Literature Review of Polypharmacy and Older Drivers: Identifying Strategies to Collect Drug Usage and Driving Functioning Among Older Drivers

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16. Abstract

This research product updates the state-of-the-knowledge regarding key factors that bear on NHTSA's ability to investigate the effects of multiple medications on safe driving among older people. First, the prevalence of medication use by older people in the population, the physiological/metabolic effects of specific drugs and drug classes, and the known effects on driving ability—principally for single substances—are reviewed. Next, the strengths and weakness of various methods that may be used to learn which prescription and over-the-counter drugs are being taken by older adults are described and contrasted; a consideration of which factors most strongly affect compliance with a medication regime, and which factors influence older people' willingness to participate in studies aimed at obtaining such information, complements this discussion. The remaining section in this review examines on-road, closed course, and simulation methods that have been applied in this arena, highlighting those that appear to hold the greatest promise for evaluating the effects of drugs on driving performance while also acknowledging shortcomings and limitations that have been reported in the literature. For the most part, this review concentrates on recent (since 2001) studies accessed through print and electronic media. A bibliography containing over 200 citations is included, plus an appendix identifying potentially inappropriate medications commonly prescribed for older, community-dwelling individuals.

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FOREWORD

The goal of this project is to determine if there are practical means to obtain information about drug usage by older drivers under everyday, "real-world" conditions that are valid and reliable, and to measure the consequences of multiple drug use for safe driving. Further goals are to identify candidate methodologies for carrying out such studies that are both cost-effective and likely to be successful in obtaining a diverse and representative sample of older drivers.

Project tasks are geared toward accomplishing these four main objectives:

1) A literature review that updates the findings in the unpublished NHTSA Task Order report "Polypharmacy and Older Drivers" (Wilkinson and Moskowitz, 2001).
2) A critical literature review of methods currently used to measure the use of prescription medications and over-the-counter drugs by older adults.
3) Identification of potential cost-effective and practical ways to obtain valid information about prescription medications and over-the-counter drug usage by older drivers.
4) Identification of potential cost-effective and valid methods to assess the impacts on seniors' everyday driving performance of the use of prescription medications and over-the-counter drugs.

This literature review updates the Wilkinson and Moskowitz (2001) unpublished report *Polypharmacy & Older Drivers -- Literature Review*. As such, it is limited to literature published since 2001 addressing polypharmacy, drugs, and older drivers. The review has been divided into three major sections to address the information needs of the current project: 1) Medication/Polypharmacy Effects on Older People; 2) Methods of Measuring/Monitoring Medication Usage; and 3) Methods to Measure Driving Performance.

Although prescription medications are the major focus of this review, over-the-counter medication use by older people is included where it was reliably documented in the literature. Additional areas that received attention in the literature review on polypharmacy include:

- Older people's use of alcohol in combination with other medications—as alcohol use per se is not the focus of this project.
- Medication management (compliance and persistence) by older people—these aspects of a patient's behavior have an impact on functional ability and safe driving, in addition to whether the medications provide the intended therapy for the presenting medical conditions.
- How polypharmacy among older adults impacts areas other than driving (such as falls).
- Techniques used to measure/test driving skills and their application to medication studies.

Searches were conducted in Embase (which includes MedLine), PsycINFO, TRIS, and SafetyLit Weekly for current literature (2001 to 2004) combining the following keywords:

▪ Polypharmacy ▪ Multiple medication use ▪ Prescription drugs ▪ Over-the-counter drugs ▪ Drug use ▪ Older drivers ▪ Older adults ▪ Elderly persons ▪ Community-dwelling elderly ▪ Medication review ▪ Brown-bag method ▪ Medication management ▪ Medication compliance ▪ Medication adherence ▪ Medication persistence ▪ Medication event monitoring ▪ Self-medication ▪ Medication side effects ▪ Driver impairing medications ▪ Driver impairing medical conditions	▪ Inappropriate prescribing ▪ Contraindicated drugs/medications ▪ Geriatrics ▪ Gerontology ▪ Medicaid/Medicare pharmacy claims ▪ Veterans administration pharmacy benefits management database ▪ Pharmaceutical claims ▪ Prescription database ▪ Medication usage/tracking ▪ Medication dispensing technology ▪ Motor vehicle crashes ▪ Motor vehicle accidents ▪ Dose administration aids ▪ Driving skills ▪ Driving ability ▪ Driving performance ▪ Falls or falling

Approximately 1,600 abstracts were identified in the original searches. A review of titles indicated that many reports focused on medications for resistant conditions. Eliminating the terms "resistance" and "resistant" and limiting the search to human subjects 65 and older, and abstracts to those in English reduced the results to 365 potentially relevant articles. In selecting articles for review, we included research only on populations of likely drivers (i.e., to "community-dwelling" populations, as opposed to residents of nursing homes or residents of group homes who suffer from developmental disabilities or conditions such as schizophrenia). Systematic differences in prescribing and in monitoring compliance in controlled settings such as nursing homes and hospitals limit the generalizability of information from such populations of older people to the population of community-dwelling older people. In addition, research on multiple medication effects was primary over research on single-medication effects; however, reports presenting the effects of single medications on driving performance were included to the degree that the research focused on the effects of the drug on driving performance or falling in older community-dwelling people. The set of 365 potentially relevant abstracts was reduced through this first screen to a set of 300 articles.

The selection of reports for review underwent further refinement with the assistance of two project consultants, Dr. Robert Raleigh and Dr. Marion Anders. Dr. Robert Raleigh is the chief of the Maryland Medical Advisory Board. He reviewed the set of 300 abstracts to assist in the prioritization of candidate documents/studies for review by Dr. Anders. This screening process reduced the number of potentially relevant articles to 143 on the topics of identifying

medication use and measuring medication adherence, measuring driver performance, and polypharmacy and older people.

Articles were then retrieved by the staff at the University of North Carolina Highway Safety Research Center (the prime contractor for this project), and through e-mail requests of authors, when articles were not available at UNC/HSRC. Reports received were screened according to selection criteria that include relevance and methodological soundness. Emphasis was placed on well-designed and controlled studies. The subset of articles dealing with polypharmacy effects on older people was mailed to Dr. M. W. Anders—a world renowned expert in interactions of single and multiple drugs. He is recently retired as chair of the Departments of Pharmacology & Physiology at the University of Rochester Medical School. He supported the research team in this task by performing a detailed review and interpretation of the literature with a specific focus on driving impairment (approximately 34 articles). TransAnalytics staff synthesized the literature pertaining to the measurement of driving performance (approximately 16 articles), and methods of measuring medication use/compliance (approximately 48 articles).

Dr. Richard Marottoli's (Yale University School of Medicine) review and comment on the "Medication/Polypharmacy Effects on Older People" section are gratefully appreciated.

SI* (MODERN METRIC) CONVERSION FACTORS

APPROXIMATE CONVERSIONS TO SI UNITS

Symbol	When You Know	Multiply By	To Find	Symbol
		LENGTH		
in	inches	25.4	millimeters	mm
ft	feet	0.305	meters	m
yd	yards	0.914	meters	m
mi	miles	1.61	kilometers	km
		AREA		
in^2	square inches	645.2	square millimeters	mm^2
ft^2	square feet	0.093	square meters	m^2
yd^2	square yards	0.836	square meters	m^2
ac	acres	0.405	hectares	ha
mi^2	square miles	2.59	square kilometers	km^2
		VOLUME		
fl oz	fluid ounces	29.57	milliliters	mL
gal	gallons	3.785	liters	L
ft^3	cubic feet	0.028	cubic meters	m^3
yd^3	cubic yards	0.765	cubic meters	m^3
NOTE: Volumes greater than 1000 l shall be shown in m^3.				
		MASS		
oz	ounces	28.35	grams	g
lb	pounds	0.454	kilograms	kg
T	short tons (2000 lb)	0.907	megagrams (or "metric ton")	Mg (or "t")
		TEMPERATURE (exact)		
°F	Fahrenheit temperature	5(F-32)/9 or (F-32)/1.8	Celcius temperature	°C
		ILLUMINATION		
fc	foot-candles	10.76	lux	lx
fl	foot-Lamberts	3.426	candela/m^2	cd/m^2
		FORCE and PRESSURE or STRESS		
lbf	poundforce	4.45	newtons	N
lbf/in^2	poundforce per square inch	6.89	kilopascals	kPa

APPROXIMATE CONVERSIONS FROM SI UNITS

Symbol	When You Know	Multiply By	To Find	Symbol
		LENGTH		
mm	millimeters	0.039	inches	in
m	meters	3.28	feet	ft
m	meters	1.09	yards	yd
km	kilometers	0.621	miles	mi
		AREA		
mm^2	square millimeters	0.0016	square inches	in^2
m^2	square meters	10.764	square feet	ft^2
m^2	square meters	1.195	square yards	yd^2
ha	hectares	2.47	acres	ac
km^2	square kilometers	0.386	square miles	mi^2
		VOLUME		
mL	milliliters	0.034	fluid ounces	fl oz
L	liters	0.264	gallons	gal
m^3	cubic meters	35.71	cubic feet	ft^3
m^3	cubic meters	1.307	cubic yards	yd^3
		MASS		
g	grams	0.035	ounces	oz
kg	kilograms	2.202	pounds	lb
Mg (or "t")	megagrams (or "metric ton")	1.103	short tons (2000 lb)	T
		TEMPERATURE (exact)		
°C	Celcius temperature	1.8C + 32	Fahrenheit temperature	°F
		ILLUMINATION		
lx	lux	0.0929	foot-candles	fc
cd/m^2	candela/m^2	0.2919	foot-Lamberts	fl
		FORCE and PRESSURE or STRESS		
N	newtons	0.225	poundforce	lbf
kPa	kilopascals	0.145	poundforce per square inch	lbf/in^2

* SI is the symbol for the International System of Units. Appropriate rounding should be made to comply with Section 4 of ASTM E380.

(Revised September 1993)

MEDICATION/POLYPHARMACY EFFECTS ON OLDER PEOPLE

Polypharmacy is the use of many medications at the same time. Other definitions include prescribing more medication than is clinically indicated, a medical regimen that includes at least one unnecessary medication, or the empiric use of five or more medications (Michocki, 2001). Lee (1998) notes that the definition of polypharmacy is controversial, with authors disagreeing on the number of drugs—varying from study to study, from the concomitant use of more than 2 drugs, 4 drugs, 5 drugs, 6 drugs, and 10 drugs—and whether to include as-needed medications, over-the-counter drugs, or herbal and alternative medications.

Within the context of the present NHTSA research on polypharmacy and older drivers, it is instructive to consider findings by Hébert, Bravo, Korner-Bitensky, and Boyer (1996) [consider shortening to "Hebert et al."] that the consumption of three or more drugs per day increases the risk of functional decline in elderly people by 60 percent (cited in Allard et al., 2001[you appear to cite this as "Allard et al." in the next paragraph, which is much better. Need to be consistent.).

The risks of polypharmacy include an increase in the number of potentially inappropriate prescriptions (PIP), cognitive disorders, falls, hip fractures, depression, and incontinence (Gurwitz, Soumerari, and Avorn, 1990). Additionally, preliminary results of a project currently underway for NHTSA suggest that there is an increased risk of motor vehicle crashes for older drivers who use multiple potentially driver-impairing medications (LeRoy, 2004). Wilkinson and Moskowitz (2001) reviewed 21 studies of multiple medication use by the community-dwelling older population in the United States and found that approximately 10 to 27 percent of community-dwelling elderly are prescribed medications on the Beer's List of Drugs that are potentially inappropriate for people over age 65. Medications on this list are deemed inappropriate because they are either ineffective or the potential for adverse outcomes is greater than the potential for benefit. Allard et al. (2001) reported on a study performed by the Quebec Health Insurance Board (1992), which found that approximately 10 percent of the elderly population of Quebec has at least one PIP that meets the criteria for therapeutic overlapping, a high daily dose, or a harmful drug interaction. The Quebec Health Insurance Board further found that the PIP risk increases exponentially with the number of drugs. For example, taking fewer than 4 drugs is associated with a 12 percent risk, whereas taking more than 5 drugs a day involves a 40 percent PIP risk. It is important to note that the prevalence of potentially driver-impairing medications in the community-dwelling population of older people is likely higher, given that many drugs not on the Beers list can impair safe driving performance.

This section of the report will describe: (1) the prevalence of prescription and over-the-counter medication use by older community-dwelling people in the United States and in other countries; (2) how these frequently used medications interact with the aging body; (3) the consequences of medication use on older person's ability to drive safely; and (4) the consequences of medication use on falls and other adverse events.

MEDICATION USE IN THE OLDER POPULATION

This section begins by summarizing recent studies conducted in the United States describing the medication use of the community-dwelling older population. The majority of data in these studies were obtained through pharmacy claims databases, although in a few studies reported below, data were obtained through subject interviews, and to a lesser degree from biochemical sampling in trauma centers. Prescription medication use is described first, followed by over-the-counter (OTC) medication use, and the concurrent use of medication and alcohol. This section concludes with summaries of studies conducted on the prevalence of medication use in the community-dwelling older population of other countries. In light of changing practice and prescribing patterns over time, it should be kept in mind that the individual medications discussed may change over time but the underlying principles may apply to other drugs in the same categories.

United States: Use of Drugs in the Community-Dwelling Older Population

Prescription Medications. In a recent and comprehensive national survey of U.S. noninstitutionalized adults, Gurwitz (2004) reported that more than 90 percent of people 65 or older use at least 1 medication per week; more than 40 percent of this population use 5 or more different medications per week; and 12 percent use 10 or more different medications per week.

In a cohort study of nearly 28,000 Medicare+Choice enrollees cared for by a multispecialty practice (an ambulatory clinic setting) during a 12-month study period during 1999 and 2000, researchers found that 75 percent of the sample received prescriptions for 6 or more prescription drugs (Gurwitz et al., 2003). Residents of long-term-care facilities were excluded from the study. The average age of the subjects in the sample was 74.7 (sd=6.7). The age and gender distribution of the sample was similar to that of the U.S. population 65 and older. Forty-nine percent of the sample was prescribed medications in four or more categories. Combinations of medication use were not reported; however, the specific prescription medication categories and percentage of enrollees receiving prescriptions were as follows:

- Cardiovascular (53.2%)
- Antibiotics/anti-infectives (44.5%)
- Diuretics (29.5%)
- Opioids (21.9%)
- Antihyperlipidemic (21.7%)
- Nonopioid analgesics (19.8%)
- Gastrointestinal tract (19.0%)
- Respiratory tract (15.6%)
- Dermatologic (14.8%)
- Antidepressants (13.2%)
- Sedatives/hypnotics (12.9%)
- Nutrients/supplements (12.3%)
- Hypoglycemics (11.5%)
- Steroids (9.7%)
- Ophthalmics (9.6%)
- Thyroid (9.4%)
- Antihistamines (9.2%)
- Hormones (9.1%)
- Anticoagulants (7.0%)
- Muscle relaxants (5.4%)
- Osteoporosis (5.3%)
- Antiseizure (3.4%)
- Antigout (3.2%)
- Antineiplastics (2.8%)
- Antiplatelets (1.3%)
- Antipsychotics (1.2%)
- Antiparkinsonians (0.9%)
- Alzheimer disease (0.9%)
- Immunomodulators (0.04%)

The objective of the study by Gurwitz et al. (2003) was to document the incidence and preventability of adverse drug events. An *adverse drug event* (ADE) was defined in the study as "an injury resulting from the use of a drug." To provide some background, adverse drug events include "expected adverse drug reactions (or side effects) as well as events due to errors" (Agency for Healthcare Research and Quality). Adverse drug events due to errors are, by definition, preventable. In contrast, an *adverse drug reaction*, according to the World Health Organization (1975) definition is "any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." It implies that there was no error in the use of the drug. Examples of an *injury* could include an event such as a rash or diarrhea caused by an antibiotic/anti-infective agent; gastrointestinal tract events such as nausea, vomiting, diarrhea, constipation and abdominal pain; anaphylaxis (a serious allergic reaction) to penicillin; a major hemorrhage from a blood-thinning agent; and kidney failure from aminoglycosides (antibiotics that are often administered into veins or muscle to treat serious bacterial infections).

In the Gurwitz et al. (2003) study, events were categorized as fatal, life-threatening, serious, or significant. Events resulting in permanent disability included stroke, intracranial bleeding events, hemorrhagic injury to the eye, and drug-induced pulmonary injury. Deaths in the study were related to fatal bleeding; peptic ulcers; neutropenia/infection; hypoglycemia; drug toxicity related to lithium or digoxin; anaphylaxis; and complications of antibiotic-associated diarrhea. There were 1,523 identified adverse drug events, of which 421 (27.6%) were considered preventable. Of the 578 serious, life-threatening, or fatal adverse drug events, 42 percent (244) were deemed preventable. Of the 945 significant adverse drug events, 19 percent (177) were deemed preventable. The most common types of preventable adverse drug events were: electrolyte/renal (27%), gastrointestinal tract (21%), hemorrhagic (16%), metabolic/endocrine (14%), and neuropsychiatric (9%). The most common medication categories associated with preventable adverse drug events are presented below:

- Cardiovascular medications (24.5% of the ADEs).
- Diuretics (22.1% of the ADEs).
- Nonopioid analgesics (15.4% of the ADEs).
- Hypoglycemics (10.9% of the ADEs).
- Anticoagulants (10.2% of the ADEs).

Errors described in the study by Gurwitz et al. (2003) most often occurred at the stages of prescribing (246 events, or 58.4%) and monitoring (256 events, or 60.8%), although patient adherence errors were also common (89 events, or 21.1%). Gurwitz et al. (2003) note that if the findings of the study are generalized to the population of all Medicare enrollees, then more than 1,900,000 [consider "1.9 million"]adverse drug events—more than a quarter of which are preventable—occur each year among 38 million Medicare enrollees. In addition, study estimates suggest that there are in excess of 180,000 life-threatening or fatal adverse drug events per year, of which more than 50 percent may be preventable.

The issue of polypharmacy in the elderly is confounded by the use of so-called "potentially inappropriate" medications. The identification of potentially inappropriate medication use has employed the Beers criteria (Fick et al., 2003); the criteria consider "…(1) medications or medication classes that *should generally be avoided* in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a

safer alternative is available and (2) medications that should not be used in older persons known to have *specific medical conditions*." The recent update of the Beers criteria found 48 individual drugs or classes of drugs to avoid in older adults and 20 diseases, conditions, and medications that should be avoided in the elderly with these conditions. The Zhan criteria extends the Beers list of drugs to identify drugs that should always be avoided, are rarely appropriate, or have indications for use in elderly patients but are frequently misused (Zhanet al., 2001). Inappropriate medications complicate polypharmacy, because many of the drugs classified as potentially inappropriate are associated with adverse drug reactions (ADRs), some offer little or no advantage over other, safer drugs, and some have a long half-life in older patients.

Several studies of the incidence of potentially inappropriate medication use have been reported. These studies are summarized below, and reinforce the view that potentially inappropriate medication use is common in the elderly and that is a significant confounding issue when assessing the effect of combinations of medicines. Appendix A provides detail about the specific drugs, their classification, and side effects relevant to a discussion of safe driving ability.

Raji et al. (2003) used home interviews to examine the prevalence and predictors of inappropriate prescription medication use by 3,050 Mexican-Americans 65 and older living in the southwestern United States Approximately 12 percent of the sample had used at least 1 of the 32 potentially inappropriate medications within two weeks of the assessment. Four drugs accounted for 54 percent of all inappropriate prescribing: chlorpropamide,[1] propoxyphene,[2] amitriptyline,[3] and dipyridamole.[4]

The following characteristics were predictive of the subjects who were prescribed at least 1 of the 32 drugs on the list of inappropriate medications: being unmarried, having 1 or more chronic diseases, having high depressive symptoms, having frequent physician visits, and having both Medicaid and Medicare insurance (Raji et al., 2003). The odds of using any inappropriate drugs were 2.4 times greater in subjects reporting 2 or more medical conditions compared with those reporting no medical conditions. The odds of using any inappropriate drugs were approximately 6 times greater in subjects reporting 2 or more physician visits, compared with those reporting no visits. Subjects with 1 or 2 visits had 4.3 times the risk of receiving at least 1 of the 32 potentially inappropriate drugs relative to those reporting no visits.

Kamal-Bahl et al. (2003) used the data from the 1998 Medicare Current Beneficiary Survey (MCBS) to provide a national prevalence estimate of the number of community dwelling Medicare beneficiaries 65 and older who are prescribed propoxyphene. In addition to the opioid-related adverse effects associated with this medication (e.g., drowsiness, dizziness, lightheadedness), several studies were cited by Kamal-Bahl et al. (2003) that have demonstrated that it is no more effective than acetaminophen, aspirin, codeine, or ibuprofen in reducing pain

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[1] Chlorpropamide ("Diabinese") is used to treat type II (noninsulin-dependent) diabetes. It lowers blood sugar by stimulating the pancreas to secrete insulin and helping the body to use insulin efficiently.
[2] Propoxyphene ("Darvon Puvules," "Darvon-N") is used to relieve mild to moderate pain. It should not be taken in combination with other drugs that cause drowsiness: alcohol, tranquilizers, sleep aids, antidepressant drugs, or antihistamines.
[3] Amitriptyline ("Elavil"; "Endep"; "Limbitrol" [combination with chlordiazepoxide]) is used to treat symptoms of depression. Amitriptyline is in a class of medications called tricyclic antidepressants.
[4] Dipyridamole ("Aggrenox") is used to lessen the chance of stroke that may occur when a blood vessel in the brain is blocked by blood clots.

and may even be inferior. This medication is listed on the Beer's list of potentially inappropriate drugs for elderly people (Beers, 1997) and is classified by the Zhan expert panel as a drug that is "rarely appropriate" (Zhan et al., 2001). The MCBS database includes statistical weights for each respondent that can be used to generate nationally representative estimates from the survey sample. The study sample consisted of all MCBS respondents 65 or older who were community-dwelling (n=9,851, weighted n = 32.5 million) during 1998. The annual prevalence of propoxyphene use was 6.8 percent. Approximately 69 percent of the propoxyphene prescriptions in the community were combination products with another analgesic, namely acetaminophen.

Aparasu and Mort (2004) examined data from the 1996 Medical Expenditure Panel Survey (MEPS) to analyze the use of psychotropic medications that generally should be avoided in the elderly and those that should be avoided in elderly patients with certain preexisting conditions, as defined by the Beers criteria. The MEPS sampling weights were used to derive national estimates. It was estimated that nationally, 6.09 million older patients (19% of 32.29 million older patients) use psychotropic medications; 64 percent are female. Further, it was estimated that 2.3 million community-dwelling older people received potentially inappropriate psychotropic medications in 1996, which represents 7.14 percent of all community-dwelling older people and 37.86 percent of all community-dwelling older people using psychotropic agents. Thirty-three percent of those taking psychotropic drugs received agents that were generally inappropriate and 10 percent received agents that were inappropriate in the presence of specific conditions. The rate of potentially inappropriate psychotropic use in those receiving antidepressants was 51 percent, for antianxiety agents was 32 percent, and for sedative/hypnotic agents was 23 percent.

The most frequently used potentially inappropriate antidepressants are amitriptyline[5] and doxepin.[6] These agents are to be avoided in the elderly because of their anticholinergic[7] and sedative effects. Use of diazepam,[8] a long half-life benzodiazepine alone (56.89%) and use of a sedative in patients with chronic obstructive pulmonary disease (COPD, 62.65%) constituted more than half of the potentially inappropriate antianxiety and sedative/hypnotic use, respectively. Age less than 75 and use of multiple psychotropic agents were correlated with the use of potentially inappropriate psychotropic agents. For older people taking antidepressants, the use of potentially inappropriate antidepressant agents was significantly higher (4 times) among those younger than 70 compared to those 85 and older. For those taking sedative/hypnotic agents, age between 70 and 79, and having only Medicare coverage were positively associated with the use of potentially inappropriate sedative/hypnotic agents. However, older patients with Medicaid coverage were significantly less likely to use potentially inappropriate sedative/hypnotic agents than those without Medicaid coverage.

A table follows on the next page containing a summary of the studies discussed above and others bearing on the use of drugs on the Beers list by community-dwelling populations in the United States.

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[5] Brand names: Elavil; Endep; Limbitrol.
[6] Brand names: Adapin; Sinequan.
[7] Anticholinergic agents diminish the effect of acetylcholine, a neurotransmitter that in many ways counteracts the effect of dopamine in the brain. Adverse anticholinergic effects include decreased cognition, sedation, blurry vision, confusion, and instability.
[8] Brand names: Valium, Valrelease, Vazepam, Diaz Intensol, Diastat, Dizac.

Over-the-Counter Medications. Although polypharmacy has been historically associated with prescription medications, any current definition of polypharmacy must also include nonprescription compounds, such as over-the-counter (OTC) products, herbal remedies, and foods or nutraceuticals. Some OTCs were formerly available by prescription, and information about potential drug interactions may be available. In contrast, relatively little reliable information is available about drug interactions associated with herbal remedies.

Memmott (2003) provides estimates of over-the-counter (OTC) medication use citing Salom and Davis (1995). Approximately 40 percent of the drugs taken by the elderly are OTC medications. Ten percent of the general population regularly uses OTC medications and 69 percent of the people over age 65 regularly use these medications. It is estimated that 15 to 20 percent of the older users do not inform their physicians of OTC use.

Bikowski, Ripsin, and Lorraine (2001) cite evidence that on average, an ambulatory older patient takes 3.4 over-the-counter medications daily. Pollow, Stoller, Forster, and Duniho (1994) reported that the most common OTC medications were analgesics and antacids.

Thirteen percent of the elderly who are regular OTC users consume alcohol and take OTC drugs concurrently (Memmott, 2003). Another 17 percent combine OTC drugs with both prescription drugs and alcohol, increasing the possibility and severity of adverse drug reactions (ADR). The risk of a serious ADR in adults age 55 to 64 is 18.5 percent; is 30.1 percent in those 75 to 84, and is 41.9 percent in those 85 and older. In a mail survey of 1,555 HMO members 65 and older, Johnson and Ried (1996) found that 18.4 percent of the sample combined a prescription drug with an OTC drug to relieve pain; 4.5 percent combined a prescription drug and an OTC drug to relieve an upset stomach; 7.1 percent combined prescription and OTC medications for cough relief; and 5.7 percent combined prescription and OTC medications to treat cold symptoms.

Concurrent Use of Alcohol and Medications. Because of age-related physiological changes, declining health and functional status, and medication use, older adults can incur problems at low levels of alcohol consumption (Fink et al., 2002). Memmott (2003) states that estimates of alcohol dependence in the population over age 65 range from 1 to 5 percent, while the prevalence of problem drinking in the elderly varies from 10 to 15 percent. Lazow (2001) reports that within the high percentage of adults 65 and older who are admitted to a hospital at least once a year (20% of the population of this age), 20 to 50 percent who entered the hospital for nonalcohol or other drug-related problems were identified as having such problems.

The prevalence of alcohol use in geriatric trauma patients may be understated as indicated by the results of a study by Zautcke et al. (2002), who found that only a small percentage of older trauma patients are tested for alcohol use. Of the 32,382 patients 65 or older who entered a Level I or Level 2 trauma center in Illinois between 1994 and 1996, only 5.2 percent were tested for the presence of alcohol. Of those tested, 49.7 percent tested positive for alcohol and 71.8 percent of those were considered intoxicated (blood alcohol concentration [BAC] level = .08 or higher). Zautcke et al. (2002) note that the decision whether to test a patient for alcohol use was likely skewed and determined by clinical signs of intoxication. Clinical signs of intoxication are often difficult to detect, especially at lower concentrations.

Inappropriate Prescription Drug Use by Older Subjects				
Study Population	**Number, age, and sex of subjects**	**Incidence of inappropriate medication use**	**Inappropriate medications most commonly identified**	**Reference**
National Ambulatory Medical Care Survey and National Hospital Ambulatory Care Survey	22,031 subjects; 25% 65–69 years old, 24.9% 70–74 years old, 23.8% 75–79 years old, 26.2% ≥ 80 years old; 59% female and 41 % male.	Ranged from 6.01% in 1996 to 7.82% in 2000	Propoxyphene, hydroxyzine, diazepam, amitriptyline, and oxybutynin	Goulding (2004)
Outpatient prescription claims database of AdvancePCS (pharmaceutical benefit manager)	765,423 subjects; 73.7 ± 6.5 (mean ± SD) years old; 58.3% female and 41.7% male	21% of the subjects filled a prescription for one or more drugs of concern	Amitriptyline and doxepin accounted for approximately 23% of the total claims for Beers list drugs	Curtis et al., (2004)
1996 Medical Expenditure Panel Survey	Sampling weights used to derive National Estimates for the population of 32.29 million community-dwelling older people age 65+	19% use psychotropic medications (64% are female). 7.14% of all older people and 37.86% of those using psychotropic medications received potentially inappropriate psychotropic medications. 32.9% of those taking psychotropic drugs received agents that were generally inappropriate and 10.2% received agents that were inappropriate in the presence of specific conditions.	Study focused on psychotropic medications that should generally be avoided, and those that should be avoided in patients with specific medical conditions. Amitriptyline, doxepin, diazepam, chlordiazepoxide, long-acting benzodiazepines w/falls, meprobamate, flurazepam, barbiturates	Aparasu and Mort (2004)
1998 Medicare Current Beneficiary Survey	9,851 age 65+	6.8% annual prevalence of propoxyphene use	Study focused only on propoxyphene	Kamal-Bahl et al. (2003)
Mexican-Americans Living in the Southwestern U.S.	3,050 age 65+	12% of the sample within 2 weeks of the home interviews assessing medication use	Four drugs accounted for 54% of the inappropriate prescribing: chlorpropamide, propoxyphene, amitriptyline, dipridamole.	Raji et al. (2003)
Duke Established Populations for Epidemiological Studies of the Elderly (fourth wave, 1989/90, seventh wave, 1992/93)	3,234 (fourth wave) and 2,508 (seventh wave); 49.1% <75 years old, 41.1% 75–84 years old, 9.8% 85+ years old; 64.8% female and 35.2% male	21.0% of the fourth wave study population and 19.2% of the seventh wave study population used one or more inappropriate medications	Benzodiazepines and NSAIDs	(Hanlon et al., 2002)

In a survey by Adams (1995) 38 percent of the elderly community dwellers reported concurrent use of alcohol and high-risk medications (e.g., antidepressants, antihypertensives, sedative-hypnotics). Six percent reported consuming seven or more drinks per week while taking a high-risk medication.

Fink et al. (2002) cite a study by Adams, Yuan, Barboriak, and Rimm (1993) who conducted a national study using 1989 Medicare claims data, and found that alcohol-related hospitalizations were more common among elderly people than hospitalizations for myocardial infarction. Fink et al. (2002) developed the Alcohol-Related Problems Survey to detect older people who are at risk for or are experiencing problems because of their use of alcohol alone or in conjunction with their comorbidities, medication use, and functional status. The Alcohol-Related Problems Survey[9] (ARPS) was administered by Fink et al. (2002) to 549 current drinkers 65 and older who were mostly Caucasian (87%) with high school or higher education (94%). Eligible participants reported drinking at least one alcoholic beverage in the past 12 months. Based on the ARPS score, drinkers were classified into three categories: harmful drinkers (alcohol abuse or dependence, or the presence of problems such as hypertension, adverse drug events, or legal problems due to drinking); hazardous drinkers (drinking poses a likely risk for problems); or nonhazardous drinkers (drinking poses no known risks for problems). Eleven percent of subjects were harmful drinkers, and 35 percent were hazardous drinkers. Most harmful drinkers were identified by their use of alcohol with their comorbidity (e.g., three or more drinks, two to three times per week and having hypertension, depression or other psychiatric condition, or gout; or, any amount of alcohol plus having had hepatitis in the past 12 months, cirrhosis or other liver condition, or gastritis in the past 12 months). More men than women were classified as harmful drinkers, and more women than men were classified as nonhazardous drinkers.[?] Most hazardous drinkers were identified by their use of alcohol with medications. Similar proportions of men and women, and older (age 75+) and younger (age 65 to 74) age groups were hazardous drinkers.

Looking at the number of medications used with potential alcohol interaction by the study sample, Fink et al. (2002) report that:

- 12 percent used no such medications;
- 46 percent used 1 to 3 such medications;
- 32 percent used 4 to 6 such medications; and
- 9 percent used 7 or more such medications.

The most common combination of alcohol use and medications was one or more drinks per day with the following medications (in hierarchical order from most common to least common): arthritis and pain medications, cimetidine[10] or ranitidine,[11] antidepressants, warfarin,[12] nitrates,

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[9] The ARPS is a self-administered questionnaire with 60 items about the presence of medical and psychiatric conditions, symptoms of disease, smoking behavior, medication use, physical function and health status, quantity and frequency of alcohol use, episodic heavy drinking, symptoms of alcohol abuse and dependence, driving after drinking, and gender.

[10] Cimetidine (brand names: Tagamet; Tagamet HB 200; Tagamet Tiltab) is used to treat ulcers, gastroesophageal reflux disease, and conditions where the stomach produces too much acid. OTC cimetidine is used to prevent and treat symptoms of heartburn associated with acid indigestion and sour stomach. Cimetidine is in a class of medications called histamine 2 receptor antagonists (H2RA).

diphenhydramine,[13] or antiseizure medication. The second most common combination of medications and alcohol use for hazardous drinkers was two or more drinks per day, and the use of aspirin (two or more) or hypertensives.

Other Countries: Use of Drugs in the Community-Dwelling Older Population

Polypharmacy is common in the older community-dwelling population of other countries. This section of the report summarizes recent studies of medication use by older community-dwelling individuals in Spain (one study), Canada (two studies), Finland (three studies), Sweden (one study), and Denmark (one study).

In one study of 65 patients with heart failure in Spain (49 males and 16 females age 60.5 ± 12.0 [mean ± SD] years), it was found that 74 percent of the subjects were taking 6 or more pills per day and that 28 percent were taking 11 or more pills per day (Martínez-Sellés et al., 2004). One key finding of the study was the high rate of homeopathic and alternative medicine use among female patients, one-third of whom reported the use of such treatments.

In a sample of 1,216,000 community-dwelling adults 66 and older in Ontario, Canada, 40,307 (3.31%) were prescribed a drug that was on the Beers list and categorized by the study authors as "drugs to always avoid" or "drugs that are rarely appropriate" (Lane et al., 2004). For the 12,162 older people who received a drug on the "always-avoid list," the majority (63%) were prescribed flurazepam.[14] Meperidine[15] accounted for 19 percent of the always-avoid prescriptions, chlorpropamide[16] accounted for 16 percent, and barbiturates accounted for 4 percent. For the 28,985 older people who received a drug categorized as "rarely appropriate," diazepam[17] accounted for 85 percent of the prescriptions and chlordiazepoxide[18] accounted for 15 percent of the prescriptions.

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[11] Ranitidine (brand names: Zantac; Zantac AR) is used to treat ulcers, gastroesophageal reflux disease, and conditions where the stomach produces too much acid. OTC ranitidine is used to prevent and treat symptoms of heartburn associated with acid indigestion and sour stomach. Ranitidine is in a class of medications called histamine 2 receptor antagonists (H2RA).

[12] Warfarin (brand name: Coumadin) is used to prevent blood clots from forming or growing larger. It is often prescribed for patients with certain types of irregular heartbeat and after a heart attack or heart valve replacement surgery.

[13] Diphenhydramine (brand names: Benadryl; Benylin) is an antihistamine that relieves red, irritated, itchy, watery eyes; sneezing; and runny nose caused by hay fever, allergies, and the common cold. It also may relieve the itching of insect bites, sunburns, bee stings, poison ivy, poison oak, and minor skin irritation. Diphenhydramine is also used to prevent and treat motion sickness, induce sleep, treat Parkinson's disease, and relieve cough caused by minor throat or airway irritation.

[14] Flurazepam (brand name: Dalmane in the United States) is a benzodiazepine derivative. It is a hypnotic agent prescribed for insomnia. Brand names in Canada include Apo-Flurazepam ; Novo-Flupam ; PMS-Flupam; Somnol; and Som Pam..

[15] Meperidine (brand names: Demerol, Isonipecaine, and Pethidine) is used to relieve moderate to severe pain. Meperidine is in a class of medications called narcotic analgesics, a group of pain medications similar to morphine. It works by changing the way the body senses pain.

[16] Chlorpropamide ("Diabinese") is used to treat type II (noninsulin-dependent) diabetes. It lowers blood sugar by stimulating the pancreas to secrete insulin and helping the body to use insulin efficiently.

[17] Diazepam **(**Brand names:Valium and Valrelease) is used to relieve anxiety, muscle spasms, and seizures and to control agitation caused by alcohol withdrawal..

[18] Chlordiazepoxide (Brand names: Libritabs; Librium; Limbitrol (combination with amitriptyline); Mitran; Reposans-10; Sereen.) is used to relieve anxiety and to control agitation caused by alcohol withdrawal.

Hogan, Maxwell, Fung, and Ebly (2003) reported on the prevalence of benzodiazepine use in Canada. In the mid 1990s, approximately 25 percent of senior citizens in Nova Scotia annually received a prescription for a benzodiazepine. In 1991, 16 percent of Saskatchewan seniors received a benzodiazepine prescription. They conducted a study to evaluate the change in benzodiazepine use in a group of 1,181 subjects 65 and older in a 5-year longitudinal study between 1990/91 (T1) and 1996 (T2). They found that although the average number of medications (prescribed, non-prescribed, and nutritional supplements) increased from 3.9 to 5.8, the proportion of subjects using benzodiazepines at T1 and T2 was similar (26.4% versus 25.2%). The most commonly used classes of medications (and percentage of subjects using them) were: analgesics (58.5%); diuretics (32.7%); anxiolytics (29.5%); cardiac drugs (24.5%); and antihypertensives (17.2%). With regard to use of benzodiazepines, at T2, 74 percent of users were taking benzodiazepines regularly and 26 percent were using them only as needed. Approximately half of the T2 benzodiazepine users had been consuming benzodiazepines at T1. A key finding between T1 and T2 was a decline in the proportion of subjects consuming long half-life benzodiazepines (nonsignificant) and triazolam[19] (significant), which, the authors suggest, may indicate better prescribing practices as physicians have been cautioned about the use of both.

It should be noted here that with hypnotic drugs such as benzodiazepines, the duration of hypnotic effect and the profile of unwanted effects may be influenced by the distribution and elimination half-lives of the administered drug and any active metabolites formed. When half-lives are long, the drug or metabolite may accumulate during periods of nightly administration and be associated with impairments of cognitive and motor performance during waking hours. If half-lives are short, the drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to sedation or CNS depression should be minimal or absent (RxMed, 2005). Furthermore, benzodiazepines or active metabolites with very long elimination half-lives can accumulate with chronic dosing and produce prolonged effects, especially in elderly or obese patients, those with liver disease, or with concurrent use of other drugs that compete for hepatic oxidation. The updated Beers criteria indicate that short- and intermediate-acting benzodiazepines are preferred over long-acting benzodiazepines, if a benzodiazepine is required (Fick et al., 2003).

Another key finding by Hogan et al. (2003) at T2 was that older people with a depressed mood (Geriatric Depression Scale score greater than 5) were more likely to be prescribed a benzodiazepine (37%) than an antidepressant (26.9%). The authors state that benzodiazepines are often used by depressed individuals, despite the fact that with the exception of alprazolam, they are believed to be ineffective for the primary treatment of depression. They cite their earlier findings that physicians appear to overprescribe benzodiazepines and underprescribe antidepressants in depressed older patients (Hogan, Ebly, and Fung, 1995). Their 2003 data showing a higher rate of benzodiazepine than antidepressant use in seemingly depressed patients suggests potentially inappropriate psychotropic prescribing.

People over 64 years of age represent 15 percent of the Finnish population, but their medication costs comprise 40 percent of the expenditures of the total Finnish population (Linjakumpu et al., 2002). These authors conducted two cross-sectional surveys among community-dwelling people 64 and older in 1990-1991 and 1998-1999 to investigate changes in

[19] Triazolam is a benzodiazepine with a very short elimination half-life (about 3 hours).

the use of prescription drugs and polypharmacy. The mean age was the same in both surveys (72 for men and 73 for women). In this study, polypharmacy was defined as the concomitant use of over 5 medications. Nonprescription drugs were not included in this study. The number of medications per person increased from 3.1 to 3.8, and polypharmacy increased from 19 percent of the sample to 25 percent of the sample. These changes were most prominent among the population 85 and older, especially women. Medication use grew from 93 percent to 97 percent in subjects 84 and older, between the two surveys. In 1998/99, women 84 and older used an average of 6.8 medications. Drug users with polypharmacy were older than those without polypharmacy, and two-thirds of those with polypharmacy were women. Cardiovascular and central nervous system (CNS) medications were used most commonly in both surveys, and CNS medication use increased significantly between surveys. Of CNS medication users, 84 percent used psychotropics or psychostimulants in 1990/91 and 72 percent in 1998/99. Main categories of medications among the elderly with polypharmacy included cardiovascular (90% of the elderly in both surveys), followed second by alimentary tract/metabolic system medications (67% in the first survey), and CNS medications (63% in the second survey). The use of medications for blood/blood-forming organs and the genitourinary system grew most significantly from the first to the second survey among people with polypharmacy (42% to 56% and 10% to 29%, respectively). Of the various subgroups of cardiovascular medications, the use of beta-blocking agents, calcium-channel blockers, agents acting on renin-angiotensin system and statines grew significantly between surveys. For those using musculoskeletal system medications, anti-inflammatory and antirheumatic medication use grew from 80 to 84 percent between surveys.

The same populations were evaluated for their use of psychotropics by Linjakumpu et al. (2002). In the data analysis, psychotropics were divided into four groups: anxiolytics, hypnotics, antipsychotics (including lithium and neuroleptics) and antidepressants. Twenty-five percent of the sample was taking at least one psychotropic drug in both surveys. Fifty percent of subjects 85 and older used psychotropics in 1998/99. Hypnotics/sedatives, which mainly consist of benzodiazepines, were the most commonly used psychotropics in both surveys, and most users were taking them regularly.

In the Linjakumpu et al. (2002) study, the use of hypnotics and antidepressants increased most during the study period. Hypnotics increased from 11 percent to 15 percent between the surveys. The use of short-acting benzodiazepines (midazolam, triazolam) decreased from 7 percent to 2 percent, while the use of non-benzodiazepine sleeping pills (zopiclone, zolpidem) increased from 1 percent to 9 percent. Eleven percent used long-acting benzodiazepines in the first survey and 8 percent in the second survey. They were taken regularly by 57 percent of the users in the first survey and 60 percent of the users in the second survey. The use of benzodiazepines increased only among the oldest subjects, from 25 percent to 28 percent. Concomitant use of two or more psychotropics increased significantly from 7 percent to 10 percent between the surveys. Approximately one-third of all psychotropic users were taking at least two psychotropic medications concomitantly; and the proportion of users of three or more psychotropics was 6 percent in 1990/91 and 8 percent in 1998/99. Of all psychotropic users, 1 percent were taking four or more psychotropics concomitantly in both surveys. Polypharmacy and the use of psychotropics were most prevalent among those 85 and older, with women predominating. Concomitant use doubled from 11 percent to 22 percent among the oldest subjects. Drug users with polypharmacy used psychotropics more commonly (53%) than those without polypharmacy (21%) across both study periods.

Linjakumpu et al. (2002) found that subjects age 64 to 71 used cyclic antidepressants equally commonly in both surveys. A key finding was that none of these subjects used the new atypical antipsychotics in 1998/99. In 1990/91, most users had a combination of a hypnotic/sedative and an antipsychotic medication (3%) while in 1998/99, the most common combination was a hypnotic/sedative and an antidepressant (5%). The authors note that concomitant use of two or more CNS medications (including psychotropics and opioids) is associated with an increased risk of falls more often than the use of CNS-active drugs in general. Linjakumpu et al. (2002) caution that long-acting benzodiazepines and cyclic antidepressants impair cognition, and cause drowsiness in the morning and tiredness in the daytime. Cyclic antidepressants also cause blurring of vision, and may cause symptoms such as parkinsonism.

Mantyselkaet al. (2002) studied multiple medication use among Finnish patients visiting their primary care physicians due to nonacute musculoskeletal pain. Study subjects included 358 adults with a mean age of 54 (37% were 60 or older). The most common pain locations were back, lower extremities, and neck. Half of the patients had scores on the General Health Questionnaire (Goldberg and Williams, 1988) and one-forth had scores on the Beck Depression Inventory [no apostrophe s, according to all sources](Beck and Beck, 1972) indicating depression. Sixty percent of the patients had used prescription drugs and approximately half had used over-the-counter drugs for pain management during the week prior to the office visit. For most analgesics, patients in Finland need a prescription; however, ibuprofen, ketoprofen, paracetamol, and acetylsalicylic acid are available as OTC drugs. Approximately one-third used more than one drug simultaneously due to pain. Depression was associated with the use of multiple medications due to pain, as well as the daily use of medications due to pain. OTC drug use was more common among females and patients who lived alone, than among males and married patients. One of six patients used sedatives or anxiolytics due to pain. The use of anxiolytics or sedatives was more common among older and less educated patients as well as those who were not employed. Mental distress and depression were independently associated with the use of anxiolytics and sedatives. A statistically significant relationship was found between depression and multiple drug use. Depression appeared to be underdiagnosed among study participants, however, as depression was recorded as a secondary reason for the visit for two patients. The authors note that excessive use of anxiolytics and sedatives among patients with prolonged pain may be an indicator of undetected and untreated mental disorders.

The prescription drug use of older, community-dwelling people in Tierp, Sweden, in 1994 was studied by Jörgensen et al. (2001). Prescription drug and diagnosis information were obtained using a computerized research register for all people 65 and older living in the community. Prescriptions purchased outside of the community are not included in the register, resulting in a estimated loss of 5 percent of the data on medication use. There were 4,642 subjects 65 and older residing in Tierp in 1994, 78 percent of whom had at least one prescription filled at the local pharmacies in that year.

Cardiovascular agents were most commonly used among both genders (47.2% of the study sample), with diuretics being the largest subgroup, followed by beta-blockers. Women used more cardiac drugs than men, and the highest use of cardiac drugs was in patients age 75 to 84. Approximately 10 percent of the elderly used cardiac glycosides. Thirty-seven percent of the sample used nervous system drugs, with opioids (14.8%) and hypnotics/sedatives (14.2%) the most commonly used subgroups. Use of anxiolytics was higher among women (17.4%) than men (7.9%). The third largest group of prescription agents was gastrointestinal drugs (34.2% of the

sample) with antiulcer drugs as the largest subgroup. Oral antidiabetic drugs were used by 7.4 percent of the subjects and 2.4 percent used insulin. Respiratory system medications were prescribed for 22.8 percent of the subjects, equally distributed between men and women except in the oldest age group (85+) where men had higher use. Cough preparations was the largest subgroup, with 15 percent of the elderly using prescribed cough suppressants and expectorants. Use of all pharmacologic groups was significantly lower for women 85 and older compared to those 75 to 84, with the exception of nervous system drugs. The largest difference in use was found for cardiovascular drugs and anti-infective agents. A similar trend was shown for the men, except that among the oldest men, use was significantly lower only for cardiovascular drugs (beta-blockers, anticoagulants, and lipid-lowering agents). The differences in prescription drug use between men and women were largest in the youngest age group (65-74), where significantly more women used 9 of the 14 pharmacologic groups than men. In this age group, more men than women used antithrombotic agents. Among the oldest subjects (85+), there were more pharmacologic classes where men had a significantly higher use than women (calcium-channel blockers, antibiotics, respiratory drugs).

In the Jörgensen et al., (2001) study, the average number of prescription drugs per subject was 4.3 (range = 0 to 34). Multiple drug use (5 or more prescription drugs) occurred in 39 percent of the population, with a higher percentage among women than men (43% versus 34%). Almost 13 percent of the sample used 10 or more drugs. It is not known if all the drugs were used simultaneously. Also, the percentage of polypharmacy could be higher if nonprescription drugs were taken into account. A multivariate analysis showed that the number of primary care visits was the greatest determinant of multiple drug use. Visiting a physician 5 times or more during the year increased the risk of using 5 or more different drugs by approximately 15 times compared with not being seen. A large number of diagnoses also increased the risk for multiple drug use. The authors note that the strong relationship could imply that the elderly were seriously ill and needed frequent follow-up and extensive drug therapy. Since the data is cross-sectional, it could also be that multiple drug use had consequences that made the elderly seek care.

In a survey of 636 drivers stopped randomly by police in Denmark and asked to take home a survey to complete and return, 5.8 percent indicated that they had used a medicinal or illegal drug within the 24-hour period prior to being stopped (Behrensdorff and Steentoft, 2002). Among them, 3 percent had taken hypnotics, tranquilizers, or analgesic drugs (e.g., "hazardous medicinal drugs"). One driver reported using cannabis. The remaining 2.8 percent reported the use of other types of "non-hazardous"[20] drugs such as drugs for high blood pressure, stomach ulcer, etc. In this study, 44 percent of the respondents were 45 or older; however, the ages of the drivers reporting having used a medicine in the prior 24-hour period were not reported. In response to the question, "Do you ever drive a few hours after having had both a hazardous medicinal drug and alcohol," 31 of the 361 respondents (8.5%) reported "yes" or "occasionally." Of these respondents, 19.3 percent were 18 to 24; 22.6 percent were 24 to 44; and 48.4 percent were 44 and older. The distribution by gender for driving after consuming alcohol and a hazardous drug showed that 84 percent of these respondents were men and 16 percent were women.

[20] In Denmark, hazardous medicinal drugs include all types of drugs that are considered a potential hazard in relation to road safety or machine handling. Such drugs are labeled with a red triangle and have a package information insert.

PHYSIOLOGICAL EFFECTS

Introduction

Polypharmacy may lead to drug interactions, *i.e.*, the alteration of clinical drug responses by the prior or concomitant administration of two or more drugs. Drug interactions may be additive, synergistic, or antagonistic. Furthermore, while drug interactions may be harmful, they also may be beneficial in achieving desired pharmacological and clinical effects.

Approximately 150 antihypertensive[21], anti-arrhythmic[22], and inotropic[23] medications—which are used to treat cardiovascular conditions—interact with alcohol. Pain killers, antihistamines, tranquilizers, anticoagulants, and antidiabetic drugs also react negatively to alcohol (Cadieux, 1989; Lamy, 1988). Interactions can produce additive, synergistic, or inhibitory effects. Alcohol and other drugs may compete for enzyme metabolism in the liver, either negating the effect of the medication or increasing the effect. Depressants such as benzodiazepines are especially affected by alcohol in this manner, as are antipsychotics, some anti-depressants, anti-coagulants, oral hypoglycemics, anti-seizure compounds, and anti-hypertensive agents. Older people who are experiencing this effect may show heightened confusion, memory loss, dizziness, incontinence, and death from a central nervous system shutdown (Pollow, Stoller, Forster, and Duniho, 1994; Lamy, 1988; Briggs, Castleden, and Kraft, 1980). Alcohol and medication use even 10 hours or more apart from each other can significantly alter the effects of the medication in the same manner that multiple medication use can cause interactions (Lazow, 2001).

There are three broad types of drug interactions: pharmaco*dynamic* drug interactions, pharmaco*kinetic* drug interactions, and physical or chemical drug interactions.

Pharmacodynamic drug interactions are usually associated with drug-drug interactions at the therapeutic target or receptor. For example, compounds may compete directly for binding to a common receptor. The administration of two drugs with anticholinergic effects, such as an antiparkinsonian drug (*e.g.*, trihexyphenidyl), and a tricyclic antidepressant (*e.g.*, amitriptyline), may result in excessive anticholinergic effects.

Pharmacokinetic drug interactions are the result of alterations in drug *absorption*, *distribution*, *metabolism*, or *elimination*. Most pharmacokinetic drug interactions are associated with altered drug metabolism, particularly with cytochromes P450 (CYPs) although other enzyme systems are also involved in pharmacokinetic drug interactions.

Physical or chemical drug interactions are the consequence of the interaction of two drugs, *e.g.*, cholestyramine and warfarin, or with OTC drugs and prescribed drugs, *e.g.*, magnesium-aluminum-based hydroxide antacids and fluoroquinolone antibiotics. Physical or chemical drug interactions often lead to therapeutic failure.

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[21] Antihypertensive drugs are medicines that help lower blood pressure.
[22] Anti-arrhythmic drugs are medicines that correct irregular heartbeats and slow down hearts that beat too fast.
[23] Inotropes are drugs that make the heart beat more strongly.

Physiological Changes That Affect How Older People Metabolize Medications

A range of physiological changes that may affect drug metabolism occurs with age. The liver plays a central role in the termination of drug action and has, therefore, been well studied. Liver size or volume and hepatic blood flow both decrease with age, but these changes are not associated with changes in liver structure (Schmucker, 2001; Zeeh, 2001). Other physiological changes that occur with aging include reduced body mass and basal metabolic rate, reduced proportion of body water, increased proportion of body fat, decreased cardiac output, altered relative tissue perfusion, decreased plasma protein binding, reduced gastric acid production and gastric emptying time, and reduced gut motility and blood flow (see Table 1, Herrlinger and Klotz, 2001).

Although the effect of aging on human drug metabolism has been much studied, few generalizations about how aging affects human drug metabolism have emerged. Such studies are complicated by several factors, including the heterogeneity of the aged population, genetic polymorphisms[24] of human drug-metabolizing enzymes, and the methodologies and selection of drugs used to quantify drug metabolism. The evaluation of *in vivo* human drug-metabolism is best expressed by the pharmacokinetic term clearance (Cl) and, more specifically, by the plasma clearance (Cl_p) (Herrlinger and Klotz, 2001). Cl_p is the virtual volume of plasma cleared of drug in a unit of time and is, therefore, related to the volume in which the drug is distributed (V_d) and the rate at which it is eliminated (k_{el}). Hence, $Cl_p = (V_d)(k_{el})$ and has the dimensions of (volume) $(\text{time})^{-1}$, *i.e.*, mL min^{-1}.

The interpretation of the clearance of a drug must also be tempered by several factors, including Phase-I versus Phase-II metabolism, activity of metabolizing enzymes, degree of hepatic extraction, extent of protein binding, hepatic blood flow, liver size or volume, and extent of extrahepatic drug metabolism (Brenner et al., 2003). Given the range of variables that affect the interpretation of human drug metabolism, it is not surprising that the literature is inconsistent on whether aging significantly affects drug metabolism.

Drug-metabolism reactions have traditionally been described as Phase-I and Phase-II reactions. The liver plays a central role in both Phase-I and -II drug-metabolism reactions, but significant extrahepatic drug metabolism also occurs. (Indeed, significant drug-metabolizing capacity is present in the intestine; the inactivation of intestinal drug-metabolizing enzymes by grapefruit juice is the basis of the increased bioavailability of some drugs (Dahan and Altman, 2004)). Phase-I reactions are functionalization reactions that insert or unmask functional groups, *e.g.*, a hydroxyl group. Cytochrome P450-catalyzed oxidative reactions are the most common Phase-I reactions, but other oxidative as well as reductive and hydrolytic reactions are also important for some drugs. Phase-II reactions enzymatically couple a drug or, more commonly, a drug metabolite produced by a Phase-I reaction with an endogenous acceptor molecule.

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[24] Genetic polymorphisms are defined as variations (mutations) in DNA that are observed in 1 percent or more of the population. Variability in the level of expression or function of enzymes, responsible for metabolizing most prescription medications, can have a profound effect on drug efficacy. Some genetic polymorphisms lead to deficiency of these enzymes in some individuals, which can result in an increased risk of concentration-related toxicity. In other individuals polymorphisms enhance enzyme activity, resulting in lower drug concentration, and decreased response to therapy. For drugs such as codeine, which must be activated by enzymes in the body, an inherited deficiency in the activating enzyme can markedly reduce drug response (such is the case for 6% to 10% of Caucasians). Source: http://www.signaturegenetics.com/sgtiles/en/download/physician_nb_5684.pdf

Glucuronide formation is most common Phase-II reaction. Significantly, both Phase-I and -II drug metabolism reactions yield products that are usually less active pharmacologically and more polar and, therefore, readily excreted. Hence, Phase-I and -II drug-metabolism reactions play a major role in the duration and termination of drug action.

As indicated above, reactions catalyzed by the cytochromes P450 family of enzymes are highly important for human drug metabolism. There are more than 50 known genes (*CYP*s) that encode the human cytochromes P450s (CYPs),[25] but approximately 15 CYPs are involved in drug and chemical metabolism and of these only six subfamilies (CYP1A, CYP2A, CYP2C, CYP2D, CYP2E, and CYP3A) are important for human drug metabolism (Kinirons and O'Mahony, 2004).

Some recent examples suffice to illustrate approaches taken to evaluate the role of the cytochromes P450 in human drug metabolism. Gorski, Vannaprasaht, Hamman, Ambrosius, Bruce, Haehner-Daniels, and Hall (2003) studied the effect of age, sex, and rifampin[26] administration on intestinal and hepatic cytochromes P450 3A (CYP3A) activity with midazolam[27] as the substrate. CYP3A catalyzes the metabolism of, say, 50 percent of clinically used drugs and is, therefore, of much importance. Rifampin is a well-known inducer of CYP3A, *i.e.*, it produces a marked increase in the activity of CYP3A. The authors observed that there was no significant difference in the systemic clearance of midazolam between young (fourteen females: 26 ± 4 years; fourteen males: 27 ± 4 years) and elderly (fourteen females: 72 ± 5 years; ten males: 70 ± 4 years) subjects and between male and female subjects. Rifampin markedly increased the clearance of midazolam in both old female and male subjects, but marked interindividual variability in the extent of induction by rifampin was observed.

Brenner et al. (2003) studied the effect of age (twelve males aged 31.7 ± 5.0 and twelve males aged 68.3 ± 2.1 years) and CYP2C9 genotype on the steady-state disposition of diclofenac[28] (a nonselective COX inhibitor) and celecoxib[29] (a selective COX-2 inhibitor). No age effect on the clearance of either diclofenac or celecoxib was observed. The area-under-the-curve (AUC)[30] for diclofenac was lower in the elderly subjects than in the younger subjects, but this was attributed to the higher bodyweight of the elderly subjects. Similarly, no association between CYP2C9 genotype and disposition of the study drug was observed.

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[25] http://drnelson.utmem.edu/cytochromep450.html.

[26] Rifampin is used to treat certain bacterial infections. It is used with other medicines to treat tuberculosis. Rifampin is also taken by itself by patients who may carry meningitis bacteria in their noses and throats (without feeling sick) and may spread these bacteria to others.

[27] Midazolam is used to produce sleepiness or drowsiness and to relieve anxiety before surgery or certain procedures. It is also used to produce loss of consciousness before and during surgery.

[28] Diclofenac is used to relieve the pain, tenderness, inflammation (swelling), and stiffness caused by osteoarthritis and rheumatoid arthritis and ankylosing spondylitis. It is in a class of medications called nonsteroidal anti-inflammatory medications (NSAIDs), and works by stopping the body's production of a substance that causes pain and inflammation.

[29] Celecoxib is used to relieve the pain, tenderness, inflammation (swelling), and stiffness caused by arthritis and to treat painful menstrual periods and pain from other causes. It is also used to reduce the number of polyps in the colon and rectum in patients with a disease called familial adenomatous polposis. Celecoxib is in a class of NSAIDs called COX-2 inhibitors that work by stopping the body's production of a substance that causes pain and inflammation. COX-2 inhibitors may cause less stomach bleeding and ulcers than similar medications.

[30] AUC plots the plasma drug concentration against time and is a measure of the bioavailability of the drug. It has the dimensions of time × concentration.

Greenblatt et al. (2004) investigated the effect of age on the pharmacokinetics of triazolam, which is metabolized by CYP3A. The 61 male and female subjects were divided into three groups each: young males (29 ± 1.6 years), intermediate-aged males (47 ± 1.6 years), and elderly males (67 ± 1.5 years); young females (29 ± 1.6 years), intermediate-aged females (44 ± 1.9 years), and elderly females (68 ± 1.5 years). No difference in the clearance of triazolam was found among the groups of female subjects. In male subjects, however, no difference in the clearance of triazolam was found between the young and elderly groups, but, when age was evaluated as a continuous variable, the AUC increased with age and the clearance decreased with age, indicating increased bioavailability and decreased elimination of triazolam, which could lead to drug accumulation and adverse reactions.

Herrlinger and Klotz (2001), Schmucker (2001), and Kinirons and O'Mahony (2004) have reviewed the relationship between age and human drug metabolism. These authors conclude that although some measures of drug metabolism are diminished in the elderly, significant interindividual variability in drug metabolism, drug action, and adverse reactions characterizes the elderly population.

While few generalizations are possible in this area, the data presently available do <u>not</u> allow us to dismiss or disregard the potential effects of aging on drug metabolism.

EFFECTS ON DRIVING ABILITY

This section of the report begins with a general overview of medication use and crash risk. Next, recently conducted epidemiological and experimental studies conducted to determine the consequences of a single class of medication on the ability to drive safely are reviewed. These studies are limited to the medications most frequently used by the older community-dwelling population (benzodiazepines, opioids, antidepressants, and antidiabetics). It concludes with three studies that analyzed multiple medication use as follows: one study that evaluated medication use and fitness to drive, one evaluation using a pharmacy database linking a recent crash event to medication use, and one study evaluating substances found in the blood of drivers killed in crashes. Unfortunately, there is a dearth of research on the effects of combinations of specific medications or even combinations of drug classes on driving ability per se.

In theory, all psychoactive compounds (depending on dose), may have detrimental effects on psychomotor performance underlying driving skills (Walsh, de Gier, Christopherson, and Verstraete, 2004). The most common psychoactive substances can be divided into depressants (e.g., alcohol, sedatives/hypnotics, volatile solvents), stimulants (e.g., nicotine, cocaine, amphetamines, ecstasy), opioids (e.g., morphine and heroin), and hallucinogens (e.g., PCP, LSD, cannabis). For some drugs, the effect may be evident for acute use, but may become reduced after tolerance has developed (Morland, 2000). Carr (2004) states that in this era of polypharmacy, there are a myriad of sedating medications that could contribute to driving impairment. A simple drug review may identify benzodiazepines, anticholinergics, narcotics, alcohol, or other medications that, once discontinued, may decrease crash risk.

In Wilkinson and Moskowitz's (2001) review of 11 epidemiological studies of medication use and traffic safety risk (primarily in older drivers) in the United States and Canada between 1991-2000, it was concluded that the prescription drugs most likely to be associated with motor vehicle crashes by older drivers include the same CNS medications found to increase

risk in adults younger than age 65—namely, benzodiazepines (especially long-acting), cyclic antidepressants, and opioid analgesics. Further, they cite a study by Stuck et al. (1994) who found that depressed, community-dwelling elderly were eight times as likely as their nondepressed counterparts to be prescribed a long-acting benzodiazepine in addition to their antidepressant medication.

Depressants: Benzodiazepines

Walsh et al. (2004) point to Berghaus and Grass (1997), who summarized more than 500 experimental studies in which the effects of benzodiazepines on driving-related performance were assessed. Benzodiazepines are central nervous system depressants used therapeutically to produce sedation, induce sleep, relieve anxiety and muscle spasms, and to prevent seizures (Jones, Shinar, and Walsh, 2003). The correlation between serum benzodiazepine concentrations and performance deficit for most of the benzodiazepines investigated was almost linear. On-road driving tests using different benzodiazepines and zopiclone[31] demonstrated adverse effects on the standard deviation of lateral position (a measure of lane keeping). Subjects tested the morning after using benzodiazepines as hypnotics showed impairment comparable to a BAC of .05 to .10 (O'Hanlon, et al., 1986). [FYI we no longer use "percent" relative to BAC numbers. Would be glad to discuss with you the reason, if you are interested.] Walsh et al. (2004) state that based on the present knowledge, benzodiazepines constitute a considerable risk to traffic safety, both in therapeutic doses and to a much higher degree at higher doses.

Depressants: Opioids

Opioid drugs are central nervous system depressants, used in the treatment of cancer pain and chronic nonmalignant pain. Although there is common acceptance that opioid-naïve patients should be instructed not to drive, there is controversy surrounding recommendations that should be made to patients taking stable opioid doses. Fishbain, Cutler, Rosomoff, and Rosomoff (2003) conducted a structured, evidence-based review of the literature between 1966 and 2001 to determine whether opioids affect the driving ability of patients who are on stable doses of this medication or who would be presumed to have developed some tolerance to the sedative effects of opioids. Twenty-three studies on the effects of stable opioid doses on psychomotor abilities were reviewed. Results indicated that 16 (70 percent) of the studies supported a conclusion of no effect on psychomotor abilities. This indicates "moderate evidence, generally consistent findings" of no impairment of psychomotor abilities according to Agency for Health Care Policy and research (AHCPR) guidelines (Institute of Medicine Committee to advise the Public Health Service on Clinical Practice, 1990).

Fishbain et al. (2003) reviewed 11 studies on the effects of stable doses of opioids on cognitive abilities. Only 5 (45 percent) of these studies supported a conclusion of no effect on cognitive function. The evidence on the effects of stable doses of opioids on the cognitive abilities necessary for safe driving may therefore be regarded as "inconclusive" according to AHCPR guidelines.

[31] Zopiclone (brand name: Imovane) belongs to the group of medicines called central nervous system (CNS) depressants (medicines that make you drowsy or less alert). This medicine is used to treat insomnia (trouble in sleeping).

Fifteen studies were reviewed to determine the effects of new opioid dosing on psychomotor abilities (Fishbain et al., 2003). As 14 (93 percent) of the studies supported a conclusion of no effect on psychomotor function, it was concluded that there was "strong evidence, consistent findings" of no impairment of psychomotor abilities for acute opioid administration, using the quantitative method described by the AHCPR guidelines.

Fishbain et al. (2003) reviewed seven studies to determine the effect of stable opioid dosing on motor vehicle crashes, violations, and convictions compared to the general population. As 6 (86 percent) of the studies supported no effect, this indicated "strong evidence, consistent findings" of no more crashes, convictions, or violations among opioid-dependent patients as compared to the general population.

Four studies were reviewed by Fishbain et al. (2003) to determine whether there were impairments on driving for patients on stable opioids, compared to controls, using driving simulators or on-road driving measures. As 3 of the 4 studies (75 percent) supported a conclusion of no effect, this indicated "strong evidence, consistent findings" for no impairment of driving performance, using simulator or on-road measures.

Fishbain et al. (2003) suggest that there may have been confounding variables to explain the inconsistent evidence in the cognitive impairment studies, which could have also confounded the results of the studies reviewed on psychomotor abilities, crashes/convictions/violations, and driving performance in simulators and on-road. Confounding factors include pain level (e.g., higher levels of pain interfere with psychomotor/cognitive function), education level, disease state (disease-associated symptoms such as fatigue), and history of drug/alcohol abuse or dependence.

Of particular interest to the present review, Fishbain et al. (2003) provided recommendations about how future research on the effects of opioid drugs and driving ability can be improved. First, future psychomotor and cognitive studies should control for pain, educational status, and history of drug/alcohol abuse/dependence, besides controlling for sex and age. In addition, studies can be improved by using different types of control groups. In the reviewed studies, a treatment group (patients placed on opioids) was compared to a control group (patients not on opioids). This leads to a situation where the effects of a patient's disease state (e.g., cancer/fatigue, pain, etc.) are not controlled for. A better control group could be to use the patients as their own controls. Then, psychomotor and cognitive studies could be performed pre-opioid placement and post-opioid placement and compared. Of the 3 studies reviewed with this design, all 3 found no opioid effect on cognitive or psychomotor abilities. Another possible improvement recommended to this type of research is to include a patient control group. In this case, include a cancer patient opioid-free control group to compare to the cancer patients placed on opioids *and* to a control group of opioid-free nonpatients. A final improvement (Zacny, 1995) is the use of a positive control as a benchmark. In this instance, a patient would be given drugs that are known to affect cognitive and psychomotor performance, such as diazepam. Opioid effects would then be compared not only to opioid-free controls, but to this positive control group. This has the advantage of comparing opioid impairment (if any) to a benchmark.

Antidepressants

Antidepressants are prescribed most often for clinical depression and severe cases of depression. Jones, Shinar, and Walsh (2003) provide a breakdown of the subclasses of antidepressants with examples. Subclasses include: the tricyclic antidepressants (e.g., amitriptyline and doxepin); the serotonin-specific reuptake inhibitors (SSRI) including fluoxetine (Prozac); monoamine oxidase inhibitors (MAOIs), including phenelzine (Nardil); and several new drugs such as venlafaxine (Effexor) and nefazodone (Serzone). With regard to antidepressants, Walsh et al. (2004) cites EMCDDA (1999) who reviewed controlled experimental studies and concluded that impaired performance is associated with the use of most sedative tricyclic antidepressants. New-generation antidepressants do not seem to interfere with performance, except when used at higher doses. Analytical epidemiological studies, using predominantly older drivers, have documented increased crash risks, with a relative risk of 2.3 [something missing here, like "according to"]Leveille, Buchner, Koepsell, McCloskey, Wolf, and Gagner (1994).

Ramaekers (2003) summarized the major results of all studies published from 1983 to 2000 that investigated the effect of antidepressants on driving performance. This report considered two broad classes of antidepressants: *sedating* antidepressants, i.e., drugs developed for the management of depression that have depressant side effects, and *nonsedating*, i.e., drugs developed for the management of depression that lack significant sedating effects. The sedating antidepressants are the tricyclic antidepressants amitriptyline, imipramine, and doxepin and the related compounds mianserin and mirtazapine. Examples of nonsedating antidepressants include the monoamine oxidase inhibitor moclobemide, the selective serotonin reuptake inhibitors fluoxetine, paroxetine, and nefazodone, and the serotonin and norepinephrine uptake inhibitor (SNRI) venlafaxine.[32] The effect of antidepressants on driving behavior was assessed with the standard deviation of lateral position (SDLP) test. A detailed description of this methodology for measuring driver performance follows in the section of this report titled "On-Road Testing."

Ramaekers (2003) found that acute doses of sedating antidepressants produced effects in the SDLP that were comparable to those seen in subjects with a blood alcohol concentration of .08 grams per deciliter. [fyi: just to keep the terminology consistent] The tricyclic antidepressants had little effect on the SDLP after one week of treatment, but the effect of mianserin persisted throughout the treatment period. Nocturnal doses of sedating antidepressants did not alter the SDLP when assessed the next day after treatment. The nonsedating antidepressants failed to alter the SDLP. Increases in the SDLP were, however, observed after the combined use of nonsedating antidepressants and benzodiazepines; these effects were attributed to pharmacokinetic drug interactions: Effects were seen when the cytochromes P450-dependent metabolism of the benzodiazepine was inhibited by the antidepressant given.

Lithium is used for the treatment of bipolar disorder, but its use is associated with impaired memory and slow reaction times (Honig et al., 1999). A recent case-control study of 5,579 subjects age 67 to 84 found that the current use of lithium was higher (rate ratio = 2.08) among subjects who had been involved in an injurious motor vehicle crash compared with

[32]It should be noted that although Ramaekers (2003) categorized paroxetine and nefazodone as nonsedating, in practice they are considered to be sedating. Personal communication from Richard Marottoli , M.D., M.P.H., Yale University School of Medicine to Kathy Lococo, 7/20/2005.

control subjects (Etminan et al., 2004). No information about drug interactions with lithium was reported in this study.

Antidiabetic Agents

Hypoglycemia is a common adverse effect of insulin treatment in people with diabetes, potentially leading to cognitive impairment, altered levels of consciousness, and delayed reactions (Diamond, Collins, and Rohl 2005). If such reactions occur while operating a motor vehicle, a crash is likely. These authors note that the gold standard of care recommended by the American Diabetes Association for the strict glycemic control of individuals with Type I diabetes to prevent long-term complications of the disease is not without risk, and has the potential to result in more frequent and catastrophic hypoglycemia.[33] Diabetic drivers are potentially at increased risk for motor vehicle crashes as a result of both their therapy (insulin induced hypoglycemia) and diabetic complications (e.g., retinopathy with visual disturbances).

Szlyk et al. (2004) queried 25 licensed drivers age 34 to 72 with diabetic retinopathy regarding the number of crashes in which they had been involved in the prior 5-year period. Blood was also drawn to determine glycosylated hemoglobin levels[consider adding: "also known as the A1c test or the glucose tolerance test"?]. Unlike blood glucose levels that vary between days, glycosylated hemoglobin levels measure hyperglycemia over a period of 2 to 3 months, and have been shown to predict the progression of diabetic retinopathy. The mean glycosylated hemoglobin level was 9.2 percent, with a range of 6.4 percent to 11.6 percent. Szlyk et al. (2004) report that the normal range of glycosylated hemoglobin in nondiabetic individuals is 4.0 to 6.0 percent, and that the American Diabetes Association recommends a target goal of less than 7.0 percent for diabetic patients. Nineteen of the 25 subjects in the study had glycosylated hemoglobin levels greater than 7.0 percent. Subjects who had one or more crashes within the past 5 years had a significantly higher glycosylated hemoglobin level than those not reporting crashes. The authors concluded that the majority of the study group had not achieved the target level for glycosylated hemoglobin recommended by the American Diabetes Association, which mirrors the findings of epidemiologists who indicate that the majority of people with diabetes do not achieve a target goal for glycosylated hemoglobin (Klein et al., 1988). This puts them at higher risk of the progression of diabetic retinopathy, as well as at higher risk of automobile crashes.

[33] HbA1C measurements of less than 7.2% and average blood glucose levels of approximately 8.0-8.5 mmol/L.

Multiple Medications

Visual, cognitive, or psychomotor impairments associated with a range of drug groups and specific drug combinations have been investigated. Although several drug groups are represented, interactions among drugs that affect the central nervous system are the most common. There are, however, relatively few studies that report the effects of combinations of mediations specifically on driving performance, although some related studies do provide insight. For example, a history of falls is associated with difficulty in driving (Lyman et al., 2001), and falls in the elderly are associated with the use of psychotropic drugs (Riefkohl, Bieber, Burlingame, and Lowenthal, 2003). In patients who failed to respond to treatment with the SSRI paroxetine and who received augmentation therapy with bupropion,[34] an increased risk of falls was seen (Joo et al., 2002). Katona (2001) has reviewed briefly drug interactions that occur with psychotropic drugs, including antidepressants, mood stabilizers, antipsychotics, and cholinesterase inhibitors. Indeed, the concomitant use of the cholinesterase inhibitor donepezil and other anticholinergics was found to be relatively common in a cohort of community-based older adults with probable dementia (Roe, Anderson, and Spivack, 2002).

As indicated elsewhere in this document, the use of sedating antidepressants is associated with driving impairment in the elderly (Ramaekers, 2003). A recent review notes a large number of clinically significant drug interactions with antidepressants in the elderly (Spina and Scordo, 2002); for example, tricyclic antidepressants and monoamine oxidase inhibitors have a high potential for pharmacodynamic drug interactions with a range of drugs, including benzodiazepines, antipsychotic agents, and other antidepressants. The newer antidepressants, such as SSRIs, SNRIs, and so-called dual-action compounds, *e.g.*, mirtazepine, exhibit fewer drug interactions than the sedating antidepressants and long-acting benzodiazepines, but pharmacokinetic drug interactions may be seen (Sheikh, 2004). Orthostatic hypotension[35] is an adverse effect seen with some antidepressants, particularly the tricyclic antidepressants and some of the so-called atypical antidepressants (Keene, Galasko, and Land, 2003). Some medications that may be prescribed along with antidepressants that may increase the risk of dizziness, syncope, and falling include antipsychotics, anxiolytics, hypnotics, opioid analgesics, diuretics, and other antihypertensive medications.

Benzodiazepine use is widespread among older adults (Gray et al., 2003); in a population of 1,505 enrollees in a health-maintenance organization (average age of 72.5; 59 % female), the prevalence and incidence of benzodiazepine use was 12.3 percent and 6.6 percent, respectively. In a cohort of 78,367 elderly subjects (average age of 73.6; 55.7 % female) in Quebec, Canada, 45 percent filled a prescription for a benzodiazepine (Bartlett, Abrahamowicz, Tamblyn, Grad, Capek, and du Berger, 2004). The mean duration of benzodiazepine use was 75.5 days.

Although the risks for traffic crashes associated with the use of benzodiazepines and related compounds have been established (for a review, see Vermeeren, 2004), little information is available about the interaction of benzodiazepines and other drugs, except alcohol. In a study of 269 patients involved in traffic crashes and admitted to the emergency room of the University Hospital of Trauma Surgery in Innsbruck, Austria, both alcohol and a benzodiazepine was

[34] Bupropion (brand name "Wellbutrin") is an antidepressant that is a norephinephrine/dopamine reuptake inhibitor.
[35] Orthostatic hypotension consists of symptoms of dizziness, faintness or lightheadedness which appear only on standing, and which are caused by low blood pressure.

present in the blood of 2.3 percent of the patients older than 60 (Kurzthaler et al., 2003). All plasma benzodiazepine concentrations were stated to be within the therapeutic range. A combination of both alcohol and psychotropic drugs was found to be involved in approximately 10 percent of the cases in a study of 3,398 fatal motor vehicle crashes in three Australian states, but the data did not allow assessment of the role of benzodiazepines (Drummer et al., 2003; Drummer et al., 2004).

In a study in The Netherlands, benzodiazepines were found to increase the risk of motor vehicle crashes. The adjusted odds ratio for benzodiazepine use amounted to 5.1 (95% CI: 1.8–14.0). Although 14 percent of the subjects in the 110 cases studied were 50 or older, the incidence of the use of both alcohol and benzodiazepines in this age group was not reported (Movig et al., 2004).

The roles of medical conditions and medications in automobile crashes in the elderly have been investigated (McGwin, Sims, Pulley, and Roseman, 2000). The cohort included 901 drivers in Alabama, and of these, there were 244 at-fault drivers, 182 not-at-fault drivers, and 475 drivers not involved in crashes. Older drivers (65 or older; 50.4 percent females) with heart disease or stroke were more likely to be involved in at-fault automobile crashes; benzodiazepine use was also associated with at-fault crash involvement (OR = 5.2, CI = 0.9–30.0), but the involvement of both benzodiazepines and other drugs was not reported.

A review of 170 positive lorazepam[36] drug-impaired driving cases in Washington was conducted (Clarkson, Gordon, and Logan, 2004). Eighty-six percent of the drivers tested positive for other drugs in addition to lorazepam, including muscle relaxants (meprobamate, carisoprodol), painkillers (methadone, hydrocodone), and alcohol; the contribution of the other drugs to drug-impaired driving was not investigated, and the ages of the drivers who tested positive for lorazepam and other drugs were not reported.

Del Rio and Alvarez (2003) evaluated the relationship between medicinal drug use and fitness to drive for 8,043 drivers attending Medical Fitness to Drive Test Centers. Spain is the only country in the European Union where it is compulsory for all new and renewing drivers to take a medical-psychological test prior to licensure. In the Medical Driving Test Centers, medical, eyesight, and psychological tests are conducted to assess fitness to drive (del Rio and Alvarez, 2001). Road tests are not part of the battery. A team of professionals working in the centers is comprised of a general practitioner, an ophthalmologist, and a psychologist. These professionals analyze aspects of sight, hearing, the locomotor system, cardiovascular diseases, diabetes mellitus, neurological disease, mental disorders, problems relating to alcohol, drugs, and medicinal products, and renal disorders. In addition, the following perceptual-motor skills are evaluated: time-movement anticipation, senso-motor coordination, and multiple reaction times. As a result of the evaluation, drivers are classified as either fit, fit with restrictions (e.g., medical-psychological check-up required at regular intervals, more frequent intervals, or vehicle adaptation), suspended for a period of time, or unfit (permission to drive is irrevocably refused for medical, psychological, or ophthalmologic reasons).

[36] Lorazepam (brand name: Ativan) is a benzodiazepine with CNS depressant, anxiolytic and sedative properties, used to relieve anxiety. Lorazepam is also used to treat irritable bowel syndrome, epilepsy, insomnia, and nausea and vomiting from cancer treatment, and to control agitation caused by alcohol withdrawal.

Analyses reported by del Rio and Alvarez (2003) showed that 24.7 percent of the drivers chronically consumed medications (used them daily for at least one month) with men consuming more medications, and medication use increasing with increases in age. Fifty-six percent of the drivers 65 and older took medications on a daily basis, and 25 percent of these reported taking medicines and drinking alcohol daily. The mean number of medications consumed among chronic users across all age groups was 1.28. The mean number consumed by drivers 65 and older was 1.42. The therapeutic groups most frequently consumed were: cardiovascular system (7.8 percent of the sample), followed by alimentary tract and metabolism (4.8 percent), and central nervous system (4.3 percent). For 20 percent of the medication-used-chronically group, there was a warning in the Summary of Product Characteristics about the effect of the medication on driving. Of the drivers considered "fit," 22 percent were taking medications with a warning. Of those considered "fit with restrictions," 38 percent were taking medications with a warning. Of the drivers considered "suspended," 51 percent were taking medications with a warning. Of the drivers who were taking medicines chronically and were deemed "unfit to drive," 100 percent (n=9) were taking medications that had a warning about driving. All nine also suffered from a pathology that could interfere with fitness to drive. The medications being taken by the nine subjects deemed "unfit to drive" were as follows (with three of the nine cases also having a diagnosed dependence on alcohol):

- Case 1: tricyclic antidepressant drug
- Case 2: tricyclic antidepressant drug + long-acting benzodiazepine
- Case 3: long-acting benzodiazepine
- Case 4: first-generation antihistamine H-1 drug
- Case 5: antipsychotic drug
- Case 6: antiepileptic drug
- Case 7: antihypertensive drug + nonsteroidal anti-inflammatory drug
- Case 8: antihypertensive drug + nonsteroidal drug + hypouricemic drug
- Case 9: antihypertensive drug + nonsteroidal anti-inflammatory drug + hypolipidemic drug + antiarrhythmic drug

The percentage of "unfit to drive" cases increased with the number of medications consumed (1 drug = 0.3%, 2 drugs = 0.5%, 3 drugs = 1.2 %, and 4 drugs 9.1 %) as did the percentage of those found "fit with restrictions" (1 drug = 16.2%, 2 drugs = 21.2%, 3 drugs = 43.2%, and 4 drugs = 45.3%).

In Leroy's (2004) case-control analysis using a pharmaceutical claims database with codes indicating services rendered as the result of a motor vehicle crash, higher percentages of crash-involved drivers were prescribed two or more prescriptions than non-crash-involved drivers. Potentially driver-impairing (PDI) medicines were used by greater percentages of crash-involved drivers than by non-crash-involved drivers (e.g., narcotic analgesics, skeletal muscle relaxants, anti-anxiety medications, NSAIDs, and COX inhibitors). The most-frequently appearing drug combinations (in descending order of frequency) in the group of crash-involved drivers 50 and older were:

- Narcotics + Non-Steroidal Anti-Inflamatory Drugs (NSAIDs)
- Skeletal Muscle Relaxants + NSAIDs
- Narcotics + Skeletal Muscle Relaxants

- Narcotics + Skeletal Muscle Relaxants + NSAIDs
- Narcotics + Antibiotics
- Gastric Acid Secretion Reducers + Narcotics
- Anti-Anxiety Drugs + Narcotics
- Serotonin Reuptake Inhibitor (SSRI) Antidepressants + Narcotics
- Narcotics + NSAIDs + Antibiotics

Preliminary results of Leroy's (2004) analysis indicate that 64 percent of the drivers 50 and older who had a motor vehicle crash had received a prescription for a potentially driver-impairing (PDI) medication within the prior 60 days. This compares to 54 percent of the non-crashed involved drivers 50 and older. To qualify as a PDI medication, the medication had to be associated with known effects on the central nervous system, blood sugar levels, blood pressure, vision, or otherwise have the potential to interfere with driving skills. Possible PDI effects include sedation, hypoglycemia, blurred vision, hypotension, dizziness, fainting (syncope), and loss of coordination (ataxia). Preliminary results are suggestive that the following medications are impairing and related to crash risk: narcotic analgesics, antidepressants, antidiabetic agents, anti-anxiety agents, antihypertensive agents, and skeletal muscle relaxants.

In a study conducted in Spain by del Rio, Gómez, Sancho, and Alvarez (2002), some type of psychoactive drug was detected in 50.1 percent of the 5,745 drivers killed in traffic crashes between 1991 and 2000, with alcohol the most prevalent (43.8%), followed by illicit drugs (8.8%) and medicinal drugs (4.7%). Among the medicinal drugs were benzodiazepines (3.4%), antidepressant drugs (0.6%), and analgesics (0.4%). In the sample, 92 percent were males and 8 percent were females; 10 percent were under age 20, 31 percent were between 21 and 30, 19 percent were between 31 and 40, 13 percent were between 41 and 50, 9 percent were between 51 and 60, and 11 percent were over 60. Age was unknown in the remaining 7 percent. Blood samples were analyzed for alcohol. All samples were also screened for the presence of illicit and medicinal drugs. Positive results after screening were confirmed by gas chromatography—mass spectrometry (GC—MS) and concentrations of psychoactive drugs or metabolites were determined.

Results indicated that in 49.9 percent of the cases (2,868), no substance was detected, and in 50.1 percent of the cases (2,877) some type of psychoactive substance was detected. Of the cases in which some psychoactive substance was detected, the following combinations of substances were found:

- Alcohol alone = 38.2 percent of the cases
- Alcohol + illicit drugs = 4.0 percent of the cases
- Alcohol + medicinal drugs = 1.2 percent of the cases
- Alcohol + illicit drugs + medicinal drugs = 0.4 percent of the cases
- Illicit drugs alone = 3.2 percent of the cases
- Illicit drugs + medicinal drugs = 1.2 percent of the cases
- Medicinal drugs alone = 1.9 percent of the cases

Considering the 4.7 percent (269 of the 5,745 drivers) with medicinal drugs, the following combinations were found:

- Medicinal drugs alone = 1.9 percent of the cases
- Medicinal drugs + illicit drugs = 1.2 percent of the cases
- Medicinal drugs + alcohol = 1.2 percent of the cases
- Medicinal drugs + illicit drugs + alcohol = 0.4 percent of the cases

In 59.1 percent (159 of the 269) cases in which medicines were found, alcohol and/or illicit drugs were present. In 18 of the 110 cases in which only medicines were detected, two or more medicines were present. Benzodiazepines represented the most commonly detected group of medicines, followed in decreasing order by antidepressants, analgesic, anti-epileptic drugs, barbiturates, H-1 antihistamines, vasodilators, calcium antagonists, antihemetic drugs, and anti-psychotic drugs. Benzodiazepines were detected alone in 27.6 percent of the cases in which medicine was found. When benzodiazepines were detected with other substances (in 72.4 % of the cases), they were found along with illegal drugs in 41.3 percent of the cases, with alcohol in 33.7 percent of the cases, and with other medicines in 14.8 percent of the cases.

FALLING AND OTHER ADVERSE EFFECTS

Although there are benefits for psychotropic medications for older people, significant adverse effects have been associated with their use, including diminished cognition, excessive sedation, and an increased risk of falls and fractures (Aparasu and Mort, 2004). This section of the report summarizes the literature on polypharmacy and falling in the older community-dwelling population, and concludes by detailing the effects of cardiac polypharmacy on visual performance.

In older people, benzodiazepines are principally used for insomnia and anxiety disorders. The acute use of benzodiazepines can lead to memory problems, perceptual errors, and impairments on tests of attention (Hogan, Maxwell, Fung, and Ebly, 2003). In a 5-year longitudinal study of subjects 65 and older, they found that benzodiazepines were associated with adverse outcomes. In particular, affect, self-rated health, cognition, function, and new institutionalization were significantly associated with benzodiazepine use. Benzodiazepine users had a lower ADL and IADL score (activities of daily living and instrumental activities of daily living), performed worse on a test of attention and psychomotor abilities (Digit Symbol Substitution Test), and had a higher likelihood of falling.

Tinetti (2004) states that each of the following conditions has been shown to increase the risk of falling in two or more observational studies:

- Arthritis
- Depressive symptoms
- Orthostasis
- Impairment in cognition, vision, balance, gait, or muscle strength
- Use of four or more prescriptions

Foster, Hillegass, and Phillips (2004) cite the *Guidelines for the Prevention of Falls in Older Persons* (2001), which includes a meta-analysis of studies examining both multiple and single risk factors for falling and medications, and found a significantly increased risk from psychotropic medications, class 1A anti-arrhythmic medications, digoxin, and diuretics. Tinetti (2004) reports that although there is a clear relation between falling and the use of a higher

number of medications, the risks associated with individual classes of drugs have been more variable (Leipzig, Cumming, and Tinetti, 1999). To date, serotonin-reuptake inhibitors, tricyclic antidepressants, neuroleptic agents, benzodiazepines, anticonvulsants, and class 1A anti-arrhythmic medications have been shown to have the strongest link to an increased risk of falling (Leipzig et al., 1999; Thapa, Gideon, and Cost, 1998). A recent meta-analysis found that the odds ratio for falls was 1.48 with benzodiazepine use, with no difference between short- and long-acting preparations (Leipzig et al., 1999). In Hogan et al.'s (2003) sample of subjects 65 and older, those not currently taking benzodiazepines were less likely to have fallen, than those who were either continuous users or new users of benzodiazepines (33.5% versus 40.3%, p=0.48).

In a sample of community-dwelling subjects age 65 to 84 who participated in the Salisbury Eye Evaluation project, multiple medication use, defined as taking four or more medications, predicted fear of falling at a 20-month follow-up clinic evaluation for 1,466 of the 2,212 participants who did not express fear of falling at the baseline clinic evaluation (Friedman et al., 2002). In this study, fear of falling at baseline was a predictor of falling 20 months later. Of the 1,597 subjects who had not had a fall at baseline, sedative use and fear of falling at baseline were independent predictors of falls at the 20-month follow-up visit. Sedatives were defined as any benzodiazepines, phenothiazines, or antidepressants.

In a cross-sectional analysis of self-reported medication use and self-reported falling over the past 12 months by high-functioning community-dwelling black and white people age 70 to 79, fallers were more likely to report more medications than nonfallers (de Rekeniere et al., 2003). Fallers took a mean of 6.1 medications (sd=4.3) and nonfallers took a mean number of 5.5 medications (sd=3.9). This difference was significant at the 0.01 level. In women, benzodiazepine use was associated with past falls. In the multivariate model, the adjusted odds ratio for benzodiazepine use versus none in women was 1.6 (1.0-2.6). Participants included 3,075 people in the Health, Aging, and Body Composition Study identified from a random sample of white Medicare beneficiaries and all age-eligible black community residents in designated ZIP code areas surrounding the Pittsburg, PA, and Memphis, TN, study centers.

In a population of 489 patients admitted to the neurology department of a hospital in Kiel, Germany, during 100 consecutive days, Stolze et al. (2004) found that the average age of the 165 patients who had experienced a fall in the past 12-month period was significantly higher than the average age of the nonfallers (62.8 $\pm$ 15.5 years versus 55.3 $\pm$ 16.6 years, $p < 0.001$). Descriptive statistics showed clear differences in the percentage of fallers and nonfallers who were being treated with medications known to be risk factors for falls, as follows:

- Antihypertensives: 39% of fallers versus 28% of nonfallers
- Diuretics: 16% of fallers versus 6% of nonfallers
- Neuroleptics: 15% of fallers versus 6% of nonfallers
- Benzodiazepines: 14% of fallers versus 7% of nonfallers
- Betablockers: 14% of fallers versus 10% of nonfallers
- Antidepressants: 13% of fallers versus 8% of nonfallers
- Digitalis: 7% of fallers versus 1% of nonfallers
- Alcohol abuse: 6% of fallers versus 2% of nonfallers

A logistic regression analysis showed a significant correlation between the occurrence of falls and medication for digitalis ($r=0.064$, $p<0.05$), diuretics ($r=0.061$, $p<0.05$), and neuroleptics ($r=0.62$, $p< 0.05$). The number of falls was correlated (Kendall's t-B) with antihypertensiva (t-B=0.15, $p<0.05$), benzodiazepines (t-B=0.12, $p<.05$), and neuroleptics (t-B=0.19, $p<0.05$). The authors conclude that medications that lower blood pressure have the potential to cause falls, irrespective of neurological diagnosis.

Kennedy et al. (2002) compared the accident types of patients admitted to trauma centers in Scotland, a percentage of whom were insulin-treated diabetics. Accidents in this study included motor vehicle crashes, assaults, falls greater than 2 meters (6.56 ft), falls of 2 meters (6.56 ft) or less, sports injuries, and other unclassified injuries. They found that insulin-treated diabetics had an accident rate (across all accidents) that was 291.2 per 100,000 population per year compared to an accident rate of 148.4 for the control population (this difference is significant, with a relative risk of 1.97). The insulin-treated patients were significantly older, more likely to be women and had a longer stay in the hospital, than control patients. The major injury type was low falls (less than 2 meters), accounting for 62 percent of the injuries to the insulin-treated group and 47 percent of the control group. Of the 151 injuries sustained by the 94 insulin-treated patients with low falls, the majority were fractures at peripheral sites (fractures of the femur, fibula, tibia, humerus, radius, ulna, calcaneus, and digit accounted for 75% of the injuries). There were only 23 motor vehicle crashes (MVCs) among the insulin-treated patients during the study period. The percentage of accidents resulting from MVCs was lower in the insulin-treated group than in the remainder of patients in the database (15%versus 24%).

Lawlor, Patel, and Ebrahim (2003) found that chronic diseases and multiple pathology are more important predictors of falling than polypharmacy. They used a cross-sectional survey design and data from the British women's heart and health study for 4,050 women ages 60 to 79. Slightly over 70 percent of the women were taking at least one drug, and 15 percent were taking five or more drugs. Although there was a strong linear association between the number of drugs taken and whether they had a fall in the previous 12 months (crude odds ratio = 1.14 for each additional drug taken), the association was not significant when the data were adjusted for chronic diseases and other potential confounding factors (fully adjusted odds ratio = 1.01). Only two classes of drugs—hypnotics or anxiolytics, and antidepressants—were independently associated with increased odds of falling, even with adjustment for chronic disease status (including ever having a diagnosis of depression) and other potential confounding factors (e.g., age, body mass index, hemoglobin concentration, heavy alcohol consumption, and social class). Each class was associated with an increase of about 50 percent in the odds of falling. In the fully adjusted analyses, analgesics, cardiovascular system drugs, endocrine system drugs, and respiratory disease were not independently associated with having a fall. Nearly 75 percent of the women had at least one chronic disease. There was a significant linear trend of increasing odds of falling with increasing number of chronic diseases, even after adjustment for drug use and other potential confounding factors. The fully adjusted odds ratio for any fall in the previous 12 months associated with having at least one of the chronic diseases was 1.81, and for each additional simultaneously occurring disease was 1.37.

Lawlor et al. (2003) found that circulatory disease, chronic obstructive pulmonary disease, depression, and arthritis were each associated with higher odds of falling. The population-attributable risk of having had at least one fall in the previous 12 months (from the fully adjusted models) was 6.2 percent for coronary heart disease, 6.2 for circulatory disease, 8.0

for chronic obstructive pulmonary disease, 9.4 percent for depression, and 17.4 percent for arthritis. When number of drugs taken and number of chronic diseases were included in the same regression model, they combined multiplicatively. The odds ratio for a fall for each additional chronic disease, adjusted for number of drugs taken, was 1.39, and that for each additional drug taken, adjusted for number of chronic diseases was 1.05. There was no strong evidence of a statistical interaction between number of drugs and number of chronic diseases, and no evidence of statistical interactions between any of the individual chronic diseases and their relevant treatment. The population-attributable risk of falling associated with having any chronic disease was 32 percent, compared to that associated with the use of psychotropic drugs (between 2% and 5%).

The South Western Sydney Area Health Service Falls Subcommittee has listed the following classes of drugs associated with falls:[37]

- Anxiolytics or sedatives (alprazolam, bromazepam, clonazepam, diazepam, lorazepam, oxazepam, flunitrazepam, nitrazepam, temazepam)
- Antipsychotics (chlorpromazine, fluphenazine, trifluoperazine, thioridazine, haloperidol, clozapine)
- Opioids (morphine, codeine, oxycodone, pethidine, methadone)
- Antidepressants (amitriptyline, nortriptyline, clomipramine, desipramine, doxepin, dothiepin, imipramine, mianserin, phenelzine, tranylcypromine, moclobemide, fluvoxamine, fluoxetine, paroxetine, citalopram)
- Antiparkinsonians (levodopa, bromocriptine, selegiline, benzhexol, benztropine, biperiden, orphenadrine, procyclidine)
- Hypoglycaemics (insulin, glibenclamide, gliclazide, glipizide, tolbutamide, metformin)
- Antihypertensives (captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, remipril, trandolapril, candesartan, irbesartan, losartan, telmisartan, amlodipine, dilatizem, nifedipine, felodipine, verapamil, atenolol, pindolol, propanolol, metoprolol, labetolol, prazosin, clonidine)
- Diuretics (frusemide/furosemide, ethacrynine/ethacrynic acid, buemtanide/bumetanide, bendrofluazide, chlorothiazide, hydrochlorothiazide, methyclothiazide)
- Laxatives/stool softeners within previous 24 hours

In consideration of "other adverse effects" of using multiple medications, cardiac polypharmacy has been associated with color vision and acuity changes in older people (Castells, Teitelbaum, and Tresley, 2002). In particular, the addition of amiodarone therapy in patients

[37] Clinical Practice Guidelines: The Assessment, Management and Prevention of Falls in the Elderly in the South Western Sydney Area Health Service. An initiative of the Injury Advisory Committee. Michael Sugrue, FRCS (1), FRACS, Chair, Injury Advisory committee. www.swsahs.nsw.gov.au/livtrauma/practice.asp

using digoxin has been associated visual "shining," glare, color vision anomalies, and decreased visual acuity. Amiodarone is a benzofuran derivative, and is an approved anti-arrhythmic agent indicated for the treatment of ventricular tachyarrhythmias and other cardiac conditions. While both drugs can cause permanent visual changes, the ocular effects are often reversible, indicating the importance of ocular examination at baseline and every 6 months for patients receiving a regimen of amiodarone and/or digoxin therapy. Digoxin (Lanoxin) is an approved treatment for congestive heart failure and certain cardiac arrhythmias. Its ocular side effects overlap with those of amiodarone, and include color vision deficits (commonly yellow-brown), and central or paracentral visual-field defects. Unique to digoxin is a reported side effect of a white or colored "snowy" or "frosted" appearance to vision. Digoxin has a low safety profile because the therapeutic and toxic serum levels are known to be close. Digoxin toxicity is a result of both dosing and cumulative effects. It is estimated that up to 20 percent of patients who receive digoxin demonstrate some level of toxicity. Up to 95 percent of patients with toxic levels of digoxin demonstrate visual symptoms (Piltz et al., 1993).

A number of drugs can significantly increase serum levels of digoxin, easily inducing toxic levels. These include amiodarone, furosemide, nifedipine, verapamil, and quinidine (American Society of Health-System Pharmacists, 2001). Amiodarone, in particular, can increase serum digoxin concentrations 70 to 100 percent, with substantial variability. In the case report of a 76-year-old man provided by Castells et al. (2002) who reported reductions in visual acuity, color vision, increased difficulty with glare, and the presence of visual shining after the initiation of amiodarone, the patient's cardiologist had reduced the dose of digoxin by the recommended 50 percent when amiodarone therapy was initiated.

The most common ocular symptom is halos or colored rings (usually blue-green) around lights, particularly at night. The incidence of colored rings or halos around lights ranges from 1.4 to 24 percent (Harris et al., 1983; Nielsen, Andraen, and Bjerregaard, 1983; Greene et al., 1983; Raeder, Podrid, and Lowan, 1985). The most common ocular finding is a type of keratopathy that consists of corneal epithelial microdeposits. A rare optic neuropathy, similar in ophthalmosopic appearance to nonarteritic ischemic optic neuropathy, has been described. The incidence of amiodarone optic neuropathy has been estimated at 1.8 percent versus a 0.3 percent risk of anterior ischemic optic neuropathy in an age- and location-matched group (Feiner et al., 1987). The severity of the vision loss from this optic neuropathy and the degree of its reversibility is variable (Harris et al., 1983; Mantyjarvi, Tuppurainen, and Ikaheimo, 1998; Ingram, 1983; Macaluso, Shults, and Fraunfelder, 1999; Sreith, Schoenfeld, and Marieb, 1999; and Feiner et al., 1987).

MEASURING/MONITORING MEDICATION USAGE

To meet the broad objectives of this research (i.e., to determine the effect of multiple medication use on driving functioning), it will be important to ensure that research subjects are complying with their medication regime. Conclusions cannot be made about the effects of medications on driving behavior if the medication is not taken, or if more or less of the medication is taken than prescribed. If the medication regimen is not followed, the intended therapy for the medical condition is not provided, resulting in confounded research results (e.g., functional impairments arising from the untreated medical condition may result in impaired driving performance, as opposed to functional impairments arising from the medications assumed to have been taken causing the impaired driving performance). As an example, Roe, Anderson, and Spivack (2002) found that the probability of a new user continuing donepezil (for mild to moderate dementia) was .797 at 90 days, and .627 at 180 days.[38] Almost 14 percent of patients 65 to 94 who continued therapy for at least 180 days showed gaps in treatment of 6 weeks or more. The significance of discontinuing therapy is a decline in cognitive and global functioning within 6 weeks of withdrawal, to the level of functioning as if the patient never took the drug.

Research indicates that specific patient-related factors affect compliance (e.g., depression). A better understanding of these factors can provide a rationale for screening potential subjects for future NHTSA research in this area.

This section of the report begins with a discussion of methods used to measure compliance, including the pros and cons associated with each method, and provides examples of recent research that has employed each method. Following the discussion of methods of measuring compliance, research describing the factors influencing compliance is reviewed. This section concludes with a discussion of older people' willingness to participate in research studies to uncover their medication use, and the professionals to whom older people are most likely to divulge their medication use.

METHODS OF MEASURING MEDICATION USE/COMPLIANCE IN THE COMMUNITY DWELLING POPULATION OF OLDER PEOPLE

Researchers across several decades have described patient compliance as "the best documented, but least understood health behavior" (Coons, 2001; Becker and Maiman, 1975). Although a variety of methods to measure compliance exist, problems with validity and reliability are inherent with every one of them (Marinker et al., 1997). Vik et al. (2004) state that presently there is no generally accepted gold standard for measuring adherence. This belief is highlighted by Steiner and Earnest (2000), who noted that the only way to be certain about a patient's compliance is to administer the medication directly to the patient.

[38] Although this example may seem extreme when considering the population of community-dwelling older people who are likely to be driving, it is not, based on the fact that in all 51 U.S. licensing jurisdictions, drivers with a diagnosis of mild dementia may continue to drive, until which time they fail a DMV road test or their physician submits an unfavorable report to the DMV.

Seven methods of measuring compliance with medication regimes are described by the American Pharmacists Association (APhA, 2003):

- Clinical judgment
- Patient self report
- Clinical response
- Biochemical measures
- Pill counts
- Pharmacy records
- Electronic medication monitors

In the pages that follow, each method is briefly described, followed by a synthesis of current literature (where present) that has employed that method for community-dwelling older people.

Clinical Judgment

Studies have shown that physicians' clinical judgment of compliance are no more accurate than predicting compliance by chance. APhA summarizes a study by Gilbert et al. (1980) who found that estimates of compliance by 10 physicians for 74 patients (58 of whom the physicians had known for at least 5 years) were accurate only for 10 percent of the patients, when compared to information obtained from a pill count and blood concentration measurements.

More recently, Bikowski, Ripsin, and Lorraine (2001) conducted a study with 50 patient-physician pairs to determine the degree of disparity between physicians' perceptions of older patients' medication regimen and patients' perceptions of their regimen. Patients consisted of individuals 65 and older who visited their physician on an index day, who had visited that physician at least three times in the past year, and were taking at least four prescription medications. Physicians were family medicine faculty and second- and third-year residents. The average number of prescription medications per patient was 7 (range= 3 to 7, sd=2.89). Congruence was defined as agreement between physician and patient regarding all prescription medications, dosages, and frequency. The focus of the study was on patient understanding of the medication regime, as opposed to medication-taking behavior (or adherence). First-year medical students interviewed patients in their homes and were asked about their understanding of what their medication regimen should be, including all prescription and nonprescription medications and their doses and schedules of administration.

Bikowski et al. (2001) found that only 14 percent of the patient-physician pairs demonstrated complete congruence. Seventy-four percent of the pairs had at least one medication that either the physician was unaware the patient was taking or the physician thought the patient was taking, but was not part of the patient's regime. Twelve percent of the pairs showed dose and/or frequency discrepancies. Overall, complete congruence between physician and patient was achieved for 60 percent (225 of 375) of the individual medications. The highest congruence was found for diabetic and other endocrine medications, with 73 percent and 74 percent congruence, respectively. Pain medications (including nonsteroidal anti-inflammatory medications) and gastrointestinal medications showed the lowest congruence (29 percent and 43 percent, respectively). Antihypertensives, the most frequently prescribed medications (36 percent

of the sample) showed a congruence of 66 percent. Other cardiac medications showed a congruence of 57 percent. Patient-physician congruence for psychiatric medications (including sleep medications) was 60 percent. Congruence for pulmonary medications was 55 percent. Study authors reported that it was not clear from the study why the physicians underreported medications; however, other researchers have demonstrated underreporting of drugs when physicians were surveyed about what medications their patients were taking (Spagnoli et al., 1989; Morrow, Leiter, and Sheikh, 1988).

Patient Self Report

In many studies, information obtained using the patient self-report method has correlated positively to information obtained from random pill counts, biochemical measures, and electronic medication monitors. In several studies reviewed by APhA (2003), querying patients about their compliance resulted in the detection of over 50 percent of patients with poor compliance, with a specificity of 87 percent. Inaccuracies in the patient self-report method arise when patients overreport actual compliance, either because they don't want to displease the provider or because they are unaware of their actual compliance. Vik et al. (2004) report that the consensus of the literature is that subjects who report nonadherence are in fact nonadherent, but other methods are required to detect those who report that they are adherent, but in fact are not. Vik et al. note that scaled questionnaires have been employed to assess self-reported adherence with success. For example, Morisky, Green, and Levine's (1986) four-item scale for assessing antihypertensive treatment demonstrated acceptable psychometric properties, and scaled scores correlated with blood pressure control.

Kaplan et al. (2004) assessed patient compliance with lipid lowering medications using the question, "In the last month, how often did you take your cholesterol medication in the way your doctor prescribed," with a five-point scale ranging from "None of the time," to "All of the time." Subjects who reported that they took their medication in the manner prescribed "some of the time," "a little of the time," or "none of the time" over the last month were defined as noncompliant. Overall, 12 percent of the subjects were defined as noncompliant, and there was a significant association between achieved cholesterol level (serum cholesterol level was measured) and self-reported noncompliance.

De Klerk et al. (2003) reported on the use of the Compliance-Questionnaire-Rheumatology (CQR) in a validation study comparing the CQR to electronic medication event monitoring, which they refer to as "the gold standard" in compliance measurement. The CQR is a 19-item instrument that measures patient compliance to drug regimens, identifies factors that contribute to suboptimal patient compliance, and may be used to measure future compliance in patients with rheumatoid arthritis (RA), polymyalgia rheumatics (PMR), and gout.[39] In a prior study, the CQR had good test-retest reliability and moderate internal consistency, and validation

[39] The 19 items were derived from a series of patient interviews and a focus group interview, and reflects statements made by individual patients regarding their drug-taking behavior. It requires approximately 12 minutes to complete. Patients are asked to indicate how much they agree with each statement on a 4-point Likert scale (1=don't agree at all; 2= don't agree; 3=agree; and 4=agree very much). One item, for example, states, "If the rheumatologist tells me to take the medicines, I do so." Six items are stated negatively, and their scoring is reversed. For example, "If I can help myself with alternative therapies, I prefer to do that to what my rheumatologist prescribes." The CQR total score is calculated by summing the items, subtracting 19, and dividing by 0.57, enabling the CQR total score to vary from 0 (complete noncompliance) to 100 (perfect compliance).

using discriminant analyses against an overall patient self-report compliance measure showed a sensitivity of 98 percent, a specificity of 67 percent, and an estimated kappa of 0.78 to detect low compliance (de Klerk et al. (1999). Treharne, Lyons, and Kitas (2004) used the CQR scale, and found good internal consistency (Chronbach's Alpha = 0.81). In their study to investigate the effects of specific psychosocial factors on adherence to medication in RA patients, CQR adherence score was used as the main dependent variable.

In the de Klerk et al. (2003) study, 85 patients visiting the outpatient rheumatology wards at three hospitals in The Netherlands completed the CQR and were given their medications in bottles fitted with Medication Event Monitoring System (MEMS) caps (Aardex Ltd., Zug, Switzerland). Multiple linear regression analyses showed that the total, weighted CQR score significantly and adequately predicted medication-taking compliance (r^2=0.46, p=0.001) and correct dosing (r^2=0.42, p=0.004). Discriminant analyses showed that specificity and sensitivity to detect good taking compliance were 95 percent and 62 percent, respectively. The predictive value to detect unsatisfactory taking compliance was 86 percent and to detect good taking compliance was 83 percent. Four items were especially predictive of taking compliance, and explained 35 percent of the variance: fear of forgetting to take the drug ("I definitely don't dare to miss my antirheumatic medications"); being able to function well ("The most important reason to take my antirheumatic medicines is that I can still do what I want to do"); routines in daily life ("My medicines are always stored in the same place, and that's why I don't forget them"); and side effects ("If you can't stand the medicines, you might say 'throw it away, no matter what'"). The predictive values for these items are somewhat lower than the predictive value of the full CQR-19, with a sensitivity of 51 percent and a specificity of 87.5 percent.

The high predictive values of the CQR-19 make it an attractive tool as a screening instrument in future studies of polypharmacy and driving, to identify subjects who are compliant with their medication regime.

Another self-report method—the "brown bag method" of medication review—entails participants collecting containers of their current prescription and over-the-counter medications in a brown paper bag (usually provided by the organization or agency conducting the review) and bringing the bag with the medications to their physicians or a pharmacists during scheduled medication review appointments. As noted by Caskie and Willis (2004), the usefulness of self-reports of medication use depends on the willingness and the ability of the individual to volunteer such information. They further state that the congruence of pharmacy records and self-reported medication use is of importance because self-reports of medications are often used as a surrogate for health status or the presence of chronic diseases, and are important when studying medication compliance, polypharmacy, and drug interactions. Self-reports of medication are frequently used in population-based studies where pharmacy records are lacking or are expensive to obtain.

In England, brown bag reviews are a component of the medicine review process, and supplement information provided by the patient's medical record and pharmacy reports. The Task Force on Medicines Partnership and the National Collaborative Medicines Management Services Programme (2002) indicates that a review of scripts in the absence of the medical record or a review of the record in the absence of the patient are screens for significant prescribing error. A medication review that does not take account of what the patient actually takes—rather than what is on the prescription or in the record—is incomplete. Patient

information leaflets describing medication reviews include a request for the patients to bring all their medications to the review clinic, including herbal remedies, medicines that are bought from a pharmacy, and medicines that are bought over the counter. Medicines are described as anything the patient takes including tablets, liquids, inhalers, creams and ointments, and any medicines that the patient has but no longer takes (Pharmacy Practice and Medicines Management Group, 2002).

Furthermore, in England the National Service Framework (NSF) for Older People (Department of Health, 2001) recommends that an in-depth evaluation of all a patient's medications (prescribed and nonprescribed) be targeted at those older people known to be at higher risk of medicine-related problems, including: those prescribed four or more medicines (polypharmacy); those discharged from a hospital, those residing in in-care homes; those for whom medicine-related problems have been identified through routine monitoring; patients 75 and older, as a part of their annual health check; and for those who have had an adverse change in health (dizziness, confusion). An NHS milestone by the year 2002 was for all people over age 75 to have their medications reviewed at least annually, and for those taking four or more medications to have a 6-month review. A 2004 milestone set by the NSF is for every Primary Care Group (PCG) or Primary Care Trust (PCT) to have schemes in place so that older people get more help from pharmacists in using their medications.

The study by Caskie and Willis (2004) included 294 members of a State pharmaceutical assistance program (PACE – Pharmaceutical Assistance Contract for the Elderly) who were also participants in a clinical trial on cognitive training at the Pennsylvania State University (ACTIVE – Advanced Cognitive Training for Independent and Vital Elderly). Subjects ranged in age from 65 to 91, with a mean age of 74.5. In this study, self-reported medication data were collected by use of the brown bag method; however, over-the-counter medications were excluded from analysis. Computerized pharmacy claims for prescription fills and refills were obtained from PACE for a time period that included the date of the brown bag data collection. Medications in the PACE pharmacy data whose supply was estimated to be depleted more than 5 days before the brown bag assessment were also excluded. Data were examined for 10 major therapeutic drug classes: antihistamines; anti-infective agents; autonomic drugs; blood formation and coagulation; cardiovascular drugs; CNS agents; electrolytic, caloric, and water balance; ear, eyes, nose, and throat preparations; gastrointestinal drugs; and hormones and synthetic substitutes. Specific drug classes within the class of cardiovascular drugs and CNS agents were examined in greater detail because of the frequency with which they are prescribed to older people and because of their possible side effects. The following specific cardiovascular drug classes were examined: ACE inhibitors, cardiac glycosides, beta blockers, calcium channel blockers, antilipemic drugs, hypotensive agents, and vasodilating agents. Specific CNS drug classes examined included: NSAIDs, opiate agonists, and benzodiazepines. For both data sets, a code was entered to indicate whether the participant had at least one medication in that class or had no medication in the class. The three most commonly occurring major therapeutic drug classes in both data sets were cardiovascular drugs (PACE = 59% of participants; self-report = 67% of participants); hormones and synthetic substances (PACE = 32% of participants; self-report = 37% of participants) and CNS agents (PACE = 28% of participants; self-report = 34% of participants).

Across the 10 major drug classes, there was an average of 91 percent agreement (9 of 10 classes) between the self-report and pharmacy records. Agreement scores ranged from 50 to 100

percent, and almost half (49%) had perfect agreement between their self-report data and their pharmacy data. Within the specific cardiovascular drug classes, agreement scores ranged from 43 to 100 percent, with an average of 96.4 percent (6.7 of 7 classes). Within the specific CNS drug classes, agreement scores ranged from 33 to 100 percent, with an average agreement of 92.7 percent (2.8 of 3 classes).

Sources of discrepancy between self-reported medications and the pharmacy database in the Caskie and Willis (2004) study most often occurred because the pharmacy records excluded medications that were contained in the self-reports. The pharmacy records did not include an average of 24 percent of the major drug classes that were self-reported, whereas on average, the study participants did not report 7 percent of the major drug classes contained in their pharmacy reports. Similarly, for the specific cardiovascular drugs, the average rate of omissions was 1 percent for self-reports, and the average rate of omissions for the pharmacy records was 13 percent. For the specific CNS drug classes, self-reports showed on average omissions for 5 percent of the drug classes, whereas the pharmacy records reported an average of 13 percent fewer CNS classes than the self-report data.

The study authors examined the variables that predicted agreement and disagreement between the self-report and the pharmacy data. They found the following significant predictors for the major drug classes:

- Participants who were married, had a lower income, and had better general health were more likely to have self-report data that agreed with the pharmacy data than subjects who were not married, had higher incomes, and poorer general health.
- Participants who were married and who were in better health were less likely to omit drug classes included in the pharmacy data.
- Married participants were less likely to report a drug class that was not in the pharmacy records.

For the cardiovascular drug classes, the following significant relationships were found:

- Individuals with better health had better agreement between their self-report data and the PACE pharmacy records.
- Individuals with better health were less likely to report a drug class that was not found in the pharmacy records.

For the CNS drug classes, the following significant relationships were found:

- Male participants had higher levels of agreement between their self-reports and the pharmacy data.
- Participants in better health had higher levels of agreement between their self-reports and the pharmacy data.
- Participants with poorer general health had more self-reported drug classes that were not represented in the pharmacy records.

Caskie and Willis's study findings support the conclusion that the brown bag method provides a reasonable substitute for pharmacy records as a measure of current medications.

In another study utilizing the brown bag method, Freml, Farris, Fang, and Currie (2004) performed an analysis of 50 randomly selected brown bag reviews performed by pharmacy students and 100 randomly selected brown bag reviews performed by pharmacists in the Iowa brown bag review to compare types of recommendations (e.g., cost savings versus therapeutic) made by pharmacists and students. The Iowa brown bag reviews were performed by community pharmacists, as well as by doctoral pharmacy students during their final year of pharmacy education. The mean age of the 150 subjects in the Freml et al. study was 77, and more than 70 percent were female. Interestingly, the number of prescription medications the subjects brought to the pharmacy in the brown bags for review was higher than the number of medications they self-reported using over the past month. There were no differences in the demographics, disease variables, or medication use variables between the pharmacist-reviewed and the student-reviewed groups. Results found that each subject used an average of 5.5 prescription drugs of which 2.2 (41%) were generic, and an average of 2.5 nonprescription drugs of which 1.6 (64%) were generic. There were no differences between pharmacist and pharmacy student groups in the rate of substitution and interchange of medications. However, there were statistically significant differences in pharmacist and student recommendations. In general, pharmacy students were more likely than pharmacists to make any recommendation. Specifically, students made significantly more "stop prescription drug," "switch to alternate brand," and substitution recommendations. Grouping recommendations into cost-saving and therapeutic categories, pharmacy students made significantly more cost-saving recommendations than pharmacists. Students also made more therapeutic recommendations, but the difference was not significant.

Freml et al. (2004) provide a few reasons why pharmacy students may have provided more recommendations, including possibly having more time than pharmacists to do reviews (as pharmacists had to time-share with other on-the-job tasks), having better interviewing skills as a result of recent clinically oriented education, unfamiliarity with patients' wishes, and lack of concern about damaging provider relations at the pharmacy site. Freml et al. (2004) concluded that students can be valuable members of the health care team by providing cost-saving and therapeutic recommendations, and by decreasing pharmacist workload. Prior research has documented that physicians frequently accept recommendations from students at a rate similar to which they accept recommendations from pharmacists (Chisholm and Hawkins, 1996; Chisholm, Taylor, and Hawkins, 1997; Slaughter, Ericson, and Thomson, 1994; Taylor, Church, and Byrd, 2000; Briceland, Kane, and Hamilton, 1993).

Nathan, Goodyer, Lovejoy, and Rashid (1999) reported on medication use of 205 patients who volunteered to participate in a brown bag review. The mean age of the participating patients was 64.45. The number of drugs reviewed per patient ranged from 1 to 14, with an average of 6.2. Pharmacists made interventions in 87 percent of the reviews. Interventions included: providing information about the purpose of at least one medication (65% of the reviews); improving or correcting usage of at least one medication (46%); providing knowledge on common or important adverse drug reactions or side effects (52% of reviews). Fifty-eight percent of patients admitted to or were suspected of either not using at least one of their medications at all or not using them according to prescribed directions. Interactions between medications (sometimes between prescribed and over-the-counter medicines) were identified in 4 percent of the reviews.

Clinical Response

For many medications, a patient's clinical response to a medication is only weakly related to compliance. In addition, while some studies suggest that the absence of predictable adverse side effects is correlated to noncompliance, the link between compliance and adverse effects has not been consistent in the literature (APhA, 2003). The APhA therefore concludes that clinical response generally is not a good measure of compliance.

Biochemical Measures

Biochemical measures of patient compliance consist of serum drug concentration and urine assay (blood and urine sampling) to measure drug presence and concentrations. Although this method is objective, it is not practical, convenient, or appropriate for most circumstances, and it is not always reliable. Serum drug concentrations detect compliance problems only for medications that have a long half-life; however, it does not account for individual differences in absorption and metabolism. Also, biochemical measures do not provide information about whether the patient took the proper amount of medication at the proper time. The costs of assays for the assessment of multidrug regimens can be prohibitive.

Behrensdorff and Steentoft (2002) conducted a roadside survey in Denmark to describe the prevalence of medicinal and illegal drugs in passenger vehicle drivers in a rural area. Police randomly stopped 1,000 drivers and requested that they provide on-the-spot saliva samples and complete a questionnaire once they returned to their homes. Drivers who were suspected of illegal driving (impaired driving, driving without a valid license) were not included in the stopped sample, as police wanted to follow their own procedures for illegal driving. Sample drivers participated voluntarily and anonymously; the refusal rate for saliva sampling was 1.9 percent and the response rate for the questionnaire study was 66 percent.

A total of 961 saliva samples were collected using the Cozart RapiScan System—a five-panel drug test designed to detect five main groups of frequently abused drugs: amphetamines, benzodiazepines, cocaine, cannabis, and opiates. Saliva screenings were performed partly by use of the Cozart RapiScan system and partly by a Cozart "Drugs of Abuse Microplate EIA" system. Both systems provide only a preliminary analytical test result (e.g., they detect the presence of a substance), and require a more specific alternative chemical method to obtain a confirmed analytical result (e.g., they do not provide a measure of the drug concentration). Saliva was chosen as the specimen for the study because it is easier, less invasive, and less time consuming for police to collect and handle than urine. In addition, the RapiScan saliva screen provided promising results in an earlier study in Scotland (Oliver and Seymour, 1998), and it was the only instrument available on the market that included five substances for screening. A drawback of the saliva screening systems used, however, is that neither is capable of tracing all types of benzodiazepines available on the Danish market. All samples were sent to the Department of Forensic Chemistry, Institute of Forensic Medicine, University of Copenhagen, for screening and confirmation by specific methods. After screening hundreds of samples using the RapiScan system, it was concluded that the test was not reliable and reproducible. Therefore, the RapiScan system was rejected and replaced by the Cozart "Drugs of Abuse Microplate EIA" system for screening of the 861 of the 961 samples with enough remaining saliva. Only the samples that screened positive were further analyzed using gas chromatography-mass spectrometry (GC-MS) for amphetamines, cannabis, cocaine/benzoylecgonine, and opiates. The benzodiazepines were

confirmed by two methods: by gas chromatography with an electron capture detector, and by liquid chromatography with a diode array detector.

In the research conducted by Behrensdorff and Steentoft (2002), 7.1 percent of the sample (64 of the 896 stopped drivers who provided saliva) screened positive using the initial screen. In the confirmatory analysis, 2 percent (18 drivers) tested positive for one or more benzodiazepines or an illegal drug (amphetamines, cannabis, cocaine, or opiates, e.g., the drugs included in the screening method). The ages of the 18 drivers were not reported. In 0.7 percent (6) of the saliva samples, one or more benzodiazepines were detected: diazepam, bromazepam, alprazolam and oxazepam (all tranquilizers). The authors note that some of the frequently used benzodiazepines (in Denmark) would not be picked up by the screens used in this study, and therefore the number of samples that screened positive for benzodiazepines underestimates the prevalence of this drug in the population of rural drivers. The great difference in the number of positive saliva samples by the initial screening compared to the confirmatory analysis underscore the importance of conducting specific confirmation methods in combination with initial screening.

Pill Counts

Pill counts measure compliance by comparing the number of doses remaining in a container with the number of doses that should remain, if the patient's compliance were perfect. This method can provide an overestimation of compliance if the patient is aware that a pill count is going to be conducted—patients may remove excess doses and discard them. Another drawback to this method is that it cannot verify that a dose removed from a container was actually consumed, or whether it was consumed at the correct time. Pill counts are not suitable for medications taken on an as-needed basis. Pill counts can provide an accurate measure of compliance under the following circumstances: when they are conducted in a patient's home; when the patient is not aware that a pill count is going to be conducted; when there are reliable records to confirm the amount of medication dispensed, the date the most recent prescription refill was begun, how much medication was left over from the previous prescription when the current prescription was begun, and whether there was any change in the prescription; and a determination can be made regarding whether the patient stores medication in other locations or has shared any of the medications with friends or family.

Kogos (2004) utilized the pill-count method to determine adherence to all medications taken by a group of 30 men age 69 to 86 who were receiving treatment at a Veteran's Administration Medical Center. Study subjects were described by their healthcare professional as nonadherent. The purpose of the study was to determine whether attendance at five support-group sessions would increase adherence. The proportion of prescribed doses taken was calculated for each medication using the following formula: number of pills dispensed minus number of pills present in the bottle/number of pills expected to be taken according to the prescription instructions. Following the initial pill count, these treatment group members brought all their prescribed medications to each of the five group meetings. The support groups for the treatment condition included the use of contracts, enlisting social support, monitoring and giving feedback, and education about healthy lifestyles. Control group members completed only an initial and final pill count; they attended five support-group sessions where issues other than treatment adherence were discussed. Treatment group members demonstrated a significant improvement in their pharmacological adherence, as measured by pre- to post-pill count;

however, there was no significant difference between members of the treatment group and control group on pill count. The failure to find a difference may have been attributed to the low number of support meetings, as most research indicates a minimum of eight meetings is necessary for a treatment effect to show. In addition, pre-treatment compliance was high compared to other studies—77.3 percent for the treatment group and 87.6 percent for the control group, despite the referral criteria for inclusion in the study. The researchers conclude that there is preliminary support for a multicomponent adherence group to increase medication compliance.

Pharmacy Records

The use of pharmacy records to estimate compliance based on pharmacy refills correlates favorably with electronic measurement, but shares some of the same problems that are intrinsic to pill counts. A refill record will provide information about how much medication was dispensed in a given interval, but it can not validate that the medication was actually consumed or consumed at the correct time. In addition, although refill records across pharmacies can be tracked in many cases, these records do not include medications obtained from other sources, such as free samples from physicians and pharmaceutical companies, or medications obtained through sharing with other family members or friends. Free samples given to patients by their physicians and pharmacists (and medications obtained from sources outside of the pharmacy network) would have the consequence of overestimating noncompliance as measured with the pharmacy database.

Some of the problems related to appropriate medication use in the elderly, such as drug-drug interactions and drug-drug duplication can be monitored using electronic pharmacy claims data and drug utilization review computer software (Fillit et al., 1999). However, exclusive use of pharmacy claims data ignores the fact that health plan members may purchase both prescription as well as over-the-counter medications outside of the plan's benefit structure. This can happen when members who need multiple medications exceed their pharmacy benefit plans and purchase some medications out-of-pocket. This may make a portion of their pharmacy usage unavailable to the health plan. In addition, administrative data does not include nonprescription medications—frequently consumed by older people with significant effects on polypharmacy.

Pharmacy records were used in some of the studies described earlier in the brown bag method, as a means of identifying members at risk for polypharmacy for inclusion in those medication-review studies. Other researchers have used pharmacy databases to determine the relative frequency of various combinations of medications, and to conduct case-control studies of the use of medications and adverse outcomes such as motor vehicle crashes (LeRoy, 2004). As noted by LeRoy, an advantage to the use of claims data is that it is not dependent on patient recall of medication and disease information. However, in interpreting results derived from analyzing administrative claims data, the following sources of error or influence must be considered:

- reporting error (including under-reporting);
- ascertainment error (correctly billed but incorrectly diagnosed); and
- detection bias (frequent visits yield increased opportunity to detect).

LeRoy used two databases, a nonproprietary database (National Ambulatory Medical Care Survey/NAMCS) and a proprietary database (PharMetrics). The content of these databases is discussed in more detail below.

The NAMCS 1998-2000 data (nonproprietary) were used to obtain information on drug use characteristics and disease prevalence for the U.S. population. NAMCS is a national probability sample survey of visits to office-based physicians, whose detailed prescription drug information is recorded by physicians. Data are obtained on patients' symptoms, physicians' diagnoses, and medications ordered or provided. Statistics on demographic characteristics, external causes of injury (e.g., motor vehicle crash) and services provided are also included in the database. The unit of analysis in the database is the number of physician visits, not the number of patients. Quality control of the data is provided by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC), which has instituted a thorough system of data completeness checks and data edits. All medical and drug coding were subjected to a two-way, 10-percent independent verification procedure. Patients were sorted into groups by age (under 50 and over 50) and whether or not they had a motor vehicle crash coded as a reason for the physician visit. The kinds of descriptive analyses that were conducted with this database, sorted by age group and motor vehicle crash versus the entire cohort included the following:

- number of physician visits by age and gender;
- number of physician visits by age, gender, and number of medications;
- number of physician visits by gender, age group, and specific combinations of drug classes;
- number of physician visits by age, gender, and number of potential driver-impairing medications;
- number of physician visits by age, gender, and number of conflict medications;
- number of physician visits by age, gender, and specific potential driver-impairing disease groups;
- number of physician visits by age, gender, and number of potential driver-impairing disease groups; and
- number of physician visits by age, gender, and number of disease-drug conflicts.

The proprietary database employed by LeRoy (2004) is owned by PharMetrics, who provides anonymized patient-specific medical and pharmaceutical claims-linked datasets derived from claims paid through health insurance programs. It includes inpatient and outpatient diagnoses and procedures, and both standard and mail-order prescription records. It also allows for the analysis of medical usage and disease treatments in a temporal relationship to a motor vehicle crash. The company uses extensive data quality review procedures that use over 100 quality measures. Queries for individuals with E-codes ("external cause of injury") for motor vehicle crashes, and three controls for each case, provide information about patient demographics, number of medications dispensed, patterns of medication combinations, and disease prevalence for patients with and without motor vehicle crashes in the enrollment population. Occurrences of drug-drug conflicts and drug-disease conflicts were also examined. The same descriptive queries were conducted as were conducted with the nonproprietary database, in addition to a matched pair case-control study. Cases were defined as all patients with one of more claims with a diagnosis code (ICD9-CM) indicative of a motor vehicle crash and with at least six months of continuous enrollment prior to their first claim(s) with a crash code.

Three control patients were randomly matched to each case patient, with matching based on the following criteria: no claims with any of the motor vehicle accident codes; age within 5 years of the case; same gender; at least 6 months of continuous enrollment prior to the Case study subject's first claim with an accident code.

A potentially relevant data set to provide information about medications dispensed to older people is the Veteran's Administration Pharmacy Benefits Management (PBM) Database. The PBM Database is a national database of information about all prescriptions dispensed within the VHA System beginning with fiscal year 1999. The database was developed by the Pharmacy Benefits Management Strategic Healthcare Group (PBM/SHG), which is a VA entity responsible for managing the national VA drug formulary process (Smith and Joseph, 2003). PBM data files are created and stored by the PBM/SHG at the Edward Hines Jr. VA Hospital in Hines, IL. Smith and Joseph (2003) state that VA data is an important resource for understanding patterns and costs of pharmacy use by a large, predominantly older population. While there are several large non-VA prescription databases that contain information on privately insured individuals, they contain relatively few people over age 65. Although many VA patients are elderly men, the numbers of younger veterans and women allows for analysis of these groups as well. Vulnerable populations, such as people with low incomes, disabilities, or mental health and substance abuse problems are present in substantial numbers. Smith and Joseph (2003) state that the number of published studies employing the VA pharmacy data sources is small but rapidly growing, as the data sources have a great potential for use in health economics and health services research.

The database contains the following common data for each prescription order dispensed for a patient: dosing instructions, National Drug Code (NDC) where applicable, product name, ordering provider, drug product costs, quantity dispensed, formulary status, and VA drug class. Other data elements are available depending on whether the order was an IV, unit dose, or outpatient prescription order. An unusual feature of PMB is the availability of dosing instructions, which is useful to researchers in studies of patient adherence to physician instructions. Data are made available to researchers as a flat file in Microsoft VisualFoxPro, Microsoft Access, or SAS format. The patient's SSN will be provided to researchers if there is a need to link the PBM data to other data sources. Researchers cannot directly access the PBM database; instead the PBM/SHG will create a custom extract for the researcher. The database is at the level of individual prescriptions, and therefore, a person can have multiple records on a given day. The PBM database contains no information about patient clinical characteristics. Two other VA databases, VISTA and the Decision Support System (DSS) National Data Extracts can be linked to obtain clinical data such as diagnosis and procedure codes for inpatient admissions and outpatient visits, as well as admission and discharge dates for inpatients. However, these linkages do not allow attribution of a prescription to a particular clinic code or diagnosis, if more than one appeared on the outpatient record for a given day. Patient demographic data may be obtained can be obtained by linking the PMB database to the VISTA database. Smith and Joseph (2003) note that obtaining data from VISTA is significantly more difficult, and therefore, unless additional clinical data is needed, the PBM database will be the better choice. VISTA requires specialized programming, permission by each of the 128 VA facilities across the United States (as opposed to the PMB database that extracts data from all facilities monthly), and careful interpretation across facilities. A planned DSS National Pharmacy Extract will contain rich data about patient characteristics, such as gender, date of birth, low-income status (based on the local threshold for federally subsidized low-income housing) and home ZIP code.

Data access requirements are as follows (Smith and Joseph, 2003): Researchers may have access only to special-use data extracts created by the PMB/SHG field office at the Hines, VA, hospital. Although both inpatient and outpatient data are extracted, only the outpatient PBM datafiles are currently available for research.

Requests for PBM data are fulfilled if the PBM/SHG confirms the following: the proposed data use will not conflict with the PBM/SHG's primary mission of managing the VA formulary process; IRB approval has been granted; all applicable laws, regulations, and VA policies are being followed, including those pertaining to data confidentiality and human rights; and the requestors have completed a use and nondisclosure agreement. Non-VA researchers are provided PBM data by the PBM/SHG only if they are collaborating with a VA employee or belong to an official oversight body. PBM/SHG will not release data for research if the design appears to favor a particular medication or class of medications or if the study is not scientifically valid. Smith and Joseph (2003) report that the time and effort needed to obtain permission to access the data sources is not trivial, especially for non-VA researchers.

In some cases, there will be a charge for PBM data. There is generally no charge to create an extract for pilot VA research projects, and VA employees may access the data for management purposes at no charge. For funded research, the PBM/SHG staff will request payment in proportion to the staff time needed to consult on protocol design and to compile, analyze, and report the data. For simple data extracts that do not require protocol design assistance, there is a nominal charge to cover programmer costs.

Smith and Joseph (2003) raise an important issue regarding patients' dual use of VA and non-VA systems. Because of the very low co-pay charged by VA pharmacies ($7 in 2002 for non-service-connected conditions), many enrollees use the pharmacy services to supplement their Medicare coverage. More than 50 percent of VA enrollees have Medicare coverage, including 22 percent of those under age 65. Consequently, researchers cannot rely on VA sources alone to present the whole picture of health care services for VA patients. One option is to obtain Medicare records for VA patients, linking them to VA encounter data through Social Security numbers. This would provide a more complete picture of health services and enable research on those who use alternative systems of care.

Another potential source of pharmacy data is the Medicare Current Beneficiary Survey (MCBS), which is a continuous, multipurpose survey of a nationally representative sample of aged, disabled, and institutionalized Medicare beneficiaries. MCBS, which is sponsored by the Centers for Medicare & Medicaid Services (CMS), is the only comprehensive source of information on the health status, health care use and expenditures, health insurance coverage, and socioeconomic and demographic characteristics of the entire spectrum of Medicare beneficiaries (http://www.cms.hhs.gov/mcbs/default.asp.) An e-mail inquiry to the Centers for Medicare and Medicaid Services regarding the use of this database in projects sponsored by NHTSA to assess the effects of polypharmacy on driving yielded the following response:[40]

> "Medicare is in the process of implementing a drug benefit. Because this benefit is so new to the program, there are no data collected by traditional claims mining; however, the MCBS is a survey that should be able to address your needs. Please visit our CMS

[40] E-mail from William Long to Kathy Lococo 1/11/2005.

research help desk for further assistance in identifying the data files, which best serve your needs. Follow this link to our help desk: http://www.cms.hhs.gov/researchers/resdac.asp?"

Information obtained from the CMS Web site for researchers' use of MCBS data is as follows. The Research Data Assistance Center (ResDAC) provides free assistance to academic and non-profit researchers interested in using Medicare, Medicaid, SCHIP, and Medicare Current Beneficiary Survey (MCBS) data for research. Primary funding for ResDAC comes from a CMS research contract. ResDAC is a consortium of faculty and staff from the University of Minnesota, Boston University, Dartmouth Medical School, and the Morehouse School of Medicine. ResDAC offers a number of services for researchers with all levels of experience using or planning to use CMS data. Services include technical data assistance, information on available data resources, and training. CMS releases MCBS data only under a data use agreement. CMS will release some billing and administrative data with the MCBS survey data, commensurate with demonstrated need. Researchers who have specific needs for more detailed geographic information or for Medicare claims data may request Limited Data Set (LDS) Files from CMS. Requests for these files must include a study protocol with specific justification for the additional data required, along with an Identifiable Data Use Agreement. The MCBS Access to Care files (1991 through 2002) and the MCBS Cost and Use files (1992 through 2001) and accompanying documentation are available. Data files are supplied in EBCDIC format on tapes with IBM standard labels. Each data file costs $480.

The Cost and Use file is a more complete file with regard to health expenditures and medical events. The MCBS Cost and Use files link Medicare claims to survey-reported events and provides complete expenditure and source of payment data on all health care services, including those not covered by Medicare. Expenditure data were developed through a reconciliation process that combines information from survey respondents and Medicare administrative files. The process produces a comprehensive picture of health services received, amounts paid, and sources of payment. The file can support a broader range of research and policy analyses on the Medicare population than would be possible using either survey data or administrative claims data alone. The strength of Cost and Use files stem from the integration of information that can be obtained only from a beneficiary and from Medicare claims data on provider services and covered charges. Survey-reported data include information on the use and cost of all types of medical services, as well as information on supplementary health insurance, living arrangements, income, health status, and physical functioning. Medicare claims data includes use and cost information on inpatient hospitalizations, outpatient hospital care, physician services, home health care, durable medical equipment, skilled nursing home services, hospice care, and other medical services.

Chrischilles et al. (2004) used claims data from 117 pharmacies participating in the Iowa Medicaid Pharmaceutical Case Management (PCM) program to identify eligible patients for an evaluation of the PCM program. Eligible patients consisted of noninstitutionalized Iowa Medicaid patients taking four or more long-term medications, including at least one medication representing 1 of 12 specified diseases (congestive heart disease, ischemic heart disease, diabetes mellitus, hypertension, hyperlipidemia, asthma, depression, atrial fibrillation, osteoarthritis, gastroesophageal reflux, peptic ulcer disease, and chronic obstructive pulmonary disease). In order to have complete claims data, patients who were not continuously eligible for Medicaid from 6 months before through 12 months after the date on which they became eligible for PCM

were excluded from analysis. The prevalence of adverse drug reactions was assessed in patient questionnaires. Of the total of 3,037 patients eligible for PCM services during the study enrollment year, approximately 28 percent were 65 or older. Of the 3,037 patients identified, 2,211 were continuously eligible and constituted the analysis data set. Surveys were sent to the 2,211 subjects, and the response rate was 39 percent (659 of 2,211 were completed and returned).

The Medical Expenditure Panel Survey (MEPS), used by Aparasu and Mort (2004) to evaluate the prevalence and correlates of potentially inappropriate medications among older community-dwelling people, is a representative national sample survey of the U.S. noninstitutionalized population. The survey is conducted by the Agency for Healthcare Research and Quality in collaboration with the National Center for Health Statistics. It uses a household component (HC) and a medical provider component (MPC). The HC consisted of three rounds of computer-assisted in-person interviews with household respondents in a year, to collect information on sociodemographic characteristics, health conditions, health status, and healthcare use. The MPC validated and supplemented the HC information through a mail survey of medical providers and pharmacies. Pharmacies provided data on prescriptions dispensed to respondents. Data provided by the 21,571 respondents to the 1996 MEPS were employed to develop national estimates of health care use. For Aparasu and Mort's (2004) study, data on the use of psychotropic medications by individuals 65 and older were extracted from the MEPS prescription file. Based on classifications described by Mort and Aparasu (2000), psychotropic medications were classified as antidepressants, antianxiety agents, sedative/hypnotics, antipsychotic agents, and stimulants. Generic product identifiers in the Price-Check PC software (First DataBank, Inc., Indianapolis, IN) were used to classify products according to their generic ingredients based on the products' prescription National Drug Codes. The data extraction procedure resulted in an unweighted total of 471 records for older patients using psychotropic medications of the 2,455 records for elderly patients (19%). This translated to an estimate of 6.09 million (19%) of the 32.29 million elderly patients.

Gurwitz et al. (2003) used administrative data regarding outpatient health service utilization and prescription medication for their sample of 27,617 Medicare+Choice Plan enrollees who were followed by a large multispecialty group practice. The group practice provides health care to more than 30,000 people 65 and older living in a single geographic area, approximately 90 percent of whom are enrolled in the Medicare+Choice Plan. The practice provides care to members of a New England-based health maintenance organization. All Medicare+Choice plan enrollees had a drug benefit plan during the study. Comparison of this population to the overall U.S. population 65 and older demonstrated very similar age and gender characteristics. The authors state that this particular setting (a large multispecialty group practice providing care to patients 65 and older who live in a single geographic area, and who have prescription drug medical coverage) is ideal for research on prescription drug use and the incidence of adverse effects, because automated data on prescription medications, laboratory results, and electronic clinic notes were readily available. At the time of the study, while only 17 percent of all Medicare beneficiaries nationally were Medicare+Choice plan enrollees, the age and sex characteristics of the study population closely mirrored the overall U.S. population 65 and older.

Hennessy, Bilker, Weber, and Strom (2002) recommend that whenever possible, researchers using administrative data should carry out macro-level descriptive analyses on the

parent data set. They reached this conclusion after examining the integrity of six Medicaid databases for use in pharmacoepidemiology research. They examined four categories of potential data errors: incomplete claims for certain time periods; absence of an accurate indicator of inpatient hospitalizations; missing hospitalizations for those 65 and older; and diagnostic codes in demographic groups in which those conditions should be rare. They found that prescription claims were missing intermittently in some States. For three of the six States, no valid marker was found for inpatient hospitalizations. Hospitalizations were missing to varying degrees for those 65 and older. They mention that studies using Medicaid data linked to Medicare data would hopefully eliminate the problem of incomplete hospitalization data, since in the United States, Medicare is almost always the primary payer for hospital claims for those 65 and older. Medicaid studies without access to Medicare data may have limited ability to study hospitalization outcomes in the elderly. There were no widespread gross errors in diagnostic codes or demographic data. In particular, Hennessy et al. recommended that researchers examine the number of claims of different types (e.g., prescription, inpatient medical, outpatient medical) over time, looking for apparent gaps. Validity of markers of hospitalization should be assessed, with comparison with an external standard undertaken whenever possible. The accuracy of diagnoses and demographic data should be evaluated by examining the frequency of select diagnoses stratified by demographic group. Further, they state that the practice of obtaining data only on the set of enrollees who will be included in the results of the study precludes the macro-level quality assurance checks that should be conducted. With regard to prescription claims, it was recommended that investigators consider the possibility of incomplete prescription claims in the execution and interpretation of studies. They cite, for example, longitudinal studies examining prescription refill patterns might incorrectly interpret incomplete claims as the failure of subjects to obtain prescription refills. Examining whether a greater number than expected of such gaps occur simultaneously in calendar time within the study cohort may help identify such study gaps.

A particular item of importance in the use of pharmaceutical databases is the time window chosen to assess drug use. Kennerfalk et al. (2002) found that use of a random date compared with a one-month period resulted in a significant underestimation of the amount of drugs used for acute conditions and, consequently, the risk of polypharmacy. Polypharmacy was defined in this study as the concomitant use of 5 or more drugs. They analyzed the number of different prescribed drugs used at the index (random) date and during the month following the index date in a sample of 5,000 patients 65 to 90 years old from the General Practice Research Database in the United Kingdom. The prevalence of polypharmacy in men at the index date was 9.7 percent compared to 15.9 percent in the month after the index date. For women, the prevalence of polypharmacy at the index date was 10.9 percent compared to 18.7 percent in the month after the index date. The difference between the two time windows was statistically significant for both men and women. The authors state that the use of a short time window will accurately include drugs for continuous use (e.g., for treatment of chronic conditions), while agents used for the treatment of acute conditions will be underestimated or even excluded. They further state that one month may be too short a time interval to reflect the risk of multiple drug use.

Electronic Medication Monitoring Devices

Electronic medication monitoring devices use microchip technology to record and download data to a computer for review and analysis describing the actual date and time that a

dose is removed from a container. Although the devices are recognized as the "gold standard" of compliance assessment, the method has drawbacks similar to the pill count method and the pharmacy refill method—electronic medication monitoring devices cannot assure that a dose that was removed was actually consumed or administered correctly (APhA, 2003). In addition to errors introduced when a bottle is opened and no medication is taken, errors may be introduced when a patient removes two doses during one opening (one for the morning and one for the afternoon) and only one event gets recorded for two doses taken (Samet, Sullivan, Traphagen, and Ickovics, 2001). Despite these limitations, electronically measured adherence has been more highly associated with clinical outcomes than self-report (Liu et al., 2001) and pill counts (Namkoong, Farren, O'Connor, and O'Mally, 1999).

Dunbar-Jacob et al. (2003) measured medication compliance by 169 community dwelling individuals age 62 and older (mean age = 70.7, range = 62 to 94) who had cardiovascular conditions in addition to other diagnoses for which medication use was monitored. Subjects were recruited from a heart failure clinic, from specialty practices in rheumatology, and through speaking to senior citizen groups in several small towns. Medication adherence (percentage of doses taken, percentage of days with the correct number of doses, and the percentage of expected doses within the correct timing interval) for three groups of patients was monitored: medications prescribed for a community sample of subjects with cardiovascular problems, medications prescribed for a clinic group of patients with heart failure, and medications for a clinic group of patients with rheumatoid arthritis. Adherence was measured with the ARDEX Medication Event Monitoring System that uses a medication bottle cap fitted with a microprocessor to capture the timing (date and time) of each medication-taking event. When the bottle is opened, the microprocessor records the date and time, and downloads the data to an ASCII file for analysis.

Sociodemographic factors included in the study to determine their ability to predict medication adherence were: gender, age, race, marital status, education, number of people living in the household, employment status, household income, insurance status for medications, and frequency of daily dosing for the medication being monitored. Sociodemographic data were pooled across the three medication study groups in the analysis.

Adherence values showed that on average, across the three groups, 89 percent of the prescribed doses were taken, the correct number of doses taken was taken on 76 percent of the days, and 64 percent of the doses were taken within the correct timing interval. When comparing groups, the subjects with rheumatoid arthritis exhibited the lowest adherence levels for each of the three adherence measures (77% for prescribed doses taken, 59% for days with the correct number of doses taken, and 44% for doses taken within the correct timing interval). The community group with cardiovascular problems and the heart failure group had similar adherence levels, with the heart failure group showing a slightly higher percentage of doses taken than the community group with cardiovascular problems (98% compared to 90%) and a higher percentage of days with the correct number of doses (87% compared to 82%). The community group had a higher percentage of doses in the correct timing interval when compared to the heart failure group (73% compared to 72%).

FACTORS AFFECTING COMPLIANCE WITH MEDICATION REGIMES

Researchers examining the medical records of approximately 28,000 Medicare enrollees 65 and older found that 89 of the 421 preventable adverse drug events (21%) were caused by "errors in patient adherence"—for example people taking the wrong dose, continuing to take medication despite instructions by the physician to discontinue drug therapy, refusal to take a needed medication, continuing to take a medication despite recognized adverse effects or drug interactions known to the patient, and taking another person's medication (Gurwitz et al., 2003).

Barat, Andreasen, and Damsgaard (2001) found that 71 percent of their sample of subjects 75 and older showed dose deviations, most commonly lower-than-prescribed dosing and less frequent drug intake. The drugs most often involved in deviations were hypnotics, analgesics, bronchodilators, and diuretics. Fourteen percent of all participants receiving low-dose aspirin, 12 percent receiving diuretics, 13 percent using nitrates, 14 percent receiving calcium antagonists, and 12 percent receiving nonsteroidal anti-inflammatory drugs exceeded the prescribed dose. Fifty-eight percent of all subjects receiving hypnotics, 54 percent using nonsteroidal anti-inflammatory drugs, and 46 percent receiving analgesics used lower doses than prescribed.

Vik, Maxwell, and Hogan (2004) performed a review of the literature (1966 to 2002) on medication compliance among community-dwelling older adults and concluded that there are few empirical data to support a simple systematic descriptor of the nonadherent patient. The evidence emerging from their review suggests that polypharmacy and poor patient-health-care-provider relationships (including the use of multiple providers) are the major determinants of nonadherence, and that the impact of sociodemographic factors is negligible. Vik et al. (2004) report that the proportion of hospitalizations among older patients attributable to nonadherence may be as high as 11 percent.

The American Pharmacists Association (APhA, 2003), in its overview of compliance research and interventions, indicates that the five most common types of noncompliance are:

- not having the prescription filled;
- taking an incorrect dose (too much or too little medication);
- taking the medication at the wrong time;
- forgetting to take one or more doses; and
- stopping the medication too soon.

The APhA lists three groups of factors that may contribute to poor compliance: *medication-related* factors, *patient-related* factors, and *prescriber-related* factors. Recent findings reported in the literature in each of three areas are presented below.

Medication-Related Factors

With regard to medication-related factors, the review by the APhA (2003) generally found that decreases in compliance have been associated with increases in:

- the complexity, cost, and duration of a medication regimen;

- the number of prescribed medications; and
- the severity of adverse side effects.

Dunbar-Jacob et al. (2003) found that medication adherence (measured as the percentage of prescribed doses taken, the percentage of days with correct dosing, and the percentage of expected doses with correct timing) in a sample of 169 community-dwelling people 62 and older with cardiovascular conditions significantly declined as the dosing frequency increased. The average adherence (percentage of prescribed doses taken) was 95 percent for once dosing daily, 84 percent for twice dosing daily, 84 percent for three doses daily, and 78 percent for four doses daily. As the number of doses per day increased, adherence to correct timing decreased. Subjects who were on a once-per-day regimen had an average compliance rate of 83 percent compared to 53 percent for those on a twice-per-day regimen and 27 percent for those on a four-times-per-day regimen.

Compliance rates for Type 2 diabetes patients taking antihyperglycemic drugs did not reach 50 percent in a study by Dailey et al. (2001), even with a simple monotherapy dosing regime; however, compliance with a monotherapy regime was 36 percent higher than compliance with a polytherapy regime. Daily et al. (2001) used pharmaceutical claims data from Medi-Cal to examine antihyperglycemic drug use patterns among Medicaid recipients with Type 2 diabetes and to compare compliance and persistence for simple one-drug antihyperglycemic regimes to more complex multiple-drug regimens. There were 37,431 patients in the 1-year follow-up period (mean age = 61.3, range 30 to 107.9 years) and 16,452 patients (mean age = 70 , range 30 to 107.9) in the 2-year follow-up period. The treatments consisted of either metformin alone or sulfonylurea alone (monotherapy) or a combination of metformin plus sulfonylurea (polytherapy). Results showed that patients on the monotherapy regime had approximately 65 percent more days of continuous (or persistent) treatment (129 days) per patient per year than did patients taking polytherapy (78 days). Monotherapy subjects had a 36-percent higher compliance rate than polytherapy subjects (177 days versus 130 days.) At the 1-year follow up period, patients on monotherapy (either metformin or sulfonylurea alone) had identical compliance rates of 49.3 percent. This compares to a compliance rate of 36 percent for patients on a polytherapy regime (metformin plus sulfonylurea). At the 2-year follow-up, compliance dropped to 42.4 percent for patients on metformin alone, 42.1 percent for patients on sulfonylurea alone, and 29 percent for patients on both metformin and sulfonylurea.

Balkrishnan et al. (2003) reported lower compliance in patients 65 and older with Type 2 diabetes who were taking injectable antidiabetic medications as compared to older Type 2 diabetic patients taking oral antidiabetic medications. Oral antidiabetic medication use was associated with a 0.28-point increase in medication possession ratio (MPR, based on pharmacy data, calculated as the number of days of antidiabetic prescription supply dispensed divided by the number of days between prescription refills, ranging from 0-1), which translates to a 62-percent increase over the MPRs of patients not using oral antidiabetics. Other factors associated with lower adherence included a self-reported emergency room visit in the year before enrollment in the Medicare HMO (a 0.43-point decrease in the MPR, or a 6% decrease versus the mean) and an increase in the severity of comorbidity (the Charleston index).

Even with a simple dosing regime (e.g., once-daily dosing), a review of studies on hypertensive patients found that on average, only 75 percent of drugs prescribed for the hypertensive condition were taken (Cramer, 2004). Cramer describes the compliance scenario as

an abrupt discontinuation of treatment, lasting several days or more, followed by abrupt resumption. She reports on the consequences of erratic compliance with antihypertensive therapy by citing Psaty et al. (1990), who found that patients who took less than 80 percent of their antihypertensive medication were at a four-fold elevated risk for an event than good compliers. As an example, when a hypertensive patient falls and breaks a hip, the cause is more likely due to missed doses that lead to very high blood pressure and lightheadedness than to an effect of the drug.

Murray et al. (2004) indicate that congestive heart failure (CHF) is an exemplary disease for illustrating difficulties associated with adherence. The incidence of CHF increases with aging, and in older adults, it is most often the result of a long history of poorly maintained hypertension, which requires multiple medications. With the onset of CHF, patients may be required to take 5 or more cardiovascular medications, in addition to any medications needed for other chronic diseases. With the greater number of medications taken by older people, and the increased likelihood that many of these individuals will have cognitive impairment, Murray et al. (2004) state that older adults with CHF would appear to be at risk for problems with medication adherence.

Although the association between higher numbers of concurrent medications and poorer adherence is the prevalent finding in the literature, the counterintuitive finding that higher numbers of medications predicted better adherence was found in a study using subjects taking cardiovascular medicines (Shalansky and Levy, 2002) and in a study using subjects taking rheumatoid arthritis medications (Treharne, Lyons, and Kitas, 2004). Subjects in both studies were patients recruited from outpatient hospital clinics (heart failure clinic, lipid clinic, and a rheumatology clinic). Attending an outpatient clinic in and of itself may be associated with greater adherence. Also, in the cardiovascular clinic study, all subjects demonstrated persistence to therapy before being surveyed (e.g., subjects who were not taking cardiovascular medications for at least 3 months were excluded). In addition, subjects' perceptions of their disease severity and their need to take medicines has been shown to be an important predictor of adherence, and subjects who believe they are more ill (e.g., through being prescribed a large number of medications) may be more likely to take steps necessary to maintain their health. Taking higher numbers of medications requires more attention to the medication-taking regime, and in the cardiac study, use of compliance aids was higher in adherent subjects. In the RA study, patients taking more medicines perceived that their medications were more necessary. These patient-related factors (described below) may explain the counterintuitive association between higher numbers of medications and greater compliance.

In a study evaluating compliance with lipid-lowering medication in 510 patients with a mean age of 64, Kaplan et al. (2004) found that medication side effects reported as "frequent and very unpleasant" were associated with noncompliance (in analyses adjusted for age, sex, and race/ethnicity).

Patient-Related Factors

With regard to patient-related factors, demographics such as age, gender, race, intelligence, level of education, marital status, and social status generally have not been found to relate to medication compliance (APhA, 2003). However, in the review by the APhA, the following demographic variables have been found to correlate with compliance: limited access to health care, financial problems, communication barriers, and lack of social support. While it may be surprising that older age has not been associated with poorer compliance, compliance-related problems associated with older people are attributed to characteristics of the medication regime as opposed to age (e.g., older people take more medications and are more susceptible to adverse drug events).

Compliance with medications is also low when patients are in denial regarding the nature/severity of their condition; when medications are prescribed for preventative reasons for conditions that are symptomless; when patients feel no benefit for taking the medication; when patients do not believe that the medication will affect their condition; when there are no immediate consequences for not taking the medication; and when patients feel that the short-term disadvantages to the medication (such as side effects) outweigh the long-term benefits (APhA, 2003). As pointed out by Treharne, Lons, and Kitas (2004), it appears that perceptions are stronger predictors of adherence that demographic factors, in the group of patient-related factors.

In a study by Kaplan et al. (2004) study, unmarried status, feelings of sadness or depression for more than two weeks of the prior year, lack of insurance, and children in the household were independently associated with poorer compliance with lipid-lowering medication. Their subjects consisted of 510 patients treated in the cardiology practices of three hospitals located in the Bronx, NY. The mean age was 64.4, and ranged from 33 to 94. Hispanics (37%), black (33%), and white non-Hispanic individuals (25%) comprised the sample. Educational attainment and household income were low, with 47 percent holding less than a high school diploma, and 78 percent reporting an annual household income of less than $20,000. More than 60 percent of subjects were covered solely by public health insurance, with 11 percent having no insurance. Approximately half had monthly out-of-pocket expenses for prescription medications, and 25 percent reported difficulty paying for medications.

In a study of 496 patients treated for hypertension, the majority of whom were 65 or older, Wang et al. (2002) found that only 29 percent of the sample had enough medication to cover at least 80 percent of the days during the 1-year study period (based on prescription refill records). Thirty-five percent of the sample had enough medication to cover between 50 and 79 percent of the days in the study period, and 36 percent had less than 50 percent of the days in the study period covered. After controlling for the potential confounding effects of demographic variables (age, gender, race, education, and employment status), use of thiazide diuretics, the presence of comorbid conditions (coronary artery disease, cerebrovascular disease, and renal failure), and locus of control, Wang et al. (2002) found that an increase in depressive symptom severity was significantly associated with a lower odds of compliance. There was no association between compliance and knowledge of hypertension, health beliefs and behaviors, social supports, or satisfaction with care. There was a trend toward compliance for patients perceiving that their health is controlled by external factors.

Dunbar-Jacob et al. (2003) analyzed sociodemographic factors to identify predictors of medication compliance for the three measures of compliance. With regard to the percentage of prescribed doses taken, only race (white versus black) was significant. Black subjects were more likely to be compliant than white subjects (98% versus 88% adherence, respectively). With regard to the percentage of days with correct dosing, only total household income predicted adherence. Adherence increased with increases in income, from 68 percent for those with incomes less than $20,000, to 87 percent for those with incomes between $20,000 and $29,999, to 86 percent for those with incomes over $30,000. With regard to the percentage of expected doses with correct timing, only income and number in household were significant. Subjects with lower incomes were less likely to be compliant to correct dose timing. As the number of people living in the household increased, adherence to correct timing decreased. Subjects living alone had an average adherence rate of 70 percent. Those living with one other person had an average adherence rate of 62 percent. Individuals living with at least two other people had an average adherence rate of 59 percent. Neither age, gender, marital status, education, employment status, nor insurance coverage significantly predicted medication compliance in the Dunbar-Jacob et al. (2003) study.

Prescriber-Related Factors

Prescriber-related factors that correlate with low compliance include: a poor prescriber-patient relationship, poor prescriber communication skills, a mismatch between the prescriber and patient regarding health beliefs, and lack of positive reinforcement from the health care provider (APhA, 2003).

FACTORS AFFECTING OLDER PEOPLE'S WILLINGNESS TO PARTICIPATE IN RESEARCH

To begin this section, several recruitment lessons were offered to increase the participation of older community-dwelling participants in frailty/injury prevention studies that appear relevant to the current research (Ory et al., 2002). These include:

- the use of official stationery with original signatures;
- keeping the initial phone contact brief; and
- informing participants early in the phone conversation of their physician's sponsorship of the study.

In addition, Ory et al. (2002) state that recruitment yields can be bolstered by working through people living in residential apartments associated with a long-term care facility. Further, many older people temporarily relocate to warmer climates during the winter months, so that needs to be taken into account when designating recruiting windows. Finally, they state that it is more efficient to accept a refusal rather than invest the effort necessary to keep an uninterested participant in the study.

Wong (2004) reported on a polypharmacy intervention by Premera Blue Cross in conjunction with the Washington State Medical Association and the Washington State Department of Health that used the brown-bag method. The intervention included: (1) a brochure mailed to members that explained the potential risk for drug interactions when multiple medications are prescribed; (2) a medication log for members to list their medications by name,

strength, directions for use, and purpose; (3) a brown bag in which members were directed to put all medications from all providers (prescription, nonprescription, and herbal) and to take to their provider; and (4) a letter mailed to providers explaining the Polypharmacy Program, and including the member brochure and the brown bag. The purpose of the medication review was to ensure that members were taking the correct medications at the appropriate doses, reduce medication duplications or interactions, and help to reduce potential adverse drug reactions. A public relations campaign was initiated to increase the effectiveness of the program by reinforcing the need for multiple-medication evaluations and to reach many individuals in the community. The PR campaign included television interviews on evening news programs, newspaper articles, and discussions on morning radio programs.

In 2001, polypharmacy material was sent to 12,000 members over age 55 who had at least five or more separate medication claims in one quarter for drugs on a custom list of medications defined as maintenance medications. In 2003, the Polypharmacy Program was expanded to include all members over age 18. As of February 2004, material had been mailed to 48,700 members and 5,000 providers in Washington, Alaska, and Oregon.

The intervention was evaluated through annual member and provider surveys. The member surveys were mailed four months after the polypharmacy mailing and consisted of questions addressing member recall of receipt of the program intervention material, and whether they read the material, completed the log, and completed a medication review with their physicians (and if so, what types of changes, if any, were made to their medication regimes). The polypharmacy material recall rate was 48 percent among members who responded to the survey. Of these, 88 percent indicated that they read the material, 36 percent completed the medication chart, and 50 percent had a medication review within four months of receiving the mailing. The study found that over two-thirds of patients (68 percent) received prescriptions from multiple physicians, and one-third of patients received prescriptions from three or more doctors. Overall, 52 percent of the respondents who recalled receiving the materials rated the program helpful or very helpful. Of those who had not visited their physician at the time of the member survey, 53 percent indicated that they plan to take their medications to their physician for review. Among those who brought their medications to their physician, one out of three had some type of medication change (add a medication, stop a medication, or change a dose). Of the providers who responded to the survey, 37 percent agreed that the program helps to reduce medication-related complications and hospitalizations. A pharmacy claims analysis indicated that in the year prior to the intervention, there was an average increase in the number of medications per person from 4.5 to 5.5. In the year following the intervention, the number of medications per person decreased from 5.5 at the time of the intervention to 5.0 after one year.

Farris et al. (2004) evaluated participants' satisfaction with the reviews conducted during the Iowa Brown Bag program. Of the 24,825 Iowa Priority enrollees, only 3,198 (13%) sought and received a review in the year 2002. Enrollees were made aware of the review program through enrollment material, the program Web site, quarterly newsletters, and pharmacists. Enrollees who participated in a review completed a survey regarding motivation for obtaining a review; medication changes related to the review; satisfaction with the review; and willingness to pay for the review. The most common reason provided by the Farris et al. (2004) study respondents for participating in the review was to save money on prescriptions (65%), followed by obtaining more information (21%) and to ensure that all medications were safe to be taken together (20%). On a scale of 1 (very dissatisfied) to 7 (very satisfied), respondents had an

average satisfaction rating for their review of 5.1, and 68 percent rated it as a 5 or higher. The percentage of respondents indicating willingness to pay some part of the cost for such a review was 48 percent for an initial review, and 29 percent for an annual review. When asked if they would have an annual review, 24 percent responded that they "definitely" or "probably" would. Survey respondents who did not seek a review provided the following reasons: they did not need a review (29%), they did not know about it (29%), or their physicians or pharmacists were not providing the reviews (11%).

Fillit et al. (1999) conducted a prospective study with a follow-up survey to examine the effects of a brown bag review by primary care physicians on prescriptions written for elderly members of a Medicare-managed care organization who were at risk of polypharmacy. Prescription drug data were obtained for 37,372 members of the Houston, Texas, area of the NYLCare 65/Gulf Coast Medicare risk health maintenance organization. Members identified at risk of polypharmacy—defined as those who had received 5 or more prescriptions during a three-month study period—were mailed a letter suggesting they make an appointment with their primary care physician for a medication review, because an electronic review of their medications indicated they were receiving multiple medications. A brown bag was provided with a label that read, "Request a medication review with your doctor. Bring your prescription and nonprescription medications to your doctor." Each primary physician in the plan received a mailing containing an introductory letter, a member-specific medication report, and clinical practice guidelines for managing polypharmacy. The medication management report for each of their patients at risk for polypharmacy listed all prescription medications captured by the administrative claims data (only those prescribed for at least 30 days), as well as the dosages and number of pills dispensed per prescription. Use of over-the-counter medications was not available in the administrative database. A follow-up survey was sent to each member considered at risk for polypharmacy and to all primary care physicians treating one or more of the members at risk for polypharmacy. The member questionnaire was anonymous and contained 36 items: 3 concerned the receipt of the brown bag and resulting actions, 7 concerned the conduct of the medication review, 11 concerned symptoms and health care usage related to medication side effects, 1 item concerned changes in overall health, and the SF-12 instrument [would the word "form" or "questionnaire" be better than "instrument"?]used to measure physical and mental health status.

Of the 37,372 member 65 or older enrolled in the Program, 5,737 (15%) were at risk for polypharmacy and were mailed the brown bag material, and later the member questionnaire. Of the 5,737 questionnaires mailed, 2,615 were returned. Of the 2,615 members who returned questionnaires, 1,087 (42%) had participated in the medication review with their physicians. Ninety-six percent of the members who participated in the medication review reported that they had a discussion concerning prescription medications and 72 percent indicated that nonprescription medications were also discussed. As a result of the medication review, 20 percent indicated that the doctor stopped or discontinued a medication, 29 percent indicated that the doctor changed the dosage of medication, 11 percent indicated that the doctor discovered medications purchased without a prescription that the doctor did not know the patient was taking, and 17 percent indicated that the doctor discovered medications prescribed by another physician that the first doctor did not know the patient was taking. Members who participated in the medication review were slightly more likely to have worse physical and mental health function scores on the SF-12 than those who did not request a medication review.

Other researchers have found the rate of self-referral for a brown bag medication review to be low. Nathan, Goodyer, Lovejoy, and Rashid (1999) distributed flyers to all households within the health authority localities of Bexley and Greenwich in southeast London, posted fliers in the 23 pharmacies within these health authorities, and trained pharmacists, nurses, and general practitioners to identify and recruit candidate subjects. Although the service was open to any member of the public, only 205 patients volunteered to participate. Ninety percent of the volunteers were actively recruited by the pharmacists. Once recruited, subjects were issued a brown bag and were asked to bring all their medication from home, including prescribed and over-the-counter medications, medications out-of-date or no longer used, and any reserve supplies. In this study, the resident pharmacist conducted the reviews, which took approximately 30 minutes each. Medications were reviewed to identify contraindications, interactions, adverse reactions, and problems with administration and compliance. The pharmacist explained the purpose of medications, and provided advice on dosage, administration, or compliance as necessary. With patients' consent, pharmacists reported any medication-related problems to the patients' general practitioner.

Follow-up interviews with patients indicated that, although they had initially been wary of the process and suspicious of the motives, they were unanimously in favor of medication reviews and thought that they should become a permanent service. Patients offered that they would have been more willing to participate had their doctor recommended that they do so. Several pharmacists recommended that closer collaboration with general practitioners was necessary to ensure the success of this type of activity. It was also recommended that pharmacists conduct the reviews in the general practitioners' surgery, as it was a more suitable environment and there could be much better liaison with the doctor—this was highlighted by the need for more information by the review panel ranking medication problem severity, which was not available to the reviewing pharmacists. Additionally, pharmacists were reluctant to provide information to general practitioners out of concern that it would be perceived as an intrusion into the general practitioner's area of clinical responsibility. The few general practitioners who responded to a follow-up survey indicated that they were in favor of the medication review activity.

Two focus groups were conducted to determine patients' views of the pharmacist-led medication reviews conducted within Greater Glasgow Primary Care Trust, described above, which began in 1999 (MacRae et al., 2003). Between 1999 and 2003, over 20,000 patients participated in the review service. The 14 focus-group participants were sampled with respect to age, gender, and number of medication changes resulting from the medication review. Focus group members were asked to provide their views about their initial expectations, positive and negative aspects of the medical review process, and potential areas for future improvement. The positive aspects of the reviews included obtaining explanations about medications and knowing the medication regime was optimized as a result of the review. Problems arising as a result of the medication reviews included concerns about changing medications, the potential to upset the physician-patient relationship, and apprehension regarding physician rationale in the past for issuing or not issuing a medication under recommendation by the pharmacist as a result of the medication review. A majority of the focus group members stated that pharmacist-let medication review should be provided on an ongoing basis; however some patients wanted reassurance that pharmacists and physicians were working collaboratively.

Levenson (2002) reported on five focus groups attended by a total of 26 women and 15 men over age 60 in the United Kingsom as part of the Medicines Partnership Program to understand their views regarding the medication review standard published in 2001 by the National Service Framework for Older People. Key issues for discussion included: whether participants had heard of medication reviews; whether they had had a medication review; whether their physicians routinely ask about how they are doing with their medications; whether they always take their medications as directed; whether they had their medications reviewed within the past year, and if so how the review went, and who was involved; whether they were asked to take their medications with them; what they would like to discuss in an upcoming medication review; with whom and where they would like to have their medications reviewed; types of information they would like to have in advance of a review; whether they would like a written discussion about their medications; and what health professionals could do to help them get the most out of a medication review. Participants in each group suffered from a range of long-term medical conditions, and many reported regularly using more than four prescribed medications. Several also indicated that they took over-the-counter medications, vitamins, and homeopathic remedies. Although most people in the groups indicated that they comply with the advice given in taking medications, their comments and anecdotal stories indicated otherwise. Many indicated that they stopped taking medications or reduced dosages in response to unpleasant side effects. In one group, all participants indicated that they altered their medication routine from what was advised, because they felt overmedicated.

Of particular interest to the present research is what participants in the focus groups conducted by Levenson (2002) thought about where medication reviews should take place and who should be involved. In general, there were no strong views regarding *where* a review should take place, however, there was support for the opinion that medication reviews should be conducted face-to-face as patients would be flustered by telephone communication about their medications. Regarding *who* should be involved in medication reviews, general practitioners, hospital doctors, pharmacists, and to a lesser extent nurses were suggested as possibilities. The consensus of the groups was that the quality of the review and the attitude of the reviewer were more important than the professional background. Most important was that people wanted someone who was knowledgeable and had time to talk and listen. Those who had good relationships with their general practitioners felt strongly that the GP or possibly the practice nurse should conduct the review. Others had low expectations about GP review because their GPs had long waiting times for scheduling appointments and long waits at the office, and given those conditions, they were doubtful that GPs could add medication reviews to their commitments. Pharmacists were considered as knowledgeable and participants were open to the possibility of pharmacist involvement, provided that there was good communication of the results to the physician. Nurses were viewed as less informed about medications and therefore less suitable to conduct reviews.

Although most of the focus group participants had not participated in a medicine review, those who had participated found the experience to be helpful. The majority of those who had not experienced a medicine review indicated that they would appreciate the opportunity to discuss their medicines with a health professional. Those who stated that they would not want to participate in a review provided the following reasons: (1) avoiding unnecessary change ("I say, if there is nothing wrong, don't mend it"), (2) fear of being taken off a medication that they depend on ("if they suggested coming off a pill—diazepam or hormone replacement treatment—

it would be difficult to come off"); and (3) concern that the medication reviews may be to save the NHS money and not primarily for the benefit of patients.

Zermansky et al. (2001) conducted a study to determine whether a pharmacist can effectively review repeat prescriptions through consultations with elderly community-dwelling patients. Proposals in the United Kingdom have recommended that pharmacists review medication use in light of the fact that general practitioners's workloads are already on the increase, and based on studies in the United States in the 1990s showing the benefits of pharmacists reviewing long-term prescriptions in community practice. Two earlier studies in the U.K. showed that pharmacists identified more drug-related problems than normal care (Granas and Bates, 1999; Mackie et al., 1999).

The Zermansky et al. study design was a randomized controlled trial of clinical medication review by a pharmacist against normal general practice review. Four general practices in Leeds Health Authority with four or more partners were recruited by random selection. The participating practices provided lists of registered patients 65 and older who received at least one drug on repeat prescription on June 1, 1999. Subjects were excluded if they were in nursing homes, had a terminal illness, or were in a clinical trial. Eligible patients were sent a letter requesting their participation; those who consented were randomly assigned to either a control group (normal care review) or an intervention group (clinical review by pharmacist). The intervention was conducted in the pharmacist's clinic, although immobile patients were visited at home, and consisted of a discussion with the patient about conditions being treated and relevant symptoms; identification of drugs being taken; identification of indications for which they are being taken; assessment of adherence; an evaluation of continuing need for the drug, suboptimal treatments, side effects, drug interactions and contraindications, and cost considerations; and an evaluation of whether major, minor, or no change is needed. Patients in the control group continued to receive normal care from their practitioner and were called in for review of treatment by their general practitioner according to normal custom in the practice. Only 44 percent of the control group patients had a documented review with a doctor. The measures of effectiveness were the number of changes to repeat prescriptions during the 12-month study period, changes in the number and cost of medicines, changes in dose frequency, and effects on healthcare workload (general practitioner consultations, hospital outpatient admissions, and acute admissions).

Results were reported for 1,131 patients with a mean age of 74. The mean number of changes in at least one repeat prescription per patient was 2.2 for the intervention group and 1.9 in the control group. This difference was significant. Changes included starting a new drug, stopping a drug, switching drugs, changing doses, changing to a generic, changing formulation, or changing frequency. The only type of change that was significant was that more patients in the control group started taking a new drug. However, a higher percentage of treatment group patients were advised to stop a drug than control group patients (41% compared to 33%). The authors point out that stopping unnecessary medications is important for two reasons: patients' compliance tends to decrease with increases in the number of drugs; and stopping unnecessary drugs reduces the risk of adverse effects and interactions. Although the number of drugs and costs rose in both groups over the 12-month period, the increase was significantly less in the intervention group. The intervention group showed no evidence of adverse health outcomes as measured by the need for consultation with a general practitioner or hospital treatment.

The authors mention that only half of the contacted patients were successfully recruited. In a follow-up study to determine why older patients declined to participate in the pharmacist-led medication reviews, Petty et al. (2001) found that consenting patients were dissimilar from consenting patients. Patients were *less* likely to participate in reviews if they were older or were female. The authors comment that the older patients may have found it more difficult to attend if they were "unwell" or were more likely than younger patients to have difficulty reading or understanding the letter. Females may have been less likely to participate because, as a rule, they visit their doctors more frequently than men and may have felt that they have ample opportunities to discuss medication use. Patients were *more* likely to consent if they were in the group taking 5 or more repeat medications (as compared to the group taking from 1 to 4 repeat medications). The researchers state that this may be due to hopes that the review would uncover medications that could be stopped, or because people taking fewer than five medications may see the review as a waste of time.

During follow-up telephone calls to nonconsenting patients, 10 themes emerged describing reasons for nonparticipation. First, several readability and comprehension difficulties were uncovered in the letter of invitation to the medication review. The font used for the letter was Times New Roman size 12. Patients with poor eyesight stated they had difficulty reading the letter, and no one in the home to read it to them. Others misinterpreted the location for the medication reviews, thinking they had to go to the researcher's university or local hospital instead of to their own physicians' practice, even though the letter was written on the physician practice letterhead. A subset believed the study involved a clinical trial, despite wording in the letter stating that the study was not a trial. Others stated that they took no medicines, due to a belief that inhalers and creams did not constitute medication. Second, a subset of invitees was unreachable either by telephone or mail. Third, cognitive impairment resulting in confusion about the study and the appointment explained some of the failure of invitees to participate. Fourth, some of the patients described themselves as "unwell" or just released from the hospital, and did not want to participate. Fifth, a subset was unavailable because they were either unwilling to change their routines, were in a hospital or daycare setting, or were moving out of the area. Sixth, several patients were uncomfortable with having a pharmacist review their medicines, thinking it could jeopardize the patient-physician relationship, while others explained they had just had their physician medication review. Others were suspicious of the motives and believed that the researchers were really checking up on the physician. Seventh, some patients were happy with their medication regime and did not want to be advised to make changes or stop medications. Eighth, patients with only one repeat medication thought it would be a waste of their time and the pharmacist's time. Ninth, some patients have a general negative feeling about the health care system, and didn't want to be bothered any more than necessary. And finally, some of the patients thought the purpose of the review was to save the government money by changing their medications to cheaper alternatives, and they felt mistrustful.

Petty, Knapp, Raynor, and O'house (2003) conducted focus groups to determine consenting patients' views about pharmacist-led medication review clinics run in their general practitioner's offices, and to identify barriers to participant participation. The mean age of the 18 participants was 73, with a range of 67 to 86. A range of socioeconomic backgrounds was represented, although none of the study practices represented rural communities. Ethnic minority groups were not recruited. Eleven of the 18 participants were males. The mean number of repeat medications they took was 5.5, ranging from 2 to 10. Perceptions before attending the clinic ranged from positive (an opportunity to gather information about the medications they were

taking) to suspicion that the reviews were being conducted to save money. After the review, many found the review informative and reassuring, while others were disappointed with the outcome of the review (e.g., they hoped they would be advised to stop long-term medications, but were not so advised). There was also some feeling that there is a hierarchy of who is responsible for managing patients: a general practitioner should not change treatments prescribed by a specialist, and a pharmacist should not change treatments prescribed by a general practitioner.

Kriska and Ross (2002) found that when general practitioners in England received training in the systematic approach used by pharmacists for medication reviews, they were better able to identify pharmaceutical care issues (PCIs) than when they reviewed case notes alone. Following training by an experienced clinical pharmacist, general practitioners and community pharmacists performed medical reviews on patients age 75. Nurses received training in a different review process to help them identify medication-related problems during an annual health check. General practitioners documented 2.7 PCIs per patient, community pharmacists 1.6 per patient, and nurses 1.0. The pharmacists and nurses made significantly fewer changes to prescribed drug therapy and monitoring than the general practitioners. The authors note that this finding may have been the result of higher general practitioner confidence in effecting changes and requesting monitoring. Follow-up questionnaire responses from the patients indicated that the reviews were useful (77%), and 42 percent identified a preference for a general practitioner review or continued general practitioner management. Kriska and Ross reported that the participation rate in their study was higher than that found in controlled studies of pharmacological review. They propose that this reflects a preference expressed by patients for review by general practitioners.

Jainkittivong, Aneksuk, and Langlais (2004) reported on the medical conditions and medications used in a sample of 510 Thai dental patients 60 and older. As dentists will be treating more elderly people in the future, and older people have more medical conditions and take more medicines than younger people, the authors highlight the importance of obtaining a patient's total health history before undertaking dental procedures. This is because some systematic diseases may influence oral health and/or dental treatment to some degree and dental treatment may have an influence on some systematic conditions. The authors include a list of medications with possible adverse effects of dental significance. In the Jainkittivong et al. (2004) study, one investigator interviewed subjects regarding their medical histories and medications. The subjects' family members were interviewed in cases where the subject's recall was poor. In addition, medications were verified whenever possible by inspection of medication container labels. In light of their findings that 68.3 percent of their subjects 65 and older took medications, and the average number of drugs increased with increasing age, the authors state that taking of a thorough medical history is especially important among older people, and should include a health questionnaire, an interview, copies of treatment records from physicians, and a careful analysis of all drugs being taken. Medical consultations with patients' physicians may also be needed for patients who provide conflicting or vague medical histories. The results of this study point to dentists as a group of professionals who routinely collect medication use from their patients, and may be a resource for future NHTSA studies of medication use by older drivers.

In the study by Linjakumpu et al. (2002), information about medication use was collected in personal interviews conducted by a trained nurse in a health center. This study involved 1,131 community-dwelling people 64 and older in 1990/91 and 1,197 community-dwelling people 64 and older in 1998/99 in Lieto, Finland. In the first survey, only 7 percent of the invitees declined,

did not respond, had moved elsewhere, or were unable to participate due to illness or disabilities. In the second survey 18 percent of the invitees did not participate for the same reasons. Subjects were asked to take their prescription forms and drugs with them to present to the nurse what they were currently taking. A close relative or caregiver provided information if the person could not answer questions, had dementia, or was not in good condition. If a subject could not visit a health center, a nurse made a home visit to check the medication in use. The brand names of all prescription drugs taken by the interviewee during the seven days prior to the interview was recorded. Both regular and irregular prescription drug use were recorded. Medication was defined as regular if it was taken daily, or at regular intervals, for example once per week or month. Irregular medication was defined as medication taken when needed. In addition to medication use, a questionnaire was administered to collect information about social background and quality of life. This study points to a relatively high participation rate (93% in the first survey and 82% in the second survey) of older community-dwelling people in medication use studies (albeit in Finland, as opposed to the United States) where nurses are the professionals recording usage.

A total of 7,543 noninstitutionalized elderly in the city of Randers, Denmark, were contacted by mail, and asked to complete a questionnaire on health problems, falls, exercise habits, and use of calcium and vitamin D, and were advised that a home visit would be offered within six months if they participated. This was a free-of-charge medication review by a nurse, a home safety inspection, an evaluation of possible health and food problems, and for some participants, distribution of free calcium and vitamin D supplements. Sixty percent of those contacted returned the completed questionnaire. Nonrespondents were recontacted twice by phone or by mail. Eighty-five percent of those who returned the questionnaire agreed to the in-home evaluation, for an overall acceptance rate of 51 percent. Females had a higher acceptance than males. Participation did not change significantly from ages 66 to 84, however, after 85, acceptance decreased significantly. Widowed people had the highest participation, starting at 62 percent among the youngest and decreasing to approximately 33 percent among the oldest. The trend was opposite for the never married, starting with 34 percent participation for the youngest and increasing to 47 percent at ages 95 to 99. Acceptance was highest (56 percent) when calcium and vitamin D were offered in combination with an evaluation of prescribed medicine (without the home safety inspection and health and food problems evaluation). Previous contact with the public service social center doing the recruiting was associated with higher acceptance than no previous contact, and more effect on acceptance than the type of intervention offered. The authors hypothesize that the low acceptance rate may have been influenced by the requirement that participants be willing to accept a visit in their own homes, which may have been regarded as unwanted.

METHODS TO MEASURE DRIVING PERFORMANCE

Alvarez and del Rio (2002) indicate that the need to identify suitable tests for evaluating the effects of drugs on driving ability has been widely recognized for over 20 years. This sentiment reflects the limitations of crash-based studies, namely, the relative scarcity of measurable events for any but the largest study samples, observed over significant periods of time; and is compounded by underreporting and irregularities in reporting practices across jurisdictions. As alternatives to crash data analysis, Roenker et al. (2003) have examined the strengths and weaknesses of two approaches for measuring driver performance—road tests and driving simulators.

Road tests have long been considered the gold standard for measuring driving ability. They have widely recognized limitations, however. In addition to inconsistencies in the administration and scoring of the results, which presents a major challenge to standardized and objective assessments, as a rule examinees are not exposed to the most risky and demanding situations where driving errors that lead to crashes are most likely. Nevertheless, Ramaekers (2003) asserts that actual driving tests are *essential* to conclusively define the potential impact of drugs on driving. This review will include both on-road (in traffic) and closed-course methods.

Driving simulators have been touted as offering experimental control for driving performance evaluation; they have also been criticized for a lack of fidelity for many aspects of actual driving (and therefore poor generalizability to conditions outside the laboratory), as well as simulator sickness (particularly for older adults). Another difficulty in evaluating the utility of this method is the ambiguity attached to the term "driving simulation." Testing systems bearing this label range from actual vehicles on motion platforms with fully interactive control over high-resolution "virtual" environments, to "driving bucks"—a single seat with basic wheel and pedal controls for user inputs—that offer a more limited display of the driving environment and little or no motion, to desktop computer graphic/video presentations of selected driving scenarios for "part-task" measurement (e.g., visual search, hazard detection). This review will consider three categories or levels of simulation, as elaborated in the following discussion.

As one additional perspective, a combination of approaches to investigate the effects of medications on the ability to drive has been advocated by Álvarez and del Río (2002). These authors note that relevant psychological and functional capabilities can be analyzed using vigilance and performance tests, psychomotor test batteries, reaction tests, etc., but should be complemented by simulator and on-road studies. Similarly, Keller, Kesselring, and Hiltbrunner (2003) offered the opinion that psychological tests in combination with an on-road test allow for a balanced judgment of a patient's fitness to drive. Their psychological assessment (including cognitive tests, a tracking task with divided attention, psychomotor tests, and assessments of impulse control and spatial orientation), when compared to the results of an on-road test, yielded consistent results in 88 percent of the cases studied (38 of 43 patients with neurological disabilities). Keller et al. (2003) also cite other researchers (Sundet, Goffeng, and Holt, 1995) in concluding that, while a psychological assessment sheds light on a subject's perceptual efficiency, goal-oriented behavior, distractibility, psychomotor efficiency, and impulse control, a road test is key to demonstrate the subject's capacity to retrieve from procedural memory the technical skills of handling a car, the capacity to allocate and shift attention, and to keep a general overview of concurrent events, all of which are required for safe and successful driving.

The following pages offer a more detailed description of driver performance measurement methods employed in recent studies, that may have value in future applications for research on medications and driving.

ON-ROAD TESTING

Naturalistic Studies (Driving In Traffic)

Ramaekers (2003) reviewed 10 studies conducted to determine the effects of anti-depressants on actual driving performance, using a standard road test. In this standard test, a subject drives over a 100-km (62 mi) circuit on a primary highway in normal traffic. A licensed driving instructor rides in the front passenger seat in a vehicle with dual controls. During the one-hour drive test, the subject is instructed to maintain a constant speed of 95 km/h (59 mph) and a steady lateral position within the boundaries of the slower-traffic lane.[41]

The primary performance measure in this road test is an index of road tracking precision or "weaving": the standard deviation of lateral position (SDLP). SDLP is measured in centimeters, using an electro-optical device mounted on the rear of the vehicle which continuously records lateral position relative to lane-line delineation. A justification for using this measure is that in studies of the effects of marijuana on driving, SDLP has been found to be a more sensitive indicator of impairment than measures of following distance and general driving proficiency (Ramaekers, Berghaus, van Laar, and Drummer (2004). Ramaekers (2003) further states that SDLP is a very reliable characteristic of an individual's normal driving behavior, with high test-retest reliability, and is very sensitive to sedative drug effects. As such, it at least deserves consideration as a fitness-to-drive outcome measure for a wider range of drug studies.

It is important to note that SDLP has <u>not</u> been validated against actual crash involvement. Instead, performance decrements on this measure have been calibrated to blood alcohol concentration (BAC), which in turn is highly correlated with crash risk. An alcohol calibration curve was established, showing that drinkers' mean SDLP rose exponentially with BAC. Epidemiologic studies have shown that a BAC greater than 0.50 mg/ml is associated with an exponential rise in the relative risk of fatal traffic crashes (Borkenstein et al., 1964).[42] Ramaekers (2003) asserts that the results from the alcohol calibration study can be used to describe drug effects on SDLP in terms of BAC equivalents. For the standard driving test—which has not changed substantially in 70 studies spanning two decades—the change in SDLP associated with a BAC of 0.5 mg/ml, a 2.4 cm deviation in lateral lane position, is taken as the lowest criterion value defining drug-induced driving impairment.

Interestingly, Ramaekers (2003) found only relatively modest correlations between subjects' performance on seven conventional laboratory tests of psychomotor performance (e.g., divided attention, perceptual motor coordination, sustained attention, and working memory), subjective ratings of drowsiness, and performance on the standard driving test. The highest intra-subject correlations were found between SDLP and tracking test performance in the laboratory.

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[41] A 1995 "Note for Guidance" on psychotropic drugs in the European Union stressed that tests for assessing driver fitness should minimally last 1 hour, because motivational factors may affect the results of the tests.

[42] To convert to BAC terminology used in the United States, divide by 10; thus, 0.50 mg/ml = .05 grams per deciliter. [Consider just plugging in the .05 BAC number and omit the mg/ml conversion problem.]

The research reported by Ramaekers (2003) is noteworthy with respect to its use of an *objective* measure of *continuous* behavior while driving. Also of interest are on-road evaluations that score behavior in categorical terms (e.g., checked mirror versus did not check mirror before lane change); such studies in this review include Roenker et al. (2003), Janke (2001), Janke and Hersch (1997), DiStefano and MacDonald (2003), Mallon and Wood (2004), and Freund et al. (2002). Finally, many road test protocols rely exclusively on examiner ratings or other subjective means of scoring driver performance; studies of this nature that are reviewed below include Richardson and Marottoli (2003), Wild and Cotrell (2003), Duchek et al. (2003), DeRaedt and Ponjaert-Kristoffersen (2001), and Mallon and Wood (2004).

Roenker et al. (2003) designed a driving evaluation based upon a review of crash literature, traditional drivers' tests, and fitness-to-drive evaluations. They employed an on-road course, consisting of two loops through a 7-mile urban/suburban route. Repetition of the route was conducted to provide an opportunity for a range of traffic conditions to occur. The route permitted observation of maneuvers identified in the literature as especially difficult for older drivers (e.g., left turns across traffic). For each location where a potentially difficult maneuver was attempted, two back-seat raters coded the extent to which the driver's behavior constituted a dangerous maneuver—one which either required the driving instructor to take control of the car or one where other vehicles had to alter their course in order to avoid a collision. Three raters were trained on a total of 455 items until all scoring criteria could be consistently applied by all raters (interrater reliability was $r \geq .92$).

The following driving behaviors were rated on a scale of 0 (very unsafe) to 2 (safe or appropriate) in this research: maintaining lane position, activating signals, stopping smoothly, searching (additional mirrors were placed in the car to assist the raters in detecting eye movement), selecting gaps, accelerating and decelerating smoothly, turning, maintaining speed, maintaining position in traffic, and dangerous maneuvers. Stopping at a stop sign was rated on a four-point scale, where running the stop sign = -1, rolling through a stop sign = 0, stopping at an inappropriate position = 1, and 2 = an appropriate stop. After the drive, the raters also provided a global rating of the drive ranging from 1 (drive aborted/very unsafe) to 6 (very competent/safe).

The Roenker et al. (2003) driving evaluations were performed in a car modified with a passenger-side brake pedal for use as needed by a driving instructor. The driver was familiarized with the car prior to beginning the evaluation. Drivers were informed that they should drive as they normally would, and would follow route instructions given by the driving instructor. The driving instructor followed a script to ensure that instructions were standardized across drivers. Drivers were directed through a 1-mile warm-up route, and then drove through both loops of the 7-mile course. The evaluation was conducted during daylight hours and required 50 to 60 minutes to complete. Subjects consisted of 95 licensed drivers ranging in age from 55 to 86 with a mean age of 71.

The driver performance data were reduced by grouping a total of 455 items into 13 composites, based on the behaviors being rated. Four composites—gap selection, acceleration, deceleration, and right-of-way—were subsequently dropped from the analysis due to ceiling effects (performance was nearly perfect on most observation opportunities). In addition, the composite measure for "search" was dropped for lack of sufficient data, reflecting difficulty in reliably scoring this behavior. The dropped measures are shaded in the list below. The remaining eight composites, italicized below, were scored according to the multilevel rating

system described earlier, except for dangerous maneuvers, which were scored as an actual number of observed events.

- **Acceleration** – smoothness in use of the accelerator pedal
- **Gap selection** – safely merging into or crossing traffic flow
- *Position in traffic* – relative position to surrounding traffic while moving
- **Search** – eye and head movements at intersections
- *Signals* – proper and timely use of turn signals
- *Speed* – vehicle speed control relative to posted speed limits
- *Stop position* – vehicle position when required to stop at a traffic control device
- **Deceleration** – smoothness of deceleration of the vehicle
- *Tracking* – position of vehicle in the proper lane
- *Turning* – position of vehicle when turning
- **Right-of-way** – yielding to traffic at four-way stops
- *Changing lanes* – changing lanes on a multilane road
- *Dangerous maneuvers* – based on the observations of raters at 17 potentially dangerous locations during the test (including 6 unprotected turns across traffic, 9 left-turn entrances to a high-traffic road, and 2 opportunities for inappropriate stopping in traffic to make a right turn)

This research deserves attention due to its careful design, seeking measures for a comprehensive range of behaviors that could be meaningful in gauging the safety of older drivers. Unfortunately, some of those measures with the highest construct validity in explaining maneuver errors at intersections, where older drivers are at greatest risk, did not yield usable data in this investigation. Their application in future studies may also be questioned, accordingly.

Specific strengths of the measurement methods employed by Roenker et al. (2003) included:

- repeating the route to allow the subject to become more comfortable with the evaluation process and to make it more likely that the driver would revert to everyday driving behavior;

- use of scales including four levels rather than a simple pass/fail judgment to allow for finer gradations in the observation of on-road driving behaviors;

- use of two raters to evaluate driving behaviors, rather than one evaluator, plus checking for (and confirming) high inter-rater reliabilities, bolstering claims that driving behavior was judged objectively;

- use of a fuller range of driving behaviors than assessed in prior research, grouped into composites which in turn were made up of numerous samples of driving behavior rather than a single instance; and

- evaluations were conducted across all daylight hours (7 a.m. to 5 p.m.) to encompass a wide range of driving conditions.

Next, an on-road standardized driving test was developed in research performed by Richardson and Marottoli (2003) to determine which driving behaviors and situations are related to cognitive risk factors such as visual attention and spatial abilities in older people. Thirty-five community-dwelling active drivers 72 and older underwent the driving evaluation, as well as tests of visual attention, executive function, visuospatial cognition, and memory. The cognitive measures included the logical memory (verbal memory) and visual reproduction (visual memory) of the Wechsler Memory Scale-Revised, the Hooper Visual Organization Test (visuospatial cognition), the number cancellation task (visual attention), the Trail-Making Test Part B (executive function), the Symbol-Digit Modalities test, and experimental measures of simple, choice, and complex reaction times. The driving test was taken from the 36-item relicensing exam used by the Connecticut Department of Motor Vehicles for individuals referred for examination because of medical reasons. The only change made to the exam was in the scoring procedure. Instead of coding items as "pass" or "fail," items were coded on a 3-point system, as follows: major errors/unsafe (0 points); minor errors (1 point); and good/no errors (2 points). The maximum number of points attainable was 72. The 36-item scale used to evaluate driving skills for a separate set of 357 older drivers showed high internal consistency when used by two evaluators.

The road test employed by Richardson and Marottoli (2003) began with parking lot maneuvers, and progressed to suburban roads in urban downtown traffic, and to driving on limited-access highways. The road course was 20 miles long and required 45 to 60 minutes to complete. A driving therapist riding in the passenger seat of a dual-brake equipped vehicle evaluated each participant's driving skills. Road test scores ranged from 14 to 72. Visual attention was associated with 25 of 36 driving items, highlighted with an asterisk in the list below, and included scanning the environment, interacting with other road users, and monitoring speed and judging distances appropriately. Visual memory was associated with 16 maneuvers, and executive function was related to 17 maneuvers. Most of these maneuvers overlapped with visual attention.

- Scan to sides*
- Scan to rear/head check
- Uses mirrors
- Uses safety belt
- Responds to traffic signals*
- Responds to vehicles/pedestrians*
- Grants right-of-way*
- Centers car in lane*
- Safe following distance*
- Uses directional signals*
- Positions car for turns*
- Proper lane selection*
- Gas-to-brake reaction time*
- Appropriate steering recovery*
- Acceleration
- Braking*
- Shifting
- Right turns
- Left turns*
- Backing up
- K turns
- Angle parking
- Low-density traffic*
- Simple traffic situations*
- Medium traffic situations*
- Limited access highway*
- Enter
- Exit*
- Merge*
- Lane change*
- Speed regulation*
- Follows directions*
- Judgment*
- Decision-making*
- Memory
- Attitudes and emotions*

Visual attention accounted for 18 percent of the variance on the road test after controlling for the effects of visual acuity, and was associated with over half of the specific driving maneuvers. The authors point out that the maneuvers with the greatest association with visual attention (scanning the visual field for potentially dangerous obstacles, maintaining one's speed and distance with respect to other vehicles, yielding the right of way, and negotiating turns or merges safely) are also those most often associated with older driver crashes. These results suggest that driving tests to determine the effects of medications should include these maneuvers, to increase sensitivity for visual attention deficits.

An on-road standardized driving test was used by Wild and Cotrell (2003) to compare actual driving performance to self-reported and caregivers' perceptions of driving ability for a sample of 15 healthy elderly subjects and 15 elderly subjects with mild Alzheimer's disease (mean age = 72.7). Caregivers generally included spouses or other family members living with the driver, or close friends (in the case of a subset of the healthy elderly). Criteria for participation by the healthy elderly controls (recruited from the Oregon Brain Aging Study) was a Clinical Dementia Rating (CDR) score of 0, independence in daily activities, no chronic medical conditions, and not taking any medications that affect cognition. Alzheimer's disease patients were recruited from the Aging and Alzheimer Disease Clinics and the Portland Veteran's Administration Medical Center. Nine of the Alzheimer's disease (AD) patients had a CDR score of 0.5 and 6 of the AD patients had a CDR score of 1. All subjects were required to have a valid automobile driver's license, health and automobile insurance, and drive a minimum of once a week.

Prior to participation in the road test, subjects in the Wild and Cotrell study were advised that they would be referred to the DMV for further evaluation if their driving performance was of concern to the evaluator. Of all patients contacted, 16 declined, giving reasons such as lack of interest in the study or inconvenience due to scheduling conflicts or distance required to travel. While acknowledging a possible selection bias against less confident or less able drivers, i.e., due to the fear of losing their driving privileges, the authors cite other researchers who have been successful in recruiting subjects with a wide range of deficits and driving abilities in similar research (Hunt et al., 1993; Carr et al., 1991).

The principal relevance of this study to the current study topic lies in the cognitive abilities necessary for safe driving. Drivers with mild dementia have been reported to have a crash rate that is only slightly higher than drivers of all ages in the United States, and well below that of drivers age 16 to 24, during the first three years of the disease (see Staplin et al., 1998 for a review of dementia and diminished driving skills). Side effects of commonly used CNS medications include cognitive impairment (sedation, decreased alertness, poor concentration, mental slowing or confusion, impaired judgment) while under the influence of the medication. The road test used in this study was sensitive to the effects of cognitive decline associated with AD, and could also, theoretically, be a sensitive measure of the effects of cognitive decline associated with medications.

The on-road driving evaluation in the Wild and Cotrell (2003) study was conducted by a certified driver rehabilitation specialist (CDRS) in a dual-controlled automobile, on a standardized test route in a residential neighborhood in an area unfamiliar to participants. The

route included intersections, lane changes, stop signs, and traffic signals, and segments at pre-determined intervals when the evaluator engaged the subjects in conversation to determine ability to attend to driving, navigation, and engaging in conversation simultaneously.

The driving evaluation began with a 30-minute familiarization with the test car, followed by approximately 60 minutes of on-road test time. Drivers were evaluated using a 10-item assessment that is an abbreviated version of the assessment used at the Portland Oregon Veteran's Administration Medical Center. Items were selected to represent the most frequent driving errors and causes of crashes among patients with AD as well as older drivers in general; many of the items follow the Oregon DMV guidelines for driving evaluations. The 10 items, listed below, were rated on a 5-point scale from "very good" to "very poor."

- Manages intersections
- Manages lane changes
- Maintains lane position
- Maintains proper speed
- Follows at a safe distance
- Signals in time
- Uses mirrors appropriately
- Responds to road conditions
- Responds to warning road signs
- Handles conversational distraction

The AD patients performed significantly worse than the healthy elderly controls on all 10 driving behaviors, as rated by the experienced CDRS, who was blinded to the subjects' cognitive status and group membership. AD patients rated their driving performance better than the evaluator's ratings on 7 of the 10 items; healthy controls evaluated their performance better than that of the driving evaluator on only one item (manages intersections), and significantly worse on one other item (handles conversational distraction). AD patients' self-reports of driving ability mirrored healthy elderly drivers' self-reports of driving ability for 9 of the 10 items, indicating that patients with AD are not cognizant of their diminished driving capabilities. Caregivers' perceptions of driving ability were similar to the evaluator's assessments in all but two areas: managing intersections and responding to warning road signs.

Another study of the driving performance of individuals with AD using on-road testing was carried out by Duchek et al. (2003). In this investigation, 41 percent of older subjects with mild dementia of the Alzheimer's type (CDR = 1) failed a 45-minute in-traffic road test, compared to 14 percent of older subjects with very mild AD (CDR = 0.5) and 3 percent of healthy older subjects (CDR = 0) . The mean age of the 108 participants was 74.9. Participants, who were recruited from the Alzheimer's Disease Research Center at Washington University School of Medicine, knew that their driving skills would be assessed. They were screened for depression, reversible dementias, and other disorders that could produce cognitive impairment. Almost half of the potential subject pool declined participation in the study (28% with CDR = 0; 44.9% with CDR = 0.5; and 27.1% with CDR = 1). No significant differences were found in age, education, gender, and Short Blessed Test of cognitive abilities (a six-item test of orientation, concentration and memory) between study participants and those who declined participation.

Driving performance in the Duchek et al. (2003) study was assessed using the Washington University Road Test in a standard car with dual brakes. This open-course test was conducted in traffic and assessed the following driving skills: maintaining speed, obeying traffic signs, signaling, turning, yielding right of way, changing lanes, reacting to other drivers, and

negotiating intersections. These skills were scored on a 2- or 3-point scale yielding a quantitative driving score between 0 and 108 (perfect performance) by a driving instructor who sat in the front passenger seat and the study investigator who sat in the back seat. In addition, the two raters independently assigned a global rating of safe, marginal, or unsafe as an expert clinical impression of driving performance. The inter-rater reliability of the global rating was high (k=0.85).

Subjects participated in four road tests, administered at 6-month intervals. Two driving behaviors—lane change and using signals—were impaired with increasing dementia severity. Only three driving behaviors showed a significant decline from the first to the second test administration—*qualitative judgments* (e.g., comprehension of directions, attention to task, awareness), *reacts to others* (e.g., an awareness of how one's driving affects others), and *speed control*. These were independent of CDR group status. The authors note that these behaviors represent the more complex cognitive skills involved in driving (e.g., awareness of the driving environment and decision making) rather than the specific mechanics of driving, such as signaling. These three behaviors were also highly correlated with the global ratings during the first test administration.

Analysis of driving performance over time indicated that subjects without AD (CDR = 0) took significantly longer to receive a rating of not safe than subjects with mild dementia (CDR=1). Subjects with very mild dementia (CDR = 0.5) fell somewhere between the healthy and mild dementia groups. The majority of drivers with mild AD were judged unsafe either at the first test administration, or during follow-up testing within the two-year period. These findings point to aspects of driving performance that should be assessed in any on-road study to measure driver functioning among older people with possible cognitive impairment—including impairment from the use of medications.

De Raedt and Ponjaert-Kristoffersen (2001) used an on-road test to evaluate fitness to drive for 84 licensed, active older drivers (age 65 to 96) who were referred by their insurance company following one or more crashes or by their physician. One of the objectives of this study was to determine whether the road test was predictive of four types of at-fault crashes: *crossroad*, *rear-end*, *side-swipe*, or *parking*.

Self-reported at-fault crashes during the prior 12-month period were assessed using a questionnaire. The number of crashes per subject ranged from 0 to 4. Sixty-three percent of the subjects reported at-fault crashes over the previous year. The road test was administered by two driving instructors from the Belgian fitness-to-drive evaluation center in a car equipped with a dual brake. The 45-minute road test was conducted over a standardized 35-km (21.7 mi) route in and outside of town areas in Brussels and on a highway, and included maneuvers such as lane changing, turning left, and merging with traffic. Examiners completed a detailed evaluation grid that consisted of 11 dimensions, as follows. Each dimension was rated on two or more 3- and 4-point subscales.

(1) Lateral position on the road: lateral positioning and steady steering control
(2) Lane position change: lane choice
(3) Distance from the car in front: style and adaptation

(4) Speed: style and adaptation
(5) Visual behavior and communication: eye/hand movements, and contact with other road users
(6) Traffic signals: perception and reaction
(7) Mechanical operations: fluency and timeliness of steering and pedal control
(8) Anticipation: tactical anticipatory behavior in changing situations
(9) Understanding, perception, and quality of traffic participation: insight, sense of context, and practical implementation
(10) Turning left: specific situation, into main road
(11) Joining the traffic stream: specific situation on the highway

The evaluation grid was developed at the neuropsychology/gerontology department of the University of Groningen (the Netherlands) by Brouwer, Ponds, and van Woffelaar (1989). Content validity was addressed using driving assessment experts from the Dutch fitness-to-drive assessment Center and the CARA department of the Belgian Road Safety Institute. Consistent with the strategic-tactical-operational conception of driving associated with Michon (1985), the 11 dimensions assessed in this study were sorted into three scales. The scores on 3 dimensions (#5, #6, and #9 above) were combined to produce a visuo-integrative scale. The scores on 2 dimensions were combined to produce an operational scale (#1 and #7 above), reflecting psychomotor aspects of driving psychomotor. The scores on 4 dimensions (#2, #3, #4, and #8 above) were combined to produce a scale reflecting tactical choices (driving style).

De Raedt and Ponjaert-Kristoffersen (2001) found that the tactical and visuo-integrative scales each predicted at-fault crashes at crossroads, the crash type in which older drivers are most strongly overrepresented. The visuo-integrative scale also predicted rear-end and side-swipe crashes, for this older sample. The operational scale failed to predict at-fault crashes of any type.

On-road measures based on a modification of the California Driver Performance Evaluation (DPE) were used in research reported by Janke (2001) and Janke and Hersch (1997). The DPE measures these constructs: visual search, speed control, and directional control. It is designed to detect a fixed number of possible errors, and features objective criteria for scoring specific (structured) maneuvers at specific locations. Examples of structured maneuver errors include “inadequate traffic check,” “poor lane position,” and “turns too wide (or too short).” The *Modified* Driver Performance Evaluation (MDPE) differs from the DPE in that it omits freeway driving, while adding a destination-finding task that requires a subject to safely return to the field office after being directed to drive a short distance past the office. The destination driving task was incorporated to test for possible cognitive impairment. Test times range from 30 to 45 minutes. The MDPE includes these maneuvers:

- 4 left turns and 4 right turns (mixed difficulty levels; 2 left turns and 2 right turns with multiple lanes requiring correct lane choice on approach and finish; 1 left and 1 right turn at signal controlled intersections; 2 additional turns, preferably at stop controlled intersections but may be uncontrolled with limit lines, crosswalks, turn lanes)

- 8 through intersections (2 controlled by a light [red, yellow, and green]; 2 controlled by a stop sign; 2 through/straight ahead intersections not involving stops; 2 additional intersections preferably controlled by traffic lights)

- Merging at a lane drop

- Curve negotiation (preferably a left curve; lanes should be marked, must require driver to adjust speed)

- 3 lane changes (1 left, 1 right, 1 located anywhere on the route, preferably at higher speeds)

- Minimum of 3 blocks of driving in a business area with moderate traffic density

- Minimum of 3 blocks of driving in a residential area preferably with narrow streets

- Performing parking lot maneuvers, backing, and a street park

A subset of errors defined as *critical driving errors* was listed in a separate section of the DMV score sheet. These are serious errors; under normal testing circumstances (i.e., other than a research situation), a driver's test would immediately be terminated. Such errors include: examiner intervention required (to avoid crash); driver strikes object; drives up/over curb or sidewalk; drives in oncoming traffic lane; disobeys sign/signal; dangerous maneuver; inappropriate reaction to school bus; inappropriate reaction to emergency vehicle; inappropriate speed; inappropriate auxiliary equipment use; turn from improper lane.

A subset of critical errors was also defined as *hazardous errors*, with the belief by the CA DMV that these errors are the strongest indicators of driving impairment. The hazardous error subset included "dangerous maneuver" and "examiner intervention required."

A weighted error score served as the primary criterion (dependent) variable for the driving performance analyses. This score was calculated by adding the total number of errors (regardless of severity) to twice the sum of critical and hazardous errors. Since hazardous errors were a subset of critical errors, and critical errors were a subset of total errors, this scheme weighted hazardous errors by a factor of five and other critical errors by a factor of three.

Confusion (concentration) *errors* were also recorded, when a subject was unable to proceed to field office at end of test, or drove past the street on which the field office was located and did not recognize their error.

In the study described by Janke (2001) and Janke and Hersch (1997), 75 subjects age 60 to 91, who were referred to the DMV from various sources for reexamination, were compared to 31 paid "volunteers" age 56 to 85, who were recruited through signs posted at study sites or word-of-mouth. Analyses were performed to determine if the MDPE could discriminate between the referral and volunteer subjects, and if it could discriminate between the cognitively impaired and cognitively unimpaired referral subjects. Results indicated significant correlations between

the following driving measures and group (referral versus volunteer): unweighted errors (.460); weighted errors (.470); hazardous errors (.388); critical errors (.386); and confusion errors (.418). Test failure was not significantly correlated with group. The following variables were also significantly correlated with age: unweighted errors (.395); weighted errors (.409); and critical errors (.355).

Cognitively impaired referrals had significantly more "confusion errors" than cognitively unimpaired referrals. However, there were no significant differences between cognitively impaired referrals and cognitively unimpaired referrals on total errors, critical errors, or hazardous errors (although every driving measure showed a directional difference in favor of the cognitively unimpaired subjects). The authors emphasize the value of "confusion" errors for predicting cognitive impairment, and suggest that a standardized test for older drivers who are experienced but possibly cognitively impaired should contain a task similar to the destination-finding task in the MDPE, i.e., a task that demands more than passively following an examiner's instructions. In future work undertaken by NHTSA to investigate drugs and driving, such a task could help identify subjects who are cognitively impaired as a consequence of taking sedating medications or medications that cause deficits in concentration, or combinations of medications that result in such cognitive deficits.

Di Stefano and Macdonald (2003) conducted a retrospective case review study using data from 533 road tests performed by drivers referred for a VicRoads (Victoria, Australia) licensing review test to obtain detailed information about the types of driver errors most characteristic of unsafe drivers. The average age of the tested drivers was 76.1, with a range of 24 to 100; 47 percent of the drivers were older than 80. The purpose was to develop an improved procedure for occupational therapy assessments of functionally impaired and older drivers, with a focus on optimizing the performance scoring system used in the tests.

The "on-road review test" was given to drivers referred to VicRoads because of a concern about their driving competence, but who had not been identified by their physician as having "complex medical conditions or significant cognitive impairment." It was administered by a VicRoads License Testing Officer (LTO) who specializes in older driver testing. The test was conducted in an automatic dual-control car, beginning at the driver's home and encompassed routine travel destinations (shopping, doctor's office, etc.). The routes were therefore not standardized. Drivers were provided with an initial familiarization period in the vehicle, and were then tested during a 30- to 45-minute period, usually in off-peak traffic conditions.

Criteria used to score driver performance included errors in each of six main categories: intersection negotiation, lane changing/diverging, speed and position on road, safety margin, car control, and low-speed maneuvers. The LTO used a scoring sheet that lists each performance category, and within each category, a list of separately scored behaviors was also scored. Behaviors were recorded as "satisfactory" or "unsatisfactory" and comments were made only to document details. If an LTO needed to intervene to maintain safety, this was recorded as "LTO intervention" in relation to the driver performance category, and the context in which the intervention was documented.

In the Di Stefano and Macdonald (2003) study, the most common errors (across all 533 tests) made during *intersection negotiation* tasks were: failure to check mirrors (69% of tests), failure to use turn signals (49% of tests), poor gap selection/judgment (43% of tests), poor positioning on the road when turning (39% of tests), failure to obey the sign or signal (30% of tests), and poor approach (unsafe speed before an intersection/rough deceleration) on 14 percent of tests. The most common errors related to *lane changing* included: failure to turn the head to check back over the shoulder (62% of tests), failure to use turn signals (31% of tests), failure to check mirrors (26% of tests), and poor gap selection (10% of tests). The most common errors related to *low-speed maneuvers* included: failure to turn the head to check back over the shoulder (45 % of tests), failure to check mirrors (13% of tests), and failure to use turn signals (12% of tests). The fail rate was 49 percent (261 of 533 tests).

On all but 9 of the tests where there was a failure, there was *at least one LTO intervention*; for tests with an intervention, the mean number per test was 3.6 with a maximum of 12. The most frequent problems causing LTO intervention involved errors associated with intersection negotiation, failing to yield or poor gap selection, failing to maintain the vehicle in the appropriate position on the road, inappropriate speed (either too fast or too slow), and problems with low-speed maneuvers. Although test outcome was almost always determined by LTO intervention, the variables most strongly associated with failing were scores relating to intersection negotiation, maintenance of position and speed, and safety margin. Not surprisingly, these are the types of performances associated with LTO intervention. The authors compared the errors leading to LTO intervention in this study to the "hazardous errors" reported by other researchers.

Di Stefano and Macdonald (2003) also looked at the influence of medical condition on road test fail rate. The most commonly reported medical conditions were cardiac (e.g., hypertension), endocrine (e.g., diabetes), musculoskeletal (e.g., soft tissue disorders), visual (e.g., only one functioning eye), arthritis (e.g., osteoarthritis), and mental/behavioral (e.g., affective disorders). There was *no relationship between number of medical conditions and test outcome, nor was there a significant relationship between category of medical condition* (primarily physical, primarily cognitive, or mixed) *and test outcome* (pass or fail). There was, however, an apparent effect of physical impairment on car control, where arthritis emerged as the condition with the highest fail rate (61% of the subjects with arthritis failed).

There was a significant relationship between age and test outcome in this research. Fail rate increased sharply from 0 percent for subjects under age 54, to 38 percent for subjects 75 to 79, to 71 percent for subjects 85 and older. The highest correlations between performance scores and age were for intersection negotiation, followed either by position and speed (with test outcome) or lane changing (with age). These were followed by low-speed maneuvers, car control, and safety margin.

Di Stefano and Macdonald (2003) concluded that the set of performance scores developed in the study provide a generally valid indicator of the unsafe behaviors most typical of older drivers. This is supported by the relationship of the performance scores and LTO interventions, and by the fact that the addition of age to the regression model after entry of the performance scores explained very little additional variance.

The last on-road study including older drivers considered in this review was conducted by Mallon and Wood (2004). In this study, 137 participants in two vision groups and three age groups underwent an on-road driving assessment in a dual-brake vehicle. Ninety participants had normal vision and were divided into three age groups: young (mean age = 27); middle-aged (mean = 52), and older (mean = 68.9). A second group of older participants (mean age = 71) were diagnosed with visual impairment resulting from ocular disease. Prior to the on-road test, subjects underwent a 20- to 30-minute cognitive assessment using the Barry Rehabilitation Inpatient Screening of Cognition.

Driver performance was assessed for each subject by an occupational therapist and a driving instructor, both with a specialization in driver assessment. The route and maneuvers are described by the authors as "having sufficient duration and complexity to allow assessment of a variety of driving situations and maneuvers, and sufficiently challenging to allow manifestation of visual or cognitive deficits or both." It was designed based on clinical open-road assessments in use by occupational therapists of a major rehabilitation center in Australia, closely matching an assessment by Odenheimer et al. (1994) where test scores correlated highly with cognitive ability, and high internal reliability was shown. The 15-km route involved particular driving situations and associated maneuvers at predetermined locations, and required approximately 50 minutes to complete. It consisted of city and suburban streets, simple and complex intersections, and exposed drivers to a range of traffic densities.

The occupational therapist recorded driving performance across a sequence of 106 locations. The associated driving situations and maneuvers were divided into the following nine categories, with number of locations noted in parentheses: roundabouts (3); merging (2); car parking (5); traffic-light-controlled intersections (20); non-traffic-light-controlled intersections, stop and yield (13); reversing (1); emergency brake (1); straight driving on single and dual carriageway (50); and lane changing (11). At each location, seven components of driving performance were assessed that included: general and blind spot observation, indication, braking-acceleration, lane positioning, gap selection, and approach. Failure of any aspect of performance resulted in failure of the whole task for a given location/maneuver.

For 84 percent of the locations (89 out of 106), the participant drove as instructed by the driving instructor ("directed navigation"). For 16 percent of the locations, participants were asked to find their way to a specific destination ("self-directed navigation"), using cues such as road signs and road markings to determine what route to take. Road test performance was defined as the overall score for the number of correct maneuvers out of a total of 106. In addition, the driving instructor provided an overall global rating of safety ranging from 1 to 10.

In Mallon and Wood's study, all subjects performed better under instructor-directed navigation tasks than under the self-directed navigation tasks. There was a significant effect of age, with the older subjects performing worse on both the instructor-directed and self-directed navigation tasks than the two younger age groups. The older drivers with visual impairments made significantly more errors under both directed and self-directed navigation. Considering the number of errors made by each group for each category of location/maneuver, there were significant group differences at all locations except emergency braking. The young and middle-aged drivers performed better than the older drivers in both vision groups, and the older drivers

with ocular disease performed worse than the normal-sighted older drivers for merging and straight driving locations. Age group differences in road test performance were greatest for traffic-signal controlled and non-signal controlled intersections, roundabouts, merging, lane changing, and straight driving.

The driving scores measured by the occupational therapist and the driving instructor were significantly positively related. The cognitive test scores and the occupational therapist's assessment of driving performance were significantly positively related, as were the cognitive test scores and the self-directed component driving score. The cognitive test scores were also significantly positively related to the driving instructor's safety rating. The cognitive tests, however, explained only 4.8 percent of the variance in the occupational therapist's scores for directed navigation and 14.4 percent of the variance in the occupational therapist's scores for self-directed navigation. This highlights the fact that cognitive tests cannot be substituted for on-road tests for determinations of fitness to drive.

The road test used in this study was sensitive to the number and types of driving errors made, and the locations/maneuvers where these errors occurred, making it a strong candidate for assessment of fitness to drive for future studies of older drivers and polypharmacy. The assessment reflected only the numbers and types of errors, however, not their severity. The study authors are currently examining a modified on-road scoring assessment that uses weighted criteria to denote degree of severity of driver errors.

Controlled Driving (Closed Course)

Wood (2002) employed a closed-circuit road test to study the effects of age and visual impairment on driving performance. Visual function was assessed with a battery of tests. The 139 participants were divided into the following five age and visual performance groups: young subjects with normal vision (mean age = 27); middle-aged subjects with normal vision (mean age = 52); older subjects with normal vision (mean age = 69); older subjects with mild ocular disease (mean age = 71); and older subjects with moderate/severe ocular disease (mean age = 71).

The test circuit was 5.1 km (3.2 mi), and participants were given a practice run in the opposite direction of the circuit to reduce familiarity effects. Two experimenters rode with each subject. The driving assessment tasks in this study were selected to provide a relatively high degree of complexity, and included road sign recognition, road hazard recognition and avoidance, lateral gap perception, a divided-attention task, a maneuvering task, and a reversing/parking task.

The road sign recognition task included 42 standard road signs located throughout the course, with a total of 65 items of information. Participants were required to report the information they saw on the signs. The total number of correctly identified items was recorded. The road hazard recognition and avoidance task employed nine 1 x 2.2 m (3 ft x 7 ft) sheets of 80-cm (30-in) thick gray foam placed on the roadway throughout the circuit. For hazard recognition, study participants were instructed to report when they saw a hazard and to avoid it by steering around it. The number of road hazards reported and the number hit were recorded.

For the gap perception task, nine pairs of traffic cones, with variable (lateral) spacing, were placed throughout the course. Six of the nine cone gaps were wide enough to drive through and three were too narrow. Participants were instructed to report when they saw a pair of cones and whether or not there was space to drive through them, and if so, to attempt the maneuver. If the gap was judged to be too narrow, participants were instructed to state so, and to drive around the cones. The number of correct gap widths was recorded, as was the subject's ability to maneuver through or around the cones without hitting them.

For the divided attention task, five LEDs were mounted on the windshield, spaced at even intervals at the driver's eye level. Each LED was illuminated three times throughout the run, and subjects were instructed to lightly tap the brake pedal in response to each LED illumination. The number of LEDs seen was recorded. The maneuvering task involved maneuvering through a series of nine cones separated by approximately 1.5 car lengths, placed on a straight section of the circuit. The cones were light gray to increase the visual requirements of the task, with the exception of the cones on each end, which were high contrast. The time to complete the task and number of cones hit were recorded. Two reverse/parking tasks were required, where participants backed the car into a standard-sized parking space marked with four high-contrast poles 1.2 m (4 ft) high, positioned at each of four corners of the parking space. Participants were instructed to reverse the vehicle so that it finished as straight and as centered within the space as possible; forward and reverse movements were allowed to accomplish this goal. The mean time to complete the task and the angle of the car within the space were measured.

Analysis of the driving measures indicated that they were not highly correlated, with the exception of hazards seen and hit. A composite driving score was derived that included road sign recognition, cone gap perception, maneuvering through cone gaps, number of divided attention lights seen, course completion time, and a combined score for hazard detection and avoidance. Older drivers with either normal vision or visual impairment had poorer driving performance compared with younger and middle-aged drivers with normal vision. Overall driving score also decreased for the older participants with ocular disease, as compared to those with normal vision. The driving tasks that involved recognition or divided attention, or that were timed (e.g., the road sign test, the LED task, and the course completion time) were most impaired in the older drivers. In contrast, the ability to recognize and avoid the road hazards was affected by visual status, but not age.

Wood (2002) notes that although the road circuit was free of other vehicles, it contained a relatively high information load in terms of the required driving tasks. A similar methodology could be applied to measure driver performance as a function of medication use, as it tests visual, perceptual, and cognitive skills as well as vehicle handling skills.

DRIVING SIMULATION

As noted earlier, the term "driving simulation" has been applied to diverse methodologies that may usefully be distinguished according to their degree of interactivity with the operator/test subject, the fidelity of the visual and/or motion cues provided to operators, and the performance measures obtained. For purposes of this review, three levels of simulation will be considered:

- Level III: Interactive, computer graphic visuals, full motion.

- Level II: Interactive, computer graphic visuals, restricted motion or no motion.
- Level I: Noninteractive, computer graphic and/or digital video visuals, no motion.

Level III: Interactive, Computer Graphic Visuals, Full Motion

This level of simulation is exemplified by NHTSA's National Advanced Driving Simulator (NADS) at the University of Iowa, and by facilities at a number of automobile manufacturers (e.g., Ford, DaimlerChrysler). A complete vehicle is mounted on a (at least) six-degrees-of- freedom motion platform that provides realistic cues for all vehicle maneuvers experienced in the simulator. A full, 360° field of view is available, using projected computer graphic images (CGI) that are redrawn at 60 Hz or better with no perceptible delay between a control input (e.g., steering wheel movement) and a change in the external (simulated) environment. Resolution of the CGI displays is not "photo-realistic," limiting certain kinds of studies (e.g., sign legibility), and real-world contrast gradients are difficult to obtain, which may pose a challenge for nighttime driving simulations; but these are fully immersive virtual environments that—theoretically—should allow measurement of almost any driver behavior that could be monitored in the real world, plus high-risk situations to which a subject can *only* be exposed to in a simulator.

Contacts with a representative of the National Advanced Driving Simulator facility at the University of Iowa were made during this review.[43] These revealed that, while this facility has been used to investigate the effects of drugs and medications on driving, all recent studies of this nature have been funded by private industry sponsors, and the specific research designs as well as the results are regarded as proprietary information. An earlier study of interest using the Iowa Driving Simulator (IDS), a precursor to NADS, was identified in the technical literature, though.

Weiler et al. (2000) used the IDS in a randomized, double-blind study to measure "coherence" – a subject's ability to continuously match variations in the speed of a car the driver is following – among individuals dosed with the antihistamines fexofenadine (60 mg) or diphenhydramine (50 mg); with alcohol (.10 BAC[query—is this the Euro mg/ml number, or the "American" number that should be divided by 10?]); or with a placebo. Secondary measures obtained in the IDS included lane keeping (steering instability and center line encroachments) and the latency of response to a vehicle that unexpectedly blocked the lane ahead. Subjects also provided self-reports of drowsiness. It should be noted, however, that *no older subjects participated in this study*; the sample ranged in age from 25 to 44.

The principal conclusions in the Weiler et al. (2000) report were that subjects had significantly better coherence in car following after taking alcohol or fexofenadine than after taking diphenhydramine. Alcohol impaired the secondary tasks, especially response time to the blocking vehicle, but overall driving performance was poorest among the study participants who took the diphenhydramine. Self-reports of drowsiness were not a good predictor of impairment on the primary or secondary tasks in this study. Based on these results, the report authors issue a special caution regarding the use of "first-generation" (sedating) antihistamines, suggesting that they "*… may have an even greater impact than does alcohol on the complex task of operating an automobile.*"

[43] *Pers. comm..* from Dr. Ginger Watson to L. Staplin via telephone conversation March 4, 2005.

While this study illustrates the potential applicability of high-end simulation methods to future investigations into the effects of medications on driving, a number of criticisms about this work voiced in letters to the editor of the *Annals of Internal Medicine*, where the study was published, also deserve mention. One body of criticism concerns the primary dependent measure, coherence, citing evidence that this measure of driver performance bears a weaker relationship to safety than the related measures of "modulus" (amplitude of response) and, especially, the *delay* in a driver's response to a speed change by a lead vehicle. Other criticisms draw attention to the fact that the research was funded by the manufacturer of fexofenadine, and that two of the authors are consultants to this company.

Perhaps more pertinent to the present discussion are problems associated with older subjects and prescription drug use that have been encountered across a wide range of studies conducted at IDS/NADS. As per the contact identified above, particular care must be taken with older people to ensure that any/all drugs/medications they are taking have been metabolized well past the point of peak concentration, because it is their experience at the Iowa facility that many medications make older people more susceptible to simulator sickness. Subjects' consumption histories for at least 12 hours prior to study participation are accordingly taken into account. This experience would seem to point to what is, at least potentially, a serious challenge to future NHTSA studies where the explicit goal is to investigate the effects of drugs and medications on the driving behavior of older people.

Level II: Interactive, Computer Graphic Visuals, Restricted or No Motion

This level of simulation is exemplified by numerous commercial platforms offering driving scene displays on one, two, or three screens that typically provide a field of view (FOV) of roughly 60° on each screen; and a "cockpit" including driver's seat plus brake and steering wheel/column assembly, sometimes from an actual vehicle. Motion cues, if any, are likely to be limited to "force feedback" on the vehicle controls and a belt tensioner system that constricts during simulated deceleration and is loosened during simulated acceleration. A high frequency "road vibration" element may be added, too. As for the realism of the visual displays – the same limitations apply as noted above for the high-level simulators. In addition, with these more modestly priced (less than $100,000) systems, problems with aliasing and with "pop-ups"—where the level of detail in a scene is such that not all elements can be redrawn without a perceptible delay, and objects, especially at the horizon, abruptly pop into the scene—are more likely to occur. An argument can be made that an equally wide range of driver behaviors at the *tactical* level could be examined in these simulators as can be examined in the high-level simulators, though of course advanced vehicle maneuvering skills at the *operational* level (e.g., recovering from a skid) cannot similarly be evaluated. Unfortunately, the increasingly wide-spread use of this class of simulators, for driver training as well as research applications, has indicated that simulator adaptation syndrome ("simulator sickness") affects a sizeable minority of subjects/trainees, with older people being especially vulnerable.

Documented research studies pertinent to NHTSA's interest in polypharmacy that are accessible to searches in the open scientific literature appear to have most often been conducted using "Level II" simulation methods.

As one example of such research, Szlyk et al. (2004) used a driving simulator to research visual deficits resulting from diabetic retinopathy. This was an interactive device that included a seat, steering wheel, gas and brake pedals. The visual display consisted of three 62.5-cm (24-inch) color monitors displaying a total 160° horizontal viewing field and a 35° vertical viewing field of a computer-generated environment to a driver sitting 57.5 cm (22 inches) from the center screen. As previously described by Szlyk, Brigell, and Seiple (1993), stimuli are computer-generated images of a simulated roadway with traffic, signs, and painted roadway lines. The visual scene is updated 20 times per second (the minimum rate to avoid a perceived "choppiness" in the visual display). Simulator performance measures of effectiveness in the research by Szlyk et al. (2004) included:

- Speed (mean speed in miles per hour)
- Gas-pedal pressure (mean force applied to gas pedal)
- Gas-pedal pressure SD (SD of the force applied to gas pedal)
- Acceleration (mean of 5 speed points after a complete stop at a stop sign)
- Brake-pedal pressure (mean force applied to brake pedal in arbitrary units)
- Brake-pedal pressure SD (SD of the force applied to brake pedal)
- Brake-response time (mean time in seconds elapsed between when a stop sign is displayed and when force is applied to the brake pedal)
- Response time (mean time in seconds elapsed between when a stop sign is objectively displayed and when no force is applied to the gas pedal)
- Brake-response slope (mean deceleration calculated as the ratio of change in speed to change in time before a complete stop at a stop sign)
- Brake duration (mean time in seconds that force is applied to the brake pedal).
- Ran stop sign (number of stop signs ran)
- Ran red light (number of red lights ran)
- Off-lane time (total time in seconds spent over the left yellow line during the course)
- Off-road time (total time in seconds spent off road to the right onto the road's shoulder)
- Near accidents (number of situations in which an accident is narrowly averted, as determined by an experienced observer)
- Accidents (number of collisions with other cars or objects)

In the Szlyk et al. (2004) study, 25 licensed drivers with diabetic retinopathy with a mean age of 53 (range = 34 to 72) practiced on the simulator for 15 minutes on a training course before completing the 8-minute evaluation course. They were instructed to "drive" as they normally would in their own cars, and to obey traffic rules. During the evaluation, subjects were required to respond to stop signs, traffic lights, and road hazards. While the particular results of the study are not relevant to the current research topic, the Szlyk et al. (2004) study illustrates the use of a simulator to measure aspects of driving performance that likely would also be of interest in NHTSA studies of the effects of multiple medications on driver behavior.

Lee, Drake, and Cameron (2002) employed a driving simulator with similar capabilities to assess the driving performance of 53 community dwelling older people ages 65 to 85. Senior drivers were classified as those 65 to 74, and advanced-age senior drivers were classified as those 75 to 89. The self-reported medical conditions and percentage of subjects self-reporting each condition were as follows: arthritis (28%), diabetes (13%), high blood pressure (47%),

visual problems (34%), hearing problems (23%), heart diseases (17%), and respiratory disease (4%).

The assessment conducted by Lee et al. (2002) involved three segments: a 30-minute initial screening; a 45-minute driving simulation; and a 25-minute post-session feedback. One-fourth of the participants understood how to use the controls with minimum instruction upon initial introduction of the simulator. The majority indicated that they felt positive about the simulator and confident in their ability to operate it, following the introduction. Four of the 53 subjects (7%) reported some degree of simulator sickness, stating that they experienced mild dizziness after completing the simulated driving. However, they did not feel a need to withdraw from the assessment. The simulated driving test was conducted over a total distance of 15 km (9.3 mi) over three speed-zone segments of 60 km/h (37 mi/h), 70 km/h (43 mi/h), and 100 km/h (62 mi/h). Driving scenarios included eight possible events (e.g., overtaking a car ahead, driving along a curved road) paired with a speed zone. Assessment criteria included "performance indicators" and "operational parameters." Performance indicators included total run length, speed violation, proper signaling, divided attention task, and off-road crash—effective performance required participants to exercise cognitive function in making interactive judgments and rapid decisions to modify their driving behavior according to the demands of the traffic scenarios. Operational parameters reflected the automatic responses of drivers to maneuver their vehicles when driving, and included curvature error, heading angle error, steering-wheel rate and lane position—effective performance required subjects to call on their "permanent" skills in driving acquired over years of driving.

Lee et al. (2002) found a strong association between age and performance on the "performance indicators." The difference between the performance of the senior drivers and the advanced-age senior drivers was significant for all five performance indicators. The senior driver group was involved in fewer crashes," used their signals more often when changing lanes, and committed fewer speed violations than the older senior drivers. The senior drivers drove faster than the older senior drivers, at speeds appropriate to traffic conditions. A weak association was found between the operational parameters and age of the participants. There was no significant difference in operational parameter performance as a function of age group. The authors concluded that in formulating assessment criteria for simulator studies with older people, that driving skills at the "controlled" processing level should be the focus, rather than "automatized" behaviors that do not deteriorate significantly with age.

In another study conducted by Lee and colleagues (Lee, Lee, Cameron, and Li-Tsang, 2003), the driving performance of 129 volunteer subjects 60 and older was examined in the simulator to determine if any of 10 performance measures were associated with self-reported crashes. Each participant received a 30-minute interview to gather data on self-reported crashes in the past year, medical conditions, and driving habits. This was followed by a 45-minute simulated driving session containing 10 performance tasks:

- Rules Compliance – Lane changing in a double-lane road, where the participant's car was in the right lane. Keep Lane signs displayed every 55 yards prompted subjects to go back to the inner lane.

- Traffic Sign Compliance – Drive through Stop, Give Way, and pedestrian crossings safely
- Driving Speed – Drive 1.5 miles along the road according to the designated speed of the double-lane straight road (40 mph speed limit)
- Use of Indicator – Drive around "road work" obstacles blocking the road and return to the inner lane as soon as possible
- Road Use Obligation – Observe traffic conditions and drive safely through T-junctions leading to main road with Stop signs
- Decision and Judgment – Avoid crashing into pedestrians 30 yards ahead running across the road hastily, car parked on the roadside moving out without signaling, and car in front suddenly slowing down
- Working Memory – Recall five street names and five maneuvers (turn right or left) after 10 minutes' simulated driving. Subjects were given 5 minutes to memorize the route to a fictitious park marked on a road map, followed by 10 minutes of unrelated driving, and then asked to recall the maneuvers and street names on the route.
- Simultaneous Tasks – Starting from 100, take away 5 every time the "SUBTRACT" billboard is seen. (15 billboards with "SUBTRACT" signs were posted along the road).
- Speed Compliance – Observe and maintain a speed close to the posted speed limits (40, 45, and 70 mph), which vary according to traffic conditions.
- Divided Attention Tasks – Signal the traffic indicator when the "diamond" shapes on the monitor screen change to "triangle" randomly and stay for 15 seconds.

Subjects in the Lee et al. (2003) study ranged in age from 60 to 88, with a mean age of 72.9, and 22 percent of the subjects were female. The self-reported medical conditions and percentages of subjects reporting each were as follows: high blood pressure (38%), visual problem (36%), arthritis (26%), hearing problem (25%), heart diseases (15%), and diabetes (10%). Over 70 percent of the subjects reported that they were suffering from multiple medical conditions and took daily medications including analgesic, anticoagulant, antihypertensive, and anti-inflammatory agents, but they perceived that such medications did not interfere with their driving abilities. Seventy-nine subjects (61.2%) reported having at least one crash in the prior year, but none of the crashes involved personal injury.

Lee et al. (2003) found a significant negative correlation between each simulated driving criterion and age of the participants, indicating that simulated driving performance worsens with increasing age. A stepwise logistic regression to determine the association between crashes and simulator criteria found that performance on driving tasks involving working memory, decision and judgment, and speed compliance was negatively associated with the occurrence of a crash. According to the fitted model, each added point on the working memory scale was associated with a 45 percent decrease in risk, on the decision and judgment scale with a 61 percent decrease in risk, and on the speed compliance scale with a 17 percent decrease in risk. The model also indicated that an increase of one year in age could elevate the crash risk by 13 percent.

Overall, 87.7 percent of the 129 participants in the Lee et al. (2003) study were correctly classified on the occurrence/nonoccurrence of a (self-reported) crash. The study finding that cognitive skills such as working memory, ability to make rapid decisions, judgment under time pressure, and confidence in driving at high speed were significantly (negatively) associated with a crash event, together with high sensitivity (82%) and specificity (91%) of the regression model,

suggests that driving simulators at this level could be useful in investigations of older drivers using multiple medications. Concerns persist about elevated levels of simulator sickness among older people under the influence of medications, however. Results indicating that age, per se, predicted performance in the simulator, while simultaneously predicting crash involvement better than 7 of 10 simulated driving measures, also raises some fundamental questions about this methodology.

Finally, Freund, Gravenstein, Ferris, and Shaheen (2002) conducted a study using four cognitively impaired older adults and five healthy older adults (ages 67 to 78) to examine the degree to which performance in a simulator compared to performance on an on-road test. The on-road testing was conducted by an occupational therapist, who was certified both as a driving rehabilitation specialist and a commercial driving instructor, using a dual-brake equipped vehicle. Performance measures for the simulator task and the on-road task included hazardous or potentially catastrophic errors, traffic violations, and rule violations. The mean scores for the simulator and on-road tests were significantly correlated at -.670. The lower the score on the simulator (identifying performance with few errors), the higher the score on the road test (identifying performance with competency ratings greater than 90 percent). There was also a strong association between hazardous and lethal errors committed on the simulator and failing the road test for hazardous errors. Subjects who failed the on-road test committed an average of 5.4 hazardous errors and an average of 4 lethal errors on the driving simulator. Subjects who passed the on-road test committed no hazardous or lethal errors in the simulator test. The authors conclude that although the sample size was small, study results support the use of driving simulation as a method to objectively evaluate driving performance of cognitively impaired and healthy older adults.

Level I: Non-interactive, Computer Graphic and/or Digital Video Visuals, No Motion

This level of simulation is exemplified by desktop systems with a computer monitor showing computer graphics or high-resolution video of a road scene, using standard controls (wheel, pedals), or sometimes only a mouse or touchscreen to allow the subject to respond to what is displayed on the monitor. The performance measures that can be obtained using such low-cost methods are strictly "part-task"─i.e., one stage or component of driver information processing assumed to underlie safe vehicle control is isolated for study, for example perceptual vigilance as a function of hours without sleep, or hazard detection latency while performing a secondary (divided attention) task.

As one example of such research, a vigilance study conducted by Mills et al. (2001) used a computerized task to study the effects of stimulants (dextroamphetamine at 10 mg), sedatives (a short half-life benzodiazepine, alprazolam at 0.5 mg), and fatigue, on single- and divided-attention responses in different parts of the visual field. Subjects included 18 healthy volunteers age 19 to 37 (no older people were tested). For all subjects, blood samples were taken at predose and at 12 postdose intervals (ranging from 0.25 hours to 12 hours) to determine alprazolam or dextroamphetamine plasma concentrations. Maximum concentrations of alprazolam occurred between 0.75 and 4 hours from dosing, with an average 1.78 hours. Maximum concentrations of dextroamphetamine concentration occurred between 1.5 and 4 hours, with an average of 2.78 hours.

The driving-related tasks in this research included a perceptual task in the center of the computer display, combined with identification of a critical (octagon shape) target presented at varying positions and eccentricities at the periphery of the display. Test stimuli were presented as described below using a 17-inch monitor and a keyboard spacebar and arrow keys were used to record subjects' responses.

For the central task, subjects were presented with a 7.3 cm by 5.6 cm box in the center of the monitor divided by a vertical double line that simulated a pavement centerline marking. Subjects saw a combination of "headlights" (two white lights) and "taillights" (two red lights) on each trial. One stimulus configuration—white lights on the left side of the line (representing an oncoming vehicle in the adjacent lane) and red lights on the right side of the line (representing a leading vehicle)—was designated as "correct." Subjects were instructed to only respond to the central task, by pressing the space bar on the computer's keyboard, if the display was "correct."

The peripheral task randomly presented 12 shapes for each trial, one of which could be an octagon. The stimulus display duration varied from 1 to 3 seconds. Each critical trial presented the octagon at each of the 12 positions (three levels of eccentricity on four radials), for single- and multiple-response displays. The subject was instructed to press the arrow key to indicate the direction of the critical stimulus (octagon) when it occurred. A "divided attention" display occurred when a subject was required to respond to both central and outer stimuli, and occurred on 33 percent of the trials. Single-response displays presented an outer octagon without a central response on 33 percent of the trials. One-sixth of all displays required only a central response, and one-sixth of the displays required no response.

Behavioral measures included the speed and accuracy of responses to the peripheral targets (at each of three angles of eccentricity) without the divided-attention requirement; the speed and accuracy of responses for the central task *and* the peripheral target identifications (at each of the three visual angles); and a composite score that calculated as a single linear combination of all measures. The composite score was the measure most sensitive to peak drug effects.

Results of the study showed that spatial "tunneling" was produced with both sedatives and stimulants, however tunneling was unique to each drug. With sedatives, tunneling was shown by decrements in both the single-task and divided-task scores, as the displays became more distant from the center. Stimulant-induced tunneling was characterized by improvements in only the divided-attention task displays near the center of the screen, with little or no changes at the outer edges. The tunneling brought on by depressants coincided with rising and peak blood levels.

The demonstrated impairment from a low dose of the sedative was similar to that observed in a study conducted by Mills, Parkman, and Spruill (1996), with significant deficits in visual scanning and divided attention at peak blood concentrations, which increased as stimuli were presented at increasing eccentricities. The computerized assessment in this research was thus sensitive to deficits caused by the medications that are important to the task of driving—the ability to spot potential hazards in the periphery and to divide attention.

One additional example of simulation methods at this level is provided by the work of Ball, Owsley, and colleagues at the Edward R. Roybal Center for Research in Applied Gerontology at the University of Alabama at Birmingham (UAB). The Roybal Center's simulator includes a car cab (front seat only) mounted on a fixed platform, with three screens (affording a roughly 120° field of view) displaying projection videos of different driving scenarios filmed (from a driver's eye perspective) to capture situations and maneuvers of particular interest to researchers (e.g., intersection negotiation). This approach (video) produces a high degree of realism in the driving scene stimuli, but limits the interactivity of the system to slight adjustments in the perceived travel speed of the driver's vehicle in response to pressure on the gas and brake pedals; this is why the UAB system is classified as 'Level 1' for the present discussion.

The UAB researchers have used this simulator since 1998, primarily in studies of aging and visual attention/visual information processing involving the "useful field of view" construct. Many hundreds of older subjects have participated in this research program; results have been widely reported, in peer-reviewed journals. Without discussing the results of any specific study, this review draws attention to the UAB researchers' experience with simulator sickness among older subjects. In their initial applications of this driving simulator, between one-quarter and one-third of older subjects became ill or 'queasy' to the extent that data collection could not proceed. However, after limiting subjects' exposure to only those driving scenarios involving straight-ahead movement—no horizontal or vertical curves—the rate of simulator sickness was reduced to under 5 percent.[44]

[44] Personal communication. Dr. Karlene Ball, Director, Roybal Center, University of Alabama at Birmingham, to L. Staplin in telephone conversation, March 24, 2005.

REFERENCES

Adams, W.L. (1995). "Potential for Adverse Drug-Alcohol Interactions Among Retirement Community Residents." *Journal of the American Geriatrics Society*, 43, 1021-1025.

Adams, W.L., Yuan, Z., Barboriak, J.J., and Rimm, A.A. (1993). "Alcohol-Related Hospitalizations in Elderly People: Prevalence and Geographic Variation in the United States." *Journal of the American Medical Association*, 270, 1222-1225.

Agency for Healthcare Research and Quality. *AHRQ Patient Safety Network: Glossary*. Accessed on June 7, 2005, from http://psnet.ahrq.gov/glossary.aspx.

Allard, J., Hébert, R.,, Rioux, M., Asselin, J., and Voyer, L. (2001). "Efficacy of a Clinical Medication Review on the Number of Potentially Inappropriate Prescriptions Prescribed for Community-Dwelling Elderly People." *Canadian Medical Association Journal,* 164(9), 1291-1296.

Álvarez, F. J., and del Río, C. (2003). "Illicit Drugs and Fitness to Drive: Assessment in Spanish Medical Driving Test Centers." *Drug and Alcohol Dependence*, 64, 19-25.

Álvarez, F. J., and del Río, C. (2002). "Medicinal Drugs and Driving: from Research to Clinical Practice." *Trends in Pharmacological Sciences*, 23(9), 441-443.

American Society *of Health-System Pharmacists. (2001). "Cardiac Drugs." In:* Drug Information 2001, 1500-1511. Bethesda, MD.

American Pharmacists Association/APhA. (2003). Medication Compliance-Adherence-Persistence (CAP) Digest. American Pharmacists Association and Pfizer Pharmaceuticals. Washington, D.C.

Aparasu, R.R. and Mort, J.R. (2004). "Prevalence, Correlates, and Associated Outcomes of Potentially Inappropriate Psychotropic Use in the Community-Dwelling Elderly." *The American Journal of Geriatric Pharmacotherapy*, 2(2), 102-111.

Australian Association of Occupational Therapists—Victoria, Inc. (1998). *Competency Standards for Occupational Therapy Driving Assessors*. Ashburton, Victoria, Australia.

Balkrishnan, R., Rajagopalan, R., Camacho, F.T., Huston, S.A., Murray, F.T., and Anderson, R.T. (2003). "Predictors of Medication Adherence and Associated Health Care Costs in an Older Population with Type 2 Diabetes Mellitus: A Longitudinal Cohort Study." *Clinical Therapeutics*, 25(11), 2958-2971.

Barat, I., Andreasen, F., and Damsgaard. (2001). "Drug Therapy in the Elderly: What Doctors Believe and Patients Actually Do." *British Journal of Clinical Pharmacology* , 51(6), 615-622.

Bartlett, G., Abrahamowicz, M., Tamblyn, R., Grad, R., Capek, R., and du Berger, R. (2004). "Longitudinal Patterns of New Benzodiazepine Use In The Elderly." *Pharmacoepidemiol. Drug Saf.* 13:669-682.

Beck, A. and Beck, R. (1972). "Screening Depressed Patients in Family Practice: A Rapid Technique." *Postgrad. Med*., 52, 81-86.

Becker, M.H., and Maiman, L.A. (1975). "Sociobehavioral Determinants of Compliance with Health and Medical Care Recommendations." *Med Care*, 13(1):10-24.

Beers, M.H. (1997). "Explicit Criteria for Determining Potentially Inappropriate Medication Use by the Elderly: An Update. *Archives of Internal Medicine*, 157, 1531-1536.

Behrensdorff, I., and Steentoft, A. (2002). "Medicinal and Illegal Drugs Among Danish Car Drivers." *Accident Analysis and Prevention*, 25, 851-860.

Berg, J.S., Dischler, J., Wagner, D.J., Raia, J.J., and Palmer-Shevlin, N. (1993). "Medication compliance: A Healthcare Problem." *Annals of Pharmacotherapy*, 27(9 Suppl), S1-24.

Berghaus, G., and Grass, H. (1997). "Concentration-Effect Relationship with Benzodiazepine Therapy. In: *Proceedings—14th International Conference on Alcohol, Drugs, and Traffic Safety*. C. Mercier-Guyon, Ed. Centre d'Etudes et de Recherchers en Médeccine du Traffic, France, pp. 705-709.

Bikowski, R.M., Ripsin, C.M., and Lorraine, V.L. (2001). "Physician-Patient Congruence Regarding Medication Regimes." *Journal of the American Geriatrics Society*, 49, 1353-1357.

Borkenstein, R.F., Crowther, R.F., Schumate, R.P., et al. (1964). *The Role of the Drinking Driver in Traffic Accidents*. Bloomington, Ind., University of Indiana, Department of Police Administration.

Brenner, S.S., Herrlinger, C., Dilger, K., Mürdter, T.E., Hofmann, U., Marx, C., and Klotz, U. (2003). "Influence of Age and Cytochrome P450 2C9 Genotype on the Steady-State Disposition of Diclofenac and Celecoxib." *Clin. Pharmacokinet*. 42:283-292.

Briceland, L.L., Kane, M.P., and Hamilton, R.A. (1992). "Evaluation of Patient-Care Interventions by Pharm.D. Clerkship Students." *Am Soc Hosp Pharm*, 49, 1130-1132.

Briggs, R.S., Castleden, C.M., and Kraft, C.A. (1980). "Improved Hypnotic Treatment Using Chlormethiazole and Tanzepam." *British Medical Journal*, 280, 601-604.

Brody, J.A. (1984). "Alcohol and Aging: The Extent of the Problem from Limited Data." In E.L. Autheil (ed.). *Combined Problems of Alcoholism, Drug Addiction, and Aging*. Springfield, IL: Charles C. Thomas.

Brouwer, W.H., Ponds, R.W., and Van Woffelaar, P.C. (1989). "Divided Attention 5-10 Years After Severe Closed Head Injury. *Cortex*, 25, 219-230.

Cadieux, R.J. (1989). "Drug Interactions in the Elderly. How Multiple Drug Use Increases Risk Exponentially." *Postgraduate Medicine*, 86(8): 179-86.

Carr, D.B. (2004). "Commentary: The Role of the Emergency Physician in Older Driver Safety." *Annals of Emergency Medicine*, 43(6), 747-748.

Carr, D., Schmader, K., Bergman, C., et al. (1991). "A Multidisciplinary Approach in the Evaluation of Demented Drivers Referred to Geriatric Assessment Centers." *Journal of the American Geriatrics Society*, 39, 1132-1136.

Caskie, G., and Willis, S. (2004). "Congruence of Self-Reported Medications with Pharmacy Prescription Records in Low-Income Older Adults." *The Gerontologist*, 44, 176-185.

Castellas, D.D., Teitelbaum, B.A., and Tresley, D.J. (2002). "Visual Changes Secondary to Initiation of Amiodarone: A Case Report and Review Involving Ocular Management in Cardiac Polypharmacy." *Optometry*, 73(2), 113-121.

Chrischilles, E.A., Carter, B.L., Lund, B.C., Rubenstein, L.M., Chen-Hardee, S.S., Voelker, M.D., Park, T., and Kuehl, A.K. (2004). "Evaluation of the Iowa Medicaid Pharmaceutical Case Management Program." *Journal of the American Pharmacists Association*, 44(3), 337-349.

Chisholm, M.A., and Hawkins, D.W. (1996). Analysis of Pharmacotherapy Recommendations Provided by Doctor of Pharmacy Clerkship Students." *J Pharm Teach*, 5, 3-12.

Chisholm, M.A., Taylor, A.T., and Hawkins, D.W. (1997). "Pharmaceutical Care Provided by Doctor of Pharmacy Clerkship Students in Geriatric Patients in an Acute Care Setting." *J Ger Ther*, 11, 43-50.

Clarkson, J.E., Gordon, A.M., and Logan, B.K. (2004). "Lorazepam and Driving Impairment." *J. Anal. Toxicol*. 28:475-480.

Coons, S.J. (2001). "Medication Compliance: the Search for Answers Continues." *Clin Ther*, 23, 1294-1295.

Cramer, J.A. (2004). "The Usefulness of Medication Compliance Data in Interpretation of Outcomes." Yale University School of Medicine, Connecticut. Accessed on November 29, 2004, at http://hiv.buffalo.edu/medcompliance.shtml.

Curtis, L.H., Østbye ,T., Sendersky, V., Hutchison, S., Dans, P.E., Wright A., Woosley, R.L., and Schulman, KA. (2004). "Inappropriate Prescribing for Elderly Americans in a Large Outpatient Population." *Arch. Intern. Med*. 164:1621-1625.

Dahan, A. and Altman, H. (2004). “Food-Drug Interaction: Grapefruit Juice Augments Drug Bioavailability–Mechanism, Extent, and Relevance.” *Eur. J. Clin. Nutr*. 58:1-9.

Dailey, G., Kim, M.S., and Lian, J.F. (2001). “Patient Compliance and Persistence with antihyperglycemic Drug Regimens: Evaluation of a Medicaid Patient Population with Type 2 Diabetes Mellitus.” *Clinical Therapeutics*, 23(8), 1311-1320.

Darnell, J.C., Murray, M.D., Martz, B.L., et al. (1986). “Medication Use by Ambulatory Elderly: An In-Home Study.” *Journal of the American Geriatrics Society*, 34, 1-4.

De Raedt, R., and Ponjaert-Kristoffersen, I. (2001). “Predicting At-Fault Car Accidents of Older Drivers.” *Accident Analysis and Prevention*, 33, 809-819.

Del Río, M.C., and Alvarez, F.J. (2003). “Medication and Fitness to Drive.” *Pharmacoepidemiology and Drug Safety*, 12, 389-394.

Del Río, M.C., and Alvarez, F.J. (2001). “Illicit Drugs and Fitness to Drive: Assessment in Spanish Medical Driving Test Centres.” *Drug and Alcohol Dependence*, 64, 19-25.

Del Río, M.C., Gómez, J., Sancho, M., and Alvarez, F.J. (2002). “Alcohol, Illicit Drugs, and Medicinal Drugs in Fatally Injured Drivers in Spain Between 1991 and 2000.” *Forensic Science International*, 127, 63-70.

Department of Health. (2001). *Medicines and Older People: Implementing Medicines-Related Aspects of the NSF for Older People*. London, England. Available at www.gov.uk/nsf/olderpeople.htm.

Diamond, T.H., Collins, J., and Rohl, P. (2005). “Motor Vehicle Accidents During Episodes of Hypoglycaemia—Case Reports and Lessons to be Learnt.” *Australian Family Physician*, 34(3), 151-154.

Di Stefano, M., and Macdonald, W. (2003). “Assessment of Older Drivers: Relationships Among On-Road Errors, Medical Conditions, and Test Outcome.” *Journal of Safety Research*, 34, 415-429.

Drummer, O.H., Gerostamoulos, J., Batziris, H., Chu, M., Caplehorn, J., Robertson, M.D., and Swann, P. (2004). “The Involvement Of Drugs In Drivers Of Motor Vehicles Killed In Australian Road Traffic Crashes.” *Accid. Anal. Prev*. 36:239-248.

Drummer, O.H., Gerostamoulos, J., Batziris, H., Chu, M., Caplehorn, J.R., Robertson, M.D., and Swann, P. (2003). “The Incidence of Drugs in Drivers Killed in Australian Road Traffic Crashes.” *Forensic Sci. Int*. 134:154-162.

Duchek, J.M., Carr, D.B., Hunt, L., Roe, C.M., Xiong, C., Shah, K., and Morris, J.C. (2003). “Longitudinal Driving Performance in Early-Stage Dementia of the Alzheimer Type.” *Journal of the American Geriatrics Society*, 51, pp. 1342-1347.

Dunbar-Jacob, J., Bobachick, P., and Sereika, S. (2003). "Medication Adherence in Persons with Cardiovascular Disease." *J Cardiovasc Nurs*, 18(3), 209-218.

Ennis, K.J., and Reinhard, R.A. (1997). "Maximizing Drug Compliance in the Elderly." *Post Grad Medical Journal*, 102, 21-212.

Etminan, M., Hemmelgarn, B., Delaney, J.A., and Suissa, S. (2004). Use Of Lithium and "The Risk of Injurious Motor Vehicle Crash in Elderly Adults: Case-Control Study Nested Within a Cohort." *Brit. Med. J*. 328:558-559.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 1999). *Literature Review on the Relation Between Drug Use, Impaired Driving, and Traffic Accidents*. Lisbon, Portugal.

Farris, K.B., Ganther-Urmie, J.M., Fang, G., Doucette, W.R., Brooks, J.M., Klepser, D.K., Fries, D.J., and Kuhle, C.L. (2004). "Population-Based Medication Reviews: A Descriptive Analysis of the Medication Issues Identified in a Medicare Not-for-Profit Prescription Discount Program." *The Annals of Pharmacotherapy*, 38, 1823-1829.

Feiner, L.A., Younge, B.R., Kazmier, F.J., et al. (1987). "Optic Neuropathy and Amiodarone Therapy." *Mayo Clinic Proceedings*, 62, 702-717.

Fick, D.M., Cooper, J.W., Wade, W.E., Waller, J.L., Maclean, J.R., and Beers, M.H. (2003). "Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults: Results of a U.S. Consensus Panel of Experts." *Arch. Intern. Med*. 163:2716-2724.

Fillit, H.M., Futterman, R., Orland, B.I., Chim, T., Susnow, L., Picariello, G.P., Scheye, E.C., Spoeri, R.K., Roglieri, J.L., and Warburton, S.W. (1999). "Polypharmacy Management in Medicare Managed Care: Changes in Prescribing by Primary Care Physicians Resulting from a Program Promoting Medication Revies." *The American Journal of Managed Care*, 5(5), 587-594.

Fink, A., Morton, S.C., Beck, J.C., Hays, R.D., Spritzer, K., Oishi, S., and Moore, A.A. (2002). "The Alcohol-Related Problems Survey: Identifying Hazardous and Harmful Drinking in Older Primary Care Patients." *Journal of the American Geriatrics Society*, 50, 1717-1722.

Foster, E., Hillegass, L.J., and Phillips, S.L. (2004). "Demonstration Program: An Interdisciplinary Approach at a Falls and Mobility Clinic." *Annals of Long-Term Care*, 12(5), 27-32.

Fishbain, D.A., Cutler, R.B., Rosomoff, H.L., and Rosomoff, R.S. (2003). "Are Opioid-Dependent/Tolerant Patients Impaired in Driving-Related Skills: A Structured Review. *Journal of Pain and System Management*, 25(6), 559-577.

Foster, E., Hillegass, L., and Phillips, S. (2004). "Demonstration Program: An Interdisciplinary Approach at a Falls and Mobility Clinic." *Annals of Long-Term Care*, 12(5), 27-32.

Freml, J.M., Farris, K.B., Fang, G., and Currie, J. (2004). "Iowa Priority's Brown Bag Medication Reviews: A Comparison of Pharmacy Students and Pharmacists." *American Journal of Pharmaceutical Education*, 68(2) article 50.

Freund, B., Gravenstein, S., Ferris, R., and Shaheen, E. (2002). "Evaluating Driving Performance of Cognitively Impaired and Healthy Older Adults: A Pilot Study Comparing On-Road Testing and Driving Simulation. *Journal of the American Geriatrics Society*, 50, 1309-1310.

Friedman, S.M., Munoz, B., West, S., Rubin, G.S., and Fried, L.P. (2002). "Falls and Fear of falling: Which Comes First? A Longitudinal Prediction Model Suggests Strategies for Primary and Secondary Prevention." *Journal of the American Geriatrics Society*, 50, 1329-1335.

Fries, D.J., and Kuhle, C.L. (2004). "Population-Based Medication Reviews: A Descriptive Analysis of the Medication Issues Identified in a Medicare Not-for-Profit Prescription Discount Program." *Annals of Pharmacotherapy,* 38:1823-1829.

Gilbert, J.R., Evans, C.E., Haynes, R.B., et al. (1980). "Predicting Compliance with a Regimen of Digoxin Therapy in Family Practice." *Can Med Assoc J*, 123, 119-122.

Goldberg, D., and Williams, P. (1988). *A User's Guide to the GHQ*. NFER-Nelson, Windsor.

Gorski, J.C., Vannaprasaht, S., Hamman, M.A., Ambrosius, W.T., Bruce, M.A., Haehner-Daniels, B., and Hall, S.D. (2003). "The Effect of Age, Sex, and Rifampin Administration on Intestinal and Hepatic Cytochrome P450 3A Activity." *Clinical Pharmacology and Therapeutics*, 74, 275-287.

Goulding, M.R. (2004). "Inappropriate Medication Prescribing for Elderly Ambulatory Care Patients." *Arch. Intern. Med*. 164:305-312.

Granas, A.G., and Bates, I. (1999). "The Effect of Pharmaceutical Review of Repeat Prescriptions in General Practice." *The International Journal of Pharmacy Practice,* 7, 264-275.

Gray, S.L., Eggen, A.E., Blough, D., Buchner, D., and LaCroix, A.Z. (2003). "Benzodiazepine Use In Older Adults Enrolled In A Health Maintenance Organization." *American Journal of Geriatric Psychiatry* 11:568-576.

Greenblatt, D.J., Harmatz, J.S., von Moltke, L.L., Wright, C.E., and Shader, R.I. (2004). "Age and Gender Effects on the Pharmacokinetics and Pharmacodynamics of Triazolam, a Cytochrome P450 3A Substrate." *Clinical Pharmacology and Therapeutics*, 76, 467-479.

Greene, H.L., Graham, E.L., Werner, J.A., et al. (1983). "Toxic and Therapeutic Effects of Amiodarone in the Treatment of Cardiac Arrhythmias." *Journal of the American College of Cardiology*, 2, 1114-1128.

Guidelines for the Prevention of Falls in Older Persons (2001)." American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention." *Journal of the American Geriatrics Society*, 49, 664-672.

"Guidelines on Psychotropic Drugs for the EC: Clinical Investigation of Medicinal Products in the Treatment of Generalized Anxiety Disorder, Panic Disorder, and Obsessive-Compulsive Disorder." (1995). *Eur Neuropsychopharmacol*, 5, 151-155.

Gurwitz, J.H. (2004). "Polypharmacy: A New Paradigm or Quality Drug Therapy in the Elderly?" *Archives of Internal Medicine*, 164, 18, 1957-1959.

Gurwitz, J.H., Field, T.S., Harrold, L.R., Rothschild, J., Debellis, K., Seger, A.C., Cadoret, C., Fish, L.S., Garber, L., Kelleher, M., and Bates, D.W. (2003). "Incidence and preventability of Adverse Drug Events Among Older Persons in the Ambulatory Setting." *Journal of the American Medical Association*, 289(9), 1107-1116.

Hanlon, J.T., Schmader, K.E., Boult, C., Artz, M.B., Gross, C.R., Fillenbaum, G.G., Ruby, C.M., and Garrard, J. (2002). "Use of Inappropriate Prescription Drugs by Older People." *Journal of the American Geriatric Society*, 50, 26-34.

Harris, L., McKenna, W.J., Rowland, E., et al., (1983). "Side Effects and Possible Contraindications of Amiodarone Use," *American Heart Journal*, 106(4 pt 2), 916-922.

Harvard Health Letter. (2004). "Bad Combinations. Drug Interactions You and Your Doctor Need To Worry About." *Harvard Health Letter*, 29(6), 1-2.

Hennessy, S., Bilker, W.B., Weber, A., and Strom, B.L. (2002). "Descriptive Analyses of the Integrity of a U.S. Medicaid Claims Database." *Pharmacoepidemiology and Drug Safety*, 12, 103-111.

Herrlinger, C., and Klotz, U. (2001). "Drug Metabolism and Drug Interactions in the Elderly." *Best Practice & Research Clinical Gastroenterology*, 15:897-918.

Hogan, D.B., Ebly, E.M., and Fung, T.S. (1995). "Regional Variations in Use of Potentially Inappropriate Medications by Canadian Seniors Participating in the Canadian Study of Health and Aging." *Canadian Journal of Clinical Pharmacology*, 2, 167-174.

Hogan, D.B., Maxwell, C.J., Fung, T.S., and Ebly, E.M. (2003). "Prevalence and Potential Consequences of Benzodiazepine Use in Senior Citizens: Results from the Canadian Study of Health and Aging." *Canadian Journal of Clinical Pharmacology*, 10(2), 72-77.

Honig, A., Arts, B.M., Ponds, R.W., and Riedel, W.J. (1999). "Lithium Induced Cognitive Side-Effects In Bipolar Disorder: A Qualitative Analysis And Implications For Daily Practice." *Int. Clin. Psychopharmacology*, 14:167-171.

Hunt, L., Morris, J.C., Edwards, D., et al. (1993). "Driving Performance in Persons with Mild Dementia of the Alzheimer Type." *Journal of the American Geriatrics Society*, 41, pp. 747-753.

Ingram, D.V. (1983). "Ocular Effects in Long-Term Amiodarone Therapy." *American Heart Journal*, 106 (4 pt 2), 902-905.

Institute of Medicine Committee to Advise the Public Health Service on Clinical Practice. (1990). *Clinical Practice Guidelines: Directions for a New Program*. National Academy Press, Washington, D.C.

Jainkittivong, A., Aneksuk, V., and Langlais, R.P. (2004). "Medical Health and Medication Use in elderly Dental Patients." *The Journal of Contemporary Dental Practice*, 5,(1), 1-10.

Janke, M.K. (2001). "Assessing Older Drivers: Two Studies." *Journal of Safety Research*, 32, 43-74.

Janke, M.K., and Hersch, S.W. (1997). *Assessing the Older Driver: Pilot Studies*. California Department of Motor Vehicles, Report No. 172. Sacramento, CA.

Johnson, R.E., and Ried, L.D. (1996). " OTC Drug Use In An HMO: Comparing The Elderly And Younger Adults." *Journal of Aging and Health,* 8(1), 114-135.

Jones, R.K., Shinar, D., and Walsh, J.M. (2003). State of Knowledge of Drug-Impaired Driving. U.S.DOT/National Highway Traffic Safety Administration Publication No. DOT HS 809 642. Washington, D.C.

Joo, J.H., Lenze, E.J., Mulsant, B.H., Begley, A.E., Weber, E.M., Stack, J.A., Mazumdar, S., Reynolds, C.F. 3rd, and Pollock, B.G. (2002). "Risk Factors For Falls During Treatment Of Late-Life Depression." *J. Clin. Psychiatry* 63:936-941.

Jörgensen, T., Johansson, S., Kennerfalk, A., Wallander, M., and Svärddudd, K. (2001). "Prescription Drug Use, Diagnoses, and Healthcare Utilization Among the Elderly." *The Annals of Pharmacotherapy*, 35, 1004-1009.

Kamal-Bahl, S.J., Doshi, J.A., Stuart, B.C., and Briesacher, B.A. (2003). "Propoxyphene Use by Community-Dwelling and Institutionalized Elderly Medicare Beneficiaries." *Journal of the American Geriatrics Society*, 51, 1099-1104.

Kaplan, R.C., Bhalodkar, N.C., Brown, E.J., White, J., and Brown, D.L. (2004). "Race, Ethnicity, and Sociocultural Characteristics Predict Noncompliance with Lipid-Lowering Medications." *Preventive Medicine*, 39(6), 1249-1255.

Katona, C.L. (2001). "Psychotropics and Drug Interactions In The Elderly Patient." *International Journal of Geriatric Psychiatry*, 16, Suppl. 1:S86-S90.

Keene, J.J. Jr., Galasko, G.T., and Land, M.F. (2003). “Antidepressant Use in Psychiatry and Medicine: Importance for Dental Practice.” *J. Am. Dent. Assoc*. 134:71-79.

Keller, M., Kesselring, J., and Hiltbrunner, B. (2003). “Fitness to Drive with Neurological Disabilities.” *Neurorehabiltation and Neural Repair*, 17(3), 168-174.

Kennedy, R.L., Henry, J., Chapman, J., Nayar, R., Grant, P., and Morris, A.D. (2002). “Accidents in Patients with Insulin-Treated Diabetes: Increased Risk of Low-Impact Falls But Not Motor Vehicle Crashes—A Prospective Register-Based Study. *The Journal of Trauma, Injury, Infection, and Critical Care*, 52(4), 660-666.

Kennerfalk, A., Ruigómez, A., Wallander, M., Wilhelmsen, L., and Johansson, S. (2002). “Geriatric Drug Therapy and healthcare Utilization in the United Kingdom.” *The Annals of Pharmacotherapy*, 36, 797-803.

Kinirons, M.T., and O'Mahony, M.S. (2004). “Drug Metabolism and Ageing.” *Br. J. Clin. Pharmacol*. 57:540-544.

Klein, R., Klein, B.E.K., Moss, S.E., Davis, M.D., and DeMets, D.L. (1988). “Glycoslated hemoglobin predicts the incidence and progression of diabetic retinopathy.” *Journal of the American Medical Association*, 260, pp. 2864-2871.

de Klerk, E., van der Heijde, D., Landewe, R., van der Tempel, H., and van der Linden, S. (2003). “The Compliance-Questionnaire-Rheumatology Compared with Electronic Medication Event Monitoring: A Validation Study.” *The Journal of Rheumatology*, 30(11), 2469-2475.

de Klerk, E., van der Heijde, D., van der Tempel, H., and van der Linden, S. (1999). “Development of a Questionnaire to Investigate Patient Compliance with Antirheumatic Drug Therapy.” *The Journal of Rheumatology*, 26, 2635-2641.

Kogos, S.C. (2004). “Support Groups and Treatment Adherence in a Geriatric Outpatient Clinic.” *Journal of Clinical Psychology in Medical Settings*, 11:4, 275-282.

Kriska, J., and Ross, S. (2002). “Medication Review: Whose Job is It?” *The International Journal of Pharmacy Practice*, 10 (suppl): R86.

Kurzthaler, I., Wambacher, M., Golser, K., Sperner, G., Sperner-Unterweger, B., Haidekker, A., Pavlic, M., Kemmler, G., and Fleischhacker, W.W. (2003). “Alcohol and/or Benzodiazepine Use in Injured Road Users.” *Human Psychopharmacol*. 18:361-367.

Lamy, P.P. (1988). “Actions of Alcohol and Drugs in Older Adults.” *Generations*, Summer, 9-13.

Lane, C.J., Bronskill, S.E., Sykora, K., Dhalla, I.A., Anderson, G.M., Mamdani, M.M., Gill, S.S., Gurwitz, J.H., and Rochon, P.A. (2004). "Potentially Inappropriate Prescribing in Ontario Community-Dwelling Older Adults and Nursing Home Residents." *Journal of the American Geriatrics Society*, 52, 861-866.

Lawlor, D.A., Patel, R., and Ebrahim, S. (2003). "Association between falls in elderly women and chronic diseases and drug use: cross sectional study." *BMJ*, 327, 712-717.

Lazow, R.B. (2001). "Alcohol and Other Drug Problems in Older Adults: Health and Human Service Professionals Need to Be Aware." *Journal of Prevention and Intervention in the Community*, 21(1), 79-96.

Lee, R.D. (1998). "Polypharmacy: A Case Report and New Protocol for Management." *Journal of the American Board of Family Practitioners,* 11(2), 140-144.

Lee, H.C., Drake, V., and Cameron, D. (2002). "Identification of Appropriate Assessment Criteria to Measure Older Drivers' Driving Performance in Simulated Driving." *Australian Occupational Therapy Journal*, 49, 138-145.

Lee, H.C., Lee, A.H., Cameron, D., and Li-Tsang, C. (2003). "Using a Driving Simulator to Identify Older Drivers at Inflated Risk of Motor Vehicle Crashes." *Journal of Safety Research*, 34, 453-459.

Leipzig, R.M., Cumming, R.G., and Tinetti, M.E. (1999). "Drugs and Falls in Older People: A Systematic Review and Meta-Analysis, I, Psychotropic Drugs." *Journal of the American Geriatrics Society*, 47, 30-39.

Leipzig, R.M., Cumming, R.G., and Tinetti, M.E. (1999). "Drugs and Falls in Older People: A Systematic Review and Meta-Analysis, II, Cardiac and Analgesic Drugs." *Journal of the American Geriatrics Society*, 47, 40-50.

LeRoy, A. (2004). *Draft Report: Exploratory Study of the Relationship Between Multiple Medicines and Vehicle Crashes—Analysis of Databases*. Unpublished manuscript, IATROGEN, Herndon, VA.

Leveille, S.G., Buchner, D.M., Koepsell, T.D., McCloskey, L.W., Wolf, M.E., and Gagner, E.H. (1994). "Psychoactive Medications and Injurious Motor Vehicle Collisions Involving Older Drivers." *Epidemiology*, 5, pp. 591-598.

Levenson, R. (2002). Medication Reviews – The Views of Patients. A Report to the Medicines Partnership. Available at www.medicines-partnership.org/medication-review.

Linjakumpu, T., Hartikainen, S., Klaukka, T., Kivelä, S., and Isoaho, R. (2002). "Psychotropics Among the Home-Dwelling Elderly—Increasing Trends." *Journal of Geriatric Psychiatry*, 17, 874-883.

Linjakumpu, T., Hartikainen, S., Klaukka, T., Veijola, J., Kivelä, S., and Isoaho, R. (2002). "Use of Medications and Polypharmacy Are Increasing Among the Elderly." *Journal of Clinical Epidemiology*, 55, 809-817.

Liu, H., Golin, C.E., Miller, L.G., Hats, R.D., Beck, C.K., Sanandaji, B.S., et al. (2001). "A Comparison Study of Multiple Measures of Adherence to HIV Protease Inhibitors." *Annals of Internal Medicine*, 134, 968-977.

Lyman, J.M., McGwin, G. Jr., and Sims, R.V. (2001). "Factors Related to Driving Difficulty and Habits in Older Drivers." *Accid. Anal. Prev*. 33:413-421.

Macaluso, D.C., Shults, W.T., and Fraunfelder, F.T. (1999). "Features of Amiodarone-Induced Optic Neuropathy*." American Journal of Ophthalmology*, 127, 610-612.

Mackie, C.A., Lawson, D.H., Campbell, A., Maclaren, A.G., and Waigh, R.A. (1999). "A Randomized Controlled Trial of Medication Review in Patients Receiving Polypharmacy in General Practice." *Pharm J*, 263, R7.

MacRae, F., Lowrie, R., MacLaren, A., Kinn, S., and Fish, A. (2003). "Patient Views of Pharmacist-Led Medication Review Clinics: A Preliminary Qualitative Study." *The International Journal of Pharmacy Practice*. September, 11:R6.

Mallon, K., and Wood, J.M. (2004). "Occupational Therapy Assessment of Open-Road Driving Performance: Validity of Directed and Self-Directed Navigational Instructional Components." *The American Journal of Occupational Therapy*, 58, 279-286.

Mantyjarvi, M., Tuppurainen, K., and Ikaheimo, K. (1998). "Ocular Side Effects of Amiodarone." *Surv Ophthalmol*, 42, 360-366.

Mäntyselka, P., Ahonen, R., Viinamäki, H., Takala, J., and Kumpusalo, E. (2002). "Drug Use by Patients Visiting Primary Care Physicians Due to Nonacute Musculoskeletal Pain." *European Journal of Pharmaceutical Sciences*, 17, 201-206.

Marinker, M., Blenkinsopp, A., Bond, C. et al. (1997). *From Compliance to Concordance: Achieving Shared Goals in Medicine Taking*. London, UK: Royal Pharmaceutical Society of Great Britain. http://www.medicines-partnership.org/about-us/history.

Martínez-Sellés, M., García Robles, J.A., Muñoz, R., Serrano, J.A., Frades, E., Dominguez Muñoa, M., and Almendra,l J. (2004). "Pharmacological Treatment in Patients with Heart Failure: Patients Knowledge and Occurrence of Polypharmacy, Alternative Medicine and Immunizations." *Eur. J. Heart Fail*. 6:219-226.

McGwin, G. Jr., Sims, R.V., Pulley, L., and Roseman, J.M. (2000). "Relations Among Chronic Medical Conditions, Medications, and Automobile Crashes in the Elderly: A Population-Based Case-Control Study." *Am. J. Epidemiol*. 152:424-431.

Memmott, J.L. (2003). “Social Work Practices with the Elderly Substance Abuser.” *Journal of Social Work Practice in the Addictions*, 3(2), 85-103.

Michocki, R.J. (2001). “Polypharmacy and Principles of Drug Therapy.” In: Daly, M.P., Weiss, B.D., and Adelman, A.M. (eds.) *20 Common Problems in Geriatrics*. New York: McGraw-Hill, 69-81.

Michon, J.A. (1985). “A critical view of driver behavior models: What do we know, what should we do?” In L. Evans and R. Schwing, editors, *Human Behavior and Traffic Safety*. New York: Plenum Press, Pp. 485-520

Mills, K.C., Parkman, K.M., and Spruill, S.E. (1996). “A PC-Based Software Test for Measuring Alcohol and Drug Effects in Human Participants.” *Alcoholism: Clinical and Experimental Research*, 20(9) 1582-1591.

Mills, S.C., Spruill, S.E., Kanne, R.W., Parkman, K.M., and Zhang, Y. (2001). “The Influence of Stimulants, Sedatives, and Fatigue on Tunnel Vision: Risk Factors for Driving and Piloting.” *Human Factors*, 43(2), 310-327.

Morisky, D.E., Green, L.W., and Levine, D.M. (1986). “Concurrent and Predictive Validity of a Self-Reported Measure of Medication Adherence.” *Med Care*, 24, 67-74.

Morland, J. (2000). “Driving Under the Influence of Non-alcoholic Drugs*.” Forensic Science Review*, 12, 80-105.

Morrow, D., Leiter, V., Shekih, J. (1988). “Adherence and Medication Instructions.” *Journal of the American Geriatrics Society*, 36, 1147-1160.

Movig, K.L., Mathijssen, M.P., Nagel, P.H., van Egmond, T., de Gier, J.J., Leufkens, H.G., and Egberts, A.C. (2004). “Psychoactive Substance Use and the Risk of Motor Vehicle Accidents.” *Accid. Anal. Prev*. 36:631-636.

Murray, M.D., Morrow, D.G., Weiner, M., Clark, D.O., Tu, W., Deer, M.M., Brater, C., and Weinberger, M. (2004). “A Conceptual Framework to Study Medication Adherence in Older Adults.” *The American Journal of Geriatric Pharmacotherapy*, 2(1), 36-43.

Nankoong, K., Farren, C.K., O’Connor, P.G., and O’Mally, S.S. (1999). “Measurement of Compliance with Naltexone in the Treatment of Alcohol Dependence: Research and Clinical Implications. *Journal of Clinical Psychiatry*, 60(7), 449-453.

Nathan, A., Goodyer, L., Lovejoy, A., and Rashid, A. (1999). “Brown Bag Medication Reviews as a Means of Optimizing Patients’ Use of Medication and of Identifying Potential Clinical Problems. *Family Practice*, 16, 278-282.

NHS. (2000). “Prescribing for the Older Person.” *MeReC Bulletin*, 11 (10), 37-40.

Nielsen, C.E., Andrasen, F., Bjerregaard, P. (1983). “Amiodarone Induced Cornea Ventricillata.” Acta Ophthalmol (Copenh), 61, 478-480.

Odenheimer, G.L., Beaudet, M., Jette, A.M., Albert, M.S., Grande, L., and Minaker, K.L. (1994). “Performance-Based Driving Evaluation of the Elderly Driver: Safety, Reliability, and Validity.” *Journal of Gerontology: Medical Sciences*, 49, M153-M159.

O’Hanlon, J.F., Brookhuis, K.A., Louwerens, J.W., et al. (1986). “Performance Testing as a Part of Drug Registration.” In *Drugs and Driving*, Eds. J.F. O’Hanlon, J.J. De Gier, Taylor and Francis: London, UK, pp. 311-320.

Oliver, J., and Seymour, A. (1998). “The Role of Drugs and Alcohol in Drivers Fatally Injured in the Strathclyde Police Region of Scotland, 1995-1997. “ In: *Proceedings of the Paper Presented at Nordic Conference on Andre Stoffer end Alkohol j Traffiken*. Copenhagen.

Ory, M.G., Lipman, P.D., Karlen, P.L., Gerety, M.B., Stevens, V.J., Singh, M.A., Buchner, D.M., Schectman, K.B., and FICSIT Group. (2002). “Recruitment of Older Participants in Frailty/Injury Prevention Studies.” *Prevention Science*, 3(1), 1-22.

Petty, D.R., Knapp, P., Raynor, D.K., and O’house, A. (2003). “Patients’ Views of a Pharmacist-Run Medication Review Clinic in General Practice.” *British Journal of General Practice*, 53, 607-613.

Petty, D.R., Zermansky, A.G., Raynor, D.K., Vail, A., Lowe, C.J., Freemantle, N., and Buttress, A.D. (2001). “No Thank You: Why Elderly Patients Declined to Participate in a Research Study.” *Pharm World Sci*, 23(1), 22-27.

Pharmacy Practice and Medicines Management Group. (2002). *Medication Review Patient Invitee Letters.* Produced on behalf of the Task Force on Medicines Partnership. Available at www.medicines-partnership.org/medication-review/room-for-review/toolkit/invitations.

Piltz, J.R., Wertenbaker, C., Lance, S.E., et al., (1993). “Digoxin Toxicity: Recognizing the Varied Visual Presentations*. Journal of Clinical Neuroophalmology*, 13, 275-280.

Pollow, R.L., Stoller, E.P., Forster, L.E., and Duniho, T.S. (1994). “Drug Combinations and Potential for Risk for Adverse Drug Reaction Among Community-Dwelling Elderly.” *Nursing Research*, 43(1), 44-49.

Pozzato, G., Moretti, M., Franzin et al. (1995). “Ethanol Metabolism and Aging: The Role of ‘First Pass Metabolism’ and Gastric Alcohol Dehydrognase Activity.” *Journal of Gerontology*, 50, B135-141.

Quebec Health Insurance Board. (1992). Régie de l’assurance-maladie du Québec. (1992). Rapport *du Comité d’analyse de la consommation médicamenteuse des personnes agées*. Québec (QC). The Gouvernment de Quebec.

Raeder, E.A., Podrid, P.J., and Lowan, B. *(1985). "Side Effects and Complications of Amiodarone Therapy. American* Heart Journal, 109(5 Pt 1), 975-983.

Raji, M.A., Ostir, G.V., Markides, K.S., Espino, D.V., and Goodwin, J.S. (2003). "Potentially Inappropriate Medication Use by Elderly Mexican Americans." *The Annals of Pharmacotherapy*, 37, 1197-1202.

Ramaekers, J. (2003). "Antidepressants and Driver Impairment: Empirical Evidence from a Standard On-the-Road Test." *Journal of Clinical Psychiatry*, 64(1), 20-29.

Ramaekers, J.G., Berghaus, G., van Laar, M., and Drummer, O.H. (2004). "Dose Related Risk of Motor Vehicle Crashes after Cannabis Use." *Drug and Alcohol Dependence*, 73, 109-119.

de Rekeneire, N., Visser, M., Peila, R., Nevitt, M., Cauley, J., Tylavsky, F., Simonsick, E., and Harris, T. (2003). "Is a Fall Just a Fall: Correlates of Falling in Healthy Older Persons. The Health, Aging, and Body Composition Study." *Journal of the American Geriatrics Society*, 51, 841-846.

Richardson, E.D., and Marottoli, R.A. (2003). "Visual Attention and Driving Behaviors Among Community-Living Older Persons." *Journal of Gerontology Series A: Biological Sciences and Medical Sciences,* 58:M832-M836.

Riefkohl, E.Z., Bieber, H.L., Burlingame, M.B., and Lowenthal, D.T. (2003). "Medications and Falls in the Elderly: A Review of the Evidence and Practical Considerations." *Pharm. Therap., P&T* 28:724-726, 733.

Roe, C.M., Anderson, M.J., and Spivack, B. (2002). "How Many Patients Complete an Adequate Trial of Donepezil?" *Alzheimer Disease and Associated Disorders*, 16(1), 49-51.

Roe, C.M., Anderson, M.J., and Spivack, B. (2002). "Use of Anticholinergic Medications by Older Adults with Dementia*." J. Am. Geriatr*. Soc. 50:836-842.

Roenker, D.L., Cissell, G.M., Ball, K.K., Wadley, V.G., and Edwards, J.D. (2003). "Speed-of-processing and driving simulator training result in improved driving performance." Human Factors, 45(2), 218-233. Slaughter, R.L., Erickson, S.R., and Thomson, P.A. (1994). "Clinical Interventions Provided by Doctor of Pharmacy Students. *Ann Pharmacother*, 28, 665-669.

RxMed. (2005). *The Comprehensive Resource for Physicians, Drug, and Illness Information*. www.rxmed.com

Salom, I.L., and Davis, K. (1995). "Prescribing for Older Patients: How to Avoid Toxic Drug Interactions." *Geriatrics*, 50(10), 37-45.

Samet, J.H., Sullivan, L.H., Traphagen, E.T., and Ickovics, J.R. (2001). "Measuring Adherence Among HIV-Infected Persons: Is MEMS Consummate Technology? *Aids and Behavior*, 5, 21-30.

Schmucker, D.L. (2001). "Liver Function and Phase I Drug Metabolism in the Elderly: A Paradox." *Drugs Aging* 18:837-851.

Shalansky, S.J., and Levy, A.R. (2002). "Effect of Number of Medications on Cardiovascular Therapy Adherence." *The Annals of Pharmacotherapy*, 36, 1532-1539.

Sheikh, J.I. (2004). "Anxiolytics, Sedatives, and Older Patients." *Primary Psychiat*. 11:51-54.

Slaughter, R.L., Ericson, S.R., and Thomson, P.A. (1994). "Clinical Interventions Provided by Doctor of Pharmacy Students." *The Annals of Pharmacotherapy*, 28, 665-669.

Smith, M., and Joseph, G. (2003). "Pharmacy Data in the VA Health Care System. *Medical Care Research and Review*, 60(3), Supplement to September 2003, 92S-123S. Available at www.herc.research.med.va.gov/pharmacy%20data.pdf.

Spagnoli, A., Ostino, G., Borga, A.D., et al. (1989). "Drug Compliance and Underreported Drugs in the Elderly." *Journal of the American Geriatrics Society*, 37, 619-624.

Spina, E., and Scordo, M.G. (2002). "Clinically Significant Drug Interactions with Antidepressants in the Elderly." *Drugs Aging* 19:299-320.

Sreih, A.G., Schonfield, M.H., Marieb, M.A. (1999). "Optic Neuropathy following Amiodarone Therapy." *Pacing Clinical Electrophysiology*, 22, 1108-1110.

Staplin, L., Lococo, K., McKnight, A.J., McKnight, A.S., and Odenheimer, G. (1998). *Intersection Negotiation Problems of Older Drivers, Volume II: Background Synthesis on Age and Intersection Driving Difficulties*. National Highway Traffic Safety Administration Publication No. DOT HS 808 850. Washington, DC.

Staplin, L., Lococo, K., Stewart, J., and Decina, L. (1999). *Safe Mobility for Older People Notebook*. National Highway Traffic Safety Administration Publication No. DOT HS 808 853. Washington, DC.

Steiner, J.F., and Earnest, M.A. (2000). "Lingua Medica: The Language of Medication-Taking." Annuals of Internal Medicine, 132, 926-930.

Stolze, H., Klebe, S., Zechlin, C., Baecker, C., Friege, L., and Deuschl, G. (2004). "Falls in Frequent Neurological Diseases: Prevalence, Risk Factors, and Aetiology," *Journal of Neurology*, 251, 79-84.

Stuck, A.E., Beers, M.H., Steiner, A., Aronow, H.U., Rubenstein, L.Z., and Beck, J.C. (1994). "Inappropriate Medication Use in Community-Residing Older Persons." *Archives of Internal Medicine*, 154(19), pp 2195-2200.

Sundet, K., Goffeng, L., and Hofft, E. (1995). "To Drive or Not to Drive: Neuropsyhological Assessment for Driver's License Among Stroke Patients." *Scandinavian Journal of Psychology*, 36(1), 47-58.

Szlyk, J. P., Brigell, M., and Seiple, W. (1993). "Effects of Age and Hemianopic Visual Field Loss on Driving." *Optometry and Vision Science*, 70, 1031-1037.

Szlyk, J.P., Mahler, C.L., Seiple, W., Vajaranant, T.S., Blair, N.P., and Shahidi, M. (2004). "Relationship of Retinal Structural and Clinical Vision Parameters to Driving Performance of Diabetic Retinopathy Patients." *Journal of Rehabilitation Research and Development*, 41(3A), 347-358.

Szlyk, J. P., Mahler, C. L., Seiple, W., Vajaranant, T. S., Blair, N. P., and Shahidi, M. (2004). "Effects of Retinal Structure and Clinical Vision Parameters on Driving Performance in Diabetic Retinopathy Patients." *Journal of Rehabilitation Research and Development*, 41:3 A, 347-357.

Task Force on Medicines Partnership and the National Collaborative Medicines Management Services Programme. (2002). *Room for Review: A Guide to Medication Review: the Agenda for Patients, Practitioners, and Managers*. London, England.

Taylor, C.T., Church, C.O., and Byrd, D.C. (2000). Documentation of Clinical Interventions by Pharmacy Faculty, Residents, and Students. *Ann Pharmacother*, 34, 843-846.

Thapa, P.B., Gideon, P., and Cost, T.W. (1998). "Antidepressants and the Risk of Falls Among Nursing Home Residents." *New England Journal of Medicine*, 339, 875-82.

Tinetti, M.E. (2004). "Preventing Falls in Elderly Persons." *The New England Journal of Medicine*, 348, 42-49.

Treharne, G.J., Lyons, A.C., Kitas, G.D. (2004). "Medication Adherence in Rheumatoid Arthritis: Effects of Psychosocial Factors." *Psychology, Health, and Medicine*, 9(3), 338-349.

Vermeeren, A. (2004). "Residual Effects of Hypnotics: Epidemiology and Clinical Implications." *CNS Drugs* 18:297-328.

Vik, S.A., Maxwell, C.J., and Hogan, D.B. (2004). "Measurement, Correlates, and Health Outcomes of Medication Adherence Among Seniors." *The Annals of Pharmacotherapy*, 38, 303-312.

Walsh, J. M., de Gier, J.J., Christopherson, A.S., and Verstraete, A.G. (2004). "Drugs and Driving." *Traffic Injury Prevention*, 5, 241-253.

Wang, P.S., Bohn, R.L., Knight, E., Glynn, R.J., Mogun, H., and Avorn, J. (2002). "Noncompliance with Antihypertensive Medications: The Impact of Depressive Symptoms and Psychosocial Factors." *Journal of General Internal Medicine*, 17(7) 504-511.

Weiler, J.M., Bloomfield, J.R., Woodworth, G.G., Grant, A.R., Layton, T.A., Brown, T.L., McKenzie, D.R., Baker, T.W., and Watson, G.S. (2000). "Effects of Fexofenadine, Diphenhydramine, and Alcohol on Driving Performance. A Randomized, Placebo-Controlled Trial in the Iowa Driving Simulator." *Annals of Internal Medicine*, 132(5), 354-363.

Wild, K., and Cotrell, V. (2003). "Identifying Driving Impairment in Alzheimer Disease: A Comparison of Self and Observer Reports Versus Driving Evaluation." *Alzheimer Disease and Associated Disorders*, 17(1), pp. 27-34.

Wilkinson, C., and Moskowitz, H. (2001). *Polypharmacy and Older Drivers: Literature Review*. Unpublished Manuscript, Southern California Research Institute, Los Angeles, CA.

Wong, E. (2004). The Polypharmacy Intervention Program. *Partnership for Improving Affordability and Quality*. BlueWorks Quarterly Application Submission. February 1, 2004.

Wood, J. (2002). "Age and Visual Impairment Decrease Driving Performance as Measured on a Closed-Circuit." *Human Factors*, 44(3), 482-494.

World Health Organization. (1975). *Requirements for Adverse Reaction Reporting*. Geneva.

Zacny, J. (1995). "A Review of the Effects of Opioids on Psychomotor and Cognitive Functioning in Humans." *Experimental and Clinical Psychopharmacology*, 3(4), 432-466.

Zautcke, J.L., Coker, S.B., Morris, R.W., and Stein-Spencer, L. (2002). "Geriatric Trauma in the State of Illinois: Substance Use and Injury Patterns." *American Journal of Emergency Medicine*, 20(1), 14-17.

Zeeh, J. (2001). The Aging Liver: Consequences for Drug Treatment in Old Age. *Arch. Gerontol. Geriat*r. 32:255-263.

Zermansky, A.G., Petty, D.R., Raynor, D.K., Freemantle, N., Vail, A., and Lowe, C. (2001). "Randomized Controlled Trial of Clinical Medication Review by a Pharmacist of Elderly Patients Receiving Repeat Prescriptions in General Practice." *BMJ*, Dec 8, 323, 1340-1343.

Zhan, C., Sangl, J., Bierman, A.S., Miller, M.R., Friedman, B., Wickizer, S.W., and Meyer, G.S. (2001). "Potentially Inappropriate Medication Use in the Community-Dwelling Elderly: Findings from the 1996 Medical Expenditure Panel Survey." *Journal of the American Medical Association*, 286, 2823-2829.

APPENDIX A:
Potentially Inappropriate Medications Commonly Prescribed for Older, Community-Dwelling Individuals

Drug Class	Particular Inappropriate Drugs Prescribed	Description & Side Effects Negatively Impacting Driving Ability
Antidepressants	Amitriptyline (“Elavil”; “Endep”; “Limbitrol” - combination with chlordiazepoxide)	Amitriptyline is a tricyclic antidepressant used to treat symptoms of depression. Amitriptyline may cause side effects including: drowsiness, weakness or tiredness; excitement or anxiety; difficulty falling asleep or staying asleep; restlessness; blurred vision; pain, burning, or tingling in the hands or feet; confusion; and unsteadiness.
	Doxepin (“Adapin;” “Sinequan”)	Doxepin is used to treat depression and anxiety. Side effects from doxepin are common: drowsiness weakness or tiredness; excitement or anxiety; and insomnia.
Benzodiazepines	Chlordiazepoxide (“Librium”)	Chlordiazepoxide is a long-acting benzodiazepine used to relieve anxiety and to control agitation caused by alcohol withdrawal. Side effects from chlordiazepoxide are common and include: drowsiness, dizziness, tiredness, and weakness.
	Diazepam (“Valium”)	Diazepam is a long-acting benzodiazepine used to relieve anxiety, muscle spasms, and seizures and to control agitation caused by alcohol withdrawal. Side effects include: drowsiness, dizziness, tiredness, and weakness
	Flurazepam (“Dalmane”)	Flurazepam is a short-acting benzodiazepine used on a short-term basis to help people fall asleep and stay asleep through the night. Side effects from flurazepam are common and include: headache, hangover effect (grogginess), drowsiness, dizziness or lightheadedness, and weakness.
Anti-Diabetic (Hypoglycemics)	Chlorpropamide (“Diabinese”)	Chlorpropamide is used to treat Type 2 (noninsulin-dependent) diabetes (formerly “adult-onset”), particularly in people whose diabetes cannot be controlled by diet alone. Chlorpropamide lowers blood sugar by stimulating the pancreas to secrete insulin and helping the body to use insulin efficiently.
Anti-Platelet Agents	Dipridamole (“Persantine”)	Dipyridamole is used with other drugs to reduce the risk of blood clots after heart valve replacement. It works by preventing excessive blood clotting. It is used in combination with blood thinners such as oumadin. Dipyridamole is also used with aspirin to reduce the risk of death after a heart attack and to prevent another heart attack. Although side effects from dipyridamole are not common, they can occur, and include: dizziness, headache, flushing (feeling of warmth), and itching.
Antihistamine	Hydroxyzine (”Atarax”; “Vistaril”)	Hydroxyzine is an antihistamine with anticholinergic (drying) and sedative properties that is used to treat allergic reactions (used to relieve the itching caused by allergies) It is also used to control the nausea and vomiting caused by various conditions, including motion sickness. It is also used for anxiety and to treat the symptoms of alcohol withdrawal. Although side effects from hydroxyzine are not common, they include: drowsiness; dizziness; chest congestion; headache.

Drug Class	Particular Inappropriate Drugs Prescribed	Description & Side Effects Negatively Impacting Driving Ability
Anti-Anxiety	Meprobamate ("Equanil;" "Meprospan;" "Miltown;" "Miltown 600;" "Neuramate")	Meprobamate is used to treat anxiety disorders or for short-term relief of the symptoms of anxiety. It is also used for muscle relaxation. Although side effects from meprobamate are not common, they can occur, and include: drowsiness; headache; difficulty coordinating movements (clumsiness and unsteadiness); excitement; and weakness.
Antispasmodic (urinary tract)	Oxybutynin ("Ditropan")	Oxybutynin is used to relieve urinary and bladder difficulties, including frequent urination and inability to control urination. It also helps to decrease muscle spasms of the bladder. Although side effects from oxybutynin are not common, they can occur, and include: blurred vision, dry eyes, and drowsiness
Narcotic Analgesic	Propoxyphene ("Darvon Puvules;" "Darvon-N")	Propoxyphene is used to relieve mild to moderate pain. Although side effects from propoxyphene are not common, they can occur, and include: dizziness, lightheadedness, drowsiness, mood changes, and headache.
Non-steroidal anti-inflammatory drugs (NSAIDs)	Specific drugs not mentioned in literature, but on the Beers List includes: indomethacin, phenylbutazone, ketorolac, mefenamic acid, and piroxicam	Nonsteroidal anti-inflammatory drugs (also called NSAIDs) are used to relieve some symptoms caused by arthritis (rheumatism), such as inflammation, swelling, stiffness, and joint pain. Certain side effects, such as confusion, swelling of the face, feet, or lower legs, or sudden decrease in the amount of urine, may be especially likely to occur in elderly patients, who are usually more sensitive than younger adults to the effects of nonsteroidal anti-inflammatory drugs. Also, elderly people are more likely than younger adults to get very sick if these medicines cause stomach problems. With phenylbutazone, blood problems may also be more likely to occur in the elderly.
Barbiturates	Specific drugs not listed in literature, but on the Beers List includes: butalbital, pentobarbital, and secobarbital.	Barbiturates belong to the group of medicines called central nervous system (CNS) depressants (medicines that cause drowsiness). Some of the barbiturates may be used before surgery to relieve anxiety or tension. In addition, some of the barbiturates are used as anticonvulsants to help control seizures in certain disorders or diseases, such as epilepsy. The barbiturates have been used to treat insomnia (trouble in sleeping); but if they are used regularly (for example, every day) for insomnia, they are usually not effective for longer than two weeks. The barbiturates have also been used to relieve nervousness or restlessness during the daytime. However, the barbiturates have generally been replaced by safer medicines for the treatment of insomnia and daytime nervousness or tension. Confusion, mental depression, and unusual excitement may be more likely to occur in the elderly, who are usually more sensitive than younger adults to the effects of barbiturates