Patient Profile for Upshaw, Jr., Marion

General Information

ID:	mujr90292011
Prescriber:	Harley Davidson M.D.
Name:	Upshaw, Jr., Marion
Address:	54 Browns Mill Road
City:	Anniston
State:	AL
Zip:	40343
Country:	USA
Phone:	home 123.456.7890 cell123.456.3456

Current Conditions

- arthralgia
- bladder obstruction
- bone pain
- depression
- gastroesophageal reflux disease (GERD)
- gouty arthritis
- hypertension
- macular degeneration
- neuropathic pain
- nutritional supplementation
- osteoarthritis
- osteoporosis prophylaxis
- pyrosis (heartburn)
- renal impairment
- restless legs syndrome (RLS)
- severe pain
- spinal cord compression
- sulfonamide hypersensitivity
- vertebral disc herniation

Current Allergies

- sulfonamide hypersensitivity

Current Medications

- Medication
- Amrix® Dosage: 15mg Sig: at bedtime
- Arthrotec® Dosage: 50mg Sig: twice a day
- Calcium Carbonate Dosage: 600mg Sig: two daily
- Centrum® Silver® Sig: daily
- Chelated Calcium Magnesium Tablets Sig: daily
- Colchicine Dosage: 0.6mg Sig: twice a day for side pain
- Cozaar® Dosage: 50mg Sig: daily
- Hydrochlorothiazide, HCTZ Dosage: 25mg Sig: Mon - Wed - Fri
- Mirtazapine Dosage: 30mg Sig: at bedtime
- Neurontin® Dosage: 400mg Sig: twice a day
- OxyContin® Dosage: 20mg Sig: every 12 hours
- Protonix® Dosage: 40mg Sig: twice a day
- Requip® Sig: one each afternoon

Dosing Parameters

Gender:	Male
Birthdate:	8/8/1928
Weight:	60 kgs
Height:	165.1 cm
Ideal Body Weight:	62.69 kgs
Body Surface Area:	1.66 m²
Serum Creatinine:	1.57 mg/dL
Creatinine Clearance:	30.25 mL/min

Notes

Title: Initial Interview & Assessment
Date:01/17/2012

This 84 year old white male presents with multiple major problems from severe GERD to severe bone and muscle pain. Of course he has problems with depression, hypertension, arthralgia, kyphosis, vertebra disc herniation, osteoporosis, neuropathy and gouty arthritis. The patient is in constant pain which requires an implant pain device along with opiates (Oxycontin 20mg twice a day and 10mg as needed for breakthrough pain. A review of his GERD medication shows that he is taking 80mg daily of Protonix which is twice the normal dose for any indication for the use of Proton Pump Inhibitors for the past 10+ years. The removal of the Protonix will be a long process but will have to be accomplished before we can work to develop a drug management program that will give him a comfortable quality of life. We started a tapering of the PPI back in the middle of June 2011 and have finally stopped the last 20mg every other day last week. This has been a very agonizing process that he has consistently stuck with even though it was very painful and difficult to continue . We used Apple Cider Vinegar and Honey (15cc of each) for reflux reduction along with Melatonin 9mg at night to try and negotiate some changes in his circadian rhythm to slow down or stop the hyper secretions consistent with PPI therapy withdrawal. This mammoth influx of additional stomach acids is uncontrollable and will persist throughout the tapering and withdrawal of the PPI therapy. Studies have shown that at normal dosing long term use of PPI therapy is not recommended due to the leaching of Calcium from the bones and other anemia problems that can be fatal. Much of his pain is arthritic in nature but most of the uncontrollable pain is due to bone pain due to the leaching of the Calcium and the deteriorating of the bones. Currently he has completed about 10 days of PPI free and no reflux. Now is the time to try and calm down the smooth muscles of the stomach and address his blood pressure problems, depression and neuropathic pains. Although use of chlordiazepoxide (Librium) in this age patient is not recommended, I plan to use it combined with Clidinium (an antimuscarinic) for the relaxation of the smooth muscles of the gut for a month or two or until the gut is more normal. Upon starting this tapering process he was also taking Arthrotec for his arthritis which we discontinued along with the muscle relaxant Amrix (cyclobenzapine). Stopping all the vitamin

supplements was done since the consistently basic stomach would not allow for any absorption of any of the vitamins and minerals. A trial change to Venlafaxine was attempted also months ago but he had such strong sweating episodes that we stopped until a few weeks ago and retried at 75mg at bedtime which has proven to be successful. We will move this dosing upwards as we make changes to most of the other medications, nutritional supplements and analgesic therapy. Also during this tapering period we had stopped the dopamine agonist (Requip) but retained his Cholchicine dose which should never have been used on a twice a day basis but has continued for the past 10 years. Stopping the colchicine will of course be slowly tapered to discontinue as we initiate the analgesic changes. Changing from the Oxycontin dosing which makes for peaks and troughs in the pain control to a fentanyl patch which will provide 24 hour pain control with less opiates problems should make his quality of life better. This tapering will be slow and should result in a successful outcome. Initiation of vitamin supplements as well as high doses of Calcium to try and supplement the deteriorating bones should eventually reduce bone pain and reduce his risk of fractures. Hopefully these changes will allow for the removal of the implanted pain control device. Review of his depression/anxiety consistent with the Geriatric Depression Scale showed a score of 8 which shows treatment is needed. Using the Mirtazepine was not appropriate due to a calculated Creatinine Clearance of 30cc/min. Additionally, using an ARB (Cozaar) is not recommended in this range of renal impairment and changes to the Venlafaxine ER up to 150mg at bedtime and benzothiazepine calcium channel blocker (Diltiazem CD) will be initiated. Also, use of hydrochlorthiazide, a thiazide diuretic is not recommended in patients with this stage of renal impairment. Once we have Venlafaxine ER to the 150mg dosing the need for the Neurontin should cease and will be removed. Additionally it was discovered that the patient takes Preservision vitamins for his macular degeneration which I stopped until we can remove the PPI therapy and then reinitiate using the individual pigmentations that are found in the macular of the eye. The Beta Carotene, Lutine, and Zeaxanthin will be individually supplemented to get the proper amount consistent with the Harvard studies on this supplementation and then a Centrum Silver (or like store brand) for the Zinc and Copper will complete the regimen.

Additionally for the physician's analysis and support of each statement made in this report, there are three (3) pages of references to substantiate all findings and recommendations.

Title: Drug Therapy Evaluation & Recommendations
Date: 01/17/2012

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

Amrix - cyclobenzapine a strong anticholinergic drug is positively contraindicated in the geriatric patient. Anticholinergic effects appear most frequently and cause the greatest morbidity in geriatric patients. Cyclobenzaprine is generally not recommended for use in patients 65 years of age and older. The use of this drug exacerbated more problems with GERD.

Arthrotec - combining an NSAID (diclofenac) with misoprostol (a drug to decrease gastric secretions) has been proven to be ineffective and especially using the (diclofenac) an NSAID that is positively contraindicated in the very old is an extremely bad choice of drug therapy. Diclofenac; misoprostol should be used with caution in patients with a history of or active GI disease including peptic ulcer disease, ulcerative colitis, or GI bleeding. It is recommended not to initiate therapy in these patients due to the likely increased frequency of adverse reactions. Other patients at increased risk for NSAID-induced GI bleeding include those receiving concurrent myelosuppressive chemotherapy, corticosteroid therapy, or anticoagulant therapy, tobacco smoking patients and geriatric patients. All patients receiving prolonged treatment should be routinely monitored for potential GI ulceration and bleeding.

Calcium Carbonate - use of calcium supplements are not of any benefit due to the PPI therapy. Calcium carbonate is acid sensitive and requires a strong acid media to break down and be absorbed. The geriatric patient is not going to produce the acids in the gut to make the calcium carbonate soluble and with the PPI therapy it is totally ineffective. After stopping the PPI therapy using Calcium Citrate which is soluble in the geriatric gut and is absorbed will be introduced.

Centrum Silver - like all the supplements are stopped due to the PPI therapy and will be restarted upon total clearance of the PPI therapy. The incorporation of the macular supplements with this excellent multivitamin will provide the additional Zinc and Copper necessary for the macular supplementation.

Chelated Calcium/Magnesium - this supplement just passed through the body consistent with the PPI therapy and was of no value. Continuation may be considered at a later date.

Colchicine - this is an excellent drug for use in acute gout attacks but long term use in not recommended and can be harmful. 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. The patient suffers from severe thrombocytopenia (PLT = 66) and although this drug was given many years ago for pain in his side an effort to taper and remove is essential. His uric acid levels were always in acceptable range but the physician allowed him to remain on this potent drug for over

10 years. Very serious health conditions are occurring consistent with the use of the Colchicine and many other drugs in his present regimen.

Cozaar - an Angiotensin II Receptor antagonist is not recommended in patients with renal impairment (CrCl = 30cc/min) due to changes in the Renin system. This changes the effects of the drug completely and exacerbates problems with electrolytes and muscle pain and myalgia. His current Serum Potassium = 4.4 or high normal. Anaphylactic reactions (anaphylactoid reactions) and angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue have been reported in patients treated with losartan. The potential of intestinal angioedema is high and can be a contributor to the GI problems experienced by this patient. Changes to a benzothiazepine calcium channel blocker which is very geriatric friendly will be suggested.

Hydrochlorthiazide - use of thiazide diuretics are not recommended in patients with this stage of renal impairment (CrCl = 30cc/min). The use of a long half life LOOP (torsemide) will be suggested and will support the patient needs with less potential for Calcium and Potassium loss.

Mirtazapine - Mirtazapine should be used cautiously in geriatric patients; the elderly exhibit reduced drug clearance and need lower initial doses and slower dosage titration compared to younger adults. Multiple problems in the very old can occur. The following events are listed by body system. Body as a whole: abdominal pain, malaise. Cardiovascular: hypertension, vasodilation (flushing). Digestive/GI: anorexia, vomiting. Metabolic: polydipsia (increased thirst). Musculoskeletal: arthralgia, myasthenia. Nervous system/Psychiatric: agitation, anxiety, amnesia, apathy, depression, dyskinesia (reported as either hypokinesia or hyperkinesia), hypoesthesia, paresthesias, twitching, and vertigo. Respiratory: increased cough, sinusitis. Skin and Appendages: pruritus, rash (unspecified). Urogenital system: urinary tract infection. Using the Venlafaxine ER will provide the antidepressant/anxiety support as well as the support of neuropathic pain.

Neurontin - an antiepileptic used in treating neuropathic pain will not be needed and will be discontinued when maximum dose of Venlafaxine ER is reached.

OxyContin - opiates, Oxycodone, may not be the drug of choice in treating this patient. Oxycodone is an oral semisynthetic opiate agonist derived from the opioid alkaloid, thebaine, and is similar to other phenanthrene derivatives such as hydrocodone and morphine. Geriatric patients are more sensitive to the analgesic effects of oxycodone and other opiate agonists as they experience higher peak serum levels and a longer duration of pain relief. In addition, elderly patients are more susceptible to adverse reactions from opiate agonists; especially sedation and respiratory depression probably as a result of altered distribution of the drug and decreased elimination. To avoid peaks and troughs in pain control, a change to a fentanyl patch to be applied every three days may result in better pain management. A trial change will be suggested.

Protonix - Use proton pump inhibitors (PPIs) in patients with or who have risk factors for osteoporosis cautiously. PPIs have been associated with a possible increased risk of bone fractures of the hip, wrist, and spine. There have been six epidemiological studies that have reported an increased risk of fractures with the use of PPIs; the studies compared claims data of

patients treated with PPIs versus individuals who were not using PPIs. Depending on the study, exposure to PPIs ranged between 1–12 years. The emergence of fractures varied among studies; one study reported an increase in fractures with use of PPIs in the previous year and another study found an increase after 5–7 years of PPI use. Increased risk was primarily observed in patients >= 50 years old (including geriatric patients), patients taking prescription PPIs for at least one year, and patients who had been taking high doses (doses greater than those recommended with OTC use). This patient was prescribed four (4) times the recommended does for the past 10 years.

Requip - a dopamine agonist is not recommended in the very old. Hallucinations have been reported in patients receiving ropinirole alone or in combination with L-dopa. Hallucinations have been reported with ropinirole use in patients with Parkinson's disease and in patients using ropinirole for Restless Leg Syndrome. The incidence of hallucinations is increased in geriatric patients as well as during concurrent use of ropinirole with other dopaminergic agents, such as entacapone or L-dopa. This drug has been stopped.

Drug Therapy Management

Stop all of the drugs listed:

Stop: Amrix 15mg (stopped several months ago)

Stop: Arthrotec 50mg (stopped several months ago)

Stop: Calcium Carbonate 600mg

Stop: Chelated Calcium Magnesium tablets

Stop: Colchicine 0.6mg
(taper to discontinue 0.6mg AM and 0.6mg every other PM x 7 days then 0.6mg AM x 7 days, then 0.6mg every other AM x 4 doses and discontinue completely)

Stop: Cozaar 50mg

Stop: Hydrochlorthiazide HCTZ 25mg

Stop: Mirtazapine 30mg

Stop: Neurontin 400mg (taper to discontinue 400mg AM x 7 days, then Stop).

Stop: Oxycontin 20mg & 10mg (Using tapering instructions listed with Fentanyl dose)

Stop: Protonix 40mg (this tapering has been done and patient free of all PPI drugs)

Stop: Requip (this drug was stopped several months ago)

Stop: All Nutraceuticals

New Drug Therapy

Start the following drugs:
Diltiazem CD 120mg daily
Torsemide 5mg daily
Venlafaxine ER 75mg at bedtime x 5 days then 150mg at bedtime
Librax (CLIDINIUM) cap 1 AM and PM daily x 30 days then AM daily x 30 days
Melatonin 9mg at bedtime
Apple Cider Vinegar & Honey 15cc of each at bedtime and as needed for heartburn
Fentanyl (Duragesic) Patch 25mcg apply every 3rd morning and remove old patch

Taper to discontinue OxyContin 10mg AM and 20mg PM x 6 days, then 10mg AM and PM x 6 days, then 10mg AM x 6 days and stop completely IF BREAKTHROUGH PAIN OCCURS: use 10mg every 8 hours and call me for further instructions) (Get 4 patches at a time until we have completed the taper/titration process since we may have to increase the patch strength or lower the strength as we progress. After we have completed the changeover then we can get a month's supply of the correct patch dosage)

Centrum Silver (or like store brand) daily
Beta Carotene 15mg (25,000 U) daily
Lutein 20mg daily
Zeaxanthin 6mg (Solray Zeaxanthin Plus) daily
Folic Acid 1mg daily
Vitamin B12 1000mcg IM weekly x 8 weeks then monthly
Fish Oil 1200mg three times a day
Citracal Plus Vitamin D tab 1 three times a day
Vitamin D2 1000 IU daily

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. It may take more or less of the Diltiazem CD depending on how your blood pressure log runs. Make sure that you get the pharmacist to dispense the Librax (CLIDINIUM) type which you will take twice a day for a month then once a day for a month then stop. You may have some breakthrough pain and if this occurs supplement with the 10mg OxyContin and call me. We can go up on the patch dose if necessary. I am planning on this controlling the pain and allowing for the removal of the implant in a few months. Keep your fingers crossed that this will work. The extra amounts of vitamins are for a start and down the road we may want to change some around or stop some based on your physical response as well as your laboratory values. I believe that the tapering of the Colchicine will work since we are removing many of the causes for the pain. Although if it doesn't we can start on Allopurinol which stops the manufacture of Uric acid as another approach to not using the Colchicine. Your current blood count values (PLT = 66) are seriously low and must improve and stopping the Colchicine and other drugs should make this value get back to normal. If in a few weeks the appetite does not return then we can look at this problem and respond. It is just like getting off the PPI therapy in that it takes much effort, discomfort and perseverance. I look for much better quality of life for you in a few months.

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 March visit. Please call in April and make an appointment for some time in March.

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 April or the first of March 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

Cyclobenzaprine (Amrix®) **and Oxycodone** (OxyContin®)

Severity: Moderate

Cyclobenzaprine may cause additive CNS depression if used concomitantly with other CNS depressants, such as opiate agonists. Combination therapy can cause additive effects of sedation and dizziness, which can impair the patient's ability to undertake tasks requiring mental alertness. Dosage adjustments of either or both medications may be necessary.[5155]

Concomitant use of oxycodone with skeletal muscle relaxants (e.g., carisoprodol, methocarbamol) may cause additive CNS effects, such as respiratory depression and/or sedation. For example, a woman was found unconscious and unarousable after taking 8-10 tablets of carisoprodol 350 mg (she was prescribed 1 tablet four times daily) plus her usual extended-release oxycodone 40 mg twice daily. Intravenous administration of naloxone 2 mg rapidly restored her alertness. She had not taken extra oxycodone and had a negative drug screen.[6430] In addition to additive CNS effects, the neuromuscular blocking action of skeletal muscle relaxants may be enhanced by concomitant oxycodone usage, which can increase the degree of respiratory depression.[6412] Caution should be exercised during concomitant use of any CNS-depressant drugs and oxycodone. Oxycodone should be initiated at one-third to one-half the usual dosage in patients that are concurrently receiving other CNS depressants.[6423]

Cyclobenzaprine (Amrix®) **and Mirtazapine**

Severity: High

Cautious use of cyclobenzaprine and drugs that increase serotonin concentrations such as mirtazapine is advised because of the possibility of serotonin syndrome. A patient taking phenelzine developed confusion, agitation, tremors, tachycardia, diaphoresis, hallucinations, delusions, and fever after the third oral dose of cyclobenzaprine 10 mg, which was prescribed every 8 hours. The patient remained symptomatic despite cyclobenzaprine and opiate discontinuation. As serotonin syndrome was suspected, phenelzine was discontinued. All of her symptoms progressively resolved over the next 3 days. Reinitiation of phenelzine was without consequences. NOTE: Concurrent cyclobenzaprine and monoamine oxidase inhibitor use is contraindicated (see Interactions). A suspected case of serotonin syndrome was also noted in a man who took duloxetine, opiates, and cyclobenzaprine. Cyclobenzaprine 10 mg orally every 8 hours was started very shortly before the onset of his confusion. Over a 5-day period, he developed worsening confusion, hallucinations, diaphoresis, tachycardia, tremors, marked agitation, spontaneous sustained clonus, and multifocal myoclonus. He recovered over several days after duloxetine and cyclobenzaprine discontinuation and cyproheptadine initiation.[10831]

Consistent with the pharmacology of mirtazapine and the drug's side effect profile, additive effects may occur with other CNS-active agents.[5366] Mirtazapine should be administered with caution with such agents because the CNS effects on cognitive performance and motor skills can be additive; the manufacturer specifically warns against coadministration of ethanol; patients should avoid combination of mirtazapine with alcoholic beverages.[5366] Use particular caution with anxiolytics, sedatives, and hypnotics; in studies, there has been an additive impairment of motor skills and impaired learning acquisition (pharmacodynamic effect) when mirtazapine is coadministered with a benzodiazepine (i.e., diazepam); mirtazapine and diazepam concentrations were not significantly affected.[5366] Additive sedative effects could also potentially occur with barbiturates, general anesthetics, sedating H_1-blockers, opiate agonists, buprenorphine, butorphanol, nalbuphine, pentazocine, dronabinol, THC, nabilone [9044], phenothiazines, skeletal muscle relaxants, tramadol, or tricyclic antidepressants. Use together with caution.

Diclofenac; Misoprostol (Arthrotec®) **and Calcium Carbonate**

Severity: Low

Antacids reduce the bioavailability of misoprostol acid and may also delay absorption of diclofenac sodium. Administration of magnesium-containing antacids can exacerbate misoprostol-induced diarrhea and is not recommended.[8758] Therefore, if an antacid is indicated during therapy with diclofenac; misoprostol combinations, an aluminum-containing antacid is preferred.

Diclofenac; Misoprostol (Arthrotec®) **and Hydrochlorothiazide, HCTZ**

Severity: Low

NSAIDs, to varying degrees, have been associated with an elevation in blood pressure (approximately 5 mm Hg) when given over a period of weeks. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs may decrease the effect of antihypertensive agents through various mechanisms including renal and peripheral vasoactive pathways. NSAIDs have been shown to attenuate the effects of diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), vasodilators, central alpha-2 agonists, peripheral alpha-1 blockers, and angiotensin II blockers. Diclofenac can reduce the natriuretic effect of furosemide and thiazide diuretics in some patients. The effect has been attributed to renal prostaglandin synthesis inhibition by diclofenac.[7813] Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs.[4087] Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.[3154] Closely observe the patient for signs of renal failure, and increased serum potassium concentrations may occur with concurrent potassium sparing diuretic usage.

NSAIDs can cause sodium and fluid retention as well as increase peripheral vascular resistance. NSAIDs can decrease the diuretic, natriuretic, and antihypertensive actions of diuretics,[5917] possibly through inhibition of renal prostaglandin synthesis. Concomitant administration of NSAIDs with diuretics can also increase the risk for renal insufficiency secondary to decreased renal blood flow. Patients should be monitored for changes in the effectiveness of their diuretic therapy and for signs and symptoms of renal impairment. Among NSAIDs, indomethacin, naproxen, and piroxicam may have the greatest pressor effect, while the effects of sulindac and nabumetone may be significantly less.

Diclofenac; Misoprostol (Arthrotec®) **and Losartan** (Cozaar®)

Severity: Low

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NSAIDs may alter the response to antihypertensive agents due to inhibition of vasodilatory prostaglandins.[805] Among NSAIDs, indomethacin, naproxen, and piroxicam may have the greatest pressor effect, while the effects of sulindac and nabumetone may be significantly less. In some patients with compromised renal function who are being treated with NSAIDs, coadministration of angiotensin II receptor antagonists, including losartan, may result in further deterioration of renal function. These effects are usually reversible. Reports suggest that NSAIDs (including selective COX-2 inhibitors) may diminish the antihypertensive effect of angiotensin II receptor antagonists. This interaction should be considered in patients receiving NSAIDs concomitantly with angiotensin II receptor antagonists.[5339]

Diclofenac; Misoprostol (Arthrotec®) **and tobacco**

Severity: Moderate

Concomitant use of diclofenac; misoprostol with tobacco may enhance the risk of gastrointestinal (GI) side effects. Patients with tobacco use may have an increased risk of GI bleeding with nonsteroidal anti-inflammatory drug usage.[7254] Patients using tobacco and diclofenac concurrently should be monitored closely for bleeding.

Calcium Carbonate and Ergocalciferol, Vitamin D2 (found in Centrum® Silver®)

Severity: Moderate

Calcium is often combined with vitamin D in nutritional supplementation products to supply the recommended RDA/RDI in the general population and to promote optimum bone health. The concurrent use of vitamin D with calcium carbonate or other calcium salts is generally beneficial; in some patients, however, because ergocalciferol can increase serum calcium concentrations,[6916] this combination may result in hypercalcemia.

The concurrent use of vitamin D analogs with calcium-containing antacids or other calcium salts may contribute to vitamin D-induced hypercalcemia.[4686] Calcium replacement or use of calcium-based phosphate binders may be required in patients receiving vitamin D analogs, but careful monitoring of serum calcium and phosphorus levels is needed.

Calcium Carbonate and Hydrochlorothiazide, HCTZ

Severity: Moderate

The simultaneous administration of thiazide diuretics and calcium salts or calcium carbonate may lead to hypercalcemia. Thiazides cause a decrease in renal tubular excretion of calcium as well as increase in distal tubular reabsorption. Moderate increases in serum calcium have been seen during the treatment with thiazides; if calcium salts are used concomitantly, careful monitoring of serum calcium in recommended.[5917]

The simultaneous administration of thiazide diuretics and calcium carbonate may lead to hypercalcemia. Thiazides cause a decrease in renal tubular excretion of calcium as well as increase in distal tubular reabsorption. Moderate increases in serum calcium have been seen during the treatment with thiazides; if calcium salts are used concomitantly, careful monitoring of serum calcium in recommended.[5917]

Calcium Carbonate and Gabapentin (Neurontin®)

Severity: High

It is recommended that gabapentin be taken at least 2 hours following the administration of antacids in order to avoid a significant interaction. While not specifically reported with calcium carbonate, antacids (e.g., aluminum hydroxide; magnesium hydroxide) have been shown to reduce the oral bioavailability of gabapentin by roughly 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after the antacid.[4703]

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Calcium Carbonate and Phosphorus Salts (found in Centrum® Silver®)

Severity: Moderate

The oral absorption of phosphorus is reduced by ingestion of aluminum-containing antacids (e.g., aluminum hydroxide) and by pharmacologic doses of calcium carbonate or other phosphate-lowering calcium salts (e.g., calcium acetate). There is, however, no significant interference with phosphorus absorption by oral dietary calcium at intakes within the typical adult range.[7800] Phosphate may bind magnesium salts as well; magnesium-containing antacids (e.g., magnesium carbonate, magnesium hydroxide) may also limit phosphorus absorption or phosphorus may limit magnesium absorption.[7800] If the patient requires multiple mineral supplements or the co-prescription of antacids, it may be wise to separate the administration of phosphorus salts from aluminum, calcium, or magnesium containing products. In some instances the administration of calcium salts, calcium carbonate, or an aluminum hydroxide product is used therapeutically (e.g., uremia) to decrease serum phosphorus levels, so the administration of phosphorus supplements would dynamically counteract the intended use of these drugs in these settings, assuming hypophosphatemia is not present. Appropriate calcium-phosphorus ratios in vivo are important for proper calcium homeostasis in tissues and bone; if the serum ionized calcium concentration is elevated, the concomitant use of calcium salts and phosphorus salts may increase the risk of calcium deposition in soft tissue.[7800]

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temperature of the solution, however, other factors such as amino acid concentration and the presence of other additives must also be observed (see IV Compatibility reports).

Calcium Carbonate and Vitamin A (found in Centrum® Silver®)

Severity: Low

Doses in excess of 1,500-2,000 mcg/day of Vitamin A may lead to bone loss and will counteract the effects of calcium supplementation. This adverse effect of Vitamin A on bone density does not apply to beta carotene or mixed carotenoids.[8242] [8257]

Calcium Carbonate and Magnesium Salts (found in Centrum® Silver®, Chelated Calcium Magnesium Tablets)

Severity: Moderate

Calcium and magnesium salts are often combined together in nutritional supplement and vitamin products. Oral calcium-containing medications may increase serum calcium or magnesium concentrations in susceptible patients, primarily in patients with renal insufficiency.[7800]

Calcium Salts (found in Centrum® Silver®, Chelated Calcium Magnesium Tablets) **and Hydrochlorothiazide, HCTZ**

Severity: Moderate

The simultaneous administration of thiazide diuretics and calcium salts or calcium carbonate may lead to hypercalcemia. Thiazides cause a decrease in renal tubular excretion of calcium as well as increase in distal tubular reabsorption. Moderate increases in serum calcium have been seen during the treatment with thiazides; if calcium salts are used concomitantly, careful monitoring of serum calcium in recommended.[5917]

Prolonged use of calcium salts with thiazide diuretics can lead to the milk-alkali syndrome.[4689] Exogenous calcium and thiazide diuretics each can cause hypercalcemia, and thiazide diuretics may cause metabolic alkalosis. These are pharmacodynamic interactions. While the use of a thiazide diuretic does not preclude administration of calcium salts, these two agents should not be administered together for prolonged periods without monitoring serum calcium and other serum electrolytes.

Cyanocobalamin, Vitamin B12 (found in Centrum® Silver®) **and Pantoprazole** (Protonix®)

Severity: Low

In a study of 10 healthy male volunteers, omeprazole, in doses of 20 mg-40 mg per day, caused a significant decrease in the oral absorption of cyanocobalamin, vitamin B12.[162] Theoretically this interaction is possible with other proton pump inhibitors (PPIs), although specific clinical data are lacking. Patients receiving long-term therapy with omeprazole or other proton pump inhibitors (PPIs) should be monitored for signs of B12 deficiency.

Cyanocobalamin, Vitamin B12 (found in Centrum® Silver®) **and Colchicine**

Severity: Low

Several drugs, including colchicine, have been reported to reduce the absorption of cyanocobalamin, vitamin B12.[7660] Colchicine has been shown to induce reversible malabsorption of vitamin B12, apparently by altering the function of ileal mucosa.[7677] Although further study of these interactions is necessary, patients receiving these agents concurrently should be monitored for the desired therapeutic response to vitamin B12 [7660] [7677]

Several drugs, including colchicine, have been reported to reduce the absorption of cyanocobalamin, vitamin B12.[7660] Colchicine has been shown to induce reversible malabsorption of vitamin B12, apparently by altering the function of ileal mucosa.[7677] Although further study of these interactions is necessary, patients receiving these agents concurrently should be monitored for the desired therapeutic response to vitamin B12 [7660] [7677]

Ergocalciferol, Vitamin D2 (found in Centrum® Silver®) **and Hydrochlorothiazide, HCTZ**

Severity: High

Concomitant use of thiazide diuretics and ergocalciferol in patients with hypoparathyroidism can result in hypercalcemia,[6916] which is likely due to increased release of calcium from the bone. This condition may be transient or require discontinuation of the vitamin D analog.

Potassium Salts (found in Centrum® Silver®) **and Losartan** (Cozaar®)

Severity: High

Concomitant use of losartan with potassium-sparing diuretics, potassium salts, or salt substitutes containing potassium may lead to increases in serum potassium.[5339]

Potassium salts [7025] should be used with caution in patients taking drugs that may increase serum potassium levels such as ACE inhibitors [5365]; angiotensin II receptor antagonists [5339]; cyclosporine [5134]; eplerenone [4707]; potassium-sparing diuretics (amiloride [5873], spironolactone [5751], or triamterene [5898]); high-doses of IV potassium penicillin G [6826]; trimethoprim (especially high dose) [5073]; or heparin [2173]. Concurrent use can cause hyperkalemia, especially in elderly patients or patients with impaired renal function. Conversely, potassium supplements should be discontinued when hypokalemia-causing agents are discontinued or re-evaluated to avoid the possibility of developing hyperkalemia. Examples of hypokalemia-causing agents include: thiazide diuretics and loop diuretics; amphotericin B; high-dose beta-agonists; and high doses of extended-spectrum penicillins (carbenicillin, mezlocillin, piperacillin, and ticarcillin).

Magnesium Salts (found in Centrum® Silver®, Chelated Calcium Magnesium Tablets) **and Hydrochlorothiazide, HCTZ**

Severity: Moderate

Diuretics may interfere with the kidneys ability to regulate magnesium concentrations. Long-term use of loop diuretics or thiazide diuretics may impair the magnesium-conserving ability of the kidneys and lead to hypomagnesemia.[7114] Conversely, long-term use of potassium-sparing diuretics has been found to increase renal tubular reabsorption of magnesium which may cause hypermagnesemia in patients also receiving magnesium supplements, especially in patients with renal insufficiency.

Magnesium Salts (found in Centrum® Silver®, Chelated Calcium Magnesium Tablets) **and Oxycodone** (OxyContin®)

Severity: Low

Because of the CNS-depressant effects of magnesium sulfate [7197], additive central-depressant effects can occur following concurrent administration with barbiturates, opiate agonists, sedating H_1-blockers, antidepressants, benzodiazepines, general anesthetics, local anesthetics, and phenothiazines.

Magnesium Salts (found in Centrum® Silver®, Chelated Calcium Magnesium Tablets) **and Mirtazapine**

Severity: Low

Because of the CNS-depressant effects of magnesium sulfate [7197], additive central-depressant effects can occur following concurrent administration with barbiturates, opiate agonists, sedating H_1-blockers, antidepressants, benzodiazepines, general anesthetics, local anesthetics, and phenothiazines.

Niacin, Niacinamide (found in Centrum® Silver®) **and Hydrochlorothiazide, HCTZ**

Severity: Moderate

Clonidine has been shown to inhibit niacin-induced flushing.[7631] This interaction is harmless unless niacin augments the hypotensive actions of clonidine. Finally, clinicians should keep in mind that cutaneous vasodilation induced by niacin may become problematic if high-dose niacin is used concomitantly with other antihypertensive agents,[5932] especially peripheral vasodilators such as epoprostenol, nitrates, calcium-channel blockers, or others, particularly in the setting of acute myocardial infarction, unstable angina, or other acute hemodynamic compromise.

Niacin, Niacinamide (found in Centrum® Silver®) **and Losartan** (Cozaar®)

Severity: Moderate

Clonidine has been shown to inhibit niacin-induced flushing.[7631] This interaction is harmless unless niacin augments the hypotensive actions of clonidine. Finally, clinicians should keep in mind that cutaneous vasodilation induced by niacin may become problematic if high-dose niacin is used concomitantly with other antihypertensive agents,[5932] especially peripheral vasodilators such as epoprostenol, nitrates, calcium-channel blockers, or others, particularly in the setting of acute myocardial infarction, unstable angina, or other acute hemodynamic compromise.

Losartan (Cozaar®) **and Hydrochlorothiazide, HCTZ**

Severity: Moderate

Losartan can enhance the hypotensive effects of other antihypertensive agents (including diuretics) if given concomitantly.[5339] This additive effect may be desirable, but dosages must be adjusted accordingly. Losartan tends to reverse the potassium loss and serum uric acid rise associated with thiazide diuretic monotherapy. Bosentan and losartan may have additive hypotensive effects. Losartan has no effect on the plasma concentrations of bosentan; however, bosentan may theoretically increase the hepatic metabolism of losartan via induction of CYP2C9 and CYP3A4 isoenzymes (clinical significance unknown).[4718] [5226]

Hydrochlorothiazide can have additive effects when administered with other antihypertensive agents or diuretics.[5917] In some patients, these effects may be desirable, but orthostatic hypotension is possible. Dosages must be adjusted accordingly. In addition, potassium-sparing diuretics (amiloride hydrochloride, spironolactone, and triamterene) can reduce the risk of developing hypokalemia because of their potassium-sparing effects; these agents have been used as therapeutic alternatives to potassium supplements.

Hydrochlorothiazide, HCTZ and Oxycodone (OxyContin®)

Severity: Moderate

Ethanol, barbiturates, or opiate agonists may potentiate orthostatic hypotension when used concurrently with hydrochlorothiazide.[5917]

Hydrochlorothiazide, HCTZ and Vitamin A (found in Centrum® Silver®)

Severity: Moderate

Thiazide diuretics may cause photosensitivity [5917] [7476] and may increase the photosensitization effects of drugs like griseofulvin, phenothiazines, retinoids [5254], sulfonamides, sulfonylureas, tetracyclines, or photosensitizing agents used in photodynamic therapy. Prevention of photosensitivity includes adequate protection from sources of UV radiation (e.g., avoiding sun exposure and tanning booths) and the use of protective clothing and sunscreens on exposed skin.[7476]

Mirtazapine and Oxycodone (OxyContin®)

Severity: Moderate

Concomitant use of oxycodone with other CNS depressants can potentiate the respiratory depression and/or sedation effects of both of these agents. Drugs that may cause additive CNS effects include amoxapine, anxiolytics, sedatives, and hypnotics, clozapine, dronabinol, THC, droperidol, entacapone, general anesthetics, sedating H_1-blockers, MAOIs, maprotiline, mirtazapine, molindone, nabilone [9044], nefazodone, olanzapine, opiate agonists, pimozide, pramipexole, pregabalin [7523], quetiapine, risperidone, ropinirole, tolcapone, tramadol, trazodone, and the tricyclic antidepressants. Caution should be exercised during concomitant use of any CNS-depressant drugs and oxycodone. Oxycodone should be initiated at one-third to one-half the usual dosage in patients that are concurrently receiving another CNS depressant.[6423]

Consistent with the pharmacology of mirtazapine and the drug's side effect profile, additive effects may occur with other CNS-active agents.[5366] Mirtazapine should be administered with caution with such agents because the CNS effects on cognitive performance and motor skills can be additive; the manufacturer specifically warns against coadministration of ethanol; patients should avoid combination of mirtazapine with alcoholic beverages.[5366] Use particular caution with anxiolytics, sedatives, and hypnotics; in studies, there has been an additive impairment of motor skills and impaired learning acquisition (pharmacodynamic effect) when mirtazapine is coadministered with a benzodiazepine (i.e., diazepam); mirtazapine and diazepam concentrations were not significantly affected.[5366] Additive sedative effects could also potentially occur with barbiturates, general anesthetics, sedating H_1-blockers, opiate agonists, buprenorphine, butorphanol, nalbuphine, pentazocine, dronabinol, THC, nabilone [9044], phenothiazines, skeletal muscle relaxants, tramadol, or tricyclic antidepressants. Use together with caution.

Mirtazapine and Ropinirole (Requip®)

Severity: Moderate

Mirtazapine has been noted to counteract levodopa-induced dyskinesias in patients with Parkinson's disease; a beneficial interaction from the pharmacodynamic effects of mirtazapine appeared to occur.[5370] [7716] Some medicines used for treatment of Parkinson's disease, like entacapone, tolcapone, ropinirole, or pramipexole, could potentially cause additive drowsiness when coadministered with mirtazapine.[5366]

Concomitant use of ropinirole with other CNS depressants can potentiate the sedation effects of ropinirole.[8018] These agents include: amitriptyline, amoxapine, clomipramine, clozapine, doxepin, general anesthetics, haloperidol, sedating H-1-blockers,

imipramine, MAOIs, maprotiline, mirtazapine, molindone, nefazodone, nortriptyline, olanzapine, opiate agonists, skeletal muscle relaxants, tolcapone, and trazodone.

Oxycodone (OxyContin®) **and Ropinirole** (Requip®)

Severity: Moderate

Concomitant use of oxycodone with other CNS depressants can potentiate the respiratory depression and/or sedation effects of both of these agents. Drugs that may cause additive CNS effects include amoxapine, anxiolytics, sedatives, and hypnotics, clozapine, dronabinol, THC, droperidol, entacapone, general anesthetics, sedating H_1-blockers, MAOIs, maprotiline, mirtazapine, molindone, nabilone [9044], nefazodone, olanzapine, opiate agonists, pimozide, pramipexole, pregabalin [7523], quetiapine, risperidone, ropinirole, tolcapone, tramadol, trazodone, and the tricyclic antidepressants. Caution should be exercised during concomitant use of any CNS-depressant drugs and oxycodone. Oxycodone should be initiated at one-third to one-half the usual dosage in patients that are concurrently receiving another CNS depressant.[6423]

Adverse Reactions

• abdominal pain (Colchicine | Hydrochlorothiazide, HCTZ | OxyContin® | Mirtazapine | Requip® | Arthrotec® | Protonix®)
• agitation (Mirtazapine)
• agranulocytosis (Colchicine | Hydrochlorothiazide, HCTZ | Mirtazapine | Arthrotec®)
• akathisia (Mirtazapine)
• alopecia (Colchicine | Hydrochlorothiazide, HCTZ | Protonix®)
• amblyopia (Neurontin®)
• amenorrhea (OxyContin®)
• amnesia (Neurontin® | Mirtazapine | Requip®)
• anaphylactoid reactions (Cozaar® | Arthrotec® | Protonix®)
• anemia (Hydrochlorothiazide, HCTZ | Requip® | Arthrotec® | Protonix®)
• angioedema (Colchicine | Cozaar® | Arthrotec® | Protonix®)
• anorexia (Colchicine | Neurontin® | Hydrochlorothiazide, HCTZ | OxyContin® | Mirtazapine | Requip®)
• anuria (Colchicine)
• anxiety (Neurontin® | OxyContin® | Mirtazapine | Requip®)
• aplastic anemia (Colchicine | Hydrochlorothiazide, HCTZ | Arthrotec®)
• appetite stimulation (Neurontin® | Mirtazapine)
• arthralgia (Neurontin® | Mirtazapine | Requip®)
• aseptic meningitis (Arthrotec®)
• asthenia (Amrix® | Neurontin® | OxyContin® | Mirtazapine | Requip®)
• ataxia (Neurontin®)
• atrial fibrillation (Requip®)
• azotemia (Hydrochlorothiazide, HCTZ | Cozaar® | Arthrotec®)
• back pain (Neurontin® | Cozaar® | Mirtazapine)
• biliary obstruction (OxyContin®)
• blurred vision (Amrix® | Neurontin® | Hydrochlorothiazide, HCTZ)
• bradycardia (OxyContin®)
• cardiac arrest (OxyContin®)
• chest pain (unspecified) (Requip® | Protonix®)
• cholecystitis (Protonix®)
• cholelithiasis (Protonix®)
• choreoathetosis (Neurontin®)
• confusion (Amrix® | OxyContin® | Mirtazapine | Requip® | Arthrotec®)
• constipation (Calcium Carbonate | Amrix® | Neurontin® | Hydrochlorothiazide, HCTZ | OxyContin® | Mirtazapine | Requip® | Protonix®)
• contact dermatitis (Protonix®)
• cough (Cozaar® | Mirtazapine)
• dehydration (Arthrotec®)
• depression (Neurontin® | Mirtazapine)
• diabetic ketoacidosis (Mirtazapine)
• diaphoresis (OxyContin® | Requip®)
• diarrhea (Colchicine | Hydrochlorothiazide, HCTZ | Cozaar® | OxyContin® | Requip® | Arthrotec® | Protonix®)
• diplopia (Neurontin® | Requip®)

• dizziness (Amrix® | Neurontin® | Hydrochlorothiazide, HCTZ | Cozaar® | OxyContin® | Mirtazapine | Requip® | Arthrotec® | Protonix®)
• drowsiness (Amrix® | Neurontin® | OxyContin® | Mirtazapine | Requip®)
• dysarthria (Neurontin®)
• dysgeusia (Amrix® | Cozaar®)
• dyskinesia (Mirtazapine | Requip®)
• dysmenorrhea (Arthrotec®)
• dyspepsia (Amrix® | Neurontin® | Cozaar® | OxyContin® | Requip® | Arthrotec® | Protonix®)
• dysphagia (Requip®)
• dysphoria (OxyContin®)
• dyspnea (Mirtazapine | Requip®)
• dystonic reaction (Neurontin®)
• ecchymosis (Protonix®)
• edema (Mirtazapine | Requip®)
• elevated hepatic enzymes (Cozaar® | Mirtazapine | Arthrotec® | Protonix®)
• emotional lability (Neurontin®)
• eructation (Calcium Carbonate | Protonix®)
• erythema multiforme (Arthrotec® | Protonix®)
• euphoria (OxyContin®)
• exfoliative dermatitis (Hydrochlorothiazide, HCTZ | Cozaar®)
• fatigue (Amrix® | Neurontin® | Requip®)
• fetal abortion (Arthrotec®)
• fever (Neurontin® | Mirtazapine | Requip®)
• flatulence (Calcium Carbonate | Neurontin® | Requip® | Arthrotec® | Protonix®)
• fluid retention (Arthrotec®)
• flushing (Mirtazapine | Requip®)
• gastric hypersecretion (Calcium Carbonate)
• gastritis (OxyContin®)
• gastroesophageal reflux (Requip®)
• GI bleeding (Arthrotec®)
• gingivitis (Neurontin®)
• glossitis (Neurontin®)
• glycosuria (Hydrochlorothiazide, HCTZ)
• gout (Hydrochlorothiazide, HCTZ)
• hallucinations (Amrix® | OxyContin® | Requip®)
• headache (Amrix® | Hydrochlorothiazide, HCTZ | OxyContin® | Requip® | Arthrotec® | Protonix®)
• heart failure (Arthrotec®)
• hematuria (Colchicine | Arthrotec®)
• hemolytic anemia (Hydrochlorothiazide, HCTZ | Arthrotec®)
• hepatic failure (Protonix®)
• hepatitis (Neurontin® | Cozaar® | Arthrotec® | Protonix®)
• hiccups (OxyContin®)
• hostility (Neurontin® | Mirtazapine)
• hyperbilirubinemia (Hydrochlorothiazide, HCTZ | Cozaar® | Protonix®)
• hypercalcemia (Calcium Carbonate | Hydrochlorothiazide, HCTZ)
• hypercholesterolemia (Hydrochlorothiazide, HCTZ)
• hyperesthesia (Requip®)
• hyperglycemia (Hydrochlorothiazide, HCTZ | Mirtazapine | Protonix®)
• hyperkalemia (Cozaar®)
• hypersalivation (Requip®)
• hypertension (Neurontin® | Mirtazapine | Requip® | Arthrotec®)
• hypertriglyceridemia (Hydrochlorothiazide, HCTZ | Mirtazapine)
• hyperuricemia (Hydrochlorothiazide, HCTZ)
• hypochloremia (Hydrochlorothiazide, HCTZ)
• hypoesthesia (Mirtazapine)
• hypokalemia (Hydrochlorothiazide, HCTZ)
• hypomagnesemia (Hydrochlorothiazide, HCTZ)
• hyponatremia (Hydrochlorothiazide, HCTZ | Cozaar® | OxyContin®)
• hypophosphatemia (Calcium Carbonate)
• hypotension (Amrix® | Hydrochlorothiazide, HCTZ | Cozaar® | OxyContin® | Mirtazapine | Requip®)
• hypothyroidism (Colchicine)
• ileus (Colchicine)

• impaired cognition (Neurontin® | OxyContin® | Mirtazapine)
• impotence (erectile dysfunction) (Neurontin® | Hydrochlorothiazide, HCTZ | Cozaar® | Requip®)
• increased urinary frequency (Mirtazapine)
• infection (Neurontin® | Cozaar® | Mirtazapine | Requip®)
• injection site reaction (Colchicine | Protonix®)
• insomnia (Cozaar® | OxyContin® | Mirtazapine | Protonix®)
• interstitial nephritis (Hydrochlorothiazide, HCTZ | Arthrotec® | Protonix®)
• involuntary movements (Neurontin®)
• irritability (Neurontin® | Mirtazapine)
• jaundice (Hydrochlorothiazide, HCTZ | Mirtazapine | Arthrotec® | Protonix®)
• lethargy (Requip®)
• leukocytosis (Arthrotec®)
• leukopenia (Colchicine | Neurontin® | Hydrochlorothiazide, HCTZ | Arthrotec® | Protonix®)
• libido decrease (OxyContin®)
• maculopapular rash (Protonix®)
• malaise (Neurontin® | Mirtazapine | Requip®)
• mania (Mirtazapine)
• meningitis (Arthrotec®)
• menorrhagia (Arthrotec®)
• menstrual irregularity (Arthrotec®)
• metabolic alkalosis (Calcium Carbonate | Hydrochlorothiazide, HCTZ)
• milk-alkali syndrome (Calcium Carbonate)
• miosis (OxyContin®)
• muscle cramps (Cozaar®)
• myalgia (Cozaar® | Mirtazapine)
• myasthenia (Mirtazapine)
• myoclonia (OxyContin®)
• myopathy (Colchicine)
• nasal congestion (Cozaar®)
• nausea/vomiting (Calcium Carbonate | Colchicine | Amrix® | Neurontin® | Hydrochlorothiazide, HCTZ | OxyContin® | Mirtazapine | Requip® | Arthrotec® | Protonix®)
• neonatal abstinence syndrome (OxyContin®)
• nephrotic syndrome (Arthrotec®)
• neuritis (Colchicine)
• neuroleptic malignant syndrome (Requip®)
• neutropenia (Colchicine | Mirtazapine)
• nystagmus (Neurontin®)
• orthostatic hypotension (Hydrochlorothiazide, HCTZ | Cozaar® | OxyContin® | Mirtazapine | Requip®)
• palpitations (OxyContin® | Requip®)
• pancreatitis (Hydrochlorothiazide, HCTZ | Mirtazapine | Protonix®)
• pancytopenia (Colchicine | Hydrochlorothiazide, HCTZ | Arthrotec® | Protonix®)
• paresis (Requip®)
• paresthesias (Neurontin® | Hydrochlorothiazide, HCTZ | Mirtazapine | Requip®)
• peptic ulcer (Calcium Carbonate)
• peripheral edema (Mirtazapine | Requip® | Arthrotec®)
• peripheral neuropathy (Colchicine)
• pernicious anemia (Protonix®)
• pharyngitis (Neurontin® | Requip®)
• phlebitis (Protonix®)
• photosensitivity (Hydrochlorothiazide, HCTZ)
• physiological dependence (OxyContin®)
• platelet dysfunction (Arthrotec®)
• polydipsia (Mirtazapine)
• polyuria (Hydrochlorothiazide, HCTZ)
• postmenopausal bleeding (Arthrotec®)
• proteinuria (Colchicine | Arthrotec®)
• pruritus (Neurontin® | OxyContin® | Mirtazapine | Arthrotec® | Protonix®)
• purpura (Colchicine | Neurontin® | Cozaar® | Arthrotec®)
• pyuria (Requip®)
• QT prolongation (Amrix®)
• rash (unspecified) (OxyContin® | Mirtazapine | Arthrotec® | Protonix®)
• renal failure (unspecified) (Arthrotec®)

• renal papillary necrosis (Arthrotec®)
• respiratory depression (OxyContin®)
• restlessness (Neurontin® | OxyContin® | Requip®)
• rhabdomyolysis (Cozaar® | Protonix®)
• rhinitis (Neurontin® | Requip®)
• seizures (Amrix® | OxyContin®)
• serotonin syndrome (Mirtazapine)
• SIADH (OxyContin®)
• sinus tachycardia (Amrix® | Requip®)
• sinusitis (Cozaar® | Mirtazapine | Requip®)
• skin necrosis (Colchicine)
• Stevens-Johnson syndrome (Hydrochlorothiazide, HCTZ | Arthrotec® | Protonix®)
• stomatitis (Mirtazapine)
• sudden sleep onset (Requip®)
• suicidal ideation (Neurontin® | Mirtazapine)
• syncope (Hydrochlorothiazide, HCTZ | Cozaar® | OxyContin® | Requip®)
• teratogenesis (Neurontin® | Cozaar® | Arthrotec®)
• thrombocytopenia (Colchicine | Hydrochlorothiazide, HCTZ | Cozaar® | Arthrotec® | Protonix®)
• tinnitus (Arthrotec®)
• tissue necrosis (Colchicine)
• tolerance (OxyContin®)
• toxic epidermal necrolysis (Hydrochlorothiazide, HCTZ | Protonix®)
• tremor (Neurontin® | Mirtazapine)
• urinary incontinence (Requip®)
• urinary retention (OxyContin®)
• urticaria (Colchicine | Arthrotec® | Protonix®)
• uterine contractions (Arthrotec®)
• uterine rupture (Arthrotec®)
• vaginal bleeding (Arthrotec®)
• vasculitis (Cozaar®)
• vertigo (Neurontin® | Hydrochlorothiazide, HCTZ | Mirtazapine | Requip®)
• visual impairment (Requip®)
• vitamin B_{12} deficiency (Protonix®)
• weakness (Hydrochlorothiazide, HCTZ | Requip®)
• weight gain (Neurontin® | Mirtazapine)
• weight loss (Requip®)
• withdrawal (OxyContin®)
• xanthopsia (Hydrochlorothiazide, HCTZ)
• xerophthalmia (Requip®)
• xerosis (Protonix®)
• xerostomia (Amrix® | Neurontin® | OxyContin® | Mirtazapine | Requip®)
• yawning (Requip®)

Precautions

Precaution: Amrix® in depression
Because of the drug's chemical similarity to tricyclic antidepressants (TCAs), use cyclobenzaprine with caution in patients being treated for psychological illness. Cyclobenzaprine is not an effective treatment for depression. Cyclobenzaprine is contraindicated for concomitant use in patients receiving *MAOI therapy* (see Drug Interactions). It is unclear if cyclobenzaprine, like the TCAs, can transform depression into mania or hypomania in predisposed individuals (e.g., some patients with bipolar disorder). Also use cyclobenzaprine with caution in patients with psychotic disorders (e.g., schizophrenia).

Precaution: Arthrotec® in hypertension
Use of diclofenac; misoprostol may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. The risk may increase with duration of use, and patients with cardiovascular disease or risk factors for cardiovascular disease (e.g., high blood pressure) may be at greater risk. Also, conditions such as congestive heart failure or hypertension can be exacerbated with diclofenac therapy. Meta-analysis have demonstrated that the effect of NSAIDs on blood pressure is the greatest in hypertensive individuals receiving antihypertensive medication. In addition, normotensive patients receiving antihypertensive therapy had higher increases in blood pressure than subjects with uncontrolled hypertension or normotensive

subjects receiving no hypertensive therapy.[4087] Patients with renal impairment, renal failure, hepatic disease, congestive heart failure, diabetes mellitus, systemic lupus erythematosus (SLE), rheumatoid arthritis, extracellular volume depletion (i.e., hypovolemia or dehydration), sepsis, those taking diuretics or nephrotoxic drugs, and the elderly are at the highest risk for this reaction. It is recommended not to initiate therapy with maximum doses in these patients due to the likely increase frequency of adverse reactions. Caution is recommended when administering diclofenac; misoprostol to patients with cardiac disease, peripheral vascular disease, cerebrovascular disease (e.g., stroke, transient ischemic attack), hypertension, pre-existing renal disease, fluid retention, or edema. Myocardial infarction has been reported (see Adverse Reactions). Use the lowest effective dose for the shortest duration possible to minimize the potential risk for an adverse cardiovascular event. Closely monitor blood pressure during the initiation of and continuation of diclofenac; misoprostol receipt. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Precaution: Arthrotec® in renal impairment
Diclofenac; misoprostol combinations should be used cautiously in patients with renal impairment. The half-life of misoprostol is prolonged in patients with renal dysfunction, and diclofenac and its metabolites are renally excreted. Accumulation of diclofenac and its metabolites can occur in patients with renal impairment; thus, the risk of potential toxicity may be increased. Diclofenac; misoprostol is not recommended for use by patients with advanced renal disease or renal failure. Due to the role of prostaglandins in renal function and hemodynamics, patients with renal disease should be closely observed during therapy with diclofenac due to an increased risk for adverse reactions during treatment.

Precaution: Centrum® Silver® in hypertension
Phosphorus salts should be administered cautiously to patients who have conditions which may be associated with hyperphosphatemia and/or hypocalcemia. These conditions include hypoparathyroidism, chronic renal disease, rhabdomyolysis, osteomalacia (rickets), or acute pancreatitis. Due to the possibility of developing hyperkalemia and subsequent cardiac arrest, potassium-containing phosphorus salts should be used cautiously in patients with cardiac disease, severe adrenal insufficiency (Addison's disease), acute dehydration, pancreatitis, renal failure or severe renal impairment (< 30% of normal), rhabdomyolysis, strenuous physical exercise (especially unconditioned persons), or extensive tissue breakdown (i.e., severe burns). Sodium-containing phosphorus salts may exacerbate conditions such as heart failure, severe hepatic disease, peripheral edema, pulmonary edema, hypernatremia, hypertension, or toxemia of pregnancy (e.g., preeclampsia). In addition, patients requiring sodium restriction should not receive sodium-containing phosphorus salts.

Precaution: Centrum® Silver® in renal impairment
Phosphorus salts should be administered cautiously to patients who have conditions which may be associated with hyperphosphatemia and/or hypocalcemia. These conditions include hypoparathyroidism, chronic renal disease, rhabdomyolysis, osteomalacia (rickets), or acute pancreatitis. Due to the possibility of developing hyperkalemia and subsequent cardiac arrest, potassium-containing phosphorus salts should be used cautiously in patients with cardiac disease, severe adrenal insufficiency (Addison's disease), acute dehydration, pancreatitis, renal failure or severe renal impairment (< 30% of normal), rhabdomyolysis, strenuous physical exercise (especially unconditioned persons), or extensive tissue breakdown (i.e., severe burns). Sodium-containing phosphorus salts may exacerbate conditions such as heart failure, severe hepatic disease, peripheral edema, pulmonary edema, hypernatremia, hypertension, or toxemia of pregnancy (e.g., preeclampsia). In addition, patients requiring sodium restriction should not receive sodium-containing phosphorus salts.

Precaution: Centrum® Silver® in hypertension
Potassium supplements should be monitored closely in patients with cardiac arrhythmias (e.g., atrial fibrillation, atrial flutter, digitalis toxicity (except due to documented hypokalemia), and ventricular arrhythmias including ventricular fibrillation and ventricular tachycardia), including patients receiving digoxin or other antiarrhythmic therapy. Based on a multidisciplinary review of literature and clinical practice trends, the National Council on Potassium in Clinical Practice recommends that serum potassium concentrations >= 4 mEq/L be achieved and maintained in patients with hypertension, heart failure, and cardiac arrhythmias to minimize complications of potassium depletion.[3085] In addition, the Council recommends potassium supplementation for patients at risk for developing hypokalemia and associated complications. Potassium supplementation is specifically recommended for patients with potential for diuretic-induced potassium loss (e.g., receiving thiazide or loop diuretics), patients with high sodium intake (unwilling to reduce salt intake), and patients with reduced GI intake (e.g., GI disturbances, laxative abuse).[3085]

Precaution: Centrum® Silver® in renal impairment
Potassium supplements are contraindicated in patients with *hyperkalemia* since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Due to the risk of developing hyperkalemia, potassium supplementation should be used with caution in patients with adrenal insufficiency (untreated Addison's disease); acute dehydration; systemic metabolic acidosis such as diabetic ketoacidosis; diarrhea; strenuous physical exercise (especially unconditioned persons); in patients receiving salt substitutes, potassium-sparing diuretics (e.g., amiloride, spironolactone, triamterene), ACE inhibitors, or angiotensin II antagonists; or in patients with renal disease, renal failure, or renal impairment. Potassium supplements should also be used cautiously in patients with severe burns because these patients are prone to hyperkalemia secondary to tissue breakdown and renal insufficiency. Serum potassium levels and renal function should be monitored closely in patients at risk for hyperkalemia. Because elderly patients are more likely to have decreased renal function, potassium salts should be dosed cautiously based on an assessment of renal function and therapeutic goals. NOTE: Potassium acetate injection contains aluminum (<= 200 mcg/L). Thus, aluminum may reach toxic levels with prolonged

administration in patients with renal impairment. Premature neonates are at particular risk for aluminum toxicity following administration of aluminum-containing injectables. Since premature neonates have immature kidneys, they may require large amounts of calcium and phosphate solutions, which contain aluminum. Research indicates that patients with renal impairment, including neonates, who receive parenteral aluminum at rates greater than 4-5 mcg/kg/day may accumulate aluminum at levels associated with CNS and bone toxicity. Tissue loading may occur at lower administration rates.

Precaution: Centrum® Silver® in renal impairment
Parenteral pyridoxine solutions contain varying concentrations of aluminum. Patients with renal impairment, especially as seen with neonatal prematurity, are at risk of aluminum accumulation which may result in toxicity. Limit intravenous pyridoxine therapy and consider the cumulative aluminum content among all therapies under administration in patients with renal impairment. It is noted that 4-5 mcg/kg/day of IV aluminum leads to accumulation at concentrations associated with CNS and bone toxicity; further, aluminum tissue loading is possible at lesser, but undefined, daily administration rates.[9771] Aluminum concentration in parenteral solutions can be obtained by direct manufacturer inquiry.

Precaution: Centrum® Silver® in renal impairment
Magnesium salts should be used with caution in patients with renal disease, including patients with renal impairment or renal failure. Magnesium salts are renally eliminated, so patients with renal impairment have an increased risk of developing magnesium toxicity from decreased excretion of magnesium. In patients with severe renal dysfunction, no more than 20 grams (162 mEq) of magnesium should be administered within a 48-hour period. Parenteral magnesium should be avoided in patients with a creatinine clearance of less than 20 mL/minute. Up to 30% of an orally administered dose is absorbed systemically.

Precaution: Centrum® Silver® in renal impairment
Use niacin with caution in patients with renal disease (renal failure or severe renal impairment) since niacin metabolites are excreted through the kidneys. It appears that no special precautions are needed when administering niacin to meet the recommended nutritional daily allowance (RDA). Use caution when administering higher dosages.

Precaution: Centrum® Silver® in renal impairment
Zinc Chloride injection contains aluminum which may reach toxic levels with prolonged administration in patients with renal impairment or renal failure. Neonates of neonatal prematurity are at particular risk for aluminum toxicity following administration of aluminum-containing injectables since they have immature kidneys. Research indicates that patients with renal impairment, including neonates, who receive parenteral aluminum at rates greater than 4-5 mcg/kg/day may accumulate aluminum at levels associated with CNS and bone toxicity. Tissue loading may occur at lower administration rates.

Precaution: Centrum® Silver® in renal impairment
Chromium elimination may be decreased in patients with renal disease or renal impairment. Dosage reductions in supplemental parenteral or oral doses may be needed. Since chromium is primarily excreted via the renal route, supplementation should be approached with caution, particularly in patients maintained on dialysis or with renal failure.

Precaution: Centrum® Silver® in renal impairment
Selenium supplements should be used cautiously in patients with GI disease or renal impairment. These conditions may cause high levels of selenium; dosage reductions may be necessary.

Precaution: Chelated Calcium Magnesium Tablets in renal impairment
Magnesium salts should be used with caution in patients with renal disease, including patients with renal impairment or renal failure. Magnesium salts are renally eliminated, so patients with renal impairment have an increased risk of developing magnesium toxicity from decreased excretion of magnesium. In patients with severe renal dysfunction, no more than 20 grams (162 mEq) of magnesium should be administered within a 48-hour period. Parenteral magnesium should be avoided in patients with a creatinine clearance of less than 20 mL/minute. Up to 30% of an orally administered dose is absorbed systemically.

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: Hydrochlorothiazide, HCTZ in renal impairment
Hydrochlorothiazide should be used cautiously in patients with renal disease such as severe renal impairment or renal failure. Drug-induced hypovolemia can precipitate azotemia in these patients. Therapy should be interrupted or discontinued if renal impairment worsens, as evidenced by an increase in concentrations of BUN or serum creatinine. With the exception of metolazone, thiazide diuretics are considered ineffective when the creatinine clearance is less than 30 ml/minute. Hydrochlorothiazide is contraindicated in patients with *anuria*.

Precaution: Hydrochlorothiazide, HCTZ in sulfonamide hypersensitivity

Thiazide diuretics are contraindicated in patients with known *thiazide diuretic hypersensitivity*. According to the manufacturer, hydrochlorothiazide is specifically contraindicated in patients with *sulfonamide hypersensitivity*. Although thiazide diuretics are sulfonamide derivatives, sulfonamide cross-sensitivity has been rarely documented.[53] [3600] [9205] Until further data are available, thiazide diuretics should be used with caution in patients with sulfonamide hypersensitivity. Thiazide diuretics do not contain the N4-aromatic amine or the N1-substituent which are present in sulfonamide antibiotics.[9204] Non-arylamine sulfonamide derivatives, such as thiazide diuretics, have been proposed to have a lower risk of allergic reactions in patients with sulfonamide allergy, presumably due to lack of an arylamine group at the N4 position (a proposed structural site of action for sulfonamide allergy).[9204] [9205] One large retrospective cohort study has reported that in patients with the presence of an allergic reaction after exposure to a sulfonamide antibiotic, 9.9% had an allergic reaction after receiving a non-antibiotic sulfonamide derivative, while in patients who lacked an allergic reaction after sulfonamide antibiotic exposure, 1.6% had an allergic reaction after administration of a non-antibiotic sulfonamide derivative (adjusted odds ratio 2.8; 95% CI, 2.1-3.7).[9206] A causal relationship between sulfonamide hypersensitivity and allergic reactions with non-arylamine sulfonamide derivatives has not been definitively established and remains controversial.[53] [3600] [9204] [9205] In general, patients with a documented sulfonamide allergy are considered to be predisposed for development of allergic drug reactions.[9204] [9206]

Precaution: Mirtazapine in renal impairment
Mirtazapine should be used cautiously in patients with renal impairment or renal failure. Compared to those with normal renal function, the oral clearance of mirtazapine is reduced by about 30% and 50% in patients with moderate [CrCl 11-39 ml/min] and severe [CrCl <= 10 ml/min] renal dysfunction, respectively.

Precaution: Neurontin® in depression
In January 2008, the FDA alerted healthcare professionals of an increased risk of suicidal ideation and behavior in patients receiving anticonvulsants to treat epilepsy, psychiatric disorders, or other conditions (e.g., migraine, neuropathic pain). This alert followed an initial request by the FDA in March 2005 for manufacturers of marketed anticonvulsants to provide data from existing controlled clinical trials for analysis. Prior to this request, preliminary evidence had suggested a possible link between anticonvulsant use and suicidality. The primary analysis consisted of 199 placebo-controlled clinical studies with a total of 27,863 patients in drug treatment groups and 16,029 patients in placebo groups (>= 5 years of age). There were 4 completed suicides among patients in drug treatment groups versus none in the placebo groups. Patients receiving anticonvulsants had approximately twice the risk of suicidal behavior or ideation (0.43%) as patients receiving placebo (0.22%), corresponding to an estimated 2.1 per 1000 (95% CI: 0.7-4.2) more patients in the drug treatment groups who experienced suicidal behavior or ideation. The relative risk for suicidality was higher in patients with epilepsy compared to those with other conditions. Age was not a determining factor. The increased risk of suicidal ideation and behavior was observed between 1 and 24 weeks after therapy initiation. However, a longer duration of therapy should not preclude the possibility of an association to the drug since most studies included in the analysis did not continue beyond 24 weeks. Data were analyzed from drugs with adequately designed clinical trials including carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide. However, this is considered to be a class effect. All patients beginning treatment with anticonvulsants or currently receiving such treatment should be closely monitored for emerging or worsening suicidal thoughts/behavior or depression. Anticonvulsants should be prescribed in the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

Precaution: Neurontin® in renal impairment
Gabapentin should be used with caution in patients with renal impairment. Gabapentin is excreted unchanged in the urine and can accumulate with decreased renal function. Dosage adjustments are recommended (see Dosage). Elderly patients are more likely to have reduced renal function and should be treated with caution. There are no specific recommendations for dosage reduction in the elderly.

Precaution: OxyContin® in bladder obstruction
Oxycodone and other opiate agonists can cause urinary retention and oliguria, due to increasing the tension of the detrusor muscle. Patients more prone to these effects include those with prostatic hypertrophy, urethral stricture, bladder obstruction, pelvic tumors, or renal disease. Drug accumulation or prolonged duration of action may occur in patients with renal failure or hepatic disease. In acute situations, patients require close monitoring to avoid excessive toxicity. In patients with renal impairment (creatinine clearance < 60 ml/min), the concentrations of oxycodone are approximately 50% higher than patients with normal renal function. Dose initiation in these patients should be conservative and dosage adjustments based on individual patient response. In patients with hepatic

impairment, oxycodone therapy should be initiated at doses one-half to one-third the usual dose and careful dose titration is warranted.

Precaution: OxyContin® in renal impairment
Oxycodone and other opiate agonists can cause urinary retention and oliguria, due to increasing the tension of the detrusor muscle. Patients more prone to these effects include those with prostatic hypertrophy, urethral stricture, bladder obstruction, pelvic tumors, or renal disease. Drug accumulation or prolonged duration of action may occur in patients with renal failure or hepatic disease. In acute situations, patients require close monitoring to avoid excessive toxicity. In patients with renal impairment (creatinine clearance < 60 ml/min), the concentrations of oxycodone are approximately 50% higher than patients with normal renal function. Dose initiation in these patients should be conservative and dosage adjustments based on individual patient response. In patients with hepatic impairment, oxycodone therapy should be initiated at doses one-half to one-third the usual dose and careful dose titration is warranted.

Precaution: Requip® in hypertension
The potential for cardiovascular-related adverse effects, including hypertension, hypotension, syncope and changes in heart rate, should be considered during ropinirole therapy. Dopamine agonists, including ropinirole, may impair the systemic regulation of blood pressure resulting in orthostatic hypotension, especially during dose escalation. In addition, Parkinson's disease patients appear to have an impaired capacity to respond to a postural challenge. Some cases of orthostatic hypotension have occurred more than 4 weeks after initiation of therapy. Orthostasis has also been observed in patients using ropinirole for restless legs syndrome (RLS). Careful titration may minimize the potential for this adverse effect. Ropinirole has been associated with syncope, sometimes with bradycardia, in both early Parkinson's disease (without L-dopa) patients and advanced Parkinson's disease (with L-dopa) patients. During clinical trials with extended-release ropinirole, severe systolic blood pressure increases (>= 40 mm Hg) and moderate pulse increases or decreases (>= 15 beats/minute) occurred in some patients. It should be noted that patients with significant cardiovascular disease were excluded from study participation. Therefore, caution is advised in those with severe cardiac disease until the safety of ropinirole in this patient population can be established.

Precaution: Requip® in renal impairment
No dosage adjustments are needed in patients with mild to moderate renal impairment (CrCl of 30-50 ml/min), however, ropinirole has not been studied in patients with severe renal disease. Administer ropinirole cautiously in patients with severe renal disease or renal impairment.

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