolemia (or dehydration) due to the risk of inducing profound hypotension. Patients with normal or low pulmonary capillary wedge pressures may be unusually sensitive to the hypotensive effects of nitroglycerin. Nitroglycerin should be used with caution in patients with hypotension or orthostatic hypotension because the drug can worsen hypotension, cause a paradoxical bradycardia, and/or exacerbate angina. Nitrate-induced hypotension has resulted in fatalities. In a controlled setting, such as during surgery, IV nitroglycerin can be used to produce hypotension. Nitrate therapy can worsen angina due to hypertrophic cardiomyopathy. The use of any formulation of nitroglycerin during the early days of acute myocardial infarction (MI) requires particular attention to hemodynamic monitoring and clinical status. Nitroglycerin should be used cautiously in patients who have had a recent MI because drug-induced hypotension and/or tachycardia can worsen ischemia. To minimize the risks of nitrates following acute myocardial infarction, nitroglycerin should not be administered to patients with systolic blood pressure < 90 mm Hg or >= to 30 mm Hg below baseline, severe bradycardia (less than 50 beats per minute), tachycardia, or suspected right ventricular infarction.[8488]

Precaution: Plavix® in renal impairment
Although no dosage adjustment is recommended in patients with renal impairment, the manufacturer warns that clopidogrel should be used with caution in patients with severe renal impairment. Experience is limited in patients with severe renal disease or renal failure.

Precaution: Prednisone in hypertension
Corticosteroids cause edema, which may exacerbate congestive heart failure or hypertension, and should be used with caution in these patients.

Precaution: Prednisone in hypothyroidism
Corticosteroids should be used with extreme caution in patients with psychosis, emotional instability, herpes simplex ocular infections, renal disease, osteoporosis, diabetes mellitus, and seizure disorder, because the drugs may exacerbate these conditions. Patients with hypothyroidism may have an exaggerated response to corticosteroids, thus any steroid should be used with caution in these patients.

Precaution: Restasis™ in females
There are no adequate and well-controlled studies of cyclosporine during pregnancy (FDA pregnancy risk category C). In animal models, cyclosporine has been shown to be embryotoxic and fetotoxic when given in maternally toxic doses. In pregnant transplant recipients who are being treated with immunosuppressants, the risk of premature births is increased. Outcomes of 116 pregnancies in women (mostly transplant patients) receiving cyclosporine throughout the entire gestational period showed premature birth (gestational period of 28 to 36 weeks) in 47% and low birth weight for gestational age in 28% of pregnancies. Sixteen fetal losses occurred. Most of the pregnancies were complicated by cyclosporine-induced disorders. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Neonatal complications occurred in 27%. A limited number of observations in children up to approximately 7 years of age exposed to cyclosporine *in utero* is available. Renal function and blood pressure in these children were normal. The risks and benefits of cyclosporine during pregnancy should be carefully weighed. Cyclosporine should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus; consider discontinuation of cyclosporine therapy in psoriasis patients. Females of childbearing age should be counseled about the potential risks of cyclosporine therapy during pregnancy and about appropriate contraceptive measures.

Precaution: Restasis™ in gout
Hyperuricemia has occurred in 84% of renal allograft patients receiving systemic cyclosporine versus 30% of those receiving azathioprine. Gout developed in 7% of patients receiving systemic cyclosporine.[36] Serum uric acid concentrations should be monitored carefully when cyclosporine therapy is initiated in patients with a known history of gout.

Precaution: Restasis™ in hypertension
Because of its effects on the sympathetic nervous system, cyclosporine can elevate blood pressure. The risk of hypertension increases with increasing dose and duration of cyclosporine therapy. In any patient with treated hypertension prior to initiating systemic cyclosporine therapy, the antihypertensive medication should be adjusted to control hypertension that may occur while receiving cyclosporine. Mild to moderate hypertension is more common than severe hypertension, and the incidence decreases over time. In renal, heart, or liver transplant patients treated with systemic cyclosporine, antihypertensive therapy may be required. However, since systemic cyclosporine may cause hyperkalemia, potassium-sparing diuretics should not be used. Calcium-channel blockers while effective treatment for cyclosporine-induced hypertension, may affect cyclosporine metabolism (see Drug Interactions). Psoriasis and rheumatoid arthritis patients with uncontrolled hypertension should not receive systemic cyclosporine therapy. Blood pressure measurements on at least two occasions should be performed to establish a baseline prior to beginning cyclosporine therapy in rheumatoid arthritis and psoriasis patients. Following initiation of systemic cyclosporine treatment in rheumatoid arthritis and psoriasis patients, blood pressure measurements should be monitored every 2 weeks during the initial 3 months and then monthly once the patient is stable. In rheumatoid arthritis patients, it is recommended to monitor blood pressure after a dosage increase of NSAIDs. In psoriasis or rheumatoid arthritis patients, the cyclosporine dosage should be reduced by 25-50% if hypertension develops. If hypertension persists, the dose of cyclosporine should be reduced further or blood pressure should be controlled with antihypertensive agents. In most cases, blood pressure returns to baseline once cyclosporine is discontinued.

Precaution: Restasis™ in renal impairment
Cyclosporine in recommended dosages can cause nephrotoxicity. The risk of developing cyclosporine-induced nephrotoxicity increases with increasing doses of cyclosporine and duration of cyclosporine therapy. Systemic cyclosporine therapy is contraindicated in rheumatoid arthritis and psoriasis patients with renal impairment or renal failure. All patients receiving other nephrotoxic drugs concomitantly with systemic cyclosporine should be carefully monitored for worsening renal function (see Drug Interactions). In all patients, serum creatinine should be monitored closely. It is not unusual for the serum creatinine and BUN to be elevated during systemic cyclosporine therapy for transplant rejection prophylaxis. The elevation of serum creatinine and BUN in renal transplant patients does not necessarily indicate rejection, and each patient must be fully evaluated before dosage adjustment is initiated. If patients are not monitored properly and doses are not adjusted correctly, systemic cyclosporine therapy can be associated with the occurrence of structural kidney damage and persistent renal dysfunction. In psoriasis and rheumatoid arthritis patients, serum creatinine and BUN should be monitored every 2 weeks during the initial 3 months of cyclosporine therapy and then monthly if the patient is stable. If the serum creatinine is >= 25% above the rheumatoid arthritis or psoriasis patient's baseline, the level should be repeated within 2 weeks. If the change remains >= 25% above baseline, the cyclosporine dose should be reduced by 25-50%. If at any time the serum creatinine increases by >= 50% above baseline, cyclosporine dosage should be reduced by 25-50%. Cyclosporine should be discontinued if reversibility (within 25% of baseline) of the serum creatinine is not achieved after two dosage reductions. It is recommended to monitor the serum creatinine after a dosage increase or addition of a NSAID during cyclosporine treatment.

Precaution: Symbicort in hypertension
Budesonide; formoterol should be used with caution in patients with cardiovascular disorders including ischemic cardiac disease, hypertension, cardiac arrhythmias, or QT prolongation. In addition, beta-agonists should be avoided in patients with congenital long

QT syndrome due to the risk of torsade de pointes. Significant changes in systolic and diastolic blood pressures could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. The risk of side effects such as tremor and tachycardia is higher in patients with preexisting coronary artery disease. Budesonide; formoterol should be used with caution in patients with untreated hypokalemia as changes in potassium concentrations have been observed during clinical trials.

Precaution: Triamcinolone in asthma
Triamcinolone inhalant therapy is contraindicated in patients with *acute status asthmaticus* or other types of asthma for which intensive therapy is warranted. Patients should be advised that triamcinolone is not to be used as a bronchodilator and is not indicated for relief of *acute bronchospasm*.

Precaution: Triamcinolone in hypertension
Systemic corticosteroids can cause edema and weight gain. Patients with congestive heart failure or hypertension can have an exacerbation of their condition. Systemic corticosteroids should be used with caution in these patients.

Precaution: Triamcinolone in hypothyroidism
Systemic corticosteroids should be used with extreme caution in patients with psychosis, emotional instability, renal disease, and seizure disorder because the drugs can exacerbate these conditions. Patients with hepatic disease, such as cirrhosis, or hypothyroidism can have an exaggerated response to systemic corticosteroids. Use systemic corticosteroids with caution in these patients.

Precaution: Triamcinolone in skin abrasion
Systemic corticosteroids can aggravate Cushing's syndrome and should be avoided in patients with *Cushing's syndrome*. Prolonged administration of pharmacological doses of systemic corticosteroids or topical preparations (resulting in systemic absorption) may result in hypothalamic-pituitary-adrenal (HPA) suppression and/or manifestations of Cushing's syndrome in some patients. However, the risk of developing HPA suppression while using inhaled or topical triamcinolone only is low. Acute adrenal insufficiency and even death may occur following abrupt discontinuation of prolonged systemic therapy. Triamcinolone should be used with caution when substituting the drug for oral corticosteroid therapy; deaths due to adrenal insufficiency have been reported in asthmatic patients during and following such a transfer. In addition, a withdrawal syndrome unrelated to adrenocortical insufficiency may occur following sudden discontinuation of corticosteroid therapy. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels (see Adverse Reactions). Withdrawal from prolonged systemic corticosteroid therapy should be gradual. HPA suppression can last for up to 12 months following cessation of systemic therapy. Recovery of HPA axis function is generally prompt and complete upon discontinuation of the topical corticosteroid. HPA-suppressed patients may need supplemental corticosteroid treatment during periods of physiologic stress, such as surgical procedures, acute blood loss, or infectious conditions, even after the corticosteroid has been discontinued. Conditions that increase systemic absorption of topical corticosteroids include use over large surface areas, prolonged use, use in areas where the epidermal barrier is disrupted (i.e., skin abrasion), and the use of an occlusive dressing. Patients receiving large doses of triamcinolone applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression and/or manifestations of Cushing's syndrome. If these effects are noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid.

Precaution: Ventolin® HFA in hypertension
Albuterol should be used with caution in patients with cardiovascular disorders including ischemic cardiac disease (coronary artery disease), hypertension, cardiac arrhythmias, tachycardia, or QT prolongation. In addition, beta-agonists should be avoided in patients with congenital long QT syndrome due to the risk of torsade de pointes.[4951] Significant changes in systolic and diastolic blood pressures and heart rate could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. As with other beta-adrenergic agonist medications, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation. Correct pre-existing hypokalemia prior to beta-agonist administration.

Precaution: Ventolin® HFA in renal impairment
The pharmacokinetics of albuterol were studied in a small number of subjects with creatinine clearances between 7-53 mL/minute in comparison to healthy volunteers. The half-life was unchanged; however albuterol clearance was decreased by 67% in those with renal impairment. The manufacturer recommends caution during administration of high doses of inhaled albuterol to patients with renal impairment.[8628]

Allergy Alerts

No warnings noted

References

36. Lin HY, Rocher LL, McQuillan MA et al. Cyclosporine-induced hyperuricemia and gout. N Engl J Med 1989;321:287-292.

51. DeVito JM, Vance JR. Furosemide-associated ototoxicity. Clin Pharm 1983;2:507-9.

52. Rupp W. Pharmacokinetics and pharmacodynamics of Lasix. Scott Med J 1974;19:5-13.

66. Putterman C, Ben-Chetrit E, Caraco Y et al. Colchicine intoxication: Clinical pharmacology, risk factors, features, and management. Sem Arth Rheum 1991;21:143-55.

70. Kuncl RW, Duncan G, Watson D et al. Colchicine myopathy and neuropathy. N Engl J Med 1987;316:1562-8.

256. Luke J, Luke DR, Williams LA et al. Prevention of cyclosporine-induced nephrotoxicity with transdermal clonidine. Clin Pharm 1990;9:49-53.

1096. Gogia H et al. Prevention of tolerance to hemodynamic effects of nitrates with concomitant use of hydralazine in patients with chronic heart failure. J Am Coll Cardiol 1995;26:1575-80.

1162. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991;115:787-96.

1163. Lanza FL, Royer Jr GL, Nelson RS et al. The effects of ibuprofen, indomethacin, aspirin, naproxen, and placebo on the gastric mucosa of normal volunteers. Dig Dis Sci 1979;24:823-8.

1525. Manson JM, Freyssinges C, Ducrocq MB, et al. Postmarketing surveillance of lovastatin and simvastatin exposure during pregnancy. Reproduct Toxicol 1996;10:439-46.

1567. Mueller EA, Kovarik JM, van Bree JB et al. Influence of a fat-rich meal on the pharmacokinetics of a new oral formulation of cyclosporine in a crossover comparison with the market formulation. Pharm Res 1994;11:151-5.

1797. Robbers JE, Tyler VE. *Tyler's Herbs of Choice: the Therapeutic Use of Phytomedicinals*. Binghamton NY: Haworth Herbal Press, Inc.; 1999.

2084. Eisenach JC, DeKock M, Kilmscha W. alpha$_2$-Adrenergic agonist for regional anesthesia. A clinical review of clonidine (1984-1995). Anesthesiology 1996;85:655-74.

2086. Rostaing S, Bonnet F, Levron JC et al. Effect of epidural clonidine on analgesia and pharmacokinetics of epidural fentanyl in postoperative patients. Anesthesiology 1991;75:420-5.

2087. Motsch J, Graber E, Ludwig K. Addition of clonidine enhances postoperative analgesia from epidural morphine: a double-blind study. Anesthesiology 1990;73:1067-73.

2088. Mjahed K, Harrar N, Hamdani M. Lidocaine-clonidine retrobulbar block for cataract surgery in the elderly. Reg Anesth 1996;21:569-75.

2090. Cigarini I, Kaba A, Bonnet F et al. Epidural clonidine combined with bupivacaine for analgesia in labor. Effects on mother and neonate. Reg Anesth 1995;20:113-20.

2305. White MH, Bowden RA, Sandler ES, et al. Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. Clin Infect Dis 1998;27:296-302.

2913. Heptinstall S, Groenewegen WA, Spangenberg P, et al. Inhibition of platelet behaviour by feverfew: a mechanism of action involving sulphydryl groups. Folia Haematol Int Mag Klin Morphol Blutforsch 1988;115:447-9.

2914. Loesche W, Mazurov AV, Voyno-Vasenetskaya TA, et al. Feverfew-an antithrombotic drug? Folia Haematol Int Mag Klin Morphol Blutforsch 1988;115:181-4.

2915. Biggs MJ, Johnson ES, Pesaud NP, et al. Platelet aggregation in patients using feverfew for migraine (letter). Lancet 1982;2:776.

3045. Divi RL, Chang HC, Doerge Dr. Anti-thyroid isoflavones from soybean; isolation, characterization, and mechanisms of action. Biochem Pharmacol 1997;54:1087-96.

3085. Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. Arch Intern Med 2000;160:2429-36.

3098. Burgess CD, Nayson M, Rajasingham S, et al. The extrapulmonary effects of increasing doses of formoterol in patients with asthma. Eur J Clin Pharmacol 1998;54:141-7.

3669. Tsunoda SM, Harris RZ, Christians U, et al. Red wine decreases cyclosporine bioavailability. *Clin Pharmacol Ther* 2001;70:462-7.

3697. Martin JE, Daoud AJ, Schroeder TJ, et al. The clinical and economic potential of cyclosporin drug interactions. *Pharmacoeconomics* 1999;15:317-37.

4064. Fored CM, Ejerblad E, Lindblad P, et al. Acetaminophen, aspirin, and chronic renal failure. *N Engl J Med* 2001;345:1801-8.

4718. Hansten PD, Horn JR. Cytochrome P450 Enzymes and Drug Interactions, Table of Cytochrome P450 Substrates, Inhibitors, Inducers and P-glycoprotein, with Footnotes. In: *The Top 100 Drug Interactions - A guide to Patient Management*. 2008 Edition. Freeland, WA: H&H Publications; 2008:142-157.

4751. McMahon M, Gerich J, Rizza R. Effects of glucocorticoids on carbohydrate metabolism. *Diabetes Metab Rev* 1988;4:17-30.

4882. VFEND® (voriconazole) package insert. New York,NY: Pfizer Inc; 2008 Mar.

4921. Matzke GR, Frye RF. Drug administration in patients with renal insufficiency. Minimizing renal and extrarenal toxicity. *Drug Saf* 1997;16:205-31.

4930. Nydrazid® Injection (isoniazid, INH) package insert. Princeton, NJ: Apothecon; 1997 Aug.

4948. Accolate® (zafirlukast) package insert. Wilmington, DE: AstraZeneca; 2004 Jul.

4951. The University of Arizona Center for Education and Research on Therapeutics (ArizonaCERT). QT drug lists. Retrieved April 15, 2004. Available on the World Wide Web at http://www.qtdrugs.org.

4964. Biaxin® (clarithromycin) package insert. North Chicago, IL: Abbott Laboratories; 2007 March.

4976. Quinidex Extentabs® (quinidine sulfate extended-release tablets) package insert. Richmond, VA: A.H. Robbins Company; 2000 Sept.

4978. Ery-tab® (erythromycin delayed-release tablets) package insert. North Chicago, IL: Abbott Laboratories 2006 Jun.

5005. Raaska K, Niemi M, Neuvonen M, et al. Plasma concentrations of inhaled budesonide and its effects on plasma cortisol are increased by the cytochrome P4503A4 inhibitor itraconazole. *Clin Pharmacol Ther* 2002 Oct;72:362-9.

5006. Falcoz C, et al. Effects of CYP4503A inhibition by ketoconazole on systemic activity of inhaled fluticasone propionate and budesonide. *Eur Respir J* 1997;10(suppl 25):175-6.

5017. Catapres® tablets (clonidine) package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 1998 Apr.

5038. Foradil® Aerolizer (formoterol) package insert. Kenilworth, NJ: Schering Corporation: 2003 Jun.

5044. Norvir® (Ritonavir) package insert. Chicago, IL: Abbott Laboratories; 2008 Aug.

5046. Celebrex® (celecoxib) package insert. New York, NY: Pfizer, Inc.; 2008 Jan.

5062. Amphocin® (amphotericin B) package insert. Kalamazoo, MI: Pharmacia Corporation; 2003 Sep.

5063. Churchill DN et al. Nephrotoxicity associated with combined gentamicin-amphotericin B therapy. *Nephron* 1977;19:176.

5068. AmBisome® (amphotericin B liposome) package insert. Deerfield, IL: Gilead Sciences, Inc.: 2005 Jul.

5106. Foscavir® (foscarnet) package insert. Wilmington, DE: AstraZenica LP; 2007 Oct.

5118. Vistide® (cidofovir) package insert. Foster City, CA: Gilead Sciences, Inc.; 2006 Aug.

5123. Platinol®-AQ (cisplatin) package insert. Princeton, NJ: Bristol-Myers Squibb Company; 2002 Nov.

5132. Termeer A, Hoitsma AJ, Koene RA. Severe nephrotoxicity caused by the combined use of gentamicin and cyclosporine in renal allograft recipients. *Transplantation* 1986;42:220.

5133. Whiting PH, et al. The enhancement of cyclosporine A-induced nephrotoxicity by gentamicin. *Biochem Pharmacol* 1983;32:2025.

5134. Neoral® (cyclosporine) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2005 Aug.

5138. Edecrin® (ethacrynic acid) package insert. Whithouse Station, NJ: Merck & Co.,INC.; 2003 April.

5159. Lasix® (furosemide) package insert. Bridgewater, NJ: Aventis Pharmaceuticals; 2004 Jan.

5163. Clarke TA, Waskell LA. The metabolism of clopidogrel is catalyzed by human cytochrome P450 3A and is inhibited by atorvastatin. *Drug Metab Dispos* 2003;31:53-9.

5164. Wodlinger AM, Pieper JA. The role of clopidogrel in the management of acute coronary syndromes. *Clin Ther* 2003;25:2155-81.

5165. Plavix® (clopidogrel) package insert. New York, NY: Sanofi-Synthelabo; 2004 Oct.

5166. Ticlid® (ticlopidine) package insert. Nutley, NJ: Roche Laboratories, Inc.; 2001 Mar.

5167. Pletal® (cilostazol) package insert. Tokushima, Japan: Otsuka Pharmaceutical Co., Ltd.; 2004 Feb.

5168. Persantine® (dipyridamole) package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2003 May.

5170. Hayes, AH. Therapeutic implications of drug interactions with acetaminophen and aspirin. *Arch Intern Med* 1981;141:301-4.

5173. Cytovene® (ganciclovir) package insert. Nutley, NJ: Roche Laboratories Inc.; 2000 Sept.

5174. Klonopin® (clonazepam) package insert. Nutley, NJ: Roche Laboratories Inc; 2001 Jul.

5177. Polymyxin B package insert. Bedford, OH: Bedford Laboratories; 2004 Feb.

5178. Synthroid® (levothyroxine sodium) package insert. North Chicago, IL: Abbott Laboratories; 2002 July.

5180. Smith CR, Lietman PS.Effect of furosemide on aminoglycoside-induced nephrotoxicity and auditory toxicity in humans. *Antimicrob Agents Chemother* 1983;23:133-7.

5192. Fortovase® (saquinavir) package insert. Nutley, NJ: Roche Pharmaceuticals; 2005 Feb.

5197. Serevent® Diskus (salmeterol xinafoate inhalation powder) package insert. Research Triangle Park, NC: GlaxoSmithKline; 2008 Mar.

5198. Sterile vancomycin hydrochloride, USP package insert. Schaumburg, IL: Abraxis Pharmaceutical Products; 2008 Jul.

5206. Rescriptor® (delavirdine) package insert. La Jolla, CA: Agouron Pharmaceuticals; 2006 Feb.

5232. Fiorinal® (butalbital; aspirin; caffeine) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 1998 Sep.

5262. Proventil® HFA (albuterol sulfate) Inhalational Aerosol package insert. Kenilworth, NJ: Key Pharmaceuticals, Inc.; 2001 Oct.

5269. Toprol-XL® (metoprolol succinate) package insert. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2007 Jul.

5314. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 1998;158:2200-11.

5335. Mevacor® (lovastatin) package insert. Whitehouse Station, NJ: Merck & Co., Inc.; 2005 Nov.

5351. Bumex® (bumetanide) package insert. Nutley, NJ: Roche Laboratories, Inc.; 2003 Mar.

5398. Saw J, Steinhubl SR, Berger PB, et al. Lack of adverse clopidogrel-atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. *Circulation* 2003;108:921-4.

5405. Diflucan® (fluconazole) package insert. New York, NY. Pfizer; 2004 Aug.

5414. Serzone® (nefazodone) package insert. Princeton, NJ: Bristol-Myers Squibb Company; 2003 Sep.

5460. Lipitor® (atorvastation calcium) package insert. New York, NY; Parke-Davis; 2007 Nov.

5462. Crixivan® (indinavir) package insert. Whitehouse Station, NJ: Merck & Co., Inc.; 2008 Apr.

5477. Lau WC, Waskell LA, Walkins PB, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction. *Circulation* 2003;107:32-7.

5492. Tran JQ, Gerber JG, Kerr BM. Delavirdine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet.* 2001;40:207-26.

5506. Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002;41:343-370.

5516. Hepsera® (adefovir dipivoxil) package insert. Foster City, CA: Gilead Sciences, Inc.; 2006 Sep.

5572. Viracept® (nelfinavir mesylate) package insert. La Jolla, CA: Agouron Pharmaceuticals, Inc.; 2008 Sep.

5635. Fluvoxamine maleate package insert. Laurelton, NY: Eon Labs, Inc.; March 2005.

5717. U.S. Department of Health and Human Services (DHHS), FDA, 21 CFR Part 343 (Docket No. 77N-094A). Internal analgesic, antipyretic, and antirheumatic drug products for over-the-counter human use; final rule for professional labeling of aspirin, buffered aspirin, and aspirin in combination with antacid drug products. Retrieved May 6, 2004. Published October 23, 1998 on the World Wide Web at: http://www.fda.gov.

5718. Bouvy ML, Heerdink ER, Hoes AW, et al. Effects of NSAIDs on the incidence of hospitalisations for renal dysfunction in users of ACE inhibitors. *Drug Saf* 2003;26:983-9.

5738. Prozac® (fluoxetine hydrochloride). Indianapolis, IN: Eli Lilly and Company; 2003 Nov.

5769. Comtan® (entacapone) package insert. East Hanover, NJ: Novartis Pharmaceuticals; 2000 March.

5825. Norvasc® (amlodipine) package insert. New York, NY: Pfizer Labs; 2005 Mar.

5911. Wang JJ, Lee CL, Pan TM. Improvement of monacolin K, gama-aminobutyric acid and citrinin production ratio as a function of environmental conditions of Monascus purpureus NTU 601. *J Ind Microbiol Biotechnol* 2003;30:669-76.

5928. DeVane CL, Donovan JL, Liston HL, et al. Comparative CYP3A4 inhibitory effects of venlafaxine, fluoxetine, sertraline, and nefazodone in healthy volunteers. *J Clin Psychopharmacol*. 2004;24:4-10.

5936. Sandimmune® (cyclosporine) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2002 Mar.

5944. Johnson RH, Eisenhofer G, Lambie DG. The effects of acute and chronic ingestion of ethanol on the autonomic nervous system. *Drug Alcohol Depend* 1986;18:319-28.

6035. Hydralazine package insert. Spring Valley, NY: Par Pharmaceutical, Inc; 2003 June.

6060. Takkouche B, Etminan M, Caamano F, et al. Interaction between aspirin and ACE inhibitors: resolving discrepancies using a meta-analysis. *Drug Safety* 2002;25:373-8.

6124. Nitro-Dur® (nitroglycerin) package insert. Kenilworth, NJ; Key Pharmaceuticals, Inc.; 2003 August.

6135. Zaroxyln® (metolazone) package insert. Rochester, NY: Celltech Pharmaceuticals, Inc.; 2001 May.

6192. Cardizem® LA (diltiazem) package insert. Mississauga, ON: Biovail Corporation; 2006 Apr.

6268. Cytomel® (liothyronine) package insert. St. Louis, MO: Jones Pharma Incorporated; 2001 Nov.

6278. Hyperstat® (diazoxide) injection package insert. Kenilworth, NJ: Schering Corporation; 1985 Feb.

6289. Hoffman BB, Lefkowitz RJ. Catecholamines and sympathomimetic drugs. Gilman AG, Rall TW, Nies AS, Taylor P, (eds.) In: Goodman and Gilman's Pharmacological Basis of Therapeutics. 8th ed., New York, Pergamon Press. 1990. 187-91.

6318. Zometa® (zoledronic acid) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2008 Mar.

6341. Seixas FA. Alcohol and its drug interactions. *Ann Intern Med* 1975;83:86-92.

6439. Guazzi M, Brambilla R, Reina G, et al. Aspirin-angiotensin-converting enzyme inhibitor coadministration and mortality in patients with heart failure: a dose-related adverse effect of aspirin. *Arch Intern Med* 2003;163:1574-9.

6473. Ambien® (zolpidem) package insert. New York, NY: Sanofi-Synthelabo Inc; 2007 Mar.

6524. Deltasone® (prednisone) package insert. Kalamazoo, MI: Pharmacia & Upjohn Co.; 2002 April.

6556. Welker HA, Wiltshire H, Bullingham R. Clinical pharmacokinetics of mibefradil. *Clin Pharmacokinet.* 1998;35:405-23.

6646. Ullmann AJ. Review of the safety, tolerability, and drug interactions of the new antifungal agents caspofungin and voriconazole. *Curr Med Res Opin* 2003;19:263-71.

6714. Lam YWF, Shepherd AMM. Drug interactions in hypertensive patients: pharmacokinetic, pharmacodynamic, and genetic considerations. *Clin Pharmacokinet* 1990;18:295-317.

6762. Hydrocotone® (hydrocortisone) package insert. Whithouse Station, NJ: Merck Co., Inc; 2001 Nov.

6763. Medrol® (methylprednisolone) package insert. Kalamazoo, MI: The Upjohn Company; 1990 Sep.

6776. Pediapred® (prednisolone) package insert. Rochester, NY: Celltech Pharmaceuticals, Inc.; 1999 Mar.

6778. Nubain® (nalbuphine hydrochloride) package insert. Chadds Ford, PA: Endo Pharmaceuticals Inc; 2003 May.

6859. Insel PA. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Molinoff PB, et al., eds. *Goodman and Gilman's the pharmacological basis of therapeutics*, 9th edn. New York: McGraw Hill, 1996;617-657.

6865. Entocort™ EC (budesonide) capsules package insert. Sodertalje, Sweden: AstraZeneca Pharmaceuticals; 2005 Apr.

6866. McLellan RA, Drobitch RK, Monshouwer M, Renton KW. Fluoroquinolone antibiotics inhibit cytochrome P450-mediated microsomal drug metabolism in rat and human. *Drug Metab Dispos* 1996;24:1134-8.

6892. Evers AS, Crowder CM. General Anesthetics. Gilman AG, Hardman JG, Limbird LE, (eds.) In: Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed., New York, McGraw-Hill Companies. 2001:337-365.

7151. Minetti EE, Minetti L. Multiple organ failure in a kidney transplant patient receiving both colchicine and cyclosporine. *J Nephrol.* 2003;16:421-5.

7152. Fam AG. Gout in the elderly. Clinical presentation and treatment. *Drugs Aging.* 1998;13:229-43.

7168. Charney DS, Mihic SJ, Harris RA. Hypnotics and sedatives. Gilman AG, Hardman JG, Limbird LE, (eds.) In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 10th ed., New York, McGraw-Hill Companies. 2001:399-427.

7181. Kaufman DW, Kelly JP, Wiholm BE, et al. The risk of acute major upper gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption. *Am J Gastroenterol* 1999;94:3189-96.

7185. Marinol® (dronabinol, THC) package insert. Marietta, GA: Unimed Pharmaceuticals, Inc.; 2003 May.

7198. Fleming M, Mihic SJ, Harris RA. Ethanol. Gilman AG, Hardman JG, Limbird LE, (eds.) In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 10th ed., New York, McGraw-Hill Companies. 2001:429-445.

7438. Emend® capsules (aprepitant) package insert. Whitehouse Station, NJ: Merck & Co., Inc.; 2007 Nov.

7523. Frampton JE, Foster RH. Pregabalin: in the treatment of postherpetic neuralgia. *Drugs.* 2005;65:111-8.

7677. Colchicine Injection, USP package insert. Bedford, OH: Bedford Laboratories; 1999 Apr.

7714. Schimmer B, Parker K. Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: Hardman JG, Limbird LE, Molinoff PB, et al., eds. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, 10th edition. New York: McGraw Hill, 2001;1649-1674.

7799. Aredia® (pamidronate) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2007 Nov.

7823. MST 600 (magnesium salicylate tetrahydrate) package insert. Hauppauge, NY: Contract Pharmacal Corporation; 2004 May.

7895. Patten BM, Oliver KL, Engel WK. Adverse interaction between steroid hormones and anticholinesterase drugs. *Neurology* 1974;24:442-9.

7896. Brunner NG, Namba T, Grob D. Corticosteroids in management of severe, generalized myasthenia gravis. *Neurology* 1972;22:603-10.

8488. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation* 2004;110;e82-e293.

8628. ProAir™ HFA (albuterol sulfate) Inhalational Aerosol package insert. Miami, Fl; IVAX Laboratories: 2005 Oct.

8629. Rhinocort® Aqua™ (budesonide) nasal spray package insert. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2001.

8783. Colchicine Tablets, USP package insert. Corona, CA: Watson Laboratories, Inc.; 2001 Jun.

8833. Bristol-Myers Squibb Company Press Release, March 12, 2006. New study furthers understanding of the role of dual antiplatelet therapy in the prevention of atherothrombotic events, including heart attack, stroke or cardiovascular death in broad population. Certain subgroups may benefit from dual therapy, for others it should be avoided.

9044. Cesamet™ (nabilone) package insert. Costa Mesa, CA: Valeant Pharmaceuticals International; 2006 May.

9371. Poon IO, Braun U. High prevalence of orthostatic hypotension and its correlation with potentially causative medications among elderly veterans. *J Clin Pharm Ther* 2005;30:173-8.

9504. Jin M, Shimada T, Shintani M, et al. Long-term levothyroxine treatment decreases the oral bioavailability of cyclosporin A by inducing P-glycoprotein in small intestine. *Drug Metab Pharmacokinet* 2005;20:324-30.

9508. Siegmund W, Altmannsberger S, Paneitz A, et al. Effect of levothyroxine administration on intestinal P-glycoprotein expression: consequences for drug disposition. *Clin Pharmacol Ther* 2002;72:256-64.

9798. Symbicort® (budesonide; formoterol fumarate dihydrate) inhalation aerosol package insert. Wilmington, DE: AstraZeneca LP; 2006 Jul.

9799. Faul JL, Cormican LJ, et al. Deteriorating diabetic control associated with high-dose inhaled budesonide. *Eur Respir J* 1999;14:242-3.

10989. Jadoul M, Hene RJ. Ranitidine and the cyclosporine-treated recipient. *Transplantation* 1989;48:359.

10990. Jarowenko MV, van Buren CT, Kramer WG, et al. Ranitidine, cimetine, and the cyclosporine-treated recipient. *Transplantation* 1986;42:311.

11130. Hsu WC, Chen WH, Chang MT, et al. Colchicine-induced acute myopathy in a patient with concomitant use of simvastatin. *Clin Neuropharmacol* 2002;25:266-8.

11131. Phanish MK, Krishnamurthy S, Bloodworth LL. Colchicine-induced rhabdomyolysis. *Am J Med* 2003;114:166-7.

11132. Baker SK, Goodwin S, Sur M, et al. Cytoskeletal myotoxicity from simvastatin and colchicine. *Muscle Nerve* 2004;30:799-802.

11133. Atasoyu EM, Evrenkaya TR, Solmazgul E. Possible colchicine rhabdomyolysis in a fluvastatin-treated patient. *Ann Pharmacother* 2005;39:1358-9.

11134. Alayli G, Cengiz K, Canturk F, et al. Acute myopathy in a patient with concomitant use of pravastatin and colchicine. *Ann Pharmacother* 2005;39:1358-61.

11135. Torgovnick J, Sethi N, Arsura E. Colchicine and HGM Co-A reductase inhibitors induced myopathy: a case report. *Neurotoxicity* 2006;27:1126-7.

11136. Tufan A, Dede DS, Cavus S, et al. Rhabdomyolysis in a patient treated with colchicine and atorvastatin. *Ann Pharmacother* 2006;40:1466-9.

11137. Justiniano M, Dold S, Espinoza LR. Rapid onset of muscle weakness (rhabdomyolysis) associated with the combined use of simvastatin and colchicine. *J Clin Rheumatol* 2007;13:266-8.

11138. Francis L, Bonilla E, Soforo E, et al. Fatal toxic myopathy attributed to propofol, methylprednisolone, and cyclosporine after prior exposure to colchicine and simvastatin. *Clin Rheumatol* 2008;27:129-31.