POTENTIALLY INAPPROPRIATE MEDICATION USE IN GEORGIA NURSING HOMES

by

RONG JIANG

(Under the Direction of Dr. Matthew Perri III)

ABSTRACT

Objectives: To determine the prevalence of potentially inappropriate medication use in Georgia nursing home residents and to examine the risk factors for potentially inappropriate medication use. **Method:** Retrospective data analysis. The Georgia Long-term Care Database was examined to evaluate for potentially inappropriate medication use in elderly residents. 1348 patient charts between March 1st and June 1st, 2002 were reviewed to establish the database. **Results:** Of the 1,161 older residents, 43.7 % of patients had at least one potentially inappropriate medication while 12.2 % patients had two or more. The most frequently used potentially inappropriate drugs or drug classes are antihistaminic agents, propoxyphene, sedative-hypnotics, iron supplements, and digoxin. Logistic regression demonstrated that the number of medications and diabetes predicted potentially inappropriate medication use. **Conclusions:** Potentially inappropriate medication use is common in Georgia nursing homes. Patients with more drugs are at the greatest risk for having a potentially inappropriate medication while diabetic patients have less risk.

INDEX WORDS: Geriatrics, Potentially inappropriate medication, Beers criteria, Nursing home, Georgia

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DEDICATION

To my family

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Chapter 1

Introduction

The world is experiencing major demographic and health-related transitions. As a consequence, in developed countries 10% or more of the population are 65 years of age or over. In the United States, the proportion aged 65 and over was 10% percent in 1971 and is currently 12% of the total population. By the year 2040, this percentage is projected to be 23% or some 68 million people over the age of 65 (Cessna et al, 1990). Given that the elderly tend to have multiple, chronic medical conditions, and that the prevalence of many diseases such as Alzheimer's disease, ischemic heart failure, Parkinson's disease, stroke, hip fractures, prostatic hypertrophy and various cancers are age-dependent, there would be increases in morbidity and mortality associated with this demographic trend (Grundy, 2000).

Accompanying the demographic and health transitions, health care continues to shift toward the elderly with chronic conditions. Drug therapy is the most frequently used therapeutic intervention in the geriatric patient. Studies have shown that the use of prescription and over-the-count (OTC) medications increases with age (Martin, 2000). Further, the elderly spend approximately $3 billion on prescription medication annually in U.S. and more than 90% of Americans aged 65 years or older take at least one prescribed drug daily with the majority taking two or more (Moellar et al., 1989). Drug use is even more frequent among institutionalized elderly patients. The U.S. nursing

home resident takes an average of six different medications, and more than 20% of nursing home residents use ten or more different drugs (Bernabei, 2000). Cardiovascular drugs, antihypertensives, analgesics, anti-inflammatory drugs, sedatives and gastrointestinal preparations are the most commonly used medications in the geriatric population (Hale et al., 1987), followed in frequency by laxatives, analgesics, sedative-hypnotics and neuroleptics as the most commonly prescribed medications in long-term care facilities (Lamy et al., 1980).

Management of drug therapy in the elderly is an important issue. Many factors unique to the aged population make drug therapy more complicated. The physiologic changes associated with aging can have an effect on how medications are handled in the body. Such changes include alterations in various volumes of drug absorption, distribution, metabolism and clearance. Elderly patients may also have increased or decreased drug effects because of alteration in receptor response. These pharmacokinetic and pharmacodynamic changes may result in a prolonged drug half-life, increased potential for drug toxicity, and greater likelihood for adverse drug reactions.

Widespread concerns have been raised about the high rate of use and quality of medication use in older people. The elderly may be at particular risk from drug-related problems such as overuse, misuse and adverse drug reactions (ADRs). It has been reported that up to one-third of the elderly have drug-related problems that have resulted in or contributed to a hospital admission (Cooper, 1997). Other research has revealed rates of hospital admissions due to ADRs from 4.2% to 16.8% in the elderly (Onder, 2002). Since ADRs obviously increase with taking multiple medications (polypharmacy) it is vital to also consider drug chosen. While important in any prescribing decision, it is

critical for the elderly that careful considerations of the benefits of a medication against the potential risks be evaluated. It has been suggested that some drugs should be generally avoided and the doses of some drugs should not be exceeded in elderly persons.

This study will examine the use of medications in long term care, elderly patients in Georgia. While utilization rates are known to be high in this population, it is unclear whether this results in inappropriate medication use in the Georgia long-term care population.

Chapter 2

Basic Principles of Geriatric Pharmacotherapy

In general, drug effects depend on the management of the drug by the body and the sensitivity of the target organ to the drug. Both of these factors change with age, and in general these changes result in longer activity duration of action, altered drug effect and increased rate of events of drug toxicity and ADRs (Montamat et al, 1989). The following is a review of studies relating to pharmacokinetics and pharmacodynamics changes in the elderly patients. The studies concerning ADRs in the elderly patients will be reviewed in this chapter.

Pharmacokinetics

In most clinical trials drugs have been tested on primarily young healthy people (less than 65 years of age). Only limited attention has been given to pharmacokinetic parameters in the elderly. Understanding of basic principles of pharmacokinetics in this group will help to reduce ADRs in clinical practice. Therefore, the Food and Drug Administration has established requirements for including specific elderly populations in clinical trials (FDA, 1992).

Drug Absorption

Various physiologic changes occur with normal aging. In general, secretion of gastric acid and gastric emptying decreases, absorptive surface decreases and splanchnic blood flow diminishes. The elderly have a 30% decrease in mucosal surface area and a

40% reduction of blood flow of the small intestine. Despite these changes, very few medications have delayed absorption after oral administration (Cusack, 1986). None of these changes seem to have a major clinical impact (Woodhouse, 1998).

Before entering the systemic circulation, many drugs exhibit a first-pass effect in that significant metabolism takes place in liver on the drug's first passage through the organ of metabolism. Bioavailability can be used to measure absorption and first-pass metabolism. Studies using water-soluble drugs such as digoxin showed that there is no significant difference in systemic bioavailability between young and elderly persons (Kinirons, 1998). Drugs with high hepatic extraction ratios undergo extensive first-pass metabolism. However, systemic bioavailability is affected by reductions in liver function with age. This results in significant higher systemic concentrations of drugs. Propranolol, nifedipine and triazalom have been noted for such age-related effects (O'Maony, 2000).

Drug Distribution

The distribution of a drug depends on the ability of the drug to cross the cell lipid membrane. This ability is determined by the composition of body tissues, blood flow to the organs and plasma protein binding to albumin and to alpha glycoprotein, or some combination of these factors, all of which change with advancing age (Chutka DS, 1995; Kinirons, 1998).

Body composition changes substantially with age, notably a relative decrease in total body water and lean body mass and a relative increase in body fat. These changes affect drug distribution differently, depending on the lipid solubility of the drug. The increase of body fat results in a large volume of distribution for lipid-soluble drugs, causing prolonged drug action because of long elimination half-lives. This is important

clinically for central nervous system drugs such as barbiturates and several benzodiazepines. On the other hand, the reduced volume of distribution for a water-soluble drug can result in increased initial serum concentration. So, a water-soluble drug can have an increased effect with advanced age, such as ethanol, digoxin, antipyrine, and cimetidine. For digoxin, its toxicity may occur in elderly patients at the therapeutic doses for younger patients. Pancuronium and tobramycin are exceptions with an increased volume of distribution in the elderly (Montamat, 1989).

Only unbound drugs are free to cross plasma membranes into tissues. Acidic drugs such as diazepam, phenytoin, warfarin, salicylic acid and phenylbutazone bind principally to albumin; many basic drugs have a higher affinity for α_1-acid glycoprotein. There is no consistent data about α_1-acid glycoprotein and age and its concentration varies with stress placed on the individual. Epidemiological studies show that serum albumin decreases slightly in normal old people. However, plasma albumin can decrease by at least 15-20% because of decreased production by the liver in chronic disease (Woodford-Williams et al., 1964). The average serum albumin in frail elderly nursing home patients was 3.0g/dl (Cooper, 1988). Drugs such as digoxin, theophylline, phenytoin, and warfarin can have increases in non-protein-bound levels and have an increased drug effect. Therefore, in such cases, measurement of the plasma free-drug concentration is a better guide to the dose requirements than the total plasma concentration (Montamat, 1989).

Drug Metabolism

Drug metabolism is determined by hepatic function and blood flow. Hepatic mass, the number of functional hepatocytes, and hepatic blood flow decrease with

advancing age. A 65-year-old person has a 40-45% reduction of the hepatic blood flow of 25-year-old person's (Wynne, 1989).

Drugs whose hepatic metabolism rate is determined by enzymatic activity have a variable capacity to be metabolized by the liver, such as warfarin, phenytoin, and barbiturates. Their metabolism is called to be "perfusion-independent". When two such kind of drugs are administered, both of then have slower metabolism rate. Some drugs' rate of metabolism is determined by the blood flow of liver and is said to be "perfusion-limited". Perfusion-limited drugs have a rapid rate of metabolism, such as propranolol, calcium channel blockers, and tricyclic antidepressants. Because old age is associated with reduction in the presystemic metabolism of drugs with a higher rate of extraction and the bioavailability of the drugs increased. So drugs with high rates of hepatic extraction, such as most major tranquilizers, tricyclic antidepressants, and antiarrhythmic agents, should be administered with caution in the elderly.

Hepatic metabolism can be classified into two phases. Phase I reactions includes oxidation, reduction, and hydrolysis. Chlordiazepoxide, diazepam, clorazepate, and prazepan all undergo oxidative metabolism and have prolonged elimination in the elderly. Phase II reactions are generally unaffected by aging and involve glucuronidation, acetylation, and sulfation. Benzodiazepines may undergo both phases I an II of metabolism depending on the agent (Bellantuono et al., 1980).

Drug Elimination

Drug clearance is mainly determined by renal function. The rate of elimination of drugs by the kidneys decreases with age. Kidney size, the number of functioning

nephrons and glomeruli, glomerular filtration rate, and renal blood flow decrease with normal aging. Renal blood flow is reduced by as much as 40% in elderly persons.

Table 1. Pharmacokinetic Changes in Elderly Patients

Drug factor	Physiologic change	Clinical effect	Example
Absorption	↑ Gastric pH	↓↑ Absorption of drugs	Ferrous sulfate
	↓ Absorptive surface	Clinical relevance unknown	
	↓ splanchnic blood flow	Clinical relevance unknown	
Distribution	↑ Adipose tissue & Vd of lipid-soluble drugs	↑$t_{1/2}$ of lipid-soluble drugs	Diazepam Flurazepam
	↓Total body water and Vd of water-soluble drugs	↑ Serum or plasma concentration	Ethanol
	↓ Lean body mass and Vd of drugs bound to muscle	↓ Loading dose required	Digoxin
	↓ Plasma albumin	↓ Protein-bond acidic drugs ↑ Free drug	Phenytoin Warfarin
	↑ Plasma α_1-acid glycoprotein	↑ Protein-bond basic drugs ↓ Free drug	Lidocaine Propranolol
Metabolism	↓Phase I hepatic Metabolism	↑ $t_{1/2}$ of drugs	Diazepam Flurazepam
	Phase II hepatic Unchanged	$t_{1/2}$ of drugs unchanged	Oxazepam Triazolam
Elimination	↓ RPF and ↓ GFR	↑$t_{1/2}$ of drugs that undergo renal elimination	Digoxin Gentamicin

GFR = glomerular filtration rate; RPF = renal plasma flow; $t_{1/2}$ = half-life; Vd = volume of distribution.

The rate of creatinine clearance (CrCl) is a useful measure of renal function in elderly patients. Drugs with appreciable renal clearance and a low therapeutic index may have potentially serious toxic effects in the elderly, including digoxin, lithium, cimetidine aminoglycosides, procainamide, and chlorpropamide (Scneider et al., 1985). The average CrCl in frail elderly nursing home residents is 40 ml/min (Cooper, 1991). Pharmacokinetic changes that have been noted in elderly patients are summarized in Table 1(Chutka, 1995; Montamat, 1989).

Pharmacodynamics

Pharmacodynamics, the study of the end-organ responsiveness to drugs has not been done as extensively as pharmacokinetics studies in the elderly. It is difficult to study pharmacodynamic changes because lack of suitable techniques and current regulatory advice relating to pharmacodynamics issues in older people (Ford, 2000).

Specific pharmacodynamic changes have been studied for some drugs. Age-associated changes may be due to a decrease in receptor number, a change in receptor binding, or altered translation of a receptor-initiated cellular response into a biochemical reaction (Chutka, 1995). It has been known that the age-associated pharmacodynamic changes produce significant effects in the cardiovascular and central nervous system. Elderly persons appear to be more sensitive to some drugs, such as benzodiazepines, opiates or warfarin than younger persons. Studies have shown that elderly patients are sedated at lower drug concentrations than those required in young adults after given diazepam (Montamat, 1989). Elderly also have increased sensitivity to nitrazepam. This increased sensitivity is due to higher receptor response that can result in an augmented drug effect and increase the possibility of an ADR. The central nervous system, heart,

bladder and bowel are more sensitive to anticholinergic drugs. Therefore, dosage reductions of these medications are recommended. Warfarin should be administered with caution in the elderly because of the increased sensitivity of receptors. In contrast, β-Adrenergic blocking agents have a diminished effect in older patients because of a reduced receptor response (Vestal, 1979).

Adverse Drug Reactions

Adverse drug reactions (ADRs) have been defined as any responses to drugs which are noxious and unintended and which occur at doses used in humans for prophylaxis, diagnosis or therapy (World Health Organization, 1969). Because of age-associated changes in pharmacokinetics and pharmacodynamics and the chronic multiple disease conditions requiring multiple-drug regimens, elderly are particularly vulnerable to ADRs. ADRs cause 3%-5% of all hospital admissions (Lazarou et al, 1998; Onder et al., 2002). ADRs accounted for 15% -24% of all admission of people in theirs 70s (Caranasos et al., 1974; Manesse et al., 1997). The overall incidence of ADRs in the elderly is two to three times that in young adults (Nolan et al., 1988).

It has been reported that ADRs are common in nursing home older population. In a four-year prospective study, Cooper (1996) reported that two-thirds of nursing home residents surveyed developed an ADR during the 4-year period and one in seven ADRs led to hospitalization (Cooper, 1999). Drugs that frequently caused ADRs in elderly people were cardiovascular drugs, drug acting on central nervous system, nonsteroidal anti-inflammatory drug (NSAIDs), and antidiabetics. The most common adverse events were digoxin toxicity, psychotropic-related fall with fracture, NSAIDs induced gastrointestinal bleeding, and insulin hypoglycemia. Numerous patients had repeated

ADRs. Polypharmacy was a significant factor noted in this study since the mean number of drugs in the group developing ADRs was 7.8 compared to 3.3 in controls. Gurwitz et al. (2000) performed a cohort study to assess the incidence and preventability of ADRs in 18 Massachusetts nursing homes. The reported incidence was 189 adverse drug events per 1000 resident-months. 51% of them could be prevented. Neuropsychiatric events were the most common types of preventable adverse drug events.

There have been fewer systematic studies reported concerning ADRs in older people in ambulatory settings. Martys (1982) found that 36% of older people interviewed at home showed at least one sign of drug toxicity. Hanlon et al. (1997) reported that in high-risk older outpatients who took multiple drugs, 35% developed an ADR over a one-year period of observation. Ninety-five percent of these were preventable. A novel large systematic study sponsored by the federal Agency for Healthcare Research and Quality (AHRQ) and the National Institute on Aging (NIA) reported that Medicare patients treated in the outpatient setting may suffer as many as 1.9 million drug-related injuries a year because of adverse drug reactions or medical errors. Approximately 180,000 of these injuries are life-threatening or fatal, and more than half are preventable. These estimates were based on a cohort study of 27,617 Medicare enrollees followed during 1999-2000 (Gurwitz et al., 2003). The researchers identified 1,523 adverse drug events. Some 38% of the adverse drug events were characterized as serious, life-threatening, or fatal. Over one-fourth of all drug injuries were considered preventable, as were 42 percent of the serious, life-threatening or fatal injuries. Examples of more severe adverse drug events included falls with associated fractures, bleeds requiring transfusion, hypoglycemia, and deterioration of kidney function. Cardiovascular drugs, followed by diuretics, analgesics,

hypoglycemic agents, and anticoagulants were the most common medication categories associated with preventable adverse drug events. The researchers found that 58 percent of all preventable adverse drug events involved errors made when prescribing medications, such as ordering the wrong drug or dose, or prescribing a medication for which there was a known interaction with another drug the patient was already taking. Sixty-one percent of preventable adverse drug events involved mistakes made in monitoring medications, such as inadequate laboratory monitoring or a delayed response to symptoms of drug toxicity in the patient; Over 20 percent of the preventable drug-related injuries were due to poor compliance.

Many factors contribute to ADRs in the elderly, including polypharmacy, alterations in pharmacokinetics and pharmacodynamics, pre-existing diseases or conditions, drug-drug interactions, and inappropriate prescribing; however, advanced age alone does not increase the risk for ADRs (Carbonin et al., 1991). Onder (2002) et al. also found the most important risk factor for ADR-related hospitalizations in the elderly is number of drugs being taken. Age, female and alcohol use were also risk factors. The drugs most frequently responsible for these ADR-related hospitalizations were diuretics, calcium cannel blockers, NSAIDs, and digoxin. Gosney et al. (1984) identified that inappropriate prescribing was a key factor for elderly patients admitted to a hospital due to ADRs. They found 3.2% of prescriptions were contra-indicated for one reason or another, such as prescribing digoxin without potassium sparing diuretics when there was serious hypokalemia.

In summary, the understanding of age and disease associated changes in pharmacokinetics and pharmacodynamics is necessary to achieve appropriate prescribing

of drugs to the elderly. Avoiding potential ADRs, unnecessary hospitalizations and drug interactions is a challenge for prescribers when it comes to selecting the best medications for elderly patients.

Chapter 3

Literature Review

Concerning Inappropriate Medication Use in the Elderly

Medication prescribing is an important medical practice. Elderly patients have multiple chronic diseases and use multiple medications. Inappropriate prescribing is a major cause of ADRs in the elderly (Lindley et al., 1992). Age-related pharmacokinetic and pharmacodynamic changes can affect the risk/benefit ratios of some medications. Prescribing inappropriate drugs may put elderly patients at greater risk of drug-related illness. It is therefore important to identify these inappropriate medications in the elderly. In order to avoid prescribing inappropriate drugs, their current use patterns and associated factors should be examined. This chapter is a review of studies relating to inappropriate medication use in the elderly.

Criteria Accessing Inappropriate Medications

Studies have paid attention to inappropriate drug use in elderly patients since the 1980s. However, uniform criteria defining the inappropriate drug use were not available. In 1989, Health Care Financing Agency (HCFA) developed Drug Utilization Review (DUR) criteria for Medicaid patients through national expert consensus panels and updated these criteria in 1992 to apply to older people (Hanlon, 2002). The HCFA DUR explicit criteria have four types of problems (dosage, duplication, drug-drug interactions, and duration) for eight prescription drug classes, including digoxin, calcium channel

blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, histamine$_2$ receptor antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, antipsychotics, and antidepressants (Appendix A). DUR criteria does not include the problem of drug-disease interactions simply because typical pharmacy claims databases do not have diagnosis information.

Beers et al published their first explicit criteria identifying inappropriate medication in 1991. These criteria were developed from the comprehensive literature review and through a consensus of 13 nationally recognized experts. They completed a two-round survey based on the Delphi method. Inappropriate medications are defined as medications in which the risk outweighs the benefit and the criteria were to consider any prescribing to a population older than 65 years and reside in a nursing home. The criteria were designed to apply to only the frailest and sickest elderly population in nursing home. The criteria consist of two types of inappropriate medications: (1) 23 medications that should generally be avoided, including: Chlordiazepoxide, diazepam, flurazepam, meprobamate, pentobarbital, secobarbital, amitriptyline, methyldopa, propranolol, reserpine, indomethacin, phenylbutazone, chlorpropamide, propoxyphene, pentazocine, cyclandelate, isoxsuprine, dipyridamole, cyclobenzaprine, orpenidrate, methocarbamol, and carisoprodol. (2) There were 13 doses, frequencies, or durations of use of specific medications that should generally not be exceeded, including: oxazepam, triazolam, haloperidol, thioridazine, hydrochlorotiazide, cimetidine, ranitidine, oral antibiotics, oxymetazoline, penylephrine, pseudoepedrine, iron, and gastrointestinal antispasmodics. The detailed description of this criteria are shown in Appendix B (Beers, 1991).

Another investigation around the same time as Beer's criteria, Hanlon et al (1992) developed an index for assessing drug therapy appropriateness. The Medication Appropriateness Index (MAI) was intended to evaluate a variety of medications. MAI consists 10-item scale, including indication, effectiveness, dosage, correct directions, practical direction, drug-drug interaction, drug-disease interaction, duplication, duration, and expense (Appendix B). It was tested that the overall sensitivity and reliability of the MAI were good (Hanlon, 1992). Although this index provided a reliable method to assess drug therapy appropriateness, it has not been used widely. Only one study has been found using the explicit criteria of Hanlon (Schmader, 1994).

The original Beers criteria were developed for the elderly in nursing homes. Beers (1997) updated and expanded the original criteria to make them more applicable to the general elderly population in 1997. The updated criteria reflect information about new drugs and include rating potential severity of outcomes. There are two sets of criteria: one is independent of diagnosis; another one is dependent of diagnosis. The diagnosis-independent set criteria define 28 medication or classes, including a total 41 drugs that should always be avoided in the general elderly population, 8 drugs whose dosage should be not exceeded. The updated diagnosis-independent criteria are shown in Table 1. Furthermore, the new criteria identify 35 drugs or categories of drugs that are inappropriate for patients with any of known medical conditions. These drug-disease state combinations also should be avoided in the general elderly people. Both diagnosis-independent and diagnosis-dependent criteria were further categorized according to whether the drugs or drug–disease interactions have high severity of potential adverse

outcomes or not. Fourteen drugs were considered severe adverse outcomes. Seventeen drug-diagnosis combinations were considered severe Appendix.

Studies Applying Drug Utilization Review Criteria

Several studies have been conducted by using DUR criteria. They have some consistent findings. Benzodiazepines and NSAIDs are the classes of drugs that are most commonly prescribed inappropriately (Hanlon et al, 2002, Briesacher et al, 1999). The prolonged duration and use of long half-life benzodiazepines were common. Recent studies revealed that benzodiazepines are associated with cognitive impairment, falls and fall-related femur fractures (Hearing et al, 1995, Hanlon et al, 1998; Ray et al, 2000). The most common drug–drug interaction was the use of digoxin with furosemide (Giron et al, 2001). The most common drugs used in excess of defined daily dose (DDD) are dihydroergotamine, laxatives, sulfonamide, and diuretics.

Studies using DUR criteria also used Beers Criteria for drug-drug interactions (Hanlon, 2002; Giron, 2001). The most common diseases involved in potential drug interaction from these studies were congestive heart failure (CHF) and peptic ulcer disease (PUD). Using beta-blockers or calcium antagonists with CHF can worsen heart failure due to systolic left-ventricular dysfunction (Krum, 1999), yet beta blockers are beneficial if carefully added to the regimen of a patient with CHF. Other common drug-disease interactions are NSAIDs and peptic ulcer disease (PUD), NSAIDs and hypertension. It is well known that NSAIDs use may elevate blood pressure, worsen pre-existing CHF and induce gastrointestinal bleeding in PUD patients (Hanlon, 2002). Hanlon (2002) also revealed that those who were caucasian and having arthritis were more likely to have inappropriate drugs prescribed. Other researchers reported that

demented patients were more likely to be exposed to drug duplication than non-demented patients (Giron, 2001).

Studies Applying Beers Criteria

In the year after the original Beers criteria was published, a further prospective cohort study was conducted using the explicit criteria by the same author (Beers et al., 1992). They found that inappropriate medication prescribing in nursing homes was common. Of a total of 1106 nursing home residents, 40.3% of residents received at least one inappropriate drug, and 10.4% received two or more. Seven percent of all prescriptions were inappropriate. The average number of medication taken by resident was 7.2. Among all of the inappropriate medications, 51% were drugs that should be generally avoided; 34% exceeded the recommended duration limits; 15% exceeded the recommended dose limitations. Long-acting benzodiazepines, persantine, propoxyphene, and tricyclic antidepressants accounted for 80.6% of drugs that should be avoided; histamine blockers were the most common drugs exceeding duration limitations (70%). Iron supplement was the most common drug with dosage limit exceeded (70%). Residents of large nursing home and female residents were more likely to receive an inappropriate prescription. Beers et al. (Beers, 1993) also found that the characteristics of prescribers associated with best prescribing quartile were predominately female, having a certificate of added qualification in geriatrics, yet no board certification, and frequent consultation with psychiatrists.

A large retrospective, cross-sectional study was conducted to investigate the relationship between inappropriate medications and related outcomes for 19,932 elderly Medicaid beneficiaries residing in nursing homes in Louisiana (Gupta, 1996). The

researchers modified the original Beers criteria by adding ergoloid mesylates and diphenhydramine and excluded two drugs that could not identified in the Medicaid data files. This study revealed that the cost of pharmaceutical services for a patient was positively correlated with the number of different inappropriate drugs prescribed ($p=0.0001$). Inappropriate drugs can have an impact on prescription cost by causing drug-related illness and increasing drug use for the treatment of ADRs. According to Gupta et al, the number of different inappropriate drugs did not significantly influence the probability of mortality. Some studies have reported that inappropriate medication can influence drug-related morbidity in the elderly (Lindley, 1992). To understand the impact of inappropriate drug use on elderly mortality and morbidity requires controlling confounders such as disease severity and complications.

Although the original criteria were developed for the elderly in nursing home, they have been applied to community-dwelling elderly population (Stuck et al. 1994, Spore et al. 1997, Willcox et al. 1994, Aparasu et al, 1997, Aparasu et al. 1999). Most researchers have slightly modified the original Beers criteria. The modified Beers criteria consisted of 20 medications from the original list, excluding antihypertensive drugs and agents that were inappropriate based on dosage or duration of therapy and clinical circumstances. Stuck et al. (1994) also included gastrointestinal antispasmodic agents, but excluded methyldopa and propranolol. Spore et al. (1997) expanded Stuck's modified Beers criteria by adding long acting benzodiazepine clorazepate and quazepam. Although all of these studies varied in study settings, data sources and sample sizes, they found some consistent patterns. Between 14.0 % and 23.5 % of elderly patients received an inappropriate medication and the majority received one inappropriate drug, less than

0.1% of outpatients received two or more inappropriate medications. Long-acting benzodiazepines, dipyridamole, propoxyphene, and amitriptyline were among the most frequently prescribed inappropriate medications. Women, patients' age older than 80 years old and Medicaid patients appeared to receive more inappropriate drugs than average. Depressive patients had a higher risk of receiving inappropriate drugs than non-depressive patients. Only higher number of medications was known to be consistently associated with inappropriate medication use. It has been noted that some medications on the Beers criteria were not prescribed. Barbiturates, secobarbital and pentobarbital were most often as agents not prescribed for the elderly. Other infrequently prescribed inappropriate drugs included phenylbutazone, cyclandelate, isoxsuprine, pentazocine, meprobamate, trimethobenzamide, and orphenadrine (Aparasu, 2000).

Five studies have been published using the updated Beers criteria to assess inappropriate drug use. Golden et al. (Golden, 1999) reported the prevalence and pattern of inappropriate medication in 2,193 nursing home eligible, homebound patients based on the Beers diagnosis-independent criteria, which included 48 drugs. This study reported similar results to the previous study that adopted the original Beers criteria in nursing home patients: 39.7% of the older people in this study were prescribed at least one inappropriate medication; 10.4% were prescribed two or more. The most commonly prescribed drug class was cardiac agents (61.5%), including beta-blockers, digoxin, ACE-inhibitors, calcium channel antagonists and antiarrhythmics (Beers, 1992). Benzodiazepines were the second most commonly prescribed medications (41.6%). A concern was expressed that the high prevalence of benzodiazepines use might correlate

with both falls and hip fractures in older people (Tinetti, 1989; Ray et al., 1989; Ried et al., 1998; Ray et al., 2000;).

A large retrospective data analysis has been done by reviewing the Systematic Assessment of Geriatric Drug Use via Epidemiology (SAGE) database (Dhall, 2002). Of 44,562 nursing home patients, 33% patients had one inappropriate medication on admission. The top six most frequently administered drugs were propoxphene (10.1%), digoxin (>0.125 mg/day, 5.2%), iron supplements (>325mg/day, 5.1%), amitriptyline (2.5), diphenhydramine (2.5%), and hydroxyzine (1.7%). This study also analyzed the frequency of discontinuation and initiation of inappropriate medications over the first 90 days after admission for 29,082 patients who had an assessment done. 16% patients had the inappropriate drugs discontinued 90 days after admission. Drugs that were discontinued most were promethazine (56.2%), meperidine (54.8%), and dexchlorpheniramine (54.6%). The discontinuation rate was higher among the drugs that have safer therapeutic alternatives. Ninety days after admission to nursing homes, 17.5% of residents not taking inappropriate drugs had new orders for their drugs. Again, propoxphene, iron supplements, digoxin, diphenhydramine, and hydroxyzine were the top five drugs begun. The finding of this study is that residents admitted from hospital were more likely to have an inappropriate drug than those admitted from others (Dhall, 2002).

Piecoro et al. (2000) conducted a cross-sectional, retrospective study. Using the updated Beers criteria, they reviewed 1996 Kentucky Medicaid Pharmacy claims data to examine the prevalence of potentially inappropriate drug use in 64,832 Medicaid recipients aged 65 years and older. It was found that 27% of patients received at least one

inappropriate drug. Amitriptyline (7.6%), propoxyhene (6.5%), doxepin (4.0%), and indomethacin (2.3%) were the most used inappropriate drugs. Compared with community dwellers, nursing home residents had higher prevalence (33%) than ambulatory patients (24%). This study found that doxepin, a drug not listed in the original criteria, is among the most commonly prescribed.

Using the Prescribed Medicines database of 1996 Medical Expenditure Panel Survey (MEPS), which is a nationally representative survey of health care use, Zhan et al. (2001) conducted the first study to use the updated explicit criteria to estimate the prevalence of potentially inappropriate medication use for community-dwelling elderly. Because MEPS does not have information on drug dosage, frequency, and duration, they restricted their analysis to 33 drugs that were listed both in Beers criteria and MEPS and classified the 33 drugs into 3 categories: drugs that (1) should always be avoided, (2) are rarely appropriate, and (3) have some indications but are often misused. Barbiturates, flurazepam, meprobamate, chlorpropamide, meperidine, pentazocine, trimethobenzamide, belladonna alkaloids, dicyclomine, hyoscyamine, and propantheline should be always avoided. Propoxyphene, the most common inappropriate medication reported, was considered rarely appropriate. The panel members agreed that propoxyphene should not be started as a new agent for pain, but it might be appropriate for the patient who has tolerated but not abusing the drug and likely to renew the prescription. Another example is long-acting benzodiazepines. In rare situations, diazepam and chlordiazepoxide may be appropriate for alcohol withdrawal. The panel for this study considered 14 drugs that had some clear-cut indications for the elderly that are often misused. For example, amitriptyline should not be used to treat depression and

antihistamines are inappropriate for sedation. In this study, researchers reported that 21.3% of community-dwelling elderly patients in the United States received at least 1 of 33 potentially inappropriate medications (PIMs) regardless of diagnosis. About 2.6% of the elderly used at least 1 of the 11 drugs that should always be avoided; 9.1 % used at least 1 of the 8 drugs that would rarely be appropriate; and 13.3% used at least 1 of 14 medications that have some indications but are often misused. Zhan et al. (2001) also assessed the trend of inappropriate drug use over 10 years from 1987 to 1996. They found that propoxyphene and amitriptyline increased in use between 1987 and 1996; otherwise some drugs decreased such as pentazocine while estimated use of barbiturates remained constant. Unlike other previous studies, this study revealed that health status was the most important predictor of inappropriate medication use. A person reporting poor health was 6 times more likely to receive PIMs after controlling for other factors. In this study, a consistent finding with previous studies was that the number of medication was a significant risk factor. They found elderly patients who used more than the median number of prescriptions (14) were 3 times as likely to receive PIMs (Odds ratio, 2.9; 95% CI 2.3 – 3.6).

The only study that used both Beers diagnosis-independent and diagnosis-dependent criteria has published recently (Edwards et al, 2003). To compare PIMs prescribing in an acute care of the elderly (ACE) unit and a general medicine service, 176 patient records from the ACE unit and 173 from the general medicine services were obtained. According to the diagnosis-independent criteria, long-acting benzodiazepines, digoxin, iron supplement, ticlopidine, and gastrointestinal antispasmodics were the most commonly prescribed drugs. Defined as diagnosis-dependent criteria, the most common

drug-disease state combination was diabetes with beta-blockers (36%), followed by syncope with beta-blockers (20%), and constipation with narcotics (11%). PIMs were less likely to be prescribed and more likely to be discontinued in the ACE unit.

In summary, inappropriate medication use in older people remains a significant problem in the United States, especially in the long-term facilities. Most studies highlighted the problems by using Beers diagnosis-independent criteria because of the limitation of existing data sources. Data sources containing drug dosage, duration, and indications will provide more valuable assessment of inappropriate medication use. More studies are needed to address drug-disease interactions. Furthermore, measurement of inappropriate drug use and associated clinical adverse outcomes is an important issue in future studies.

Chapter 4

Research Objectives and Hypotheses

Nursing homes play an important role in the medical care of disabled older people. In 1996, approximately 1.42 million people over 65 years old resided in the 14,743 long-term care nursing homes in the US (Melnicket al., 2001). Elderly nursing home residents tend to use more medications than any other group of patients (Chutka, 1995). Multiple drug use and polypharmacy has been associated with increased number of ADRs (Cooper, 1996; Cooper, 1999; Gurwitz et al., 2000). Knowledge of inappropriate drug use and associated risk factors will help physicians improve the outcomes of medication treatment and prevent future ADRs. The literature review reveals that the inappropriate use of medication in Georgia nursing homes has not been investigated. It is hoped that this study may provide insight to the magnitude of inappropriate medication use within Georgia nursing homes.

Objectives

This study sought to:

1. Identify inappropriate use of medications in Georgia nursing home by using updated Beers diagnosis independent criteria
2. Examine patterns of inappropriate drug use and assess frequencies of inappropriate medication prescribing in nursing home elderly patients.

3. Examine if a relationship between patient demographics and inappropriate use of medications exists.
4. Assess the numbers of medications used per patient and determine if polypharmacy is associated with higher incidence of inappropriate drug use in the long-term care population.
5. Investigate the relationship between inappropriate medication prescribing and the most frequent disease conditions, including dementia, heart disease, hypertension, arthritis, stroke, depression, diabetes, and anemia.
6. Determine if the length of stay in nursing home is related to higher incidence of inappropriate medication use in the population.
7. Investigate if there is an association between patients' DNR codes and inappropriate medication prescribing.

Hypotheses

The main purpose of the study is to investigate the relationship between inappropriate medication prescribing and age, gender, length of stay, patients DNR status, number of medication, common disease groups in the elderly. The following hypothesis is proposed based on the objective of the study.

H_0: Inappropriate medication prescribing is not related to: age, gender, LOS, DNR status, number of drugs, and common diseases groups.

H_a: Inappropriate medication prescribing is related to: age, gender, LOS, DNR status, number of drugs, and common disease groups.

Chapter 5

Methodology

Data Source

This study is a retrospective data analysis using the data of Georgia Long- term Care Database, which was established by the University of Georgia College of Pharmacy Long Term Care Intervention Study. A review team, consisted of clinical pharmacists and physicians, conducted a retrospective drug utilization review of patient records in selected long-term facilities in the state of Georgia. The Georgia Department of Community Health provided a sample of nursing facilities in the state, which had an average medication utilization rate greater than 9 medications per patient per month. Fifteen Georgia nursing homes and 1527 patients at high risk of polypharmacy in the Georgia Medicaid long-term care population were identified.

Of the 1527 patients, 1348 patient chart review were completed. Patient chart records were obtained between March 1st, 2002 and June 1st, 2002. The database contains patient age, gender, length of stay, resuscitation status (Do not resuscitation), drugs and diagnosis information. Drugs include prescription and OTC medications, containing drug names, dose and frequency of usage. It was noted that this database only contains chronic medication utilization information. Therefore, the use of acute medications in this population was not examined.

Exclusion and Inclusion Criteria

The 1348 patients in the dataset were comprised of all nursing home patients for the facilities reviews. For this analysis we examined only patients who were older than 65 years as of June 1st, 2002.

Operational Definitions

For this study, potentially inappropriate medications (PIMs) are defined as any medication contained in the Beers criteria drug list. By using Beers criteria developed for application to nursing home residents and to community-dwelling elderly (Beers criteria, 1997), 49 potentially inappropriate drugs that are independent of diagnosis were selected. A detailed drug list is shown in appendix C. Among the 49 drugs, 21 drugs were considered having high severity adverse outcomes. This list includes all the generic and trade name medications identified by Beers criteria. Patient was assigned as having received an inappropriate drug if they had received one or more of the medication listed in appendix C.

The variables included in the study were operationalized as follows:

1). ***Dependent variable***

PIMs. Using of PIMs was the major outcomes of interest in this study. The PIMs were identified by the updated Beers diagnosis independent criteria (Beers, 1997). Any medication contained in appendix C was considered a potentially inappropriate medication. The cases of using potentially inappropriate medication for every patient were analyzed as dichotomous or dummy variable, coded '1' for presence of PIMs and '0' for absence of PIMs.

2). ***In dependent variables***

Age. The date of birth was recorded in the patient chart and the covariate 'AGE' was a continuous variable, calculated in number of years from birth to the date of June 1st, 2002.

Gender. The covariate 'GENDER' is a dichotomous, dummy variable coded '1' for male and '0' for female.

LOS. The admission dates for patients were recorded in the review charts. The length of stay in the 15 nursing homes was calculated in number of years form date of admission to the date of June First, 2002. The covariate 'LOS' is a continuous variable.

DNR. The 'do not resuscitation' status was recorded in the patient review chart. The covariate 'DNR' is a dichotomous, dummy variable, coded as '1' if patients refused future resuscitation and '0' if patient accepted future resuscitation.

Number of medications. The number of medications is a continuous covariate that was calculated according to the records of drug in the charts, including prescription and OTC drugs together. Patients may have up to 30 numbers of medications.

Dementia. The covariate 'DEMENTIA' presents all types of dementia recorded in the review charts, including Alzheimer's disease, multi-infarction dementia, organic brain syndrome, and other dementia. Dementia is a dichotomous, dummy variable coded as '1' for presence of any type dementia and '0' for absence of dementia.

Arthritis. The covariate 'Arthritis' presents several kinds of joint disease, including arthritis, arthralgia, degenerative arthritis, degenerative joint disease and orsteoarthritis. Arthritis is a dichotomous, dummy variable coded as '1' for presence of any type joint disease mentioned above and '0' for absence of these diseases.

Diabetes. Diabetes is a dichotomous, dummy variable that includes insulin dependent diabetes mellitus and non-insulin dependent diabetes mellitus. Diabetes was coded as '1' for presence of the disease and '0' for the absence of the disease.

Depression. The covariate 'DEPRESSION' presents depressive disease, depression, and major depression recorded in patient charts. Depression is a dichotomous or dummy variable, coded as '1' for presence of the disease and '0' for the absence of the disease.

Heart disease (CVD). This covariate 'CVD' presents congestive heart failure, cardiac dysrhythmias, cardiovascular disease, and arteriosclerotic disease recorded in patient charts. CVD is a dichotomous or dummy variable, coded as '1' for presence of the diseases and '0' for the absence of the diseases.

Hypertension. The covariate ' HYPERTENSION' is a dichotomous or dummy variable, coded as '1' for presence of the disease and '0' for the absence of the disease.

Stroke (CVA). The covariate 'CVA' presents all type of cerebrovascular accident, including introcerebral hemorrhage, cerebral infarction, hemiparesis, hemiplegia, and transient ischemic attacks. CVA is a dichotomous or dummy variable, coded as '1' for presence of the diseases and '0' for the absence of the diseases.

Anemia. The covariate ' ANEMIA' was a medical condition that was recorded in the patient chart. Anemia included all types of anemia. Anemia is a dichotomous or dummy variable, coded as '1' for presence of the anemia and '0' for the absence of anemia.

Data Analysis

Descriptive analysis was carried out to obtain the patient-based prevalence of inappropriate drug use and the frequencies of inappropriate drug use for each drug listed in table 2. The nursing home resident was the unit of analysis in all computations.

The prevalence of potentially inappropriate drug use was calculated as below:

$$\frac{\text{The number of patients received PIMs}}{\text{The total number of the studied population}} *100\%$$

Testing Hypotheses: The logistic regression method was applied to evaluate the relation between demographic, the clinical variables and the use of potentially inappropriate drugs. Age, gender, DNR status, LOS, the number of medications, and certain group of diseases were set up as independent variables. The logistic regression model for testing the hypothesis was presented as below:

$$\begin{aligned}\text{Log } (p/1\text{-}p) = {} & \beta_0 + \beta_1 (\text{age}) + \beta_2 (\text{gender}) + \beta_3 (\text{number of drugs}) \\ & + \beta_4 (\text{LOS}) + \beta_5 (\text{DNR}) + \beta_6 (\text{dementia}) \\ & + \beta_7 (\text{CVD}) + \beta_8 (\text{HTN}) + \beta_9 (\text{arthritis}) + \beta_{10} (\text{CVA}) \\ & + \beta_{11} (\text{depression}) + \beta_{12} (\text{DM}) + \beta_{13} (\text{anemia})\end{aligned}$$

The dependent variable for the model was PIMs that was dichotomized as 1 or 0. The expression on the left-hand side of the model was log-odds, where P was the probability of having potentially inappropriate medication use. This model was predicting

the probability that the dependent variable PIMs was equal to 1. On the right side of the model, independent variables gender was a binary variable (male =1, female = 0). The variable of certain diseases and DNR were dichotomized variables (Yes =1, No =0). The variables age, number of drugs, and the length of stay were continuous variables. A detailed describing of all the variables used in the logistic regression models is shown in Table 2. Measures of statistical significance (p-values) and odds ratios (OR) were computed for the predictor variables.

All data review and analysis were conducted using SPSS 11.0 software. The level of significance was set at 0.05 level.

Table 2. Variables in the Logistic Regression Model

Variables	Description	Identification
Response variable	PIM status	Dichotomized (Yes =1, No = 0)
Age	Age in years	Continuous
Gender	Gender	Dichotomized (Male =1,Femae = 0)
LOS	Length of stay in years	Continuous
No. of drugs	No.of drugs(Rx+OTC)/patient	Continuous
DNR	'Do not resuscitate' status	Dichotomized (Yes =1, No = 0)
Dementia	Dementia	Dichotomized (Yes =1, No = 0)
CVD	Heart disease	Dichotomized (Yes =1, No = 0)
HTN	Hypertension	Dichotomized (Yes =1, No = 0)
Arthritis	Arthritis	Dichotomized (Yes =1, No = 0)
CVA	Cerebrovascular accident	Dichotomized (Yes =1, No = 0)
Depression	Depression	Dichotomized (Yes =1, No = 0)
DM	Diabetes	Dichotomized (Yes =1, No = 0)
Anemia	Anemia	Dichotomized (Yes =1, No = 0)

Chapter 6

Study Results

Study Population Descriptive Statistics

Between March 1, 2002 and June 1, 2002, there were 1348 residents in 15 Georgia nursing homes who had their review of chart for drug utilization completed. 139 people who aged less than 65 years were deleted from the study according to the exclusion criteria. 48 patients were also excluded because age information was unavailable. Therefore, 1,161 individuals were included as the study cohort.

This study population demonstrated similar age and sex characteristics comparing to the overall US nursing home population aged 65 and older (Melnick et al., 2001). Women dominated the study population with 81% of residents were female; Residents had an average age of 84 years at June 1st, 2002 (STD=8.09) while the maximum age was 105. Those who aged 85 years and older comprised 51.5% of the total study population, compared with 49.3% of the US nursing home population. 35.6% of residents had "do not resuscitate" status. The most common disease conditions in the study population included dementia (70.7%), heart disease (66.6%), hypertension (57.1%), depression (33.8%), arthritis (39.3%), stroke (30%), diabetes (26.7%), fractures (30.3%), and anemia (25.1%). Table 3 summarizes the principle characteristics for the study population.

Overall, residents were prescribed an average of 8.6 medications, and had an average of 2.8 OTC drugs. The average of total number of medications per patient taken was 11.4 with a standard deviation of 5.04. Male and female residents had a similar average of total number of medication per patient (11.495 vs. 11.487, P = 0.53).

Table 3. Characteristics of the Study Population

Characteristics	n	Percentage
Age, years		
65 - 84	562	44.4
> 85	599	51.6
Gender		
Female	938	81.3
Male	216	18.7
DNR		
Yes	405	35.6
No	733	64.4
No. of medication*		
0 - 7	248	21.4
8 -10	287	24.7
11-14	339	29.2
15-30	287	24.7
Disease Conditions		
Dementia	821	70.7
Heart disease	773	66.6
Stroke	348	30.0
Hypertension	663	57.1
Diabetes	310	26.7
Arthritis	456	39.3
Anemia	291	25.1
Depression	392	33.8

* The number of medications was categorized by quartiles.

Residents had an average of 3.8 years length of stay in the nursing homes with a range from 0.08 to 34 years. The average number of diagnoses per patient is 9 (range 0 to

15). The detailed descriptive statistics for all interval or ratio data were shown in table 4.

Table 4. Summary of Descriptive Statistics for Continuous Variables.

Variables	Mean	Std. deviation	25 Percentile	Median	75Percentile
Age	84.555	8.0918	79.0630	85.2438	90.2973
LOS	3.3617	3.8949	1.4025	2.6795	4.5055
No. of Rx Drugs	8.6064	4.2363	6.000	8.000	11.000
No. of OTC Drugs	2.8148	2.1151	1.000	3.000	4.000
Total No. of Drugs	11.4212	5.0415	8.000	11.000	14.000
No.of PIMs	0.5960	0.8038	0.000	0.000	1.000

Table 5. Frequency of Patients by Total Number of PIMs per Patients

Number of PIMs	Frequency	Percent	Cumulative percent
None	697	56.3	56.3
1.00	366	31.5	87.9
2.00	103	8.9	96.7
3.00	32	2.8	99.5
4.00	6	0.5	100
Total No. of patients	1161	100	

PIMs Exposure Descriptive Statistics

According to the updated Beers criteria (independent of diagnosis), 507 patients were found to have at least one potentially inappropriate medication, accounting for 43.7 % of all patients in the study Georgia nursing homes; 141 patients (12.2 %) had two or more PIMs. Among the 141 patients, 103 patients had 2 PIMs and 32 patients had 3 PIMs. There were 6 patients with 4 PIMs noted. No potentially inappropriate drug use

Table 6. Frequency of PIMs by Patient Characteristics

Variables		n	No. of patients with PIMs (%)
Age (in years)	65 - 84	562	250 (44.5)
	> = 85	599	256 (42.8)
Gender	Male	216	87 (40.3)
	Female	938	420 (44.8)
DNR Status	Yes	405	187 (46.2)
	No	733	313 (42.7)
LOS (in years)	0 - 2	423	192 (45.4)
	3 -5	280	118 (42.1)
	6-10	113	43 (38.1)
	>11	53	17 (32.1)
No. of Rx Drugs	0 - 7	482	131 (27.2)
	8-10	329	168 (51.1)
	11-14	252	140 (55.6)
	15 - 30	98	68 (69.4)
No. of OTC Drugs	0 - 1	346	142 (41.0)
	2 - 3	439	190 (43.3)
	4 - 5	243	104 (42.8)
	> 6	133	71 (53.4)
No. of Rx + OTC	0 - 7	248	62 (25.0)
	8 - 10	287	101 (35.2)
	11 - 14	339	166 (49.0)
	15 - 30	287	178 (62.0)
Hypertension	Yes	663	267 (40.3)
	No	498	195 (39.2)
Dementia	Yes	821	348 (42.4)
	No	340	159 (46.8)
Heart disease	Yes	773	348 (45.0)
	No	388	159 (41.0)
Stroke	Yes	348	140 (40.2)
	No	813	367 (45.1)
Diabetes	Yes	310	133 (42.9)
	No	851	374 (43.9)
Arthritis	Yes	456	216 (47.4)
	No	705	291 (41.3)
Depression	Yes	392	169 (43.1)
	No	769	338 (44.0)
Anemia	Yes	291	143 (49.1)
	No	870	364 (41.8)

was noted for 654 (56.3 %) patients. The table 5 shows the total number of PIMs per patients. The average of PIMs per patient was 0.596 with a standard deviation 0.8038 (see table 4).

Table 6 presents the percentage of patient with PIMs by patient characteristics. For those residents with 0 to 7 total numbers of prescriptions and OTC drugs, 25 % had at least one inappropriate medication. For those with 8 to 10 total numbers of prescriptions and OTC drugs, 35.2% had at least one inappropriate medication; for those with 11 to 14 total numbers of prescriptions and OTC drugs, 49 % had at least one inappropriate medication. For those with 15 or more total number of prescriptions and OTC drugs, 62 % had at least one inappropriate medication (see table 6). Similar changes were found for the prescription drugs alone. Other patient characteristics did not show significant changes in percentage of potentially inappropriate medication use. For example, 44.8 % female versus 40.3 % male had PIMs.

Table 7. Specific List of Drugs Accounted for 87% of All PIMs Use in the Population

Drug name	No. patients with PIMs	Percent*
Propoxyphene	164	23.7
Promethazine	113	16.3
Hydroxyzine	80	11.6
Iron Supplements	78	11.3
Digoxin	46	6.6
Cyproheptadine	36	5.2
Oxybutynin	35	5.1
Lorazepam	30	4.3
Amitriptyline	22	3.2
Total	604	87.3

* The total number of patients with PIMs by drugs was 692.

There were total 29 medications found inappropriately used by the residents of the 15 nursing homes in Georgia. The top five most frequently prescribed inappropriate drugs included propoxyphene, promethazine, hydroxyzine, iron supplements and digoxin, followed by cyproheptadine, oxybutynin, lorazepam, and amitriptyline. These nine drugs were accounted for 87.3 % of all inappropriate medication use (table 7).

Antihistaminic agents, sedative-hypnotics, muscle relaxants and antidepressants were the most common drug classes. Antihistaminic agents were administered to 238 patients, accounting for 20.5 % of all residents. These antihistaminic agents were promethazine, hydroxyzine, cyproheptadine, and diphenhydramine. 113 patients used promethazine, and 80 patients had hydroxyzine. Among the sedative-hypnotics, long-acting benzodiazepines were prescribed to 1.6 % of residents, including lorazepam, alprazolam, and diazepam. Over doses of the short-acting benzodiazepine lorazepam, alprazolam, zolpidem and temazepam were prescribed to 59 patients (5.1%). Eight drugs may have adverse outcomes of high severity. These drugs include digoxin chlordiazepoxide, diazepam, flurzepam, amitrityline, doxepin, methyldopa, and butababital. Digoxin was the most frequently used drug which may cause severe ADRs. There were 49 patients who were prescribed digoxin over 0.125mg daily. Among those patients, only 3 patients were diagnosed cardiac arrhythmia. Therefore, 46 patients were using digoxin inappropriately. Table 8 shows the prevalence of inappropriate medication use by drugs in Georgia nursing homes.

No potentially inappropriate medication use was noted for 20 of the drugs listed in Beers updated criteria in this study. These medications were most barbiturates (amobarbital, pentobarbital, and secobarbital), all dementia treatments (ergot mesyloids

Table 8. Prevalence of Inappropriate Drug Use by Drugs or Drug Classes in Georgia Nursing Homes

Drugs by classes	No. of patients with PIMs	Percentage
Propoxyphene	**164**	**14.1**
Sedative-hypnotics (Total)	**78**	6.7
Chlordiazepoxide*	2	0.2
Diazepam*	15	1.3
Flurazepam*	1	0.1
Meprobamate	1	0.1
Lorazepam	30	2.6
Alprazolam	15	1.3
Zolpidem	13	1.1
Temazepam	1	0.1
Antidepressants (Total)	**28**	**2.4**
Amitriptyline	22	1.9
Doxepin	6	0.5
Antihypertensive agents (Total)	5	0.4
Reserpine	1	0.1
Methyldopa	4	0.3
Digoxin	**46**	**4.0**
Gastrointestinal antispasmodics (Total)	**9**	0.8
Dicyclomine	3	0.3
Hyoscyamine	6	0.5
Belladonna alkaloids	1	0.1
Antihistaminic Agents (Total)	**238**	**20.5**
Diphenhydramine	9	0.8
Hydroxyzine	80	6.9
Cyproheptadine	36	3.1
Promethazine	113	9.7
Muscle Relaxants (Total)	**46**	**4.0**
Methocarbamol	2	0.2
Carisoprodol	1	0.1
Oxybutynin	35	3.0
Metaxalone	2	0.2
Cyclobenzaprine	6	0.5
Butabarbital	**1**	**0.1**
Trimethobenzamine	**1**	**0.1**
Iron Supplements	**78**	**6.7**
Total No. of PIMs by patients**	**692**	

* Long-acting benzodiazepines

** The total No. of patients with at least one PIMs was 507.

and cyclospasmol), and cyclospasmol), analgesics (pentazocine and meperidine) and NSAIDs (indomethacin, and phenylbutazone)**,** all platelet inhibitors (dipyridamole and ticlopidine), the antidiabetic agent chlorpropamide, the gastrointestinal antispasmodic (propantheline), the antihistaminic agent (dexchlorpheniramine), the cardiovascular agents disopyramide, the antiemetic agent trimethobenzamide, and two short-acting benzodiazepines (oxazepam and trizolam).

Logistic Regression Results

The logistic regression model of inappropriate medication was employed on all the independent variables listed in the table 3. The odds ratio for each variable is an estimated multiplicative effect of a one-unit increase in that variable on the odds of using inappropriate drugs, holding all the other covariates constant. Coefficient, odds ratio, 95% CI for odds ratio, and p-value were displayed in the table 9.

Table 9. Results from the Logistic Regression

Variables	B	Odds ratio	95% CI for odds ratio		P-value
Age	-0.002	0.998	0.982	1.015	0.857
LOS	-0.021	0.980	0.948	1.013	0.183
Sex	-0.191	0.826	0.594	1.149	0.264
DNR	0.043	1.044	0.798	1.366	0.751
No. Of drugs	0.140	1.150	1.117	1.185	<0.0001
Disease conditions					
Heart disease	-0.152	0.859	0.650	1.134	0.283
Dementia	-0.086	0.917	0.693	1.214	0.545
Stroke	-0.183	0.833	0.632	1.099	0.196
Diabetes	-0.432	0.649	0.482	0.874	0.004
Anemia	0.261	1.298	0.975	1.729	0.074
Hypertension	-0.066	0.936	0.720	1.217	0.620
Arthritis	0.102	1.108	0.853	1.439	0.444
Depression	-0.309	0.734	0.559	0.966	0.027

Hosmer & Lemeshow test: Chi-square = 4.561, Sig.=0.797

$R^2 = 0.133$

C-statistic = 0.682 (Obtained by using SAS version 8.2)

From the table 9, the following inferences can be made:

(1) With number of medication increase in one unit, patients were 1.15 times more likely to get potentially inappropriate medications.

(2) Compared to non-diabetic patients, diabetic patients were 0.649 times less likely to have PIMs.

(3) Patients with a diagnosis of depression were 0.734 times less likely to get potentially inappropriate medications, compared to patients without diagnosis of diabetes.

(4) Age, sex, LOS, and patient DNR status have no significant association with potentially inappropriate medication use.

(5) Inappropriate medication use is not related to dementia, heart disease, hypertension, arthritis, stroke, and anemia.

Chapter 7

Discussion

Even though numerous studies have addressed the problems of inappropriate medication use in the elderly, almost most studies modified the Beers criteria or used only part of the Beers criteria. This is the first study that investigated the inappropriate medication use in Georgia nursing homes by using a complete diagnosis-independent drug list defined by the updated Beers criteria. The following sections of this chapter discussed the statistical inference of the results presented in chapter 6, the strength and limitations, and final conclusions of this study.

Statistical Inferences

Using a population in 15 Georgia nursing homes that had an average of medications above 9, this study found that the use of potentially inappropriate medications was prevalent. 43.7 % of residents were prescribed at least one potentially inappropriate medication, while 12.2 % had two or more potentially inappropriate medications.

The prevalence and the patterns reported in this study are consistent with other studies concerning inappropriate drug prescribing among nursing homes or homebound older people (Beers et al., 1992; Golden et al., 1999; Dhall et al., 2002; Edwards et al., 2003). The detailed comparisons were shown in table 10. The prevalence of present study was slightly higher than other studies. In the study of Beers et al. (1992), residents were

Table 10. Summary of Major Findings from the Present and Previous Studies of Long -Term Care Patients

References	Criteria	N	Prevalence (%)	Most prevalent PIMs
Present	Beers 1997	1161	43.7	Antihistamines Propoxyphene Iron supplements Benzodiazepines Muscle relaxants Digoxin
Beers et al. (1992)	Beers 1991	1106	40.3	Iron supplements Benzodiazepines Dipyridamole Propoxyphene Antihistamines Antidepressants
Golden et al. (1999)	Beers 1997 (Excluding digoxin)	2193	39.7	Benzodiazepines Antihistamines Dipyridamole Ergot mesyloids Propoxyphene Doxepin
Dhall et al. (2002)	Beers 1997	44562	33	Propoxyphene Antihistamines Iron supplements Digoxin Amitriptyline

N: Sample size

prescribed an average of 7.2 medications, even though they used the original Beers criteria. Both studies had similar study settings and sample size (1161 vs. 1106) and used diagnosis-independent criteria. However, these two studies varied slightly in the prevalence of certain inappropriate medications. Iron supplement, long-acting

benzodiazepines, dipyridamole, and propoxyphene were the most prescribed inappropriate drugs in Beers et al.'s study, while in present study antihistamine agents, propoxyphene, iron supplement, benzodiazepines, and digoxin were the top five drugs or drug classes in descending order. The variation may be explained by the difference between the two different criteria since the updated Beers criteria added antihistamic agents and digoxin.

In the study of Dhall et al. (2002), by using the updated criteria in large population of nursing homes, researchers found that the six most frequently administered drugs were propoxyphene, digoxin, iron supplements, amitriptyline, diphenhydramine, and hydroxyzine. We can see the similar inappropriate medication prescribing patterns in the present study. Propoxyphene, which offers no benefit over acetaminophen or salicylates, can lead to sedation and confusion. Analgesic medication use are common in older patients may be due to higher prevalence of fractures and arthritis. Although safer and more effective alternatives exist, 164 patients were still given propoxyphene, ranking the highest number of PIMs. Different from Dhall et al.'s, in the present study there were more residents using long-acting benzodiazepines, which could lead to CNS toxicity such as confusion, oversedation, falls, and fractures in the elderly because of prolonged drug half-lives (Beers et al., 1989).

Although high-severity drugs are contained in the HCFA interpretive guidelines for nursing home facilities since July 1, 1999 (Dhall et al., 2000), digoxin usage exceeding suggested dosage limits were still common in our study. There were 49 patients whose daily dose exceeded 0.125mg, among them 46 had a daily dose of 0.25mg, only 3 patients had cardiac arrhythmias. Digoxin is used in the treatment of

congestive heart failure and atrial arrhythmias. It is considered adequate only when digoxin was used to treat atrial arrhythmias at dosage greater than 0.125mg. Because of decreased renal clearance, digoxin toxicity is common in the elderly patients (Beers et al, 1997). There were 43 patients who were prescribed digoxin inadequately in this study.

This study found that the use of first-generation antihistamines was the most common drug class with 20.5% of patients using antihistamines (see table 8). The first-generation antihistamines are lipophilic and may cross blood-brain barrier and cause central nervous system side effects such as confusion, dyskinesia, dizziness, and blurred vision. They also have anticholinergic side effects such as confusion, urinary retention, and constipation (Kaliner et al., 1997). Most OTC cold remedies contain antihistamines, which are highly anticholinergic. This study may be the first study including assessment of OTC drugs, which may explain the higher prevalence of antihistamines.

Some variations of inappropriate medication pattern have been detected in this study. 20 drugs listed in Beers diagnosis independent drug list were not used in the elderly in this study. Dipyridamole and ergot mesyloids, which were among the most common prescribed agents in some previous studies, were among these 20 drugs. Cardiovascular disease and dementia were the most common diseases in the elderly (Melnick et al., 2001) .One possibility is that these two drugs may be not in the drug formulary for nursing homes. Another reason is that attention to inappropriate prescribing is changing doctors prescribing habits.

There are no consistent findings concerning the relationship between patient demographical factors and inappropriate medication use. As previously reported (Aparasu et al., 1999), the current study does not show any statistical difference between

males and females with inappropriate medications use. Zhan et al (2001) and Dhall et al. (2002) found female were 1.2 or 1.3 times more likely than men to be prescribed an inappropriate drug, respectively. Consistent with previous studies (Zhan et al., 2001; Dhall et al., 2002), age was not significantly associated with inappropriate medication use (Odds ratio 1.044, CI 0.982 - 1.015). The present study may be the first to assess the relationship between inappropriate medication use and patient "Do not resuscitate" status. No significant statistical difference found between patients with or without "Do not resuscitate" status (Odds ratio 1.208, CI 0.798 – 1.366).

Previous studies consistently found that the number of medications patients taken was positively associated with inappropriate medication prescribing. The present study provided further evidence to support this finding. Furthermore, this study included OTC drugs into the total number of medications. The more medications the patients taken, the more chance they get inappropriate medications. Similar finding was reported in previous studies (Golden et al., 1999; Zhan et al., 2001; Dhall et al. 2002). In other words, doctors and pharmacists should be aware of this problem in practice when patients take multiple drugs.

In this study, it was noted that the median number of diagnosis per patient was nine. Inappropriate medication use may associate with some particular chronic medical conditions in the elderly. Similarly, Stuck et al (1994) reported that the number of self-reported chronic health conditions had no statistically significant association with inappropriate drug use. However, they revealed the depressive patients were more than twice likely to use inappropriate medications than nondepressive subjects. It was explained that depressive patients suffering from sleep or anxiety problems might get

long-acting benzodiazepines rather than specific antidepressive therapy. Hanlon et al. (2002) reported patients with arthritis were more likely to have inappropriate drugs (Odds ratio 1.74; 95% CI 1.27 – 2.38).

The present study has assessed the effect of some common disease conditions on inappropriate medication use. It was noted that depression and arthritis patients had no significant difference from patients without these diseases to have inappropriate medications. The variation may be partially explained by the differences of study populations and assessing criteria. Table 8 indicated that there were no large differences of the number of PIMs between patients with and without these disease conditions. Although propoxyphene as an analgesic accounted for 23.7 % of all PIMs, arthritis patients may have less other conditions and have no more drugs than patients without arthritis. The same explanation could be applied to depression patients. The present study also found that dementia, heart disease, hypertension, stroke, and anemia patients had no significant differences from the patients without these diseases on inappropriate medication use.

The present study may be the first to assess the relationship between inappropriate medication use and the disease condition of dementia. In the study population, more than 70 % of all nursing home residents suffered from Alzheimer's disease and other kinds of dementia, with which patients may have emotional and behavioral disturbances such as agitation, anxiety, depression and sleep/wake disturbances (Cummings et al., 1987). Benzodiazepines, clonazepam, temazepan, triazolam and amitriptyline, which were on the Beers criteria list, were reported to be used in clinical practice or clinical trial to treat these problems of dementia patients (Smeroski et al., 1988; Stern et al., 1991; Reynolds

et al., 1988; Reding et al., 1983). However, in the study of Dhall et al (2002), by using patient cognitive function as predictor variables, they found residents with severe cognitive impairment were less likely to be taking an inappropriate drug than those with no cognitive impairment. In present study, demented patients were not significant different from non-demented patients to have PIMs.

The present study may be the first to assess the relationship between inappropriate medication use and the disease condition of diabetes. Although 40% of diabetic patients were given potentially inappropriate medications, multivariate analysis showed that diabetic patients were less likely to get inappropriate medications (Odds ratio 0.649; 95% CI 0.482 – 0.874), compared to the patients with no diabetes mellitus. It is hard to explain this result. Diabetic and nondiabetic patients had similar prevalence of inappropriate medication use. This result may be partially explained by lack of controlling for some confounding factors.

Strength of the study

The strength of the study is the uniqueness of the data source, the sample size, and the study itself. Unlike other previous studies, the data used in this study is a retrospective drug utilization review of patient records. Not only does each record contain all of the prescription drugs and dosage used, but it also contains OTC drug information. Therefore, this study is the first inappropriate drug prescribing study specifically including the analysis of OTC drugs. It will provide medical providers with valuable information regarding the prevalence of inappropriate prescribing in the nursing home population.

In addition, no studies of inappropriate drug prescribing have been published concerning Georgia long-term care facilities patients. The data was collected from 15

nursing homes; our study sample size is relatively larger than previous studies. This large sample size should provide more reliable results.

Limitations of the Study

Several limitations should be noted for this study. One is the operational definition of inappropriateness of drug use, which is completely based on Beers diagnosis independent criteria. Although Beers' explicit criteria are useful methods for assessing the quality of drug prescription for the elderly, it has limitations in both sensitivity and specificity. Not all of the inappropriate drug use can be identified by these criteria. Beers criteria are only a subset of all inappropriate medication use. This study has not measured inappropriate drug use related to drug-disease interactions, drug-drug interactions, and drug durations. Therefore, using Beers' diagnosis independent criteria may underestimate the prevalence of inappropriate drug use. And sometimes the criteria may identify the appropriate prescribing as inappropriate

The design of this study is retrospective study. Limitations are inherent in this non-experimental study. Potential selection bias exists due to lack of randomization and an equivalent control group. Those who were prescribed inappropriately may be inherently different from those who were prescribed appropriately. Sample bias exists in this study because the study population was come from the nursing homes that had higher average of drug utilization rates.

The assessment of inappropriate prescribing of medication can be challenging because of the high frequency of comorbid conditions in the elderly patients. We are unable to control all of the confounders. Although multiple logistic regression was used to control for some of the confounding variables such as demographic characteristics,

other confounding factors such as disease severity and duration of disease can not be modeled because these variables don't exist in the data and therefore can not be modeled.

Finally, although inappropriate of drug use can have severe clinical consequences in the elderly, we won't able to explore the relationship between the inappropriateness of medication proscription and drug related problems and ADRs related hospitalization. Simple just no such kind of data exists in the records.

Conclusion

The study results demonstrate that inappropriate medication use is a common problem among the elderly in the 15 nursing homes of Georgia. About 40.1% of residents were prescribed at least one potentially inappropriate medication, while 10.5% had two or more potentially inappropriate medications. Among the inappropriate medications, propoxyphene, antihistamic agents, iron supplement, digoxin, and long-acting benzodiazepines were the most commonly prescribed agents. Consistent with previous researches, the present study provided further evidence that the number of medications is positively associated with inappropriate drug use. Furthermore, it also found that diabetes patients are less likely received inappropriate medications. This study did not find any evidence that inappropriate medication use was associated with arthritis, depression and other common disease conditions.

High prevalence of potentially inappropriate medication prescribing may indicate higher risk for ADRs and poor clinical outcomes. Future studies should include assessment of ADRs and medical outcomes of inappropriate medication use.

Considering the results of the current study and previous inappropriate medication prescribing studies in geriatric population, it may be suggested that inappropriate

medication use continues to be a serious problems, especially in long-term care facilities. Health care providers need to be aware of this common problem in practice, particularly in nursing homes. Inappropriate prescribing as a cause of ADRs is preventable. Knowing the basic principles of appropriate prescribing for elderly, periodical assessment of drug used by older people to eliminate unnecessary drug and reduce doses to a safe and effective dose may help to improve the quality of prescribing for the elderly patients.

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Appendices

Appendix A

Health Care Financing Administration Drug Utilization Review Criteria

By Therapeutic Class and Domain

Therapeutic class	Drug-drug-interaction	Duration
Digoxin	Amiodarone, Quinidine, propafenone, verapamil	not applicable
Calcium	Cyclosporine, digoxin, verapamil with beta blockers, disopyramide, flecainide	not applicable
ACE-I	Potassium supplement potassium-saving diuretic lithium	not applicable
H2 receptor antagonist	Ketoconazole, warfarin cimetidine with phenytoin theophylline, procainamide	> 3 months
NSAIDs	Lithium, warfarin methotrexate(>30mg/d) indomethacin with triamterene saliclates with probenecid saliclates with antidiabetics	not applicable
Benzodiazepines	not applicable	>4 months
Antipsychotics	>= 3 other anticholinergics with antiparkinson drugs	>6 months without dose reduction
Antidepressants	Monoamine oxidase inhibitors >=2 other anticholinergics, tricyclic antidepressants with clonidine guanethidine, guanadrel, type 1 antiarrhythmics	not applicable

Appendix A

Health Care Financing Administration Drug Utilization Review Criteria by Therapeutic Class and Domain (Continued)

Therapeutic class	Dose	Duplication
Digoxin	Maximum daily dose	>= 2 digitalis glycosides
Calcium	Maximum daily dose	>= calcium channel blockers
ACE-I	Maximum daily dose	>=2 ACE-I
H2 receptor antagonist	Maximum daily dose for gastroesophageal reflux disease	>=2 H2 receptor antagonists or with sucralfate, omeprazole or misoprostol
NSAIDs	Maximum daily dose	>= 2 NSAIDs
Benzodiazepines	Maximum daily dose or contraindicated duo to long half-life	>=2 benzodiazepines or use with other anxiolytics or sedative/hypnotics
Antipsychotics	Maximum daily dose	>=2 antipsychotics
Antidepressants	Maximum daily dose	>= 2 antidepressants or use with stimulants

Appendix B

The Beers Inappropriate Medication Criteria 1991

Drugs should be avoided	Drugs with specific dose and duration
Sedative-hypnotics	
Long-acting benzodiazepines	Short-acting benzodiazepines nightly >4wk
Chlordiazepoxide	Alprazolam
Diazepam	Oxazepam single dose>30mg
Flurazepam	Triazolam single dose>0.25mg
Meprobamate	
Short-duration barbiturates	Antipsychotics
Pentobarbital	Haloperidol >3mg/d
Secobarbital	Thioridazine >30mg/d
Antidepressants	
Amitriptyline	
Antihypertensives	Antihypertensives
Methyldopa	Hydrochlorothiazide >50mg/d
Propranolol	
Reserpine	
NSAIDs and analgesics	Histamine2 blockers
Indomethacin	Cimetidine >900mg & >12wk
Phenylbutazone	Ranitidine >300mg & >12wk
Propoxyphene	
Pentazocine	
Oral Hypoglycemics	Antibiotics
Chlorpropamide	Oral antibiotics >4wk
Dementia treatments	
Cyclandelate	
Isoxsuprine	Decongestants Daily >2 wk
Platelet inhibitors	Oxymetazoline
Dipyridamole	Phenylephrine
Muscle relaxants-antispasmodics	Pseudoephedrine
Cyclobenzaprine	
Orphenidrate	
Methocarbamol	Iron >325mg/d
Carisoprodol	
Antiemetics	
Trimethobenzamide	GI antispasmodics Long-term

Appendix C

Beers Criteria Drug List: Independent of Diagnosis (Beers, 1997)

Drugs by classes	Should generally be avoided* (Daily doses should not exceed)	High severity
Analgesics and NSAIDs		
Propoxyphene	*	No
Indomethacin	*	No
Phenylbutazone	*	No
Pentazocine	*	Yes
Meperidine	*	Yes
Sedative-hypnotics		
Chlordiazepoxide	*	Yes
Diazepam	*	Yes
Flurazepam	*	Yes
Meprobamate	*	Yes
Lorazepam	(3 mg)	No
Oxazepam	(60 mg)	No
Alprazolam	(2 mg)	No
Zolpidem	(5 mg)	No
Temazepam	(15 mg)	No
Triazolam	(0.25 mg)	No
Antidepressants		
Amitriptyline	*	Yes
Doxepin	*	Yes
Antihypertensive agents		
Reserpine	*	No
Methyldopa	*	Yes
Cardiovascular agents		
Digoxin	(0.125mg)	Yes
Disopyramide	*	Yes
[#]GI. antispasmodics		
Dicyclomine	*	Yes
Hyoscyamine	*	Yes
Propantheline	*	Yes
Belladonna alkaloids	*	Yes

GI. Gastrointestinal

Appendix C

Beers Criteria Drug List: Independent of Diagnoses (Beers, 1997)

(Continued)

Drugs by classes	Should generally be avoided* (Daily doses should not exceed)	High severity
Antihistaminic Agents		
Clorpheniramine	*	No
Diphenhydramine	*	No
Hydroxyzine	*	No
Cyproheptadine	*	No
Promethazine	*	No
Tripelennamine	*	No
Dexchlorpheniramine	*	No
Muscle Relaxants		
Methocarbamol	*	No
Carisoprodol	*	No
Oxybutynin	*	No
Chlorzoxazone	*	No
Metaxalone	*	No
Cyclobenzaprine	*	No
Dementia Treatments		
Ergot mesyloids	*	No
Cyclospasmol	*	No
All Barbiturates except Phenobarbital		
Secobarbital	*	Yes
Pentobarbital	*	Yes
Butabarbital	*	Yes
Amobarbital	*	Yes
Iron Supplements		
Ferrous sulfate	(325mg)	No
Antidiabetic agent		
Chlorpropamide	*	Yes
Platelet Inhibitors		
Dipyridamole	*	No
Ticlopidine	*	Yes
Antiemetic		
Trimethobenzamine	*	No

Appendix D

Beers Criteria Considering Diagnoses (Beers, 1997)

Disease and conditions	Drug	High severity
Heart failure	Disopyramide	Yes
	Drugs with High sodium content	No
Diabetes	beta-blockers(Limited to people taking oral hypoglycemics or insulin)	No
	Corticosteroids(Limited in recent started use)	No
Hypertension	Diet pills; Amphetamines	Yes
Chronic obstructive pulmonary disease	Beta-blockers	Yes
	Sedative/hypnotics	Yes
Asthma	Beta-blockers	Yes
Ulcers	NSAIDs	Yes
	Aspirin(>325mg)	No
	Potassium supplements(all)	No
Seizures or epilepsy	Clozapine,thioridazine, thorazine,chlorprothixene	No
	Metoclopramide	Yes
Peripheral vascular disease	Beta-blockers	Yes
Blood-clotting disorders	Aspirin or NSAIDs	Yes
	Dipyridamole and ticlopidine	Yes
Benign prostatic hyperplasia	Anticholinergic antihistamines	Yes
	Gastrointestinal antispasmodic drugs	Yes
	Muscle relaxants	No
	Narcotic drugs(Including propoxphene)	No
	Flavoxate, oxybutynin	No
	Bethanechol	No
	Anticholinergic antidepressant drugs	Yes
Incontinence	alpha-blockers	No
Constipation	anticholinergic drugs	No
	Narcotic drugs	No
	Tricyclic antidepressant drugs	Yes
Syncope or falls	Beta-blockers	No
	Long-actin benzodiazepines	Yes
Arrhythmias	Tricyclic antidepressant drugs	Yes*
Insomnia	Decongestants or Theophylline	No
	Desipramine, SSRIs, Methylphenidate, MAOIs	No
	Beta-Agonista	No

* If started recently