

## Top Ten Dangerous Drug Interactions in Long-Term Care

One of the important initiatives in the [Multidisciplinary Medication Management Project](#) is the development and promotion of a list of ten drug interactions that are particularly problematic in long-term care settings. Each of these drug interactions involves medications that are commonly used in long-term care, and has the potential to cause significant harm if not managed appropriately.

Hundreds of drug interactions have been reported in the medical literature. Studies and reports often conflict in description or evaluation of the clinical significance or relevance of the interaction. The combination of these two elements makes the identification and management of drug interactions a difficult challenge for the clinician.

Statistically, if you take six different drugs, you have an 80 percent chance of at least one drug-drug interaction.  
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In response to this challenge, the Medication Management Project [Advisory Committee](#) undertook to identify ten drug interactions that are commonly regarded as important, and involve medications that are commonly used in older adults in long-term care settings. The committee believes that if health professionals in long-term care can focus on preventing or managing these ten drug interactions, a significant impact can be made on improving care for these older adults.

A survey instrument was prepared with the drug interactions identified. The survey was distributed at the AMDA Annual Meeting in March 2001, and was distributed on ASCP's geriatric pharmacotherapy listserv. The [advisory committee](#) reviewed the survey results and compiled the list of 10 drug interactions.

Once the list was finalized, the next step was to develop practical information for health professionals to use to help manage these drug interactions. This final list of drug interactions and management information is provided below.

### List of Top Ten Drug Interactions in Long-Term Care

Medications chosen for the Top Ten list were based on their frequency of use in older adults in the long-term care setting, and on the potential for adverse consequences if used together. Due to individual variability, not every older adult who takes these medications together will experience an adverse reaction. However, these combinations have the potential to produce harmful effects.

The purpose of this Top Ten list is to alert the interdisciplinary team to the possibility that a negative interaction may occur, so that steps may be taken to choose alternative medications, adjust doses, monitor the patient carefully, or take other such actions as may be appropriate.

Click on the drug interaction of interest to see more details.

1. [Warfarin — NSAIDs\\*](#)
2. [Warfarin — Sulfa drugs](#)
3. [Warfarin — Macrolides](#)
4. [Warfarin — Quinolones\\*\\*](#)
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8. [Digoxin — Amiodarone](#)
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\* NSAID class does not include COX-2 inhibitors

\*\* Quinolones that interact include: ciprofloxacin, enoxacin, norfloxacin, and ofloxacin

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| Warfarin           | NSAIDs   |
|--------------------|--|
| Coumadin, warfarin | Aleve, Anaprox, Anaprox DS, Ansaid, Arthrotec, Cataflam, Clinoril, Daypro, diclofenac, diclofenac/misoprostol, diflunisal, Dolobid, etodolac, Feldene, flurbiprofen, ibuprofen, Indocin, Indocin SR, indomethacin, ketoprofen, ketorolac, Lodine, Lodine XL, mefenamic acid, meloxicam, Mobic, Motrin, nabumetone, Naprelan, Naprosyn, naproxen, Orudis, Oruvail, oxaprozin, piroxicam, Ponsel, Relafen, sulindac, Tolectin, Tolectin DS, tolmetin, Toradol, Voltaren, Voltaren XR |

**IMPACT:** Potential for serious gastrointestinal bleeding

**MECHANISM OF INTERACTION:** NSAIDs increase gastric irritation and erosion of the protective lining of the stomach, assisting in the formation of a GI bleed. Additionally, NSAIDs decrease the cohesive properties of platelets necessary in clot formation.

**PREVENTION:** Avoid concomitant use of an NSAID with warfarin. Identify reason for NSAID therapy. If anti-pyretic effects are desired, then consider acetaminophen. Acetaminophen in doses less than 2g/day on a short-term basis does not appear to affect the INR. Long-term use of acetaminophen for anti-pyretic and analgesic effects is controversial. If anti-inflammatory effects are necessary, then consider cyclooxygenase-2 (COX-2) inhibitor therapy. The minimization of gastric irritation with these agents combined with the lack of anti-platelet action, support the cautious use of COX-2 inhibitors in anticoagulation patients. There are some case reports discussing the elevation of INRs with COX-2 inhibitors. If analgesic effects are desired, caution should also be exhibited with the use of tramadol; there are a few case reports describing an elevation of the INR with concomitant administration of tramadol with warfarin.

**MANAGEMENT:** Prothrombin time and INR should be monitored every week with co-administration of warfarin with an NSAID. Signs and symptoms of an active bleed should be monitored with particular attention to the appearance and patterns of bruises. Signs of an active bleed include: coughing up blood in the form of coffee grinds (hemoptysis), gum bleeding, nose bleeds, cola- or tea-colored urine (hematuria), or black, tarry stools (hemocult positive).

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| Warfarin           | Sulfa Drugs  |
|--------------------|--|
| Coumadin, warfarin | Bactrim DS, Bactrim SS, Cotrim DS, Cotrim SS, erythromycin/sulfisoxazole, Gantanol, Gantrisin, Pediazole, Septra DS, Sulfatrim, sulfamethizole, sulfamethoxazole, sulfisoxazole, Thiosulfil Forte, trimethoprim/sulfamethoxazole |

**IMPACT:** Increased effects of warfarin, with potential for bleeding

**MECHANISM OF INTERACTION:** Currently, the mechanism for interaction with sulfa drugs is unknown; however, clinicians hypothesize that warfarin's activity is prolonged due to a decreased production of vitamin K by intestinal flora affected by systemic antibiotic administration.

**PREVENTION:** Avoid concomitant use of a sulfa drug with warfarin, particularly sulfamethoxazole-trimethoprim. Identify microbial pathogen prior to initiation of antibiotic therapy. Consider culture sensitivity screening as research indicates cautious use of any antibiotic with warfarin. If use of a sulfa drug is imperative, then reduce warfarin dose by 50% during antibiotic administration and for one week following completion of the antibiotic. If sulfamethoxazole-trimethoprim therapy is required, then monitor INR every other day for elevating trends.

**MANAGEMENT:** Prothrombin time and INR should be monitored every week during co-administration of warfarin with a sulfa drug. Signs and symptoms of an active bleed should be monitored daily with particular attention to the appearance and patterns of bruises. Signs of an active bleed include: coughing up blood in the form of coffee grinds (hemoptysis), gum bleeding, nose bleeds, cola- or tea-colored urine (hematuria), and black, tarry stools (hemocult positive).

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| <b>Warfarin</b>    | <b>Macrolides</b>  |
|--------------------|--|
| Coumadin, warfarin | azithromycin, Biaxin, clarithromycin, Dynabac, dirithromycin, E-Mycin, erythromycin base, EES, erythromycin ethyl succinate, Ery-Tab, Eryc, EryPed, Erythrocin, erythromycin stearate, Ilosone, erythromycin estolate, Pediazole, erythromycin/sulfisoxazole, Tao, troleandomycin, Zithromax |

**IMPACT:** Increased effects of warfarin, with potential for bleeding

**MECHANISM OF INTERACTION:** Erythromycin inhibits the metabolism and subsequent clearance of warfarin from the body. The activity of warfarin may also be prolonged due to alterations in the intestinal flora and its production of vitamin K for clotting factor production.

**PREVENTION:** The interaction between warfarin and macrolide antibiotics is highly probable and often delayed. Concomitant use of a macrolide with warfarin should be avoided; switch to an alternative antibiotic. Microbial pathogen identification prior to antibiotic initiation will decrease the prevalence of unnecessary drug interaction risk. Consider culture sensitivity screening as research indicates cautious use of any antibiotic with warfarin.

**MANAGEMENT:** If use of a macrolide is imperative, then monitor INR every other day and adjust warfarin dosing as necessary. Signs and symptoms of an active bleed should be monitored daily with particular attention to the appearance and patterns of bruises. Signs of an active bleed include: coughing up blood in the form of coffee grinds (hemoptysis), gum bleeding, nose bleeds, cola- or tea-colored urine (hematuria), and black, tarry stools (hemocult positive).

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**NOTE:** Although caution may be warranted when using warfarin with all quinolones, Drug Interaction Facts notes that problems have been documented especially with ciprofloxacin, ofloxacin, and norfloxacin. In addition, the Medication Management Project committee has received a number of reports of INR elevations with levofloxacin.

| Warfarin           | Quinolones   |
|--------------------|--|
| Coumadin, warfarin | alatrofloxacin, Avelox, Cipro, ciprofloxacin, enoxacin, Floxin, gatifloxacin, Levaquin, levofloxacin, lomefloxacin, Maxaquin, moxifloxacin, Noroxin, norfloxacin, ofloxacin, Penetrex, sparfloxacin, Tequin, trovafloxacin, Trovan, Trovan IV, Zagam |

**IMPACT:** Increased effects of warfarin, with potential for bleeding

**MECHANISM OF INTERACTION:** The exact mechanism for the warfarin-quinolone drug interaction is unknown. Reduction of intestinal flora responsible for vitamin K production by antibiotics is probable as well as decreased metabolism and clearance of warfarin.

**PREVENTION:** Culture and identify microbial pathogen prior to initiation of antibiotic therapy. Consider culture sensitivity screening. The metabolism of warfarin may be delayed in patients administered enoxacin, ciprofloxacin, norfloxacin, or ofloxacin; thus, quinolone selection should focus on one of the newer agents that has not demonstrated significant impairment of warfarin metabolism. Additionally, microbial pathogen identification and sensitivity prior to antibiotic initiation will decrease the prevalence of unnecessary drug interaction risk.

**MANAGEMENT:** Prothrombin time and INR should be monitored during co-administration of warfarin with a quinolone. If use of ciprofloxacin is imperative, then monitor INR every other day and adjust warfarin dose as necessary. Signs and symptoms of an active bleed should be monitored daily with particular attention to the appearance and patterns of bruises. Signs of an active bleed include: coughing up blood in the form of coffee grinds (hemoptysis), gum bleeding, nose bleeds, cola- or tea-colored urine (hematuria), and black, tarry stools (hemocult positive).

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| Warfarin           | Phenytoin           |
|--------------------|---------------------|
| Coumadin, warfarin | Dilantin, phenytoin |

**IMPACT:** Increased effects of warfarin and/or phenytoin

**MECHANISM OF INTERACTION:** Currently unknown, but one theory suggests a genetic basis involving liver metabolism of warfarin and phenytoin.

**PREVENTION:** Obtain baseline phenytoin levels prior to initiation of warfarin. Monitor INR during co-administration. Target INR should be towards the lower end of the therapeutic range.

**MANAGEMENT:** Prothrombin time, INR, and phenytoin levels should be monitored during co-administration. Signs and symptoms of an active bleed should be monitored daily with particular attention to the appearance and patterns of bruises. Signs of an active bleed include: coughing up blood in the form of coffee grinds (hemoptysis), gum bleeding, nose bleeds, cola- or tea-colored urine (hematuria), and black, tarry stools (hemocult positive).

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| <b>ACE Inhibitors</b>   | <b>Potassium Supplements</b>   |
|---|--|
| Accupril, Aceon, Altace, benazepril, Capoten, captopril, enalapril, fosinopril, lisinopril, Lotensin, Mavik, moexipril, Monopril, perindopril, Prinivil, quinapril, ramipril,trandolapril, Univas, Vasotec, Zestril | K+ Care ET, Kaon, K-dur, Klor-Con, K-Phos, Micro-K, potassium acetate, potassium acid phosphate, potassium bicarbonate, potassium chloride, potassium citrate, potassium gluconate, Urocit-K |

**IMPACT:** Elevated serum potassium

**MECHANISM OF INTERACTION:** Inhibition of ACE results in decreased aldosterone production and potentially decreased potassium excretion.

**PREVENTION:** Draw potassium level prior to initiation of ACE-inhibitor in a patient.

**MANAGEMENT:** Potassium levels greater than 5 should be monitored carefully due to risk of severe hyperkalemia and EKG changes. Watch renal function (BUN, SCr) also. Adjust potassium supplementation if levels increase.

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| <b>ACE Inhibitors</b>   | <b>Spirolactone</b>       |
|---|---------------------------|
| Accupril, Aceon, Altace, benazepril, Capoten, captopril, enalapril, fosinopril, lisinopril, Lotensin, Mavik, moexipril, Monopril, perindopril, Prinivil, quinapril, ramipril,trandolapril, Univas, Vasotec, Zestril | Aldactone, spironolactone |

**IMPACT:** Elevated serum potassium levels

**MECHANISM OF INTERACTION:** Unknown, possibly an additive effect.

**PREVENTION:** Draw potassium level prior to initiation of spironolactone in a patient.

**MANAGEMENT:** Potassium levels greater than 5 should be monitored carefully due to risk of severe hyperkalemia and EKG changes. Watch renal function (BUN, SCr) also. Avoid potassium supplements in patients taking this combination of medications, unless the need is documented and the patient is monitored closely for hyperkalemia.

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| <b>Digoxin</b>   | <b>Amiodarone</b>     |
|------------------|-----------------------|
| digoxin, Lanoxin | amiodarone, Cordarone |

**IMPACT:** Digoxin toxicity

**MECHANISM OF INTERACTION:** Multiple theories exist, but actual mechanism is unknown. Amiodarone may decrease the clearance of digoxin, resulting in prolonged digoxin activity. There may also be an additive effect on the sinus node of the heart.

**PREVENTION:** Obtain digoxin level prior to initiation of amiodarone therapy. Then, decrease dose of digoxin by 50% and monitor digoxin levels once weekly for several weeks.

**MANAGEMENT:** Maintain digoxin level between 1-2. Monitor for signs and symptoms of digoxin toxicity (abdominal pain, anorexia, bizarre mental symptoms in the elderly, blurred vision, bradycardia, confusion, delirium, depression, diarrhea, disorientation, drowsiness, fatigue, hallucinations, halos around lights, reduction in visual acuity, mydriasis, nausea, neuralgia, nightmares, personality changes, photophobia, restlessness, vertigo, vomiting, and weakness).

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| Digoxin          | Verapamil   |
|------------------|---|
| digoxin, Lanoxin | Calan, Calan SR, Covera-HS, Isoptin, Isoptin SR, verapamil, Verelan |

**IMPACT:** Digoxin toxicity

**MECHANISM OF INTERACTION:** Synergistic effect of slowing impulse conduction and muscle contractility, leading to bradycardia and possible heart block.

**PREVENTION:** Monitor heart rate and EKG–PR interval. Evaluate selection of verapamil and digoxin. If patient has CHF, note that verapamil has no proven benefit in reducing mortality or morbidity; furthermore, digoxin offers no additional benefit in mortality, but does improve symptomatology.

**MANAGEMENT:** Monitor heart rate and EKG–PR interval. Monitor for signs and symptoms of digoxin toxicity (abdominal pain, anorexia, bizarre mental symptoms in the elderly, blurred vision, bradycardia, confusion, delirium, depression, diarrhea, disorientation, drowsiness, fatigue, hallucinations, halos around lights, visual acuity, mydriasis, nausea, neuralgia, nightmares, personality changes, photophobia, restlessness, vertigo, vomiting, and weakness).

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**NOTE:** Although caution may be warranted when using theophylline with all quinolones, Drug Interaction Facts notes that problems have been documented especially with ciprofloxacin, enoxacin, and norfloxacin.

| Theophylline   | Quinolones   |
|--|--|
| aminophylline, Choledyl SA, oxtriphylline, Phyllocontin, Slo-Bid, Slo-Phyllin, Slo-Phyllin 125, Theo-24, Theo-Dur, Theolair, theophylline, Uniphyll, Uniphyll CR | alatrofloxacin, Avelox, Cipro, ciprofloxacin, enoxacin, Floxin, gatifloxacin, Levaquin, levofloxacin, lomefloxacin, Maxaquin, moxifloxacin, Noroxin, norfloxacin, ofloxacin, Penetrex, sparfloxacin, Tequin, trovafloxacin, Trovan, Trovan IV, Zagam |

**IMPACT:** Theophylline toxicity

**MECHANISM OF INTERACTION:** Inhibition of hepatic metabolism of theophylline by the quinolones.

**PREVENTION:** Obtain theophylline level prior to initiation of a quinolone. Of the quinolones, enoxacin and ciprofloxacin reduce theophylline clearance by 30-84%. Consider switching to gatifloxacin, levofloxacin, moxifloxacin, or trovafloxacin; these agents appear not to inhibit theophylline metabolism.

**MANAGEMENT:** Monitor theophylline levels. Maintain level within targeted range of 5-15mcg/mL; however, theophylline toxicity may result even when the level is within the targeted range. Signs and symptoms of theophylline toxicity include seizures, nausea, and vomiting.

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