

## **Louisiana Drug Utilization Review (LADUR) Education**

### **Polypharmacy: Consequences and Management**

By: Corbin Turpin, M.D., Melissa L. Dear, R.Ph., and Pam Walters, R.Ph.

#### **Issues...**

- Polypharmacy is the use of multiple prescriptions and/or over-the-counter medications simultaneously.
- ...in order to identify polypharmacy, it is necessary to evaluate a patient's medication profile for "excessive" or "unnecessary" medications.
- At times, polypharmacy may be necessary in order to treat patients with multiple chronic diseases...

#### **Introduction**

Polypharmacy has been defined in a number of ways, one of which is the use of multiple prescriptions and/or over-the-counter medications simultaneously. Although "polypharmacy" may have a negative connotation, in certain situations, using multiple prescriptions may be appropriate, such as when treating several chronic disease states concurrently. Another definition states that polypharmacy is the excessive or unnecessary use of prescription or nonprescription medications. In this instance, in order to identify polypharmacy, it is necessary to evaluate a patient's medication profile for "excessive" or "unnecessary" medications. It is estimated that approximately 34% of prescriptions written in the United States are unnecessary. These could be medications without an appropriate indication, duplicate therapy to treat a specific condition, interacting medications, inappropriate dosages, or the use of drug therapy to treat adverse drug reactions.

#### **Potential Causes and Risk Factors**

At times, polypharmacy may be necessary in order to treat patients with multiple chronic diseases and should be done with careful monitoring and patient follow-up. However, the use of multiple medications is inappropriate when the risks outweigh the benefits. Inappropriate use may be due to varying factors. The patients contribute to the problem by:

- Taking over-the-counter medications, herbal remedies, vitamins, or other supplements without notifying the physician
- Seeing multiple physicians without providing each of them an accurate medication list
- Using multiple pharmacies
- Demanding medications to address every complaint or symptom. It is estimated that 75% of physician visits results in a written prescription.

Physicians also contribute to the problem when they have excessive or inappropriate prescribing practices, such as continuing the use of a medication that should have been discontinued because it has lost its effect, or using medication to alleviate adverse reactions to other medications.

Advanced age is the greatest risk factor for polypharmacy because many elderly patients suffer from multiple chronic disease states. Fifty percent of patients over the age of 65 have more than one chronic condition. Another contributing factor for the elderly population is that one-fourth of these patients are under the care of four or more physicians. Other risk factors include:

- Number of drugs taken daily
- Socioeconomic factors (such as living arrangements)
- Female gender
- Factors related to the patient's health care provider.

### **Adverse Consequences of Polypharmacy**

There are numerous consequences to the patient from the practice of polypharmacy. These consequences include decreased social activity, decreased cognition, increased risk of depression, and increased morbidity. Also, the risk is multiplied in the elderly because of reduced renal or hepatic function and altered functional status. Polypharmacy has also been shown to be an independent risk factor for eventual nursing home placement.

Another result of polypharmacy is increased medical costs. Increased costs cause financial strain for many, often leading to a decrease in patient compliance when patients may not be able to afford all the drugs they have been prescribed. Poor compliance rates are also compounded by complex drug regimens from multiple prescriptions.

### **Adverse Drug Reactions**

The most dangerous outcome of polypharmacy is the increased risk of adverse drug reactions (ADRs) which includes drug-drug interactions. Each drug has potential adverse side effects; thus the greater the number of drugs being used, the greater the likelihood of an adverse reaction.

The potential for ADRs has been estimated at:

- 6% when patients take two medications
- 50% when patients take five different medications, and
- 100% when patients take eight or more medications.

Over 2 million serious drug reactions and 100,000 deaths occur yearly due to adverse drug reactions. Adverse drug reactions are the fourth leading cause of death, ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents and automobile deaths.

### ***ADRs in the Elderly***

Seventeen percent (17%) of hospitalizations in elderly patients are due to adverse drug reactions (ADRs). These ADRs cause significant problems in the elderly since these adverse effects often mimic the aging process and/or diseases such as anxiety, depression, Parkinson's disease, CHF with fluid retention, gastroenteritis, and many others.

These reactions occur more frequently in the elderly due to the fact that age-related factors alter drug metabolism in several ways, including:

- Altered absorption. Drug absorption is affected by alterations in gastric pH and gastrointestinal motility, which may delay the absorption of drugs.
- Altered distribution. Distribution is affected by the alterations in protein binding that occur when drugs compete for the same protein-binding sites, particularly in the elderly, who have decreased protein-rich lean body mass or low serum albumin levels.
- Decreased hepatic metabolism. Many commonly prescribed drugs are metabolized by the liver, specifically cytochrome P450 enzymes. Since hepatic metabolizing capability slows with age, elderly individuals may be particularly vulnerable to toxicity from drugs that induce or inhibit the P450 isoenzymes used during drug metabolism.
- Decreased renal elimination. The majority of the elderly experience a decline in renal function (i.e. decreased renal blood flow, renal mass, glomerular and tubular function). Therefore, drugs eliminated through the kidneys require monitoring of renal function to determine if downward dosage adjustment is necessary to prevent potentially toxic accumulation of active compounds.

The categories of medications most commonly associated with adverse reactions in elderly patients are listed below.

- Psychotropic medications (particularly the benzodiazepines)
- Antihypertensives (including diuretics)
- Nonsteroidal anti-inflammatory medications
- Systemic steroids
- Theophylline
- Warfarin
- Cimetidine
- Digoxin.

### ***Drug-Drug Interactions***

When discussing ADRs, it is important to remember that ADRs include drug-drug

interactions. Drug interactions represent 3-5% of preventable in-hospital ADRs and play a large part in many emergency room visits. Drug interactions can occur by several mechanisms.

- Interactions could occur even before drugs enter the body due to formulation incompatibility. For example, when phenytoin is added to dextrose, a precipitate forms turning phenytoin into an insoluble salt which makes it unavailable to control seizures.

- Drug binding could take place in the GI tract which would prevent absorption and reduce systemic availability. An example would be the ability of aluminum-containing medicines, such as sucralfate and antacids, to reduce the absorption of antibiotics like ciprofloxacin and azithromycin.

- An interaction could occur in the liver or GI tract due to changes in the rates of drug metabolism caused by other medicines that are inducers or inhibitors of drug metabolism. The interaction between fluoxetine and amitriptyline is an example of this. The combination of these two drugs results in increased plasma levels of amitriptyline with an increased potential for side effects due to the fact that fluoxetine is a potent inhibitor of the CYP2D6 enzyme.

- An interaction could also happen at the level of drug action, such as the combination of verapamil, a calcium channel blocker, and a beta-blocker. Both slow the heart rate by different mechanisms which could result in heart block.

The table (TABLE 1. Overview of Selected Serious Drug Interactions) on the following page represents an overview of selected serious drug interactions that should be monitored closely in patients with multiple medications.

Interaction	Potential effect	Time to effect	Recommendations and comments
Warfarin (Coumadin) plus ciprofloxacin (Cipro), clarithromycin (Biaxin), erythromycin, metronidazole (Flagyl) or trimethoprim-sulfamethoxazole (Septra, Sepse)	Increased effect of warfarin	Generally within 1 week	Select alternative antibiotic
Warfarin plus acetaminophen	Increased bleeding, increased INR	Any time	Use lowest possible acetaminophen dosage and monitor INR
Warfarin plus acetylsalicylic acid (aspirin)	Increased bleeding, increased INR	Any time	Lowest aspirin dosage is 100 mg per day and monitor INR
Warfarin plus NSAID	Increased bleeding, increased INR	Any time	Avoid concurrent use if possible. If concurrent use is necessary, use a cyclooxygenase-2 inhibitor and monitor INR
Fluoroquinolone plus divalent cation (magnesium or calcium) (Calmace)	Decreased absorption of Fluoroquinolone	Any time	Space administration by 2 to 4 hours
Carbamazepine (Tegretol) plus cimetidine (Tagamet), erythromycin, clarithromycin or fluconazole (Diflucan)	Increased carbamazepine levels	Generally within 1 week	Monitor carbamazepine levels
Phenytoin (Dilantin) plus cimetidine, erythromycin, clarithromycin or fluconazole	Increased phenytoin levels	Generally within 1 week	Monitor phenytoin levels
Phenobarbital plus cimetidine, erythromycin, clarithromycin or fluconazole	Increased phenobarbital levels	Generally within 1 week	Clinical significance has not been established. Monitor phenobarbital levels
Phenytoin plus rifampin (Rifadin)	Decreased phenytoin levels	Generally within 1 week	Clinical significance has not been established. Monitor phenytoin levels
Phenobarbital plus rifampin	Decreased phenobarbital levels	Generally within 1 week	Monitor phenobarbital levels
Carbamazepine plus rifampin	Decreased carbamazepine levels	Generally within 1 week	Clinical significance has not been established. Monitor carbamazepine levels
Lithium plus NSAID or diuretic	Increased lithium levels	Any time	Decrease lithium dosage by 50% and monitor lithium levels
Oral contraceptive pills plus rifampin	Decreased effectiveness of oral contraception	Any time	Avoid if possible. If combination therapy is necessary, have the patient take an oral contraceptive pill with a higher estrogen content (17.5 µg of ethinyl estradiol) or recommend alternative method of contraception
Oral contraceptive pills plus antibiotics	Decreased effectiveness of oral contraception	Any time	Avoid if possible. If combination therapy is necessary, recommend use of alternative contraceptive method during cycle
Oral contraceptive pills plus progesterone (Rexulin)	Decreased effectiveness of oral contraception	Any time	Have the patient take an oral contraceptive pill with a higher estrogen content or recommend alternative method of contraception
Cisapride (Propulsid) plus erythromycin, fluconazole, itraconazole (Sporanox), ketoconazole (Nizoral), nifedipine (Procardia), indinavir (Crixivan) or ritonavir (Norvir)	Prolongation of QT interval along with arrhythmias secondary to inhibited cisapride metabolism	Generally within 1 week	Avoid. Consider whether metoprolol (Irgel) therapy is appropriate for the patient
Cisapride plus class Ia or class III antiarrhythmic agents, cyclic antidepressants or phenothiazines	Prolongation of QT interval along with arrhythmias	Any time	Avoid. Consider whether metoprolol therapy is appropriate for the patient
Sildenafil (Viagra) plus nitrates	Ornate hypotension	Soon after taking sildenafil	Absolute contraindication
Sildenafil plus cimetidine, erythromycin, itraconazole or ketoconazole	Increased sildenafil levels	Any time	Increase sildenafil to a 25-mg dose
H <sub>2</sub> O-ATP reductase inhibitor plus niacin, gemfibrozil (Lopid), erythromycin or itraconazole	Possible rhabdomyolysis	Any time	Avoid if possible. If combination therapy is necessary, monitor the patient for toxicity
Losartan (Mavacor) plus warfarin	Increased effect of warfarin	Any time	Monitor INR
SSRI plus tricyclic antidepressant	Increased tricyclic antidepressant level	Any time	Monitor for anticholinergic effects and consider lower dosage of tricyclic antidepressant
SSRI plus selegiline (Eldepryl) or nonselective monoamine oxidase inhibitor	Hypertensive crisis	Soon after ingestion	Avoid
SSRI plus enalapril (Lipitor)	Increased potential for seizures, serotonin syndrome	Any time	Monitor the patient for signs and symptoms of serotonin syndrome
SSRI plus St. John's wort	Serotonin syndrome	Any time	Avoid
SSRI plus nortriptyn (Anerge), risperidone (Mavone), sumatriptan (Imitrex) or zolmitriptan (Zelmac)	Serotonin syndrome	Possibly after initial dose	Avoid if possible. If combination therapy is necessary, monitor the patient for signs and symptoms of serotonin syndrome

## Management of Polypharmacy

Due to the extensive number of problems that can arise from the practice of polypharmacy, it is crucial for prescribers to manage it aggressively. This can be done by carefully analyzing all aspects of drug therapy, including the prevention of drug interactions.

The following is a stepwise approach that can be used by prescribing providers to prevent drug interactions:

- Take a good medication history.
- The "**AVOID Mistakes**" mnemonic can help with this process.
  - o Allergies?
  - o Vitamins and herbs?
  - o Old drugs and OTC? (as well as current medications)
  - o Interactions?
  - o Dependence? Contract? Consider the possibility of needing a behavioral contract between the provider and the patient in an effort to help the patient reach the therapeutic goal, either in the case of drug dependence or adherence to a therapeutic regimen.
  - o Mendel: Family History? A family history of benefits or problems with drugs will help determine whether pharmacogenetics should play a role in the selection of drug therapy.
- Identify high risk patients, such as those taking a high number of medications.
- Check pocket references for possible interactions.
- Consult pharmacists/drug information specialists.
- Check one of the up-to-date computerized drug information databases.

In order to analyze an entire drug regimen, another method was developed to ensure appropriate prescribing. This method, known as the "**SAIL**" protocol, is summarized below. Although this method has not been tested in clinical practice, its application could help physicians and other prescribers minimize polypharmacy in their practices.

**Table 2. The SAIL Protocol for Appropriate Prescribing**

<b>Simple</b>	Keep drug regimen as simple as possible. Prescribe combination drugs when possible. Aim for once-daily regimens.
<b>Adverse</b>	Possible adverse effects of each drug must be clearly understood. Drugs must have a wide therapeutic window and must not interact with other drugs in the regimen.
<b>Indication</b>	The indication for each drug must be clear and each drug must have a clearly defined therapeutic goal.
<b>List</b>	The list of the drugs in the regimen must be accurate and must include prescriptions, OTC medications, and herbs or alternative medications.

Lee RD. Polypharmacy: A Case Report and New Protocol for Management. The Journal of the American Board of Family Practice 1998; 11: 140-44

## Conclusion

Although polypharmacy is appropriate in certain situations, regimens of multiple

medications should be reviewed routinely to ensure that the patient is receiving maximum benefit with the least amount of risk. By carefully reviewing drug regimens and being aware of the risks, physicians can provide the highest level of care for their patients.

**References available upon request.**