TOP 10 PARTICULARLY DANGEROUS DRUG INTERACTIONS IN PA/LTC

Recent studies have shown that adverse drug reactions (ADRs) are common among nursing home residents, and frequently go unrecognized or the symptoms attributed to another condition. Many ADRs are due to drug-drug interactions. The occurrence of an interaction depends on many factors, including the inherent pharmacological properties of the drugs, the resident's medical condition and presence of co-morbidities, the dose of the drugs, and the presence of other drugs.

The severity and clinical significance of the interactions vary from mild and clinically unimportant to severe and life-threatening. Some combinations of drugs cause interactions more often than others.

The likelihood of an interaction is also increased for drugs that are more commonly prescribed in nursing homes. While most residents take various combinations of drugs without experiencing interaction-related ADRs, they nonetheless have a risk which is higher for certain combinations as discussed above.

A group of experts was convened by AMDA, in collaboration with the American Society of Consultant Pharmacists (ASCP), to develop strategies for medication management in nursing homes, identify the need to alert members of the interdisciplinary team of the need to anticipate the risk of ADRs related to drug interactions, and promptly recognize the symptoms of such interactions, so appropriate action can be taken on a timely basis.
There are numerous possible interactions. To identify those on which the care team should focus, the group conducted a survey among physicians and pharmacists to identify drug-drug interactions according to:

1. the clinical significance and potential to cause harm;
2. the frequency with which the interaction occurs, and
3. the frequency with which these drugs are prescribed in nursing homes.

Three lists emerged, and then those that were present in all three lists were chosen for the first round. The list will be publicized to members of the interdisciplinary teams via AMDA and ASCP publications, and will include the symptoms to identify. It is hoped that this will help members of the team with both increasing surveillance and prompt identification of symptoms.

Disclaimer: The information below serves only as a guide for use by qualified medical practitioners in understanding, handling and avoiding frequent and potentially dangerous drug interactions that occur in long-term care. This presentation is not intended to instruct a practitioner how to treat any medical condition, nor is it intended to replace a practitioner's best clinical judgment. AMDA expressly disclaims responsibility and liability for any adverse effects, damages or other consequences resulting from the use of any of the information contained in this presentation.

ACE INHIBITORS-POTASSIUM SUPPLEMENTS

benazepril (*Lotensin*)
captopril (*Capoten*)
enalapril (*Vasotec*)
fosinopril (*Monopril*)
lisinopril (*Prinivil, Zestril*)
moexipril (*Univasc*)
perindopril (*Aceon*)
quinapril (*Accupril*)
ramipril (*Altace*)
trandolapril (*Mavik*)

potassium acetate/potassium bicarbonate/potassium citrate (*Tri-K*)
potassium acid phosphate (*K-Phos*)
potassium bicarbonate (*K + Care ET*)
potassium bicarbonate/potassium citrate(*Effer-K, Effervescent Potassium, Klor-Con/EF, K*Lyte*)
potassium bicarbonate/potassium citrate/citric acid (*K*Lyte DS*)
potassium chloride (*Cena-K, Gen-K, K+8, K+10, K+Care, K-Dur 10, K-Dur 20, K-Lease, K-Lor, K-Norm, Kaochlor 10%, Kaochlor S-F, Kaon-Cl 20%, Kaon Cl-10, Kay Ciel, Klor-Con, Klor-Con 8, Klor-Con 10, Klor-Con/25, K*Lyte/Cl, Klotrix, K-Tab, K-vescent Potassium Chloride, Micro-K Extencaps, Micro-K 10 Extencaps, Micro-K LS, Potasalan, Rum-K, Slow-K, Ten-K*)
potassium chloride/potassium bicarbonate/lysine hydrochloride (*Klorvess*)
potassium chloride/potassium bicarbonate/potassium citrate/lysine hydrochloride (*Klorvess Effervescent Granules*)
potassium chloride/potassium bicarbonate/l-lysine monohydrochloride/citric acid (*K*Lyte/Cl, K*Lyte/Cl 50*)
potassium citrate (*Urocit-K*)
potassium gluconate (*Kaon, Kaylixir*)
potassium gluconate/potassium citrate(*Twin-K*)
potassium gluconate/potassium chloride(*Kolyum*)

Brand names appear in parentheses above and are trademarks of their respective manufacturers/owners.

Impact: Potential for elevated serum potassium levels.[1]

Mechanism of Interaction: Inhibition of ACE results in decreased aldosterone production and potentially decreased potassium excretion.

Alternatives to Patient Management: Draw potassium level prior to initiation of ACE-inhibitor in a patient.

Monitoring/Precautions: Potassium levels greater than 5.0 mmol/L 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.

ACE INHIBITORS-SPIRONOLACTONE

benazepril (*Lotensin*)
captopril (*Capoten*)
enalapril (*Vasotec*)
fosinopril (*Monopril*)
lisinopril (*Prinivil, Zestril*)
moexipril (*Univasc*)
perindopril (*Aceon*)
quinapril (*Accupril*)
ramipril (*Altace*)
trandolapril (*Mavik*)

spironolactone (*Aldactone*)

Brand names appear in parentheses above and are trademarks of their respective manufacturers/owners.

Impact: Potential for elevated serum potassium levels.[1]

Mechanism of Interaction: Unknown.

Alternatives to Patient Management: Evaluate need for additional drug therapy. ACE inhibitors are recommended in diabetic patients for nephroprotection. Spironolactone increased survival in patients with severe CHF. Prior to initiation, obtain a potassium level with a serum creatinine and BUN to further evaluate use of these agents in combination.[7]

Monitoring/Precautions: Potassium levels greater than 5.0 mmol/L and serum creatinine concentrations greater than 2.5mg/dL should be monitored carefully due to risk of severe hyperkalemia and EKG changes.[7]

DIGOXIN-AMIODARONE

digoxin (*Lanoxin*) **amiodarone (*Cordarone, Pacerone*)**

Brand names appear in parentheses above and are trademarks of their respective manufacturers/owners.

Impact: Potential for digoxin toxicity.[1]

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.

Alternatives to Patient Management: Obtain digoxin level prior to initiation of amiodarone therapy. Then, decrease dose of digoxin by 25-50% and monitor digoxin levels once weekly for several weeks.[8,9] Digoxin therapy should be cautiously started in with hypokalemia, hypomagnesemia or hypothyroidism due to the potential for adverse drug reactions at lower digoxin levels.[10,11]

Monitoring/Precautions:

1. Maintain digoxin level below 2ng/mL (2.6nmol/L).[12]
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, visual acuity, mydriasis nausea, neuralgia, nightmares, personality changes, photophobia, restlessness, vertigo, vomiting, and weakness).
3. Monitor heart rate for bradycardia and EKG-look for elongated PR interval.
4. Monitor calcium, magnesium and potassium levels.

DIGOXIN-VERAPAMIL

digoxin (*Lanoxin*) **verapamil (*Calan, Calan SR, Covera-HS, Isoptin, Isoptin SR, Verelan, Verelan PM*)**

Impact: Potential for digoxin toxicity.[1]

Mechanism of Interaction: Serum digoxin concentration rise by 60-75% due to decreased renal tubular secretion and nonrenal clearance mechanisms.[12,13] Biliary clearance of digoxin is reduced by 42-43% when administered with verapamil.[14,15]Additionally, there appears to be a synergistic effect of slowing impulse conduction and muscle contractility, leading to bradycardia and possible heart block.[8,16]

Alternatives to Patient Management: Monitor heart rate and EKG-PR interval. Evaluate selection of verapamil and digoxin. If patient has CHF, note that verapamil has not proven any benefit in mortality or morbidity; furthermore, digoxin offers no additional benefit in mortality, but does improve symptomatology. Digoxin therapy should be cautiously started in patients with hypokalemia, hypomagnesemia or hypothyroidism due to the potential for adverse drug reactions at lower digoxin levels.[10,11]

Monitoring/Precautions:

1. Maintain digoxin level below 2ng/mL (2.6nmol/L).[12]
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3. Monitor heart rate for bradycardia and EKG-PR interval.
4. Monitor calcium, magnesium and potassium levels.

THEOPHYLLLINE-QUINOLONES

Impact: Possible epileptogenic activity; possible theophylline toxicity; inhibition of hepatic metabolism of theophylline by quinolones.

Mechanism of Interaction: Inhibition of gamma-aminobutyric acid (GABA) binding to the GABA receptor, resulting in general excitation of the central nervous system.

Prevention: Obtain theophylline level prior to initiation of a quinolone. Of the quinolones, exoxacin and ciproflaxin reduce theophylline clearance by 30-84%. Consider switching to gatifloxacin, levofloxacin, moxifloxacin, or trovafloxacin; these agents appear not to inhibit theophylline metabolism.Drug interactions are often clinically unrecognized and responsible for increased morbidity in elderly patients. Prudent use of medications and vigilant drug monitoring are essential to avoid drug–drug interactions.

Management: Attention should be paid to the possible epileptogenic activity of the simultaneous administration of quinolones with theophylline.

Quinolones

List Of Quinolone Antibiotics -
ofloxacin(Floxin®), levofloxacin(Levaquin®, Tavanic®), ciprofloxacin(Cipro®,Baycip®, Cetraxal®, Ciflox®, Cifran®, Ciplox®, Cyprobay®, Quintor®),norfloxacin(Noroxin®, Amicrobin®, Anquin®, Baccidal®, Barazan®, Biofloxin®,Floxenor®, Fulgram®, Janacin®, Lexinor®, Norofin®, Norxacin®, Orixacin®,Oroflox®, Urinox®, Zoroxin®), enoxacin(Penetrex®), lomefloxacin(Maxaquin®),grepafloxacin(Raxar®), trovafloxacin(Trovan®), sparfloxacin(Zagam®),temafloxacin(Omniflox®), moxifloxacin(Avelox®), gatifloxacin(Tequin®), gemifloxacin

List of Theophyllines
Aminophylline, Choledyl SA, moxtriphylline, Phyllocontin, Slo-Bid, Slo-Phyllin, Slo-Phyllin 125, Theo-24, Theo-Dur, Theolair, theophylline, Uniphyl, Uniphyl CR

WARFARIN-MACROLIDES

warfarin (*Coumadin*)	**azithromycin (*Zithromax*)** **clarithromycin (*Biaxin*)** **dirithromycin (*Dynabac*)** **erythromycin base (*E-Mycin, Ery-Tab, Eryc*)** **erythromycin estolate (*Ilosone*)** **erythromycin ethyl succinate (*EES, EryPed*)** **erythromycin lactobionate (*Erythrocin*)** **erythromycin gluceptate (*Ilotycin Gluceptate*)** **erythromycin stearate (*Erythrocin*)** **erythromycin/sulfisoxazole (*Pediazole*)** **troleandomycin (*Tao*)**

Brand names appear in parentheses above and are trademarks of their respective manufacturers/owners.

Impact: Potential for increased effects of warfarin.[1]

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.

Alternatives to Patient Management: 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.

Monitoring/Precautions: If use of a macrolide is imperative, then monitor INR every other day and adjust warfarin dosing as necessary.[2] 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), gingival bleeding, nose bleeds, cola- or tea-colored urine (hematuria), and black, tarry stools (hemoccult positive?).

WARFARIN-NSAIDS

warfarin (*Coumadin*)	**diclofenac (*Arthrotec, Cataflam, Voltaren, Voltaren XR*)** **diflunisal (*Dolobid*)** **etodolac (*Lodine, Lodine XL*)** **flurbiprofen (*Ansaid*)** **ibuprofen (*Advil, Genpril, Haltran, Menadol, Motrin, Motrin IB, Motrin Migraine Pain, Nuprin*)** **indomethacin (*Indocin, Indocin SR*)** **ketoprofen (*Orudis, Orudis KT, Oruvail*)** **ketorolac (*Toradol*)** **mefenamic acid (*Ponstel*)** **meloxicam (*Mobic*)** **nabumetone (*Relafen*)** **naproxen (*Aleve, Anaprox, Anaprox DS, Naprelan, Naprosyn*)** **oxaprozin (*Daypro*)** **piroxicam (*Feldene*)** **sulindac (*Clinoril*)** **tolmetin (*Tolectin, Tolectin DS*)**

Impact: Potential for serious bleed[1] (GI, hemorrhage).

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.

Alternatives to Patient Management: Avoid concomitant use of an NSAID with warfarin.[2] 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 do not appear to affect the INR.2 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 reduction of prevalence of gastric adverse advents with these agents combined with the lack of anti-platelet action, support the cautious use of COX-2 inhibitors in anticoagulation patients.[2] **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.

Monitoring/Precautions: 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), gingival bleeding, nose bleeds, cola- or tea-colored urine (hematuria), or black, tarry stools (hemoccult positive?).

WARFARIN-PHENYTOIN

warfarin (*Coumadin*) **phenytoin(*Dilantin Infatab, Dilantin-125*)**

Brand names appear in parentheses above and are trademarks of their respective manufacturers/owners.

Impact: Potential for increased effects of warfarin and/or phenytoin.[1]

Mechanism of Interaction: Currently unknown, but one theory suggests a genetic basis involving liver metabolism of warfarin and phenytoin. Phenytoin may increase the effects of warfarin.[6]

Alternatives to Patient Management: 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 goal range.

Monitoring/Precautions: 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), gingival bleeding, nose bleeds, cola- or tea-colored urine (hematuria), and black, tarry stools (hemoccult positive?).

WARFARIN-QUINOLONES

warfarin (*Coumadin*)	**alatrofloxacin (*Tolectin, Tolectin DS*)** **cinoxacin (*Cinobac*)** **ciprofloxacin (*Cipro*)** **enoxacin (*Penetrex*)** **gatifloxacin (*Tequin*)** **levofloxacin (*Levaquin*)** **lomefloxacin (*Maxaquin*)** **moxifloxacin (*Avelox*)** **nalidixic acid (*NegGram*)** **norfloxacin (*Noroxin*)** **ofloxacin (*Floxin*)** **sparfloxacin (*Zagam*)** **trovafloxacin (*Trovan, Trovan IV*)**

Brand names appear in parentheses above and are trademarks of their respective manufacturers/owners.

Impact: Potential for increased effects of warfarin.[1]

Mechanism of Interaction: The exact 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.

Alternatives to Patient Management: 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,[4] ciprofloxacin,[4,5]norfloxacin,[4] or ofloxacin[4]; thus, quinolone selection should focus on one of the newer agents that has not demonstrated significant impairment of warfarin metabolism, such as levofloxacin. Additionally, microbial pathogen identification and sensitivity prior to antibiotic initiation will decrease the prevalence of unnecessary drug interaction risk.

Monitoring/Precautions: 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.2 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), gingival bleeding, nose bleeds, cola- or tea-colored urine (hematuria), and black, tarry stools (hemoccult positive?).

WARFARIN-SULFA DRUGS

warfarin (*Coumadin*)	**erythromycin/sulfisoxazole (*Pediazole*)** **sulfamethizole (*Thiosulfil Forte*)** **sulfamethoxazole (*Gantanol*)** **sulfisoxazole (*Gantrisin*)** **trimethoprim/sulfamethoxazole (*Bactrim DS, Bactrim SS, Cotrim DS, Cotrim SS, Septra DS, Sulfatrim*)**

Impact: Potential for increased effects of warfarin.[1]

Mechanism of Interaction: Currently, the interaction with sulfa drugs is unknown; however, clinicians hypothesize that warfarin's activity is prolonged due a decreased production of vitamin K by intestinal flora affected by systemic antibiotic administration. Additionally, a hypoprothrombinemic effect may occur when S-warfarin is combined with sulfaethoxazole/trimethoprim.[3]

Alternatives to Patient Management: 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.[2]

Monitoring/Precautions: INR should be monitored during co-administration of warfarin with a sulfa drug other than sulfamethoxazole-trimethoprim and warfarin dose adjustments made as necessary.[1] 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), gingival bleeding, nose bleeds, cola- or tea-colored urine (hematuria), and black, tarry stools (hemoccult positive?).

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